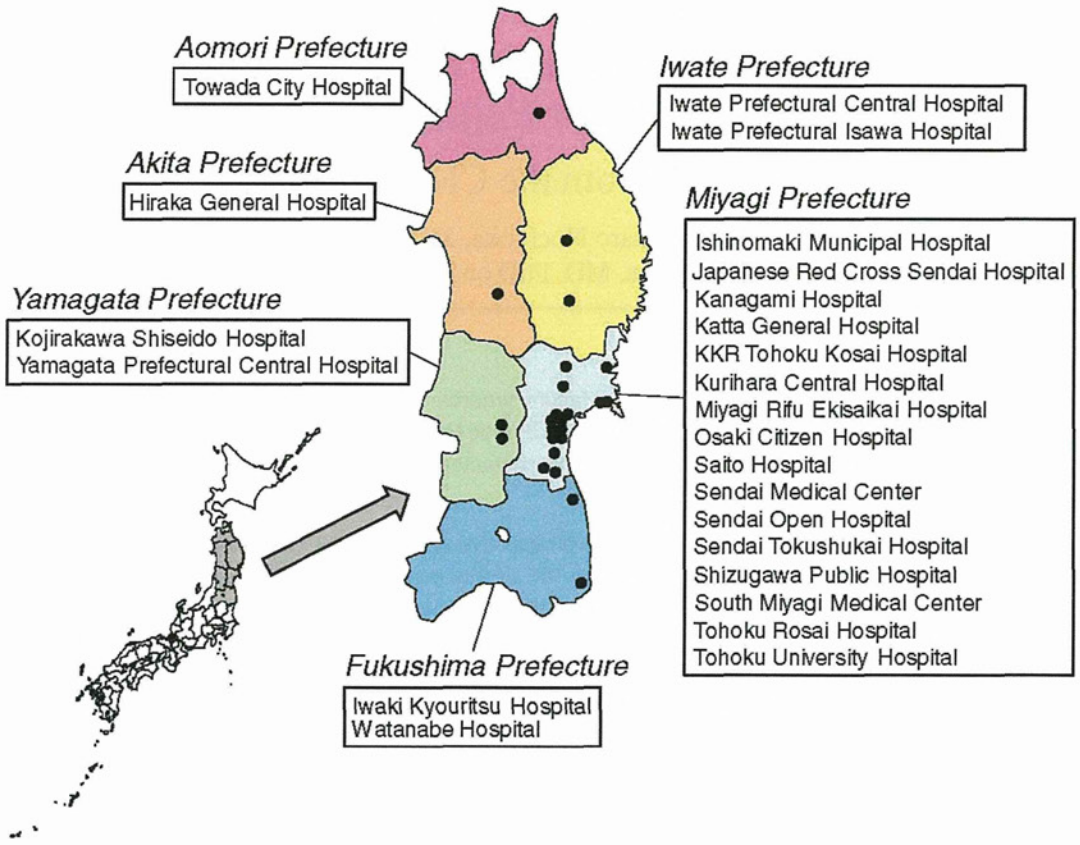

Figure 1. Map of the distribution of 24 collaborating hospitals in the Tohoku district.

patients with HF have preserved ejection fraction (pEF), as observed in the outpatient clinic, there is no evidence-based treatment guideline for such patients.[10,11] Patients with HFpEF are characterized as being more likely to be elderly, to be female and to have more comorbidities (eg, chronic kidney disease [CKD], chronic obstructive pulmonary disease, history of stroke and malignancy). Indeed, the pathophysiology of HFpEF is considered to be more closely related to those extracardiac factors compared with HF with reduced EF (HFrEF).[12,13] Another factor that is associated with the acceleration of the progression of CVD is the lower rate of achievement of clinical guideline-recommended treatment goals.[14,15] We need to regularly evaluate the penetration rate of evidence-based treatment and emphasize the appropriate adherence to the guidelines by physicians and patients.

Editorial p775

Thus, we started a large-scale multicenter prospective cohort study, named the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study, of consecutively enrolled patients at high risk for disease progression of CVD or HF due to the development of AHFS. In this first report of the CHART-2 Study, we examined the trend of etiology of HF patients and their characteristics as compared with the CHART-1 Study.[4,5]

Methods

Study Design and Specific Objectives

The CHART-2 Study is a prospective observational multicenter cohort study to identify the characteristics, mortality and prognostic risks of patients with overt HF and patients without HF but who are at high risk for disease progression of CVD. The purpose of the study was to evaluate the following: (1) characteristics of patients with overt HF and the associated prognostic risks; (2) characteristics of patients at risk for HF and the factors associated with CVD progression; (3) factors associated with the development of AHFS; (4) prevalence and prognostic impact of metabolic syndrome (MetS) in patients with overt HF; (5) the association between MetS and the development of AHFS; (6) the prevalence and prognostic impact of malignancy in patients with CVD; and (7) the prevalence of patients needing home nursing care and the characteristics of bedridden patients with CVD.

Information Disclosure

Rationale, design, and objectives of the CHART-2 Study were registered in clinicaltrials.gov (NCT00418041) and the University Hospital Medical Information Network (UMIN000000562) on the commencement of patient enrollment, and were updated instantly when modifications were made. Detailed information on the CHART-2 Study is available to the public on the Tohoku Heart Failure Association website (http://tohoku.cardiovascular-medicine.jp).

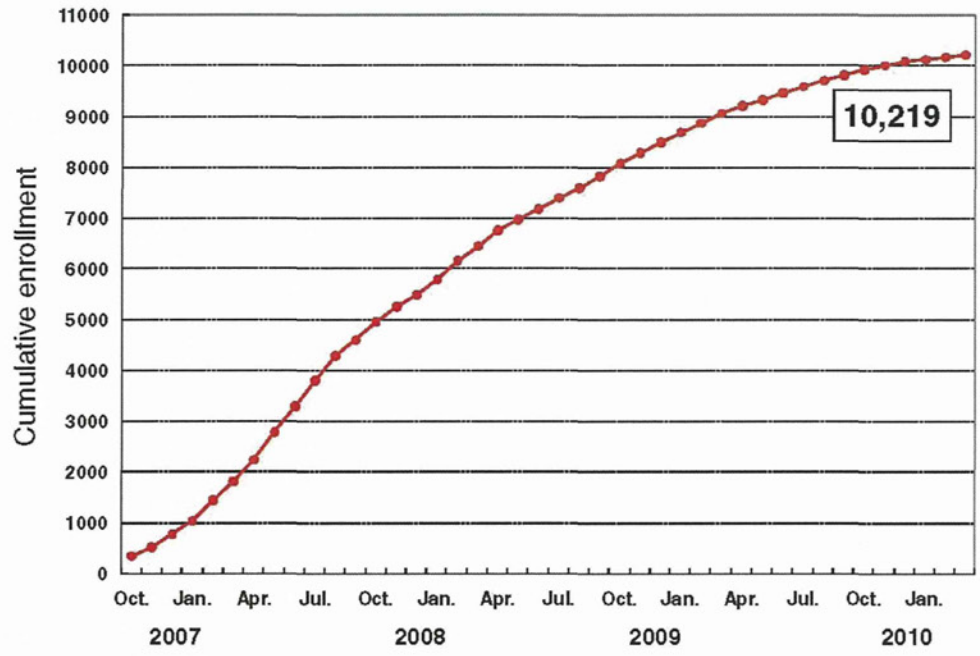

Figure 2. CHART-2 Study cumulative enrollment, showing a total of 10,219 registrations.

