Table 6 Proposed definitions of cardiorenal syndrome [34].

CRS type 1 (acute CRS)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

CRS, cardiorenal syndrome.

(AKI) and pre-morbid chronic renal dysfunction has been reported as a common precursor for AKI in HF patients [30,31]. Worsening renal function, defined as a rise in serum creatinine level >0.3 mg/dl, during hospitalization for HF is observed in 20–30% of HF patients [29]. Any change in serum creatinine has been reported to be associated with longer hospital stay, increased costs, and increased short-term/long-term mortality [29]. Lower estimated GFR on HF admission was also an independent predictor for long-term mortality in AHF patients [32]. The mechanisms of the relationship are multiple and complex including persistent vasoconstriction, high renal venous pressure, elevated intra-abdominal pressure, adenosine and tubuloglomerular feedback, and medicine perturbing intrarenal hemodynamics (Table 5) [29,33].

Classification of cardiorenal syndrome

The bidirectional natures of heart and kidney interaction represent the pathophysiological basis for a clinical entity that has been called cardiorenal syndrome (CRS) (Fig. 1). Ronco et al. proposed the new classification of CRS to help physicians characterize groups of patients, to provide the rationale for specific management strategies, and to allow the design of future clinical trials [34]. They defined CRS as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other, and divided CRS into 5 different subtypes (Table 6). The proposed mechanism of kidney–heart interaction is also shown in Table 5. The benefit and validity of using this classification should be confirmed in future studies.

Anemia in patients with CKD and/or HF

Anemia develops relatively early in the disease course of CKD and worsens with CKD severity. McClellan et al. reported that anemia was present in 47.7% in 5222 enrolled patients with CKD [35] and the prevalence of anemia was strongly associated with decreased GFR. The major mechanisms of the development of anemia are decreased erythropoietin production and increased erythropoietin resistance, and other causes include decreased red blood cell life span due to uremic toxins, chronic blood loss caused by platelet dysfunction, nutritional deficiencies [36], iron deficiency, and elevated inflammatory cytokines [37] that may cause bone marrow suppression.

Anemia also frequently occurred in HF patients, with reports ranging widely from 9.0% to 79.1% [38,39], but the majority of studies described more than 20% [40]. Previous reports suggested that decreased hemoglobin level was associated with increased rates of death and HF-related admission [23]. Anemia observed in HF patients mainly is attributed to kidney-related factors described above, and is also related with bone marrow suppression by frequent angiotensin-converting enzyme (ACE) inhibitor use in HF patients [41]. Because CKD and anemia frequently co-exist and worsen the prognosis in patients with HF, CRS is also named as ''cardio-renal-anemia syndrome'' [40].

Whether the correction of anemia using erythropoiesis-stimulating agents is beneficial or not in patients with CKD or HF is still controversial. Previous trials have reported that the complete normalization of hemoglobin levels in CKD patients did increase adverse outcomes, although it might improve cardiac function [42]. The CHOIR study revealed the surprisingly higher rates of adverse events in CKD patients targeted for the high hemoglobin level (13.5 g/dl) compared with those in the low hemoglobin group (11.3 g/dl) [43]. The CREATE and the TREAT studies also showed that the complete correction of hemoglobin level did not demonstrate any improvement in cardiovascular events [44,45]. Meanwhile, some previous studies evaluating patients with HF showed a beneficial impact of anemia correction on HF symptoms, left ventricular ejection fraction, and quality of life [46,47]. However, in a recent trial in HF patients (STAMINA-HeFT), darbepoetin alfa treatment did not significantly improve exercise duration, NYHA functional class, or even health-related quality of life [48]. A large-scale, double-blind, randomized morbidity and mortality trial (RED-HF) is currently ongoing and it may demonstrate the impact of anemia correction on mortality in those patients [49].

Treatments of CKD patients with HF and of HF patients with CKD

A complete description or details of treatment in patients with CKD or HF are beyond the scope of this article, which may appear in the authoritative clinical practice guidelines for the treatment of CKD or HF [1,10,11]. The following part highlights the issue regarding the treatment using RAS inhibitors, which is the most commonly recommended therapy in patients with HF or CKD.

Reduction of proteinuria or albuminuria by treatment is associated with the slowing of the progression of CKD and is associated with reducing the cardiovascular events [50–52]. Major clinical practice guidelines recommended RAS inhibitors as the first-line therapy for patients with proteinuric nephropathy [53–55]. However, several researchers indicated that RAS blockade was not effective in patients with early-stage CKD [56,57]. Furthermore, O'Hare et al. estimated that 40.6% of the US population older than 70 years had stage 3 or 4 CKD, most of whom were diagnosed only by the decreased estimated GFR with lower urinary protein excretion. They noted that such a population was poorly represented in randomized controlled trials of CKD progression [58] and thus, whether there is a benefit of RAS inhibitors in such elderly CKD patients is still unknown.

Many studies have shown that the use of ACE inhibitors increased survival in HF patients with reduced left ventricular function [59–61]. Angiotensin II receptor blockers (ARB) provide comparable beneficial effect on cardiovascular outcomes in those patients [62,63]. Several researchers have shown that the beneficial effect of RAS inhibition on HF and CKD seems to be independent to lowering blood pressure (BP) [64,65].

Whether the interventions aimed at lowering BP by way of RAS inhibition and lowering protein excretion are beneficial simultaneously to both cardiovascular and renal outcome is still controversial. The IDNT trial revealed that the relative risk for reaching a renal end point progressively decreased with the lowering in achieved systolic BP using irbesartan, and the group below 120 mmHg did not show the increased risk [64]. However, the risk for both all-cause mortality and cardiovascular mortality rose in patients who achieved less than 120 mmHg of systolic BP by a relative risk of 3.05 and 4.06, respectively, and the decrements of diastolic BP were significantly associated with the increased rate of myocardial infarction [65]. Meanwhile, the RENAAL trial showed that patients with more than 30% reduction in urine protein excretion were associated with a significantly reduced risk for renal outcome compared with those without such a reduction. Furthermore, the reduction in proteinuria was also associated with reduced cardiovascular event rates [51].