Site Selection

A total of 24 institutions, located in the Tohoku district, participated in the CHART-2 Study (**Figure 1**). A society was organized for the collaborating members and institutions, named the Tohoku Heart Failure Association, before the commencement of the study. The Tohoku district is located in the north-east of Japan and is composed of 6 prefectures, which include approximately 9.8 million individuals in total. The participating institutes and all collaborating members are listed in **Appendix 1**. Of 24 collaborating institutions, 15 hospitals also participated in the CHART-1 Study (**Appendix 1**). Patients enrolled in those 15 institutions accounted for 74.0% and 75.8% of the total subjects included in the CHART-1 and CHART-2 Studies, respectively.

Study Group

Stable patients were eligible for enrollment in the CHART-2 Study if they were aged ≥20 years with CAD or were in stage B, C or D defined according to the Guidelines for the Diagnosis and Management of Heart Failure in Adults authorized by the American College of Cardiology Foundation/American Heart Association.[2] In the present cohort study, patients who were asymptomatic but who had structural heart disease and/or impaired left ventricular (LV) function were categorized as being in stage B (**Appendix 2**). Stage C was defined as current or past symptoms of HF associated with underlying structural heart disease; and stage D was defined as refractory HF in which specialized and advanced treatment strategies were indicated.[2] HF was diagnosed according to the criteria of the Framingham Heart Study.[16] Patients who had been enrolled in the CHART-1 Study were not included in the CHART-2 Study. There were no other exclusion criteria in the present study. The CHART-2 Study was approved by the local ethics committee in each institution. Significant CAD was defined as either organic CAD requiring revascularization or vasospastic angina documented on electrocardiography or angiography. Eligible patients were consecutively recruited after written informed consent was obtained.

Data Collection and Processing

Eight clinical research coordinators (CRC) who belonged to the head office of the CHART-2 Study at Tohoku University visited collaborating hospitals regularly. They fully assisted attending physicians in registration, including candidate screening, explanation of the study design, obtainment of written informed consent, and data extraction from medical charts. Data were entered using a Web-based data collecting system (newly developed by Fujitsu Tohoku Systems) by CRC and trained keypunchers. An identification number was assigned to each enrolled patient and personal information was completely excluded. Data were recorded with regard to demographics, medical history, smoking history, alcohol use, family history of CVD, comorbidities for cardiovascular risks, laboratory findings, echocardiography reports, findings of coronary angiography, previous surgical treatments, and medications at entry. Anemia was defined as hemoglobin <12 g/dl in women and <13 g/dl in men, following the World Health Organization definition.[17] CKD was diagnosed when estimated glomerular filtration rate was $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$, which was calculated using the formula for Japanese individuals.[18] MetS was defined according to the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome.[19]

Follow-up Survey and Study Outcomes

All follow-up data and events are surveyed once a year during the study period. Collected data were monitored at least twice yearly. Planned completion of the follow-up period is March 2013. Several predefined outcomes including development of AHFS, mortality and other events worsening HF status will be collected in the CHART-2 Study.

Table 1. Baseline Characteristics of the CHART-1 and CHART-2 Patients vs. HF Stage

	CHART-1 (Stage C/D, 2004)	P value*	CHART-2 (2010)				
			Total	Stage B or CAD without HF	Stage C	Stage D	P value**
No. patients	1,078		10,219	5,484 (53.7)	4,640 (45.4)	95 (0.9)	
Age (years), mean±SD	68.7±13.4	0.8	68.2±12.3	67.6±12.2	68.8±12.3	74.2±12.5	<0.001
<40 (%)	3.5	0.4	3.1	3.4	2.7	1.1	<0.001
40–64 (%)	29.2		29.0	29.6	28.5	21.1	
65–74 (%)	31.7		33.7	35.6	31.8	22.1	
≥75 (%)	35.6		34.2	31.4	37.0	55.8	
Male (%)	64.5	0.01	69.8	71.0	68.5	64.2	0.01
Outpatients (%)	NA	NA	79.5	80.3	79.0	60.6	<0.001
NYHA functional class (%)							
I	6.7	<0.001	47.4	68.3	23.4	9.5	<0.001
II	72.9		46.9	30.8	66.5	21.1	
III	19.5		5.3	0.8	9.8	43.2	
IV	0.9		0.4	0.0	0.3	26.3	
Blood pressure (mmHg), mean±SD							
Systolic	126.3±19.1	0.9	128.3±18.6	130.1±17.9	126.4±19.1	119.1±22.4	<0.001
Diastolic	71.5±11.0	0.08	73.5±11.8	74.5±11.5	72.3±11.9	69.2±13.2	<0.001
Heart rate (/min), mean±SD	74.7±14.3	<0.001	71.0±14.1	69.7±13.2	72.4±15.0	72.7±14.5	<0.001
BMI (kg/m^2), mean±SD	23.0±3.7	<0.001	24.0±3.6	24.2±3.5	23.8±3.9	21.6±3.4	<0.001
<18.5 (%)	9.2	<0.001	6.6	4.8	8.3	20.0	<0.001
18.5–22.9 (%)	42.9		33.9	32.3	35.5	47.4	
23.0–24.9 (%)	20.6		23.5	25.0	21.9	21.1	
25.0–29.9 (%)	23.5		30.7	33.0	28.4	9.5	
≥30 (%)	3.7		5.3	4.9	5.9	2.1	
Waist circumference (cm), mean±SD	NA	NA	85.9±9.9	86.6±9.5	85.3±10.3	81.4±8.5	<0.001
Male	NA	NA	87.2±9.0	87.7±8.8	86.6±9.2	82.6±8.1	<0.001
Female	NA	NA	83.1±11.2	83.9±10.4	82.4±11.9	79.2±9.0	<0.001
Smoking (%)							
Never	NA	NA	52.7	51.7	53.7	63.2	0.052
Current	NA	NA	18.2	18.3	18.3	14.9	
Former	NA	NA	29.1	30.1	28.0	21.8	
Alcohol (%)							
Never	NA	NA	49.8	48.5	51.1	60.5	<0.001
Regular	NA	NA	27.7	30.0	25.1	19.8	
Chance	NA	NA	14.7	14.4	15.2	4.7	
Former	NA	NA	7.8	7.1	8.5	15.1	
Cardiothoracic ratio (%), mean±SD	NA	NA	52.1±6.5	50.7±5.8	53.6±6.9	57.0±8.1	<0.001
Laboratory findings, mean±SD							
Hemoglobin (g/dl)	13.0±2.2	0.007	13.4±2.0	13.6±1.8	13.2±2.2	12.0±2.5	<0.001
eGFR (ml·min^{-1}·1.73m^{-2})	60.9±30.7	0.9	64.5±22.6	67.5±21.2	61.1±23.5	53.2±29.6	<0.001
HDL-cholesterol (mg/dl)	NA	NA	52.2±15.4	52.9±15.3	51.5±15.6	50.8±14.9	<0.001
LDL-cholesterol (mg/dl)	NA	NA	105.7±30.0	106.3±29.4	105.3±30.9	93.7±26.2	0.001
Fast plasma glucose (mg/dl)	NA	NA	116.7±36.8	115.6±35.4	118.0±38.1	115.6±49.3	0.01
Hemoglobin A_{1c} (%)	NA	NA	5.8±1.0	5.8±0.9	5.9±1.0	5.8±1.1	<0.001
Uric acid (mg/dl)	NA	NA	5.9±1.6	5.7±1.5	6.2±1.8	6.6±2.2	<0.001
Other intervention							
CRT/ICD (%)	1.5	0.002	1.9	0.9	2.9	15.8	<0.001
Heart surgery (%)	NA	NA	14.4	10.9	18.6	18.9	<0.001
PCI (%)	NA	NA	36.8	40.6	32.6	26.3	<0.001
BNP (pg/ml), mean±SD	273.0±352.6	<0.001	145.4±249.3	97.6±188.1	191.4±283.5	454.3±555.6	<0.001
Urine albumin (mg/g·Cre), mean±SD	NA	NA	129.6±476.7	106.5±429.9	157.6±530.1	180.9±330.0	0.001

HF, heart failure; CAD, coronary artery disease; NYHA, New York Heart Association; BMI, body mass index; NA, not applicable; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; BNP, B-type natriuretic peptide; Cre, creatinine.
*Comparison of stage C/D patients in the CHART-1 Study with those in the CHART-2 Study. **Comparison of stage B/CAD, stage C, and stage D in the CHART-2 Study.

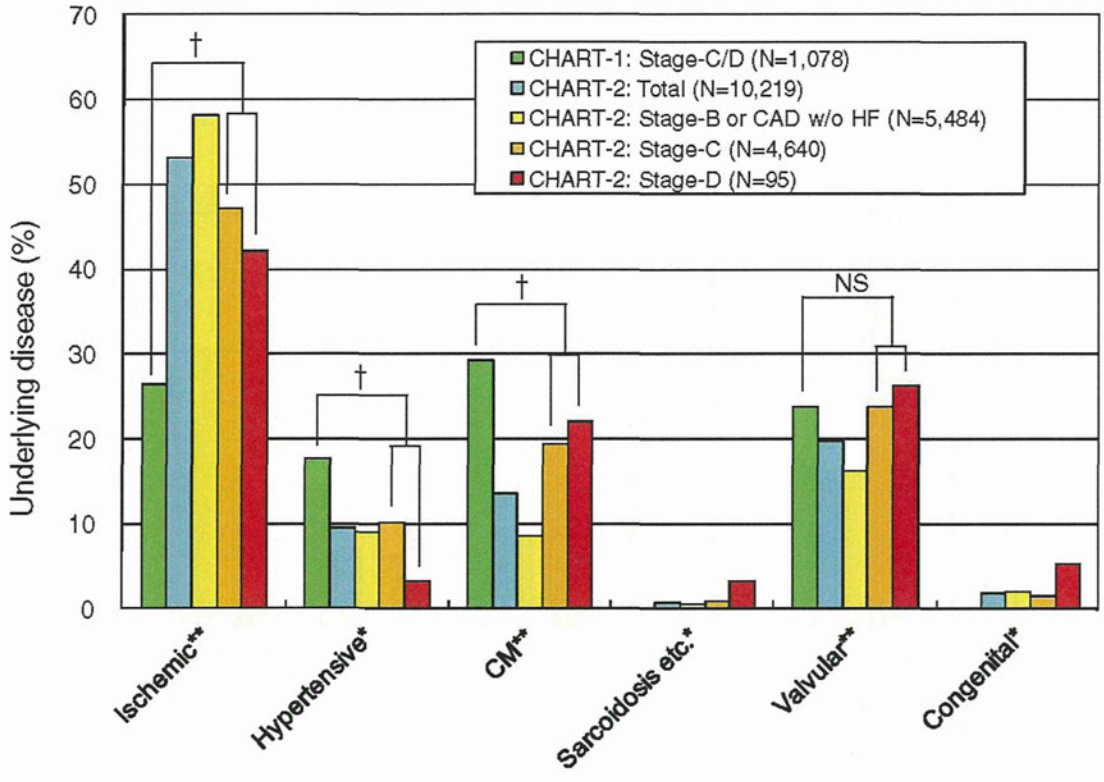

Figure 3. Underlying disease of the CHART-1 and the CHART-2 patients. CAD, coronary artery disease; CM, cardiomyopathy; HF, heart failure; w/o, without. *P<0.05 and **P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.001 between stage C/D patients in the CHART-1 Study and those in the CHART-2 Study.

Statistical Analysis

We divided the study patients into 3 groups: patients with CAD but without HF or who were in stage B; those in stage C; and those in stage D. Comparisons of data between the 3 groups were performed using ANOVA test for continuous variables and chi-squared test for dichotomous variables. Continuous data are given as mean±SD. In order to elucidate the trend of HF in Japan, we selected overt HF patients from the CHART-1 Study (n=1,078, 84.4% of the total cohort), who were categorized as being in stages C or D. We then compared the characteristics of the stage C/D patients in the CHART-1 Study with those in the CHART-2 Study.[4,5] All statistical analyses were performed using IBM SPSS Statistics 19.0, and statistical significance was defined as 2-sided P<0.05.

Results

The enrollment of patients in the CHART-2 Study was started in October 2006. The registration period was prolonged once to achieve the target enrollment number. As of March 2010, a total of 10,219 patients have been enrolled at 24 institutions and the recruitment of patients has been closed, making the Study the largest multicenter prospective cohort of HF patients in Japan (**Figure 2**).

Clinical Profiles of the CHART-2 Patients at Registration

The mean age of the total study population was 68.2±12.3 years. Male patients accounted for 69.8%, and 79.5% of the total subjects were outpatients. In the present study, 5,484 patients (53.7%) did not have HF but had CAD or cardiac structural disorder. The stage C group included 4,640 patients and accounted for 45.4% of the entire cohort, while 95 patients (0.9%) were classified as being in stage D. Baseline characteristics of the CHART-1 stage C/D patients and the total CHART-2 subjects are given in **Table 1**. These data including age, sex, vital signs, HF symptoms, anthropometric data, history of smoking, alcohol use, and laboratory findings illustrate the difference in patient characteristics between the 2 studies performed at approximately 6-year intervals. Etiology, comorbidity, medication and echocardiographic findings at registry in the 2 studies are also given in **Figures 3–6**, respectively.

Baseline Characteristics and Different Clinical Profile vs. HF Stage

Clinical profiles of the CHART-2 patients were considerably different between the 3 HF stages. Mean age increased and HF symptoms became more severe as HF stage progressed (**Table 1**). Mean systolic/diastolic blood pressure at registration was 128.3/73.5 mmHg and decreased significantly with progression of HF stage. Mean body mass index was 24.0±3.6 kg/m^2 and mean waist circumference was 87.2±9.0 cm in men and 83.1±11.2 cm in women. The factors for obesity status significantly decreased with HF severity (**Table 1**). MetS as defined by the Japanese criteria was also significantly less frequent in patients in stage C or D compared with those in stage B or those who had CAD but without HF