Medical recommendations in treating HF patients with renal impairment

Because HF patients with CKD have been not adequately represented in randomized controlled trials of HF, most treatments in such patients are not usually prescribed in an evidence-based manner. The following recommendations must be validated in future studies [10,11].

1. General principles
   (1) Evaluate the CKD stage using estimated GFR and urine albumin:creatinine ratio.
   (2) Check etiology of CKD.
   (3) Control BP appropriately using anti-hypertensive medicines including RAS-inhibitors and/or beta-blockers (<130/80 mmHg).
   (4) Appropriate management of other traditional cardiovascular risks including diabetes, dyslipidemia, smoking, etc. is necessary.
   (5) Check all CKD-related risks including anemia, serum electrolyte abnormality, serum albumin level, renotoxic agents, etc.
   (6) When using ACE inhibitors/ARB, contraindications in patients must be checked thoroughly and consider reducing dose in patients with moderate-severe CKD.
   (7) Aldosterone antagonists should be used with caution as they may cause significant hyperkalemia.
   (8) Renal dysfunction is usually associated with impaired clearance of HF medicines. The start or maintenance doses should be reduced and plasma levels must be monitored frequently to avoid toxicity, if possible.
   (9) HF patients with CKD often have excessive salt and water retention, which needs more intensive diuretic treatment. In patients with severe CKD, loop diuretics are more effective than thiazide diuretics.
2. AHF Patients with AKI (CRS Type 1)
   (1) Evaluate status of cardiac output and renal congestion.
   (2) A gradual diuresis is recommended and extracorporeal ultrafiltration may be considered in case of severely decreased diuretic responsiveness [66].
   (3) Close monitoring of renal function and hyperkalemia is necessary especially when RAS inhibitors are used [67].
   (4) The administration of beta-blockers is not recommended until the patient has stabilized physiologically [68].
   (5) The radiocontrast agent should be used in the careful consideration for nephropathy and needs appropriate prophylaxis [69].
3. Chronic HF Patients with CKD (CRS Type 2)
   (1) Attention needs to be paid to reducing risk factors and optimizing medication.
   (2) Diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension are contributing factors for renal impairment [29].
   (3) In patients with diabetic nephropathy and overt proteinuria, the risk for congestive HF may increase when systolic BP is decreased to less than 120 mmHg [65].
   (4) Peritoneal dialysis may be a therapeutic option for refractory HF patients with severe CKD [70].

Current status of CKD in Japan

Iseki et al. reported that the prevalence of CKD was higher in Japan than in other Asian countries and the USA and that individuals with a low GFR (<60 ml/min/1.73 m^2) were estimated to be 20% of the adult population [71]. According to the Japanese Society for Dialysis Therapy, the prevalence of patients with ESRD was greater than 2000 per million population since 2005. CKD is also a major public health problem in Japan and the Japanese Society of Nephrology published a CKD Practice Guideline in September 2007 [72].

Most patients with CKD are diagnosed by decreased GFR, which is usually estimated from serum creatinine level, age, sex, and ethnicity by using the Modification of Diet

Table 7 The equation for estimated GFR in Japan [72,74].

Estimated GFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female)

GFR, glomerular filtration rate.

in Renal Disease (MDRD) Study equation. Several studies have revealed that the equation for estimated GFR must be modified properly in non-white individuals, because of the variation in serum creatinine caused by the difference in muscle mass, the calibration difference in serum creatinine assay, or the different method to measure true GFR [73]. Matsuo et al. reported the revised GFR-equation in 2009 to enable more accurate estimation of GFR in the Japanese population (Table 7) [74]. Imai et al. re-evaluated the prevalence of CKD patients using this new equation in 74,024 members of the adult population who participated in a large-scale annual health check-up program in 2005. They concluded that about 13% of Japanese adult population, approximately 13.3 million people, were predicted to have CKD in 2005 [3].

Conclusions

CKD is frequently observed in HF patients and GFR had an inverse graded association with HF severity. CKD is one of the major predictors for admission for worsening HF and cardiovascular/all-cause mortality in such patients. Although a major focus of HF treatment has been on the heart, treatment strategies also should be targeted on the kidney. Evaluation of GFR should be performed in all patients with HF and patients with CKD must be treated carefully considering common pathophysiologic nature between two organs. Given the increased incidence of both diseases which pose significant impact on public health, patients with CKD should be appropriately included in future trials of HF to develop clinical evidence, which will improve the prognosis and quality of life in patients with HF.

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Trend of Westernization of Etiology and Clinical Characteristics of Heart Failure Patients in Japan

– First Report From the CHART-2 Study –

Nobuyuki Shiba, MD, PhD; Kotaro Nochioka, MD, PhD; Masanobu Miura, MD; Haruka Kohno; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators

Background: Hospitalization due to acute heart failure syndrome (AHFS) is an indicator of worsened prognosis for patients with cardiovascular disease (CVD). The Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study was designed to elucidate characteristics and prognosis of patients at high risk for CVD progression due to AHFS.

Methods and Results: The CHART-2 Study is a prospective observational multicenter cohort study. Patients with overt HF, structural cardiac disorder but without HF, or with coronary artery disease (CAD) have been consecutively enrolled from October 2006. As of March 2010, a total of 10,219 patients have been recruited, making the Study the largest multicenter prospective cohort of HF patients in Japan. The mean patient age was 68.2± 12.3 years and male patients accounted for 69.8%. Overt HF was observed in 46.3% of patients; and 53.7% did not have HF but were at high risk for AHFS. As HF stage progressed, the prognostic risks (eg, chronic kidney disease, reduced ejection fraction, and increased B-type natriuretic peptide level) became more prominent. Compared with the previous CHART-1 study, the prevalence of ischemic etiology and risk factors (hypertension, diabetes) have increased, as in Western studies.

Conclusions: This first report demonstrates the trend of westernization of ischemic etiology and clinical characteristics of HF patients in Japan, indicating the importance of appropriate management and prevention of CAD to prevent AHFS. (*Circ J* 2011; **75:** 823–833)

Key Words: Coronary artery disease; Heart failure; Prognosis; Risk factors

Cardiovascular disease (CVD) is the leading cause of death in most developed countries.[1] Furthermore, many developing countries are now catching up with regard to this trend.[1] Heart failure (HF) is the end-stage of CVD and is becoming more common all over the world because of the westernization of lifestyle, the rapid aging of the population, and the increased number of survivors of serious cardiovascular illness due to recent advances in medical and surgical treatment.[2,3] We previously performed a multicenter prospective cohort study of HF patients (Chronic Heart Failure Analysis and Registry in the Tohoku District 1 Study: CHART-1) from February 2000 to December 2005 (n=1,278). The CHART-1 Study found that HF patients were also prevalent in Japan and that the prognosis was similarly poor compared with that in Western countries.[4,5] The most prevalent etiology of HF in the CHART-1 Study was non-ischemic cardiomyopathy (28.6%), and coronary artery disease (CAD) accounted for only 25.4% of the total HF patients, which was considerably low compared with a Western HF study.[3] Hospitalization due to the onset of acute heart failure syndrome (AHFS) is a key event in the disease progression of HF and CVD. Thus, it is important to avoid the decompensation of chronic HF and prevent de novo development of congestive HF in CVD patients in order to improve their long-term quality of life.[6,7] Western studies reported that the most frequent etiology of AHFS was ischemic in origin,[8,9] but the characteristics of such patients at high risk in Japan and the type of pathophysiologic derangement that causes decompensation from stable HF remain uncertain. Furthermore, although a large number of studies have shown that most

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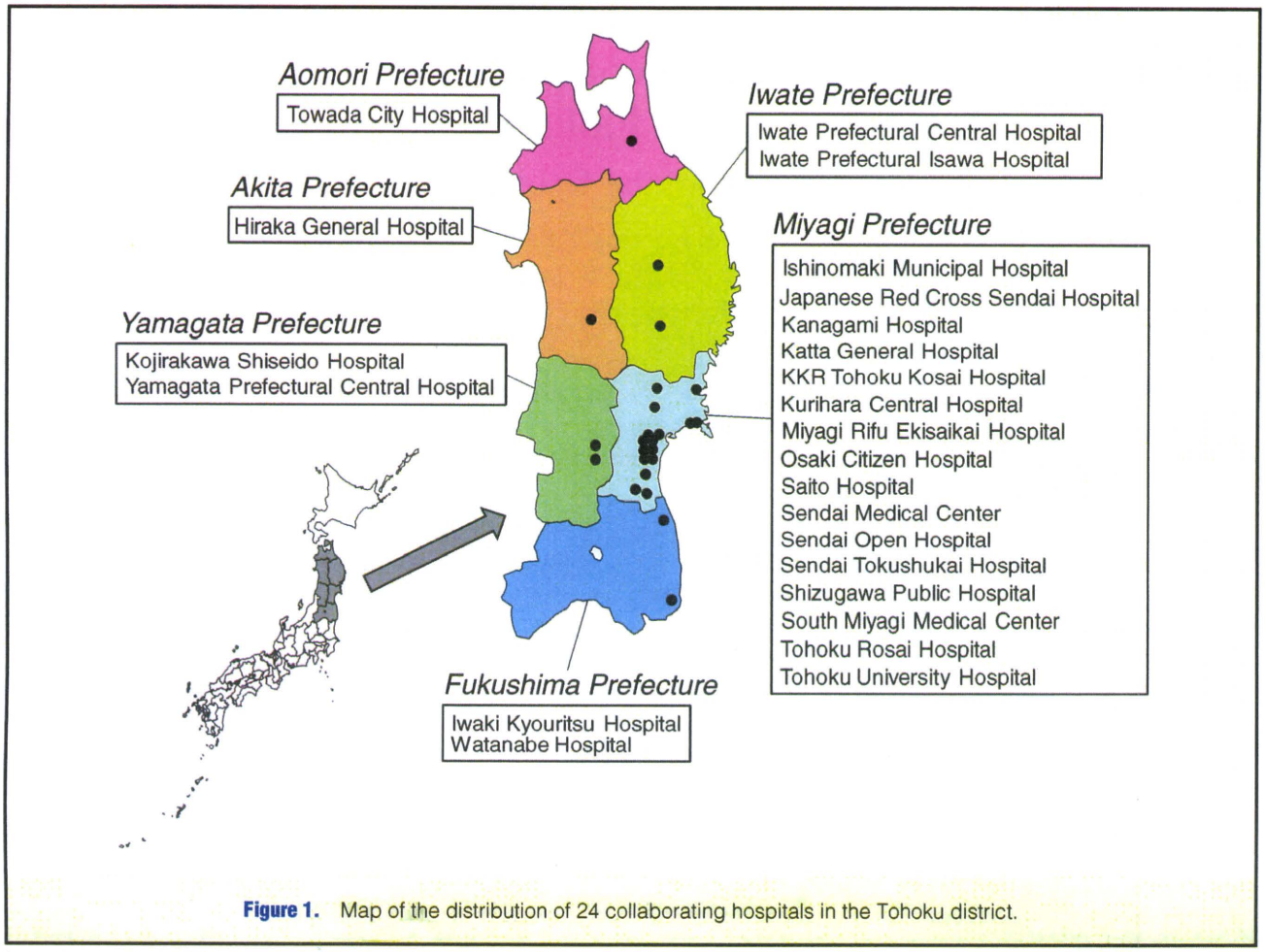

Figure 1. Map of the distribution of 24 collaborating hospitals in the Tohoku district.