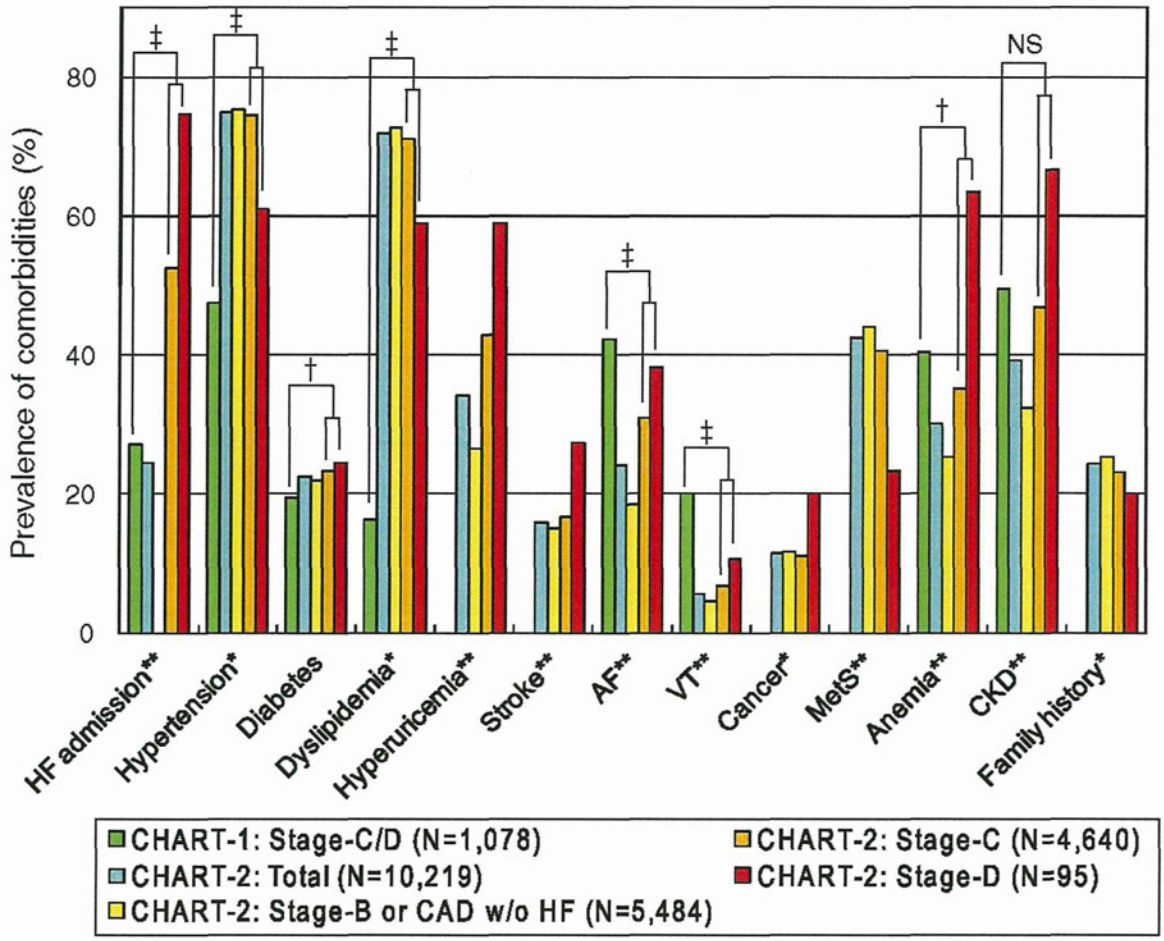

Figure 4. Comorbidities of the CHART-1 and the CHART-2 patients. AF, atrial fibrillation/flutter; CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; MetS, metabolic syndrome; VT, ventricular tachycardia; w/o, without. *P<0.05 and **P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.05 and ‡P<0.001 between stage C/D patients in the CHART-1 Study and those in the CHART-2 Study.

(**Figure 4**). Approximately 18% of patients with CVD had a smoking habit and approximately 28% of the total patients were regular alcohol drinkers (**Table 1**).

Etiology of CVD in the CHART-2 patients is shown in **Figure 3**. CAD was the most prevalent etiology of CVD (53.1%), and approximately 20% of patients had valvular abnormalities as a cause of CVD. Cardiomyopathy accounted for 13.6% of the CHART-2 patients, and the prevalence increased as HF stage progressed. Myocardial diseases due to sarcoidosis or amyloidosis were observed in 0.7% of the total population.

Figure 4 illustrates comorbidities of the CHART-2 patients. The proportion of patients with a history of hospitalization for HF was 52.5% in stage C and 74.7% in stage D. Histories of hypertension or dyslipidemia were very common (74.9% and 71.8%), and diabetes was observed in 22.5% of the total population. Approximately 12% of patients had malignant neoplasm at enrollment. The prevalence of CKD increased significantly as HF stage progressed, accompanied by an increased percentage of patients with anemia and elevated urine albumin excretion (**Table 1**). Patients with overt HF, who were categorized in stages C or D, were also characterized by higher prevalence of atrial fibrillation/flutter, ventricular tachycardia and a history of stroke.

Heart surgery and percutaneous coronary intervention were performed in 14.4% and in 36.8% of the study population, respectively. The rates of use of implantable cardioverter defibrillator and cardiac resynchronization therapy were the highest in stage D (**Table 1**).

Figure 5 shows the usage rates of medication in the CHART-2 patients. A total of 64.6% of patients were treated with renin–angiotensin system (RAS) inhibitors, and β-blockers were used in 40.4% of patients. The penetration rates of such standard medication for HF were the highest in stage C but decreased in stage D patients. Aldosterone inhibitors, digitalis, warfarin, and amiodarone were used most frequently in stage D patients.

Echocardiographic findings and LVEF are shown in **Figure 6**. As HF stage progressed, LV end-diastolic dimension was increased, LVEF was decreased, and the percentage of patients with low EF was increased. Patients with HFpEF comprised 69.1% and 51.1% of stage C and D subjects, respectively. B-type natriuretic peptide (BNP) level was also increased as HF stage progressed (**Table 1**).

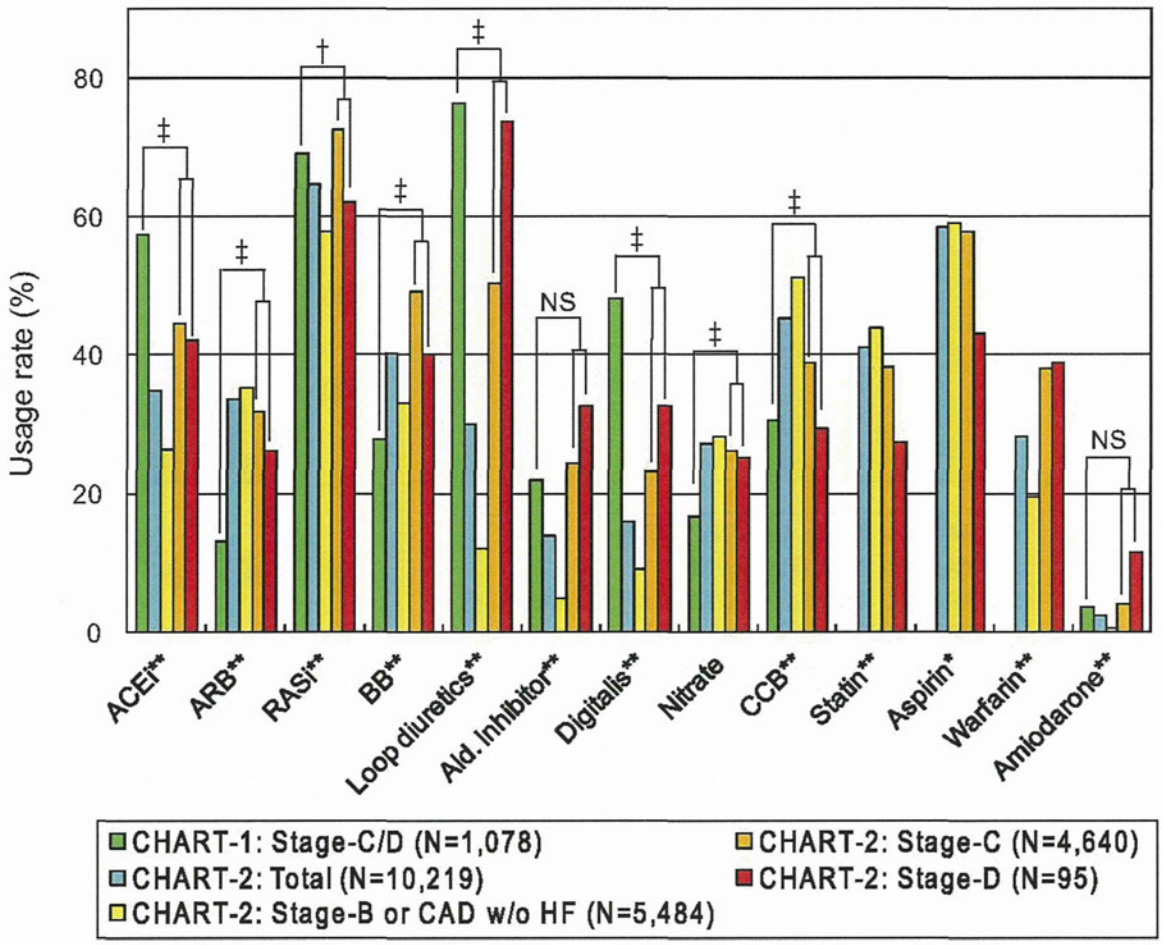

Figure 5. Medication of the CHART-1 and CHART-2 patients. ACEi, angiotensin-converting enzyme inhibitor; Ald., aldosterone; ARB, angiotensin II receptor blocker; BB, β-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; RASi, renin–angiotensin system inhibitor; w/o, without. *P<0.05 and **P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.05 and ‡P<0.001 between stage C/D patients in the CHART-1 Study and those in the CHART-2 Study.

Comparisons of Baseline Characteristics Between the CHART-1 Patients and the CHART-2 Patients or Those in Western Studies

The baseline characteristics of stage C/D patients enrolled in the previous CHART-1 Study[4,5] are given in **Table 1** and **Figures 3–6**. **Table 2** lists the comparisons of registration data in overt HF patients between CHART-1, CHART-2, and several observational Western cohort studies.

Mean age, blood pressure, and prevalence of CKD were similar between overt HF patients in the CHART-1 Study and those in the CHART-2 Study (**Tables 1,2**). As compared with the CHART-1 patients, however, those in the CHART-2 Study were characterized by a higher proportion having CAD as an etiology of HF (47.1%), the higher prevalence of histories of hypertension and diabetes (74.3% and 23.3%, respectively), more frequent HF admission history (53.0%), and a higher proportion having HFpEF (68.7%; **Table 2**; **Figures 3–5**). The usage rate of RAS inhibitors and β-blockers for overt HF patients in the CHART-1 and CHART-2 Studies increased from 69.1% to 72.3% and from 27.9% to 49.0%, respectively. In contrast, the usage rate of loop diuretics and digitalis decreased from 76.3% to 50.9% and from 48.1% to 23.5%, respectively (**Figure 5**).

Table 2 summarizes the baseline characteristics of overt HF patients in the CHART-1 Study, the CHART-2 Study, and Western observational cohort studies. Compared with Western patients, the CHART patients were characterized by less frequent ischemic etiology of HF, lower systolic blood pressure, less frequent diabetes, lower body mass index, and more frequent HFpEF. Usage rates of RAS inhibitors and β-blockers were similar between the CHART-2 patients and the Western HF patients except for the use of diuretics.

Characteristics of Patients in Stage B or Having CAD but Without HF

Patients in stage B or having CAD but without HF were characterized by younger age (67.6 years), a higher proportion of male patients (71.0%), less severe symptoms, and higher EF compared with patients in stages C or D (**Table 1**; **Figure 6**). The prevalence of cardiovascular risks such as hypertension, diabetes, and dyslipidemia, however, was similarly high (**Figure 4**), BNP was mildly elevated (**Table 1**), and the usage rate of standard HF treatment, such as RAS inhibitors and β-blockers, was too low in those patients (**Figure 5**).

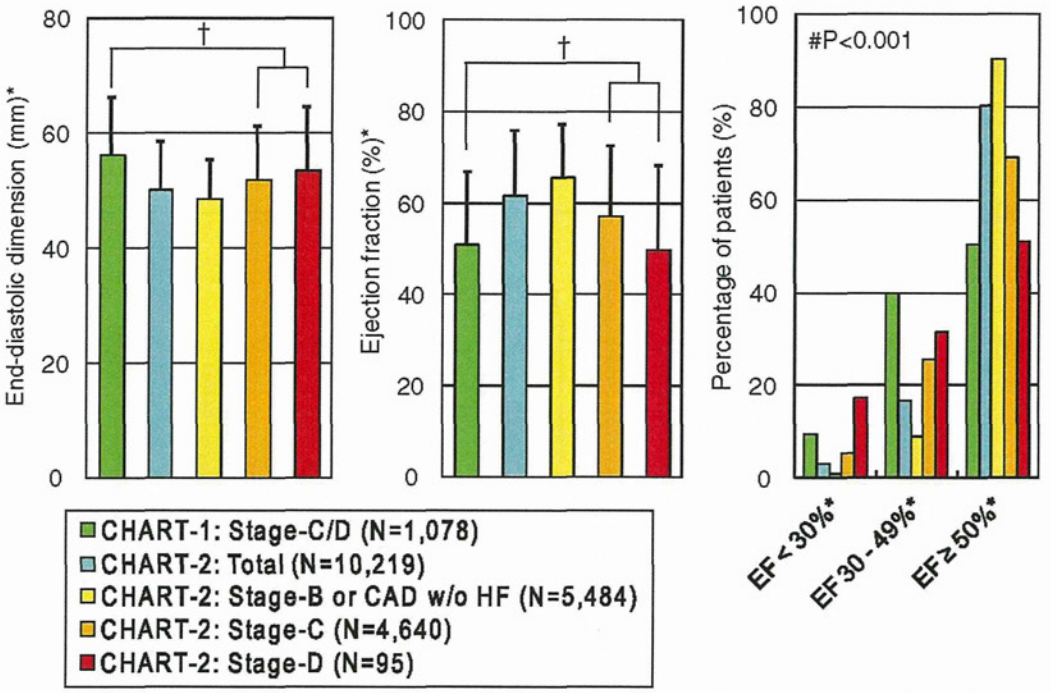

Figure 6. Left ventricular dimension and ejection fraction of the CHART-1 and CHART-2 patients. CAD, coronary artery disease; EF, ejection fraction. *P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.001 between stage C/D patients in the CHART-1 Study and those in the CHART-2 Study. #P-value for the difference in distribution of ejection fraction between stage C/D patients in the CHART-1 Study and those in the CHART-2 Study.

Discussion

The clinical characteristics and prognosis of patients at high risk for disease progression due to development of AHFS have been poorly described, and thus epidemiological research involving such patients is extremely important in preventing the disease progression of HF and CVD. The CHART-2 Study is the first and the largest multicenter prospective cohort of consecutively enrolled patients at high risk for CVD progression due to AHFS in Japan. The Tohoku University head office and the CRC fulfilled their function to enroll patients in collaborating hospitals located in the Tohoku area, and the newly developed Web-based entry system also supported smooth entry of patient data.

Major Findings of the Present Analysis

Analysis of the registration data provides several new findings regarding patients with HF and those at risk of disease progression due to development of AHFS. First, when the CHART-2 patients were compared with the CHART-1 patients, a trend of increasing ischemic etiology and comorbidities of diabetes and hypertension was evident in Japanese patients with HF, whereas those risks had been more prominent in Western patients with HF (**Table 2**; **Figures 3,4**). Second, in the CHART-2 Study approximately 54% of patients were classified as being in stage B or having CAD without overt HF. In those patients, the plasma BNP concentration was mildly elevated and the cardiovascular risk profile was also similar to that of patients in stages C or D (**Table 1**; **Figures 3–5**). Third, the severity of prognostic risks including reduced EF, elevated BNP, comorbidity of CKD, and low hemoglobin level were exacerbated progressively as HF stage progressed in the CHART-2 patients (**Table 1**; **Figures 4,6**). Fourth, the prevalence of HFpEF patients was higher (68.7%) in the CHART-2 Study compared with the CHART-1 Study, demonstrating the trend of increasing prevalence of HFpEF (**Figure 6**).[12,13] Finally, the usage rates of standard medications in the CHART-2 patients were increased compared with the CHART-1 patients, but the usage was still too low, especially in the stage B patients (**Figure 5**).