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.

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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).

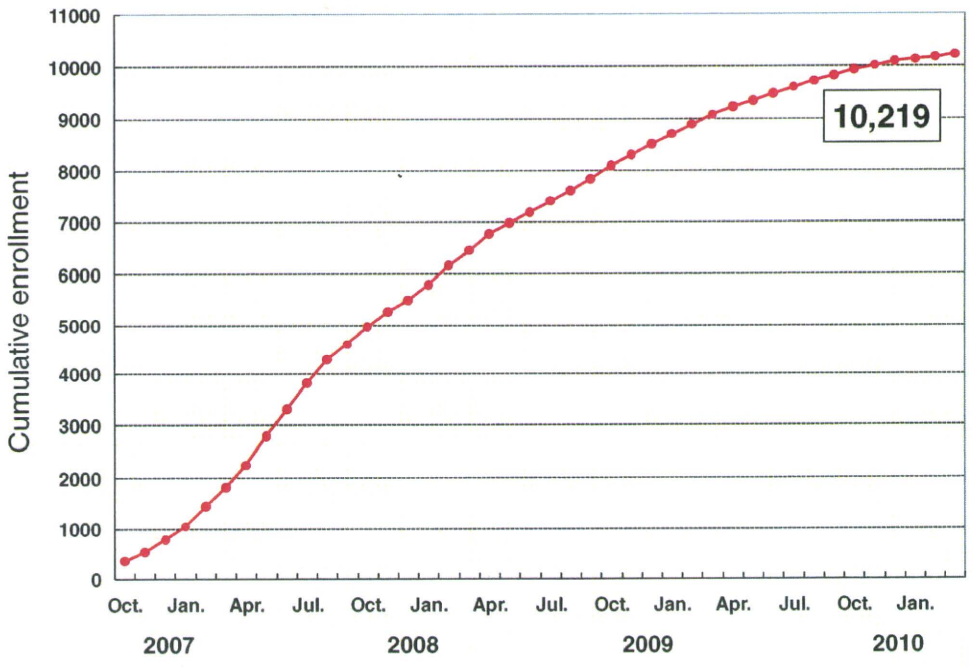

Figure 2. CHART-2 Study cumulative enrollment, showing a total of 10,219 registrations.

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/m²), 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}·1.73 m^{-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.

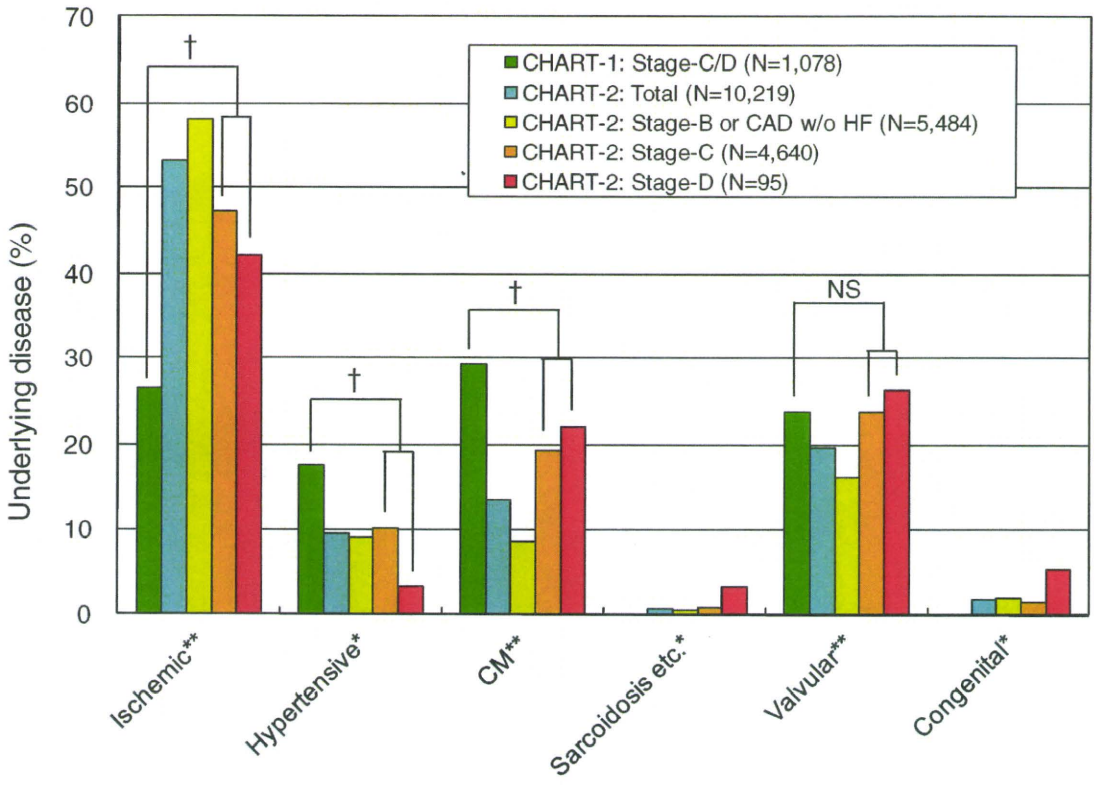

Figure 3. Underlying disease of the CHART-1 and the CHART-2 patients. CAD, coronary artery disease; CM, cardiomyopathy; HF, heart failure; w/o, without. *P<0.05 and **P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.001 between stage C/D patients in the CHART-1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