Clear Trend of Increasing Prevalence of Ischemic HF in Japan

Several observational studies have previously demonstrated that the prevalence of CAD as an etiology in HF patients was 25–32% in Japan.[3,4,20,21] The prevalence of HF patients with ischemic etiology in the CHART-2 Study was dramatically increased compared with that in the CHART-1 Study, approaching the prevalence observed in Western subjects (**Table 2**, **Figure 3**). The prevalence of hypertension and diabetes, which are significant risks for developing CAD, similarly increased in the CHART-2 patients compared with the CHART-1 patients (**Table 2**, **Figure 4**). The report of the MIYAGI-AMI Registry Study showed the steady trend of increasing incidence of acute myocardial infarction in 30 years in Japan.[22] We speculate that the clear trend of increasing prevalence of CAD as an etiology of HF is due to the following reasons: (1) the number of CAD patients has been increasing due to accelerated westernization of lifestyle in Japanese people; and (2) the number of survivors after acute coronary event has dramatically increased due to the recent progress in treatment.

Table 2. Baseline Characteristics: CHART Patients vs. Previous Western HF Studies

	Framingham Study (1993)[16]	ADHERE (2005)[8]	EuroHeart Failure Survey II (2006)[9]	Owan et al (2006)[12]	Bhatia et al (2006)[13]	CHART-1 (Stage C/D, 2004)[4]	CHART-2 (Stage C/D, 2010)
No. patients	652	105,388	3,580	4,596	2,450	1,078	4,735
Age (years), mean±SD	70.0±10.8	72.4±14.0	69.9±12.5	73.0	73.1	68.7±13.4	68.9±12.3
Male (%)	51	48	61.3	55.5	52.4	64.5	68.4
Blood pressure (mmHg), mean±SD							
Systolic	150.9±27.6	144±32.6	NA	NA	150.0	126.3±19.1	126.3±19.2
Heart rate (/min), mean±SD	78.6±14.6	NA	NA	NA	NA	74.7±14.3	72.4±14.9
Comorbidity (%)							
Hypertension	74	73	NA	54.9	51.3	47.4	74.3
Diabetes	19	44	NA	33.7	36.3	19.5	23.3
Atrial fibrillation/flutter	NA	31	NA	34.5	26.6	42.3	31.0
Ventricular tachycardia	NA	8	NA	NA	NA	20.1	6.8
CKD	NA	30 (renal insufficiency)	NA	NA	20.1 (Cre <1.7 mg/dl)	49.5	47.3
History of HF admission	NA	NA	NA	NA	NA	27.2	53.0
Underlying disease (%)							
Ischemic	53.5	57	53.6	58.6	44.0	26.4	47.1
Hypertensive	23.6	NA	62.5	NA	NA	17.7	9.9
Valvular	16.0	NA	34.4	4.7	NA	23.8	23.8
BMI (kg/m^2), mean±SD	27.2±5.3	NA	26.8	29.1	NA	23.0±3.7	23.8±3.9
LVEF (%), mean±SD	NA	34.4±16.1	38±15	44.1	39.0	50.9±16.0	56.9±15.5
≥50% (%)	NA	37†		47.2	35.9†	50.6	68.7
Medication (%)							
ACEI	NA	41	55.0	NA	NA	57.4	44.6
ARB	NA	12	9.3	NA	NA	13.1	31.8
β-blocker	NA	48	43.2	NA	NA	27.9	49.0
Loop diuretics	NA	70 (all diuretics)	71.2 (all diuretics)	NA	NA	76.3	50.9
Digitalis	NA	28	26.6	NA	NA	48.1	23.5
Nitrate	NA	26	NA	NA	NA	16.8	26.3
Amiodarone	NA	11 (all anti-arrhythmics)	12.9 (all anti-arrhythmics)	NA	NA	3.6	4.2

CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Other abbreviations see in Table 1.
†Ejection fraction >40%.

Patients at High Risk for AHFS in the CHART-2 Study

Heart failure is classified according to the 4 stages of HF syndrome.[2] Stage A and stage B are pre-HF stages but appropriate identification and treatment are needed to prevent the progression to overt HF, which is equivalent to the development of de novo AHFS. In the present study, we enrolled patients without HF but with CAD, patients with structural heart disease but without HF (stage B), and patients with overt HF (stages C and D) in order to include patients at high risk for developing AHFS.

In Western HF patients, approximately 60–80% of patients hospitalized due to AHFS have a previous history of HF,[8,9,23] and the re-hospitalization rate following HF admission is 25% at 30 days after admission.[24] These findings suggest that patients in stages C or D are the most susceptible group to AHFS. Approximately one-third of AHFS cases are considered to be de novo AHF,[8,9,23] and the majority were related to CAD.[24,25] Other major comorbidities or cardiovascular risks in patients admitted with AHFS included hypertension, diabetes, arrhythmia and renal insufficiency.[8,9,23,25] In the present study, the stage B patients were characterized by a high number of cardiovascular risks along with some cardiac structural abnormalities, and 58.2% of those patients had CAD (**Figures 3,4**). For these reasons, we also enrolled stage B patients and those with CAD but without HF, as patients at high risk for developing AHFS.

HF Stage Progression and Exacerbation of Cardiovascular Risk

Baseline characteristics of the CHART-2 patients showed the graded effects of HF stage on cardiovascular risk and comorbidity. As the HF stage progressed from stage B to stage D, mean age, number of female patients, heart rate, cardiothoracic ratio, LV dimension, and plasma BNP concentration increased significantly; whereas blood pressure, hemoglobin level, body mass index, waist circumference and EF decreased significantly (**Table 1**; **Figures 3–6**). In the present study the BNP level was mildly elevated in patients with CAD but without HF or in those in stage B, and was significantly increased with the decline of EF and exacerbation of HF stage (**Table 1**; **Figure 6**). It has also been reported that stage B patients had increased BNP level with heightened risk of mortality or cardiovascular events.[26,27] CKD is also an extensive public health problem and is more prevalent in patients with CVD or with CVD-related risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and MetS.[28,29]

Furthermore, CKD is also a significant aggravating factor in those patients. As shown in **Figure 4**, the number of patients with CKD increased with the severity of HF stage. Anemia or low hemoglobin level is associated with poor prognosis in HF patients.[30] Hemoglobin level was decreased in the CHART-2 patients, reflecting the worsening in severity of HF and CKD in those patients (**Table 1**; **Figure 4**). MetS involves a cluster of important risk factors, including central obesity, elevated fasting plasma glucose, dyslipidemia, and high blood pressure and has become a leading health concern due to the strong link to CVD.[19] A recent meta-analysis of 87 studies reported that MetS is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality.[31] Otherwise low body mass index has been consistently considered to be associated with the increased number of deaths in HF patients,[32] and the prognostic influence of MetS in those patients remains uncertain. The present study demonstrates that both body mass index and the prevalence of MetS in the CHART-2 patients were significantly decreased as HF stage progressed (**Table 1**; **Figure 4**).

Increasing Prevalence of HFpEF in the CHART-2 Study

Approximately half of the HF patients have normal or preserved EF, called HFpEF.[12,13,20] In the CHART-2 Study the prevalence of HFpEF was increased compared with the CHART-1 Study (68.7% vs. 50.6%; **Table 2**; **Figure 6**). Although the reason for the increasing prevalence of HFpEF remains unknown, we suggest the following: (1) the Japanese population is rapidly aging and the percentage of elderly HF patients has increased;[3] (2) the prevalence of hypertension has increased as a comorbidity of HF (**Table 2**); and (3) the recent progress in reperfusion therapy has contributed to preservation of EF after acute coronary events.[22]

Use of Standard Medication for CVD in the CHART-2 Patients

It has previously been reported that standard HF treatments were not used in patients who would have benefited from such medications.[33] The overall usage rates of RAS inhibitors or β-blockers in the CHART-2 patients were 64.6% and 40.4%, respectively (**Figure 5**). Although the penetration rate of such treatment was increased in overt HF patients in the CHART-2 Study compared with the CHART-1 Study (**Table 2**), it was still too low, especially in stage B patients (**Figure 5**). Further investigation is necessary to evaluate how such a low treatment rate of evidence-based medicine affects the prognosis of stage B patients.