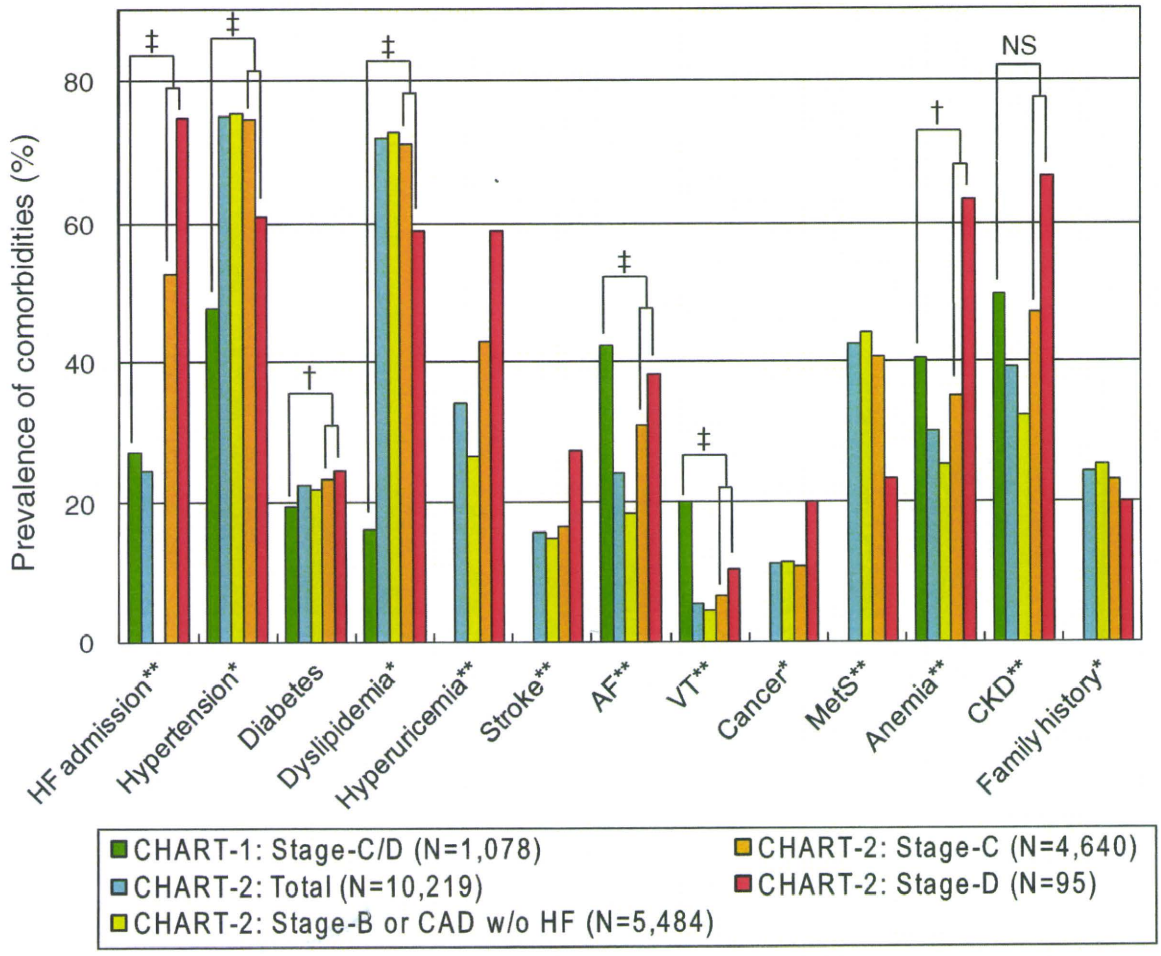

Figure 4. Comorbidities of the CHART-1 and the CHART-2 patients. AF, atrial fibrillation/flutter; CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; MetS, metabolic syndrome; VT, ventricular tachycardia; w/o, without. *P<0.05 and **P<0.001 between patients in stage B/CAD, stage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