Study Limitations

Several limitations in the design of the CHART-2 Study should be mentioned. First, the present study did not include data regarding physical inactivity, diet or nutrition, all of which are important modifiable risks for developing CVD. Second, all subjects in the CHART studies were Japanese people, which may limit extrapolation of the results to patients in Western countries. Third, the difference of the entry criteria in the CHART-1 and CHART-2 Studies might limit accurate comparison of enrolled patients in those 2 studies. Fourth, the primary design of the present study did not cover chronic lung disease, which has been recently recognized as one of the important cardiovascular risks.[34] In order to address this important issue, we started a retrospective survey on chronic obstructive pulmonary disease in the CHART-2 patients from April 2010.

Conclusions

The CHART-2 Study demonstrates the trend of increasing westernization of etiology, and the prevalence of hypertension and diabetes in HF patients in Japan. Although the number of HF patients is predicted to increase dramatically in the near future, the usage rate of standard medications in patients with CVD or HF is still too low, especially in stage B patients. Given the growing number of patients with CVD and HF in Japan, strategies preventing the development of CAD must be given top priority.

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Appendix 1

Study Organization of The CHART-2 Study

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*Fifteen hospitals were collaborating institutions in the CHART-1 Study.

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Appendix 2

Subjects in stage B must meet at least one of the following criteria and must not have signs, symptoms, or history of hospitalization for heart failure.

(1) Enlarged left ventricular end-diastolic dimension (≥55 mm) measured on echocardiography.
(2) Impaired left ventricular ejection fraction (≤50%) measured on echocardiography.
(3) Thickened interventricular septum (>12 mm) and/or thickened left ventricular posterior wall (>12 mm) measured on echocardiography.
(4) Significant valvular stenosis/insufficiency.
(5) Significant myocardial abnormalities.
(6) Congenital abnormalities.
(7) Previous cardiac surgery.

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

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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 predicition 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.[1] Furthermore, there are no authorized treatment guidelines for HFpEF due to its pathophysiological heterogeneity.[2,3] Recent guidelines recommend the inclusion of objective evidence of diastolic dysfunction in diagnosing HFpEF;[4] 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.[5] The co-existence of HF and chronic kidney disease (CKD) carries an extremely poor prognosis.[6] Furthermore, the prognosis of

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HFpEF patients may be more influenced by the existence of CKD compared with for those with HFrEF.[5,7] 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,[8] and in those with hypertension[9] and diabetes,[10] 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.[11] 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 (≥30 mg/g) was ~30%.[12,13] Furthermore, HF patients with albuminuria (≥30 mg/g) had poorer prognosis.[13–16] 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).[17] Briefly, eligible patients were aged ≥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.[18] Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[19] 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 ≥50% were classified as having HFpEF, whereas those with LVEF <50% were classified as having HFrEF.[1] 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.[20] 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

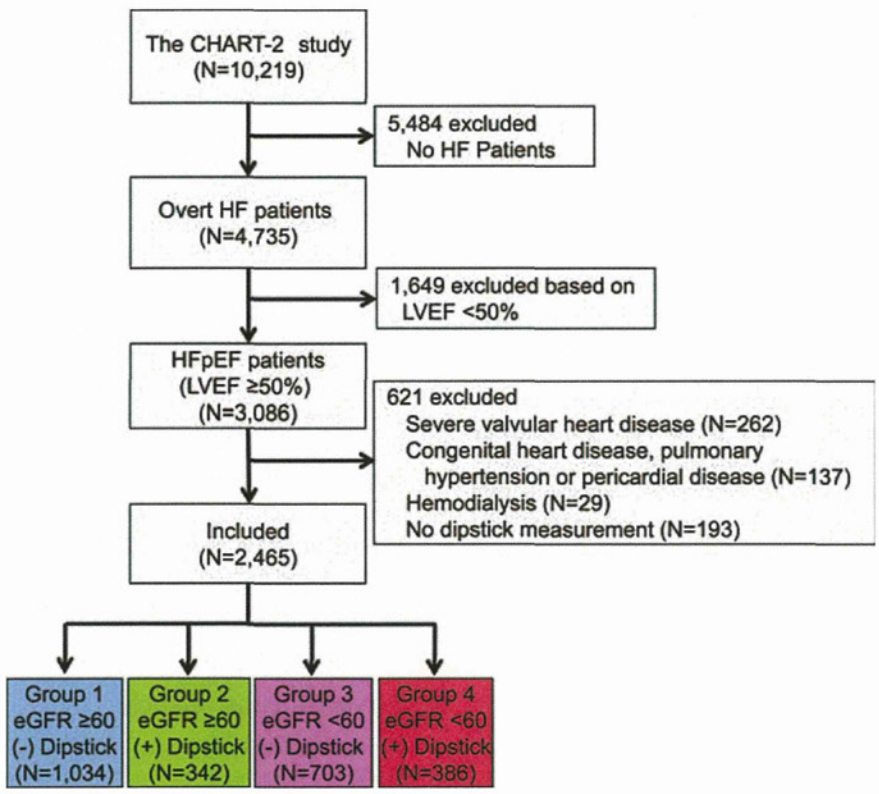

Figure 1 Study flow diagram. eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction.

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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 ≥0.3 g/L. The dipsticks of the four corporations (ARKELEY, Siemens AG, Eiken Chemical, and SYSMEX) were calibrated to indicate trace proteinuria at ≥0.15 g/L, ≥0.1 g/L, ≥0.15 g/L, and ≥0.1 g/L, respectively.

It has been reported that trace proteinuria evaluated by UDT could be a useful indicator of albuminuria (≥30 mg/g) in subjects at high risk of cardiovascular disease.[21] Furthermore, a recent study reported that trace UDT could identify urine albuminuria (≥30 mg/g) with high specificity and negative predictive value.[22] 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^2) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[23] at the time of enrolment. We defined reduced eGFR as <60 mL/min/1.73 m^2 according to the guideline.[11]

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 ± 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.[17]

Statistical analysis

To evaluate the usefulness of UDT, we divided the 2465 patients into the following four groups: group 1 (G1) with eGFR ≥60 with a negative UDT (n=1043), G2 with eGFR ≥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 ± 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,[24] heart rate,[25] serum sodium, serum potassium, co-morbidities[24] (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<δελ>β</δελ>-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 ≥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 ± 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 ± 9.0% and 62.4 ± 24.3 mL/min/1.73 m^2, 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 ≥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 ≥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 ≥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 ± 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 1 Baseline characteristics of the study patients

	Group 1 ($n=1034$)	Group 2 ($n=342$)	Group 3 ($n=703$)	Group 4 ($n=386$)	*P*-value among the four groups	ANOVA		
Reduced eGFR	–	–	+	+				
Urine dipstick test	**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^2)	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^2)	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

Continued

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Medications								
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			
Calcium channel blocker (%)	41.8	48.0	48.4	59.3	0.03	<0.001	<0.001	0.28
Loop diuretics (%)	32.8	34.8	52.3	52.8	<0.001	<0.001	0.56	0.73
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	0.51
Aldosterone inhibitor (%)	14.1	16.1	23.8	17.4	<0.001	0.001	0.19	0.01
Statin (%)	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.