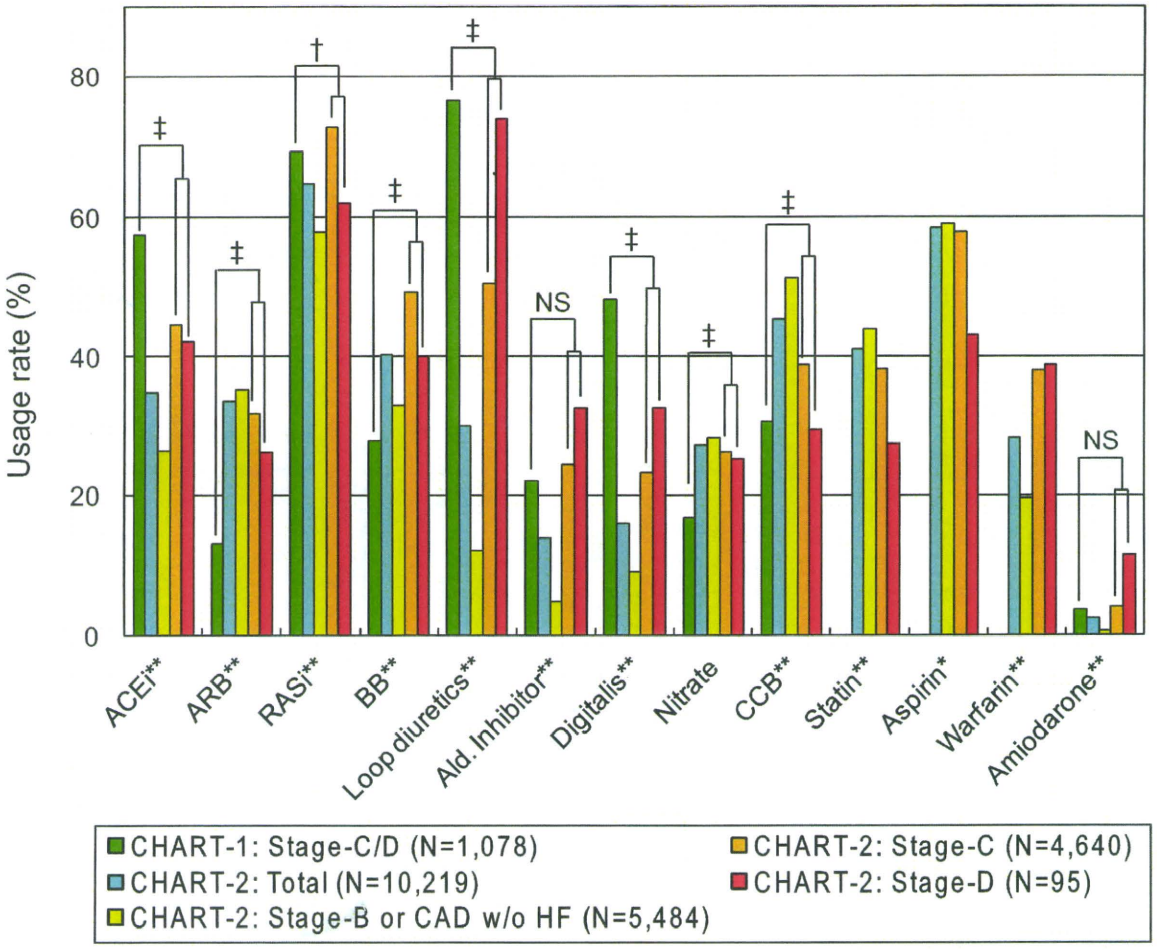

Figure 5. Medication of the CHART-1 and CHART-2 patients. ACEi, angiotensin-converting enzyme inhibitor; Ald., aldosterone; ARB, angiotensin II receptor blocker; BB, β-blocker; CAD, coronary artery disease; CCB, calcium channel blocker; RASi, renin–angiotensin system inhibitor; w/o, without. *P<0.05 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).

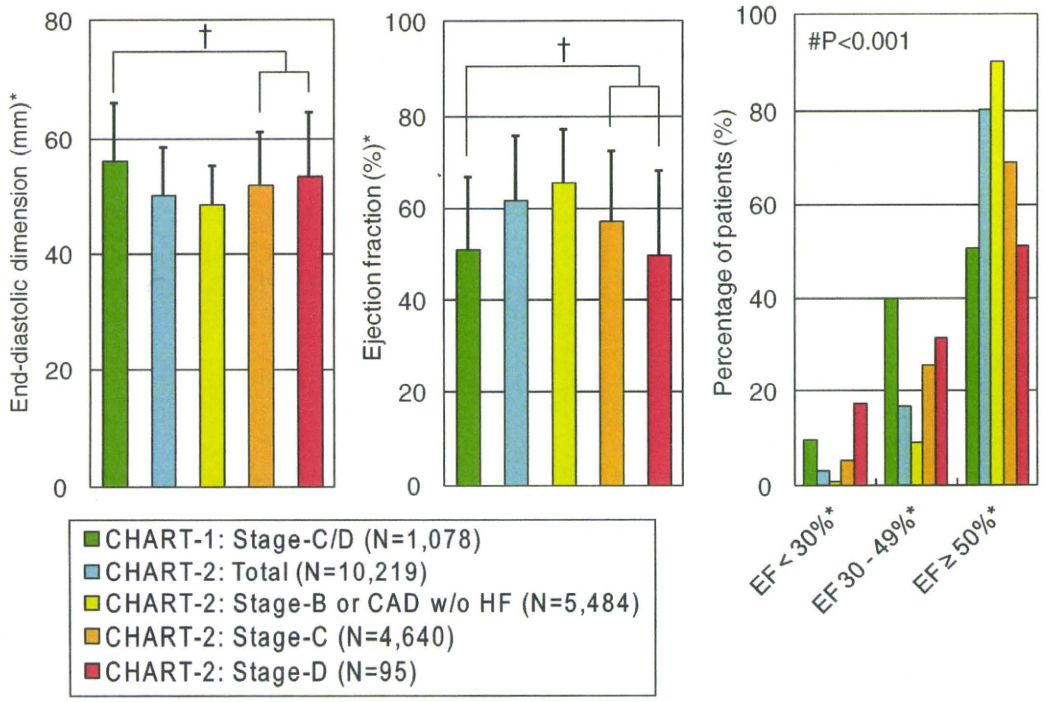

Figure 6. Left ventricular dimension and ejection fraction of the CHART-1 and CHART-2 patients. CAD, coronary artery disease; EF, ejection fraction. *P<0.001 between patients in stage B/CAD, stage C, and stage D in the CHART-2 Study. †P<0.001 between stage C/D patients in the CHART-1 Study and those 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/m²), 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

Executive Committee

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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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東北医学会
仙台

心不全予防を目的とした大規模コホート研究：第二次東北慢性心不全登録研究

A Large Cohort Study to Prevent the Development of Congestive Heart Failure : The CHART-2 Study

柴　信行

東北大学大学院　循環器EBM開発学寄附講座
東北大学大学院　循環器病態学分野

1. はじめに

エビデンスに基づいた医療行為Evidence-Based Medicine（EBM）の重要性がようやく我が国においても浸透してきている．EBMの実践においては，① 問題の抽出，② 問題解決のための情報検索，③ 情報の批判的な吟味，④ 患者への適用，⑤ 全体の評価と将来へ向けての改善，の5つのステップが重要とされている．しかしながらわが国では，根幹となるべき情報：エビデンスの蓄積が未だに不十分であると考えられる．エビデンスの創造のためには，正しく施行された臨床研究が必須である．本稿では，東北大学大学院循環器EBM開発学寄附講座で現在進行中である第二次東北慢性心不全登録研究を中心にして今後のエビデンス開発への展望を概説する．

2. 心不全の現状と今後の動向

1) 心不全の定義

心不全は全ての心疾患の最終像であると考えられている．日本循環器学会のガイドラインによると，慢性心不全とは（狭義の意味から）は，「慢性の心筋障害により心臓のポンプ機能が低下し，末梢主要臓器の酸素需要量に見合うだけの血液量を絶対的にまた相対的に拍出できない状態であり，肺または体静脈系にうっ血をきたし生活機能に障害を生じた病態」とされている[1]．一方，急性心不全とは，「心臓に器質的および/あるいは機能的異常が生じて急速に心ポンプ機能の代償機転が破綻し，心室充満圧の上昇や主要臓器への灌流不全をきたし，それに基づく症状や徴候が急性に出現した状態」をいうとされているが[2]，現在では両者を区別せずに同じ病態の時間的な差として捉えられるようになっている．その共通点は① 心ポンプ機能に障害があること，② 末梢主要臓器の灌流不全があること，③ 生活機能に障害があること，と考えられ理学所見や症状をもとにした臨床症候群であることが理解できる．

2) 心不全の進行とステージ分類

近年，心不全は進行する疾患であることが強調されるようになった．AHA/ACCの慢性心不全診療ガイドラインでは，心不全を4つのステージに分けている．息切れや動悸といった顕性の心不全症状を有する段階はステージCないしDとされ，高血圧やメタボリックシンドロームのようなリスクがあるが未だ心臓の器質的な異常のないものをステージA，軽症の心筋梗塞や無症状の弁膜疾患などのように軽度の器質的異常があるが心不全症状のないものをステージBとし，十分な治療を行わなければ一方通行的に進行する疾患であると定義している（図1）[3,4]．この病態の進行に寄与しているのは全身における神経体液性因子，特にレニン・アンジオテンシン系と交感神経系の活性化である．また，心不全のステージが進行するうえで特に重要であるのは急性心不全の発生であると考えられている．

3) 心不全は増加している

アメリカ合衆国では約500万人の心不全患者がいて毎年55万人が新規に発症していると報告されている[3]．日本における心不全の有病率や罹患率の明確な疫学データは存在しないが，おおおそ100-200万人の心不全患者が存在すると推定されている．心不全患者は先進国の多くで近年増加傾向にあると報告されているが，この原因は主に，① 急性心筋梗塞症の急性期

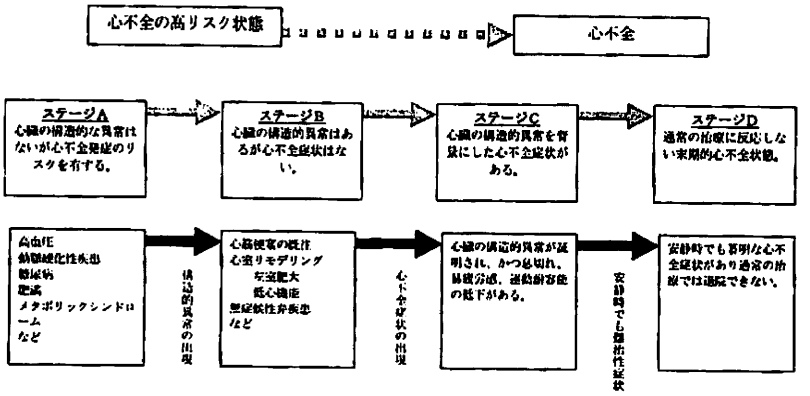

図1. 慢性心不全のステージ分類（AHA/ACCガイドラインより）[4]

救命率の増加，② 高齢者人口の増加によると考えられている．厚生労働省の高齢社会白書によると，わが国の高齢化率は2008年は22.1%であったが，2055年には40.5%に達すると推定されており，未曾有の超高齢社会を背景にして心不全患者は爆発的に増加すると危惧されている[5]．

3. 第一次東北慢性心不全登録：CHART-1研究

1) 東北心不全協議会発足とCHART-1研究の開始

本邦における心不全患者の疫学的知見は不十分であったため東北大学大学院循環器病態学分野では関連26教育病院と共同して東北心不全協議会を組織した．本協議会の最初の事業が，前向きコホート研究：第一次東北慢性心不全登録（Chronic Heart Failure Analysis and Registry in the Tohoku District：CHART-1研究）である．登録対象は安定期慢性心不全患者で目標登録数は1,000名とした．対象は文書による同意取得後に連結可能なIDを与えられ，主治医によって臨床データが紙ベースで登録され集計された．アウトカムの追跡は主治医によって年に一回施行された．詳細は表1に示すが，2000年2月に開始され2005年12月に追跡終了した[6]．

2) CHART-1研究の主な結果

総登録数は1,278例で男性が66.2%を占め，平均年齢は68.1±13.4歳であった．平均追跡期間は3.25±1.62年で全死亡が23.6%に，うっ血性心不全入院が28.1%に認められた．全コホートの生存曲線を図2に示した．予後を予測する臨床的因子の多くは欧米で報告されているものと共通であり，心不全症状・高齢・糖尿病の合併・左室リモデリング・B型利尿ペプチド上昇・心室頻拍合併・低血圧が死亡と有意な関連を示した．心不全の標準治療薬として国内外の診療ガイドラインで推薦されているレニン・アンジオテンシン系（RAS）抑制薬とβ遮断薬の使用頻度はそれぞれ69.8%，27.5%と特に後者で十分と言えなかった．標準薬物浸透度の低い症例は高齢者，女性，弁膜症症例，心機能温存症例などの診療エビデンスの不足した対象で著明であった．CHART-1研究から得られた知見の一部を文献に示した[7-13]．

4. 第二次東北慢性心不全登録：CHART-2研究

1) 心不全診療のパラダイムシフト

前述したように心不全は進行する疾患である．ステージC/Dの段階にある，すでに心不全を発症した患者を治療することは勿論であるが，むしろ心不全のハイリスク群であるステージA/Bの段階から心不全発症を予防することが重要であると考えられるようになってきた．このため，ステージBの症例を多数含んだコホート研究を企画した．これが2006年10月に開始された第二次東北慢性心不全登録（CHART-2研究）である．