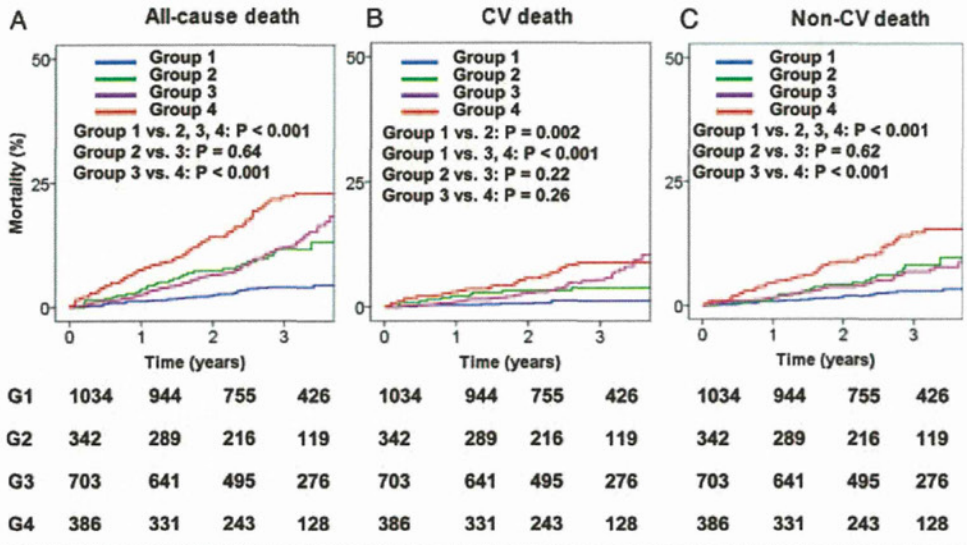

Figure 2 Kaplan–Meier survival curves for all-cause death (*A*), cardiovascular (CV) death (*B*), and non-CV death (*C*). The four groups were categorized based on the estmated glomerular filtration rate (eGFR) and urine dipstick test (UDT): group 1 (G1) (eGFR ≥60, negative UDT), G2 (eGFR ≥60, positive UDT), G3 (eGFR <60, negative UDT), and G4 (eGFR <60, positive-UDT). *P*-values indicate the comparison between each groups.

Discussion

The novel findings of the present study are as follows. First, ~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 ≥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.[8–10] In HF patients, the prevalence of patients with albuminuria (≥30 mg/g) is ~30%.[12,13] Furthermore, HF patients with albuminuria (≥30 mg/g) had a poorer prognosis independent of diabetes, hypertension, or renal function.[13–16] 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.[14] Furthermore, RAS activation and inflammation have been suggested to play causal roles in increasing albuminuria.[16] Therefore, HF patients with albuminuria (≥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 (≥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).[26] Both CKD and HF are associated with an increased activity of the sympathetic nervous system, and RAS activation, oxidative stress, and inflammation.[26] Therefore, we usually pay attention to renal function in HF patients. Compared with HFrEF patients, HFpEF patients were considered to have lower RAS activity.[27] However, according to the pathophysiology of elevated albuminuria in HF patients, HFpEF patients with albuminuria (≥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 (≥30 mg/g) may be greater than in HFpEF patients with normal albuminuria. So, the measurement 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.[1] In most clinical settings, eGFR is calculated by age, sex, and serum creatinine.[23] Therefore, some HFpEF patients may have an eGFR <60 without significant renal damage. Indeed, in the present study,

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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								<0.001			<0.001			<0.001			<0.001
	Group 1 (reference)	−	−	34 (3.3)	1.5	1.00			1.00			1.00			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								<0.001			<0.001			<0.001			<0.001
	Group 1 (reference)	−	−	10 (1.0)	0.4	1.00			1.00			1.00			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								<0.001			<0.001			<0.001			<0.001
	Group 1 (reference)	−	−	24 (2.3)	1.1	1.00			1.00			1.00			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).

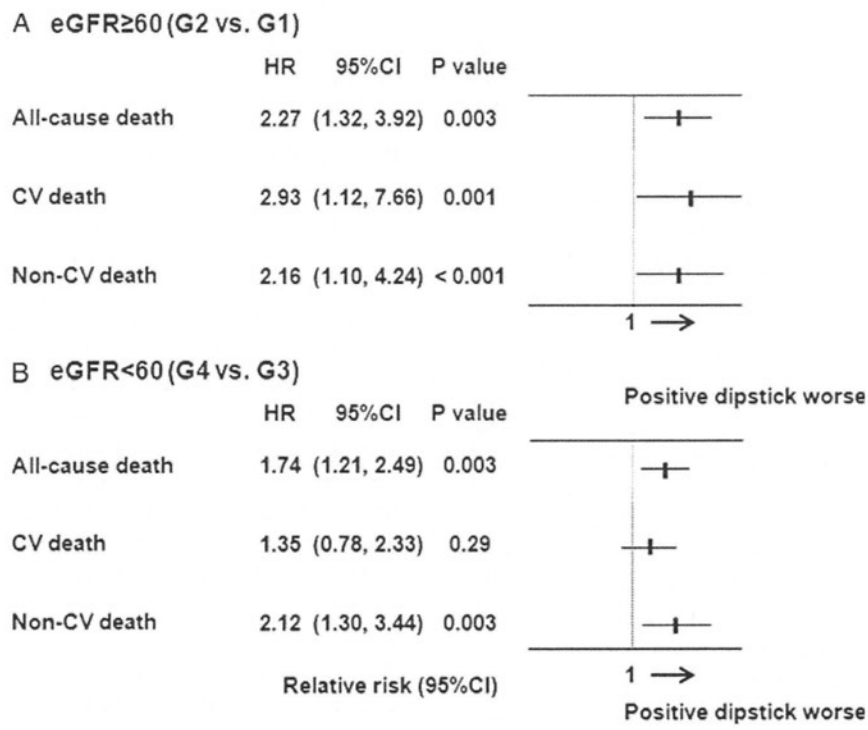

Figure 3 Hazard ratios (HRs) for all-cause death, cardiovascular (CV) death, and non-CV death after adjustment by multiple covariates including estimated glomerular filtration rate (eGFR). (*A*) eGFR ≥60 (G2 vs. G1), (*B*) eGFR <60 (G4 vs. G3). 95%CI, 95% confidence interval.

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.[22] Furthermore, UDT is very sensitive to albumin but is less sensitive to globulins and secreted proteins.[22] Konta *et al.* reported the significant usefulness of trace or more UDT to predict albuminuria (≥30 mg/g) in the general population.[21] Furthermore, the negative predictive value of UDT for identification of albuminuria (≥30 mg/g) was higher than the threshold of ≥1+.[21] Thus, in the present study, we defined positive UDT for albuminuria (≥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%.[14] 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 (≥30 mg/g) is observed in approximately one-third of HF patients.[12,13] Thus, our findings indicate that a positive UDT defined as trace or more is useful for detection of albuminuria (≥30 mg/g) and could be a reasonable surrogate of UACR measurement in HFpEF patients.

In HFpEF patients with eGFR ≥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,[28] 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.[29] 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

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patients were CVDs.[30] Albuminuria reflects glomerular injury, systemic inflammation, and endothelial dysfunction that lead to cardiovascular events.[13] Furthermore, albuminuria has been associated with changes in coagulation factors.[31] 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.[32] 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.*[31] 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.[33]

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.[7] Importantly, these mechanisms are also involved in the pathogenesis of albuminuria.[7] 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.[34] On the other hand, RAS inhibition in HFpEF is not associated with a consistent reduction in HF admission or mortality.[27] 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.[27] 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.[35] Thus, the baseline albuminuria level may be an important factor when selecting patients for treatment with RAS inhibitors.[36] 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.[4] 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.*[2] (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.[5] (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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