2) CHART-1研究とCHART-2研究の相違点

CHART-1研究との比較を表1に示した．主な相違点は，CHART-2研究では，① ステージB/C/Dの段階にある症例と冠動脈疾患患者を連続登録して一万人のデータベースを形成し，臨床データは毎年一回追跡される，② 研究コーディネーターによるカルテ調査，③ Web登録システムの開発，④ 症例の一部に薬物介入臨床試験を同時進行する，である．

表1. CHART-1研究とCHART-2研究の比較[6]

	CHART-1	CHART-2
主な目的	慢性心不全患者の治療・予後	慢性心不全発症の予防
研究デザイン	前向きコホート研究	前向きコホート研究
参加施設	関連26施設	関連24施設
登録対象	① 左心室駆出率 <50% ② 左心室拡張末期径≧55 mm ③ 心不全エピソードの既往 ①～③のいずれかを満たすもの	① 慢性心不全のハイリスク症例 ② 慢性心不全症例 ①②のいずれかを満たすもの
対象症例のStage分類など	Stage-C/Dが92.6%	Stage-B/C/Dと冠動脈バイパスあるいは冠動脈インターベンションを必要とする冠動脈疾患
年齢	満18歳以上	満20歳以上
総登録数	1,278	10,000（目標）
研究期間	2000年2月～2005年12月	登録：2006年10月から4年間 追跡：登録終了後3年間
登録方法	主治医による登録用紙記入	研究コーディネーターによるWeb登録

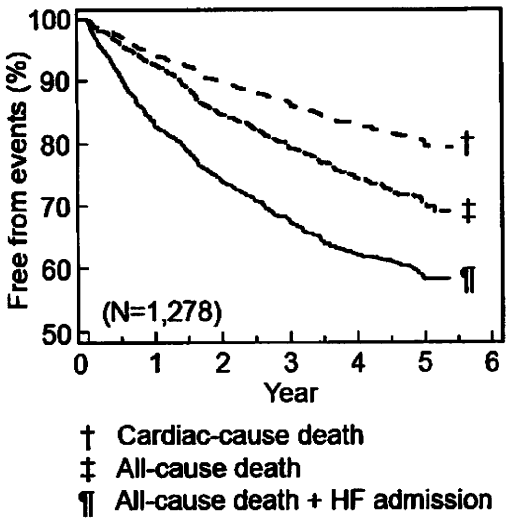

図2. 日本人心不全患者の予後[5]
HF, heart failure

3) 臨床研究コーディネーターとWeb登録システム

目標登録数の増加にともない医師のみによる登録は現実的に不可能となったため，研究実務を補助する研究コーディネーターを中心とする研究事務局の整備を行った．主な業務内容を表2に示した．参加24施設は東北地区に広く分布するため，研究コーディネーターが施設訪問時に携帯型パーソナルコンピューターからリアルタイムにデータを登録するWeb登録システムを新たに開発した．開発にあたっては実際に運用するコーディネーターの意見を大きく取り入れ使い易いユーザーインターフェースを目指した．研究プロトコールの概要は心不全協議会ホームページ上に公開されている（http://tohoku.cardiovascular-medicine.jp/）．また，本研究はUMIN-CTR（UMIN000000562）とClinicalTrials.gov（NCT00418041）に登録されている．

表2. CHART事務局における研究コーディネーターの主な業務

1. 試験準備
2. 倫理委員会準備
3. 各施設でのインフラ整備やプロトコール説明会開催
4. 研究協議会の準備
5. 試験実施の補助
6. データ収集
7. データのモニタリング
8. 有害事象やイベントの調査

4) 東北心不全協議会報告会

多施設研究においてデータ品質や研究プロトコール運用が均一に保たれるようにするため年に4回の報告会を開催している．研究内容や遂行に関わる現実的な

表3. 東北心不全協議会組織

1.	内部組織
	代表世話人
	プロトコール検討委員
	運営委員
	倫理委員
2.	外部組織
	割り付け責任者
	解析委員
	イベント評価委員
	外部モニタリング委員

問題点が討議されている．2009年12月6日に第3年次合同報告会が開催されたが，CHART-2研究の総登録数は10,030例に達し2010年3月に新規登録を終了する予定である．

5) SUPPORT試験

CHART-2研究に登録された症例のうち，高血圧を合併した安定期慢性心不全患者に対して薬物介入臨床試験を施行している．この試験はSUPPORT試験（高血圧を合併した安定期慢性心不全患者に対するアンジオテンシンII受容体拮抗薬オルメサルタンの有効性に関する薬物介入臨床試験：SUPplemental Benefit of ARB in Hypertensive Patients with Stable Heart Failure using OlmesaRTan (UMIN 000000561, NCT00417222)）と名づけられ，目標登録数1,000名を達成し2010年3月に新規登録を終了する予定である．

5. 今後の臨床研究推進に必要なもの

東北慢性心不全登録研究は研究者主導臨床試験と位置づけられる．厚生労働省による「疫学研究に関する倫理指針」と「臨床研究に関する倫理指針」に従って遂行される．企業主導の臨床試験は「医薬品の臨床試験の実施の基準（GCP）」によって，より厳格に運営される．このGCPの骨子として① 倫理性の確保，② 科学性の確保，③ 信頼性の確保が重要であるが，我々は研究者主導臨床試験であってもこれらのルールを可能な限り遵守するように努めている．東北心不全協議会では外部組織として解析委員，イベント評価委員，外部モニタリング委員などを設置している（表3）．近年わが国においても，循環器領域の大規模臨床試験が複数行われるようになったが，欧米諸国に比較すれば不十分であると言わざるをえない．診療エビデンスを日本から発信していくためには，医師主導型臨床試験をサポートする臨床試験センターの設置が必要であると考えられる．

6. 最 後 に

東北大学大学院循環器EBM開発学寄附講座で現在進行中の大規模コホート研究：CHART-2研究と，大規模薬剤介入臨床試験：SUPPORT試験の概要と今後の展望について述べた．大規模臨床試験の需要は今後ますます増加すると思われ，国家的レベルでの環境作りが急務である．

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