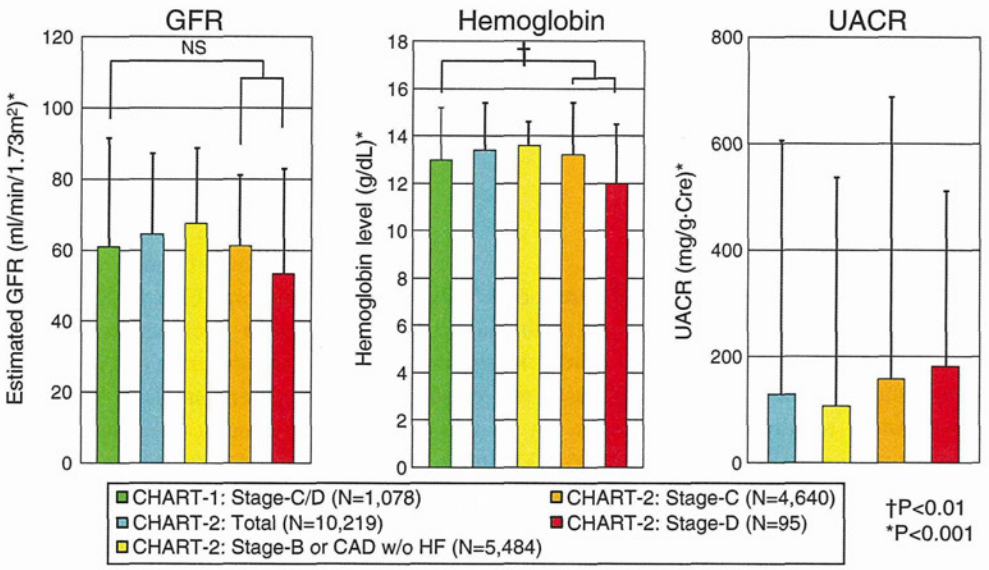

Fig. 13 GFR, hemoglobin level, and urine albumin creatinine ratio of CHART-1 and CHART-2 patients [14]. CAD, coronary artery disease; GFR, glomerular filtration rate; UACR, urine albumin creatinine ratio

The accumulation of prognostic risks with HF stage included significant increases in age, heart rate, cardiothoracic ratio, and uric acid level, as well as significant decreases in BP, BMI, and LDL-C level [14].

Characteristics of Japanese patients with HF

The stage-C and -D groups, which were considered to be patients with overt HF, accounted for 45.4% and 0.9% of the total number of enrolled patients, respectively. The most prevalent etiology of HF in the CHART-2 Study was CAD (47.1%) and it was almost comparable with the prevalence of HF etiology in Western observational cohort studies of HF (Fig. 14) [8, 65–69]. CAD as an etiology of HF has dramatically increased compared with that in the CHART-1 Study, which was undertaken approximately 6 years before the CHART-2 Study. The prevalence of hypertension and DM as comorbidities in CHART-2 patients was similar to that in Western studies (Fig. 15). Meanwhile, left ventricular EF at study entry was relatively higher and the prevalence of patients with preserved EF was considerably higher when HF patients in the CHART-2 Study were compared with those in studies of Western countries (Fig. 16). HF patients with preserved EF in the CHART-1 and −2 Studies were observed more frequently among elderly patients, just as in previous studies in Western countries [14, 58, 68, 69]. Comparisons of the usage rates of medical treatments for HF patients are shown in Fig. 17. HF patients in the CHART-2 Study were characterized by lesser use of loop diuretics and a higher use of angiotensin-II receptor blockers, but usage of β-blockers and RAS inhibitors was similar compared with that in Western studies.

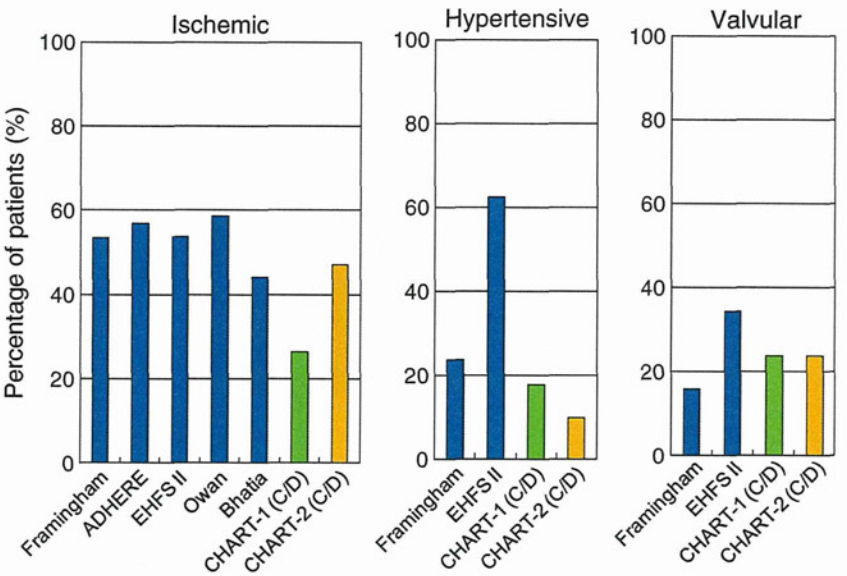

Fig. 14 Etiology of HF in Western patients and CHART patients [14]. Framingham, reference [65]; ADHERE, reference [66]; EHFS II, reference [67]; Owan, reference [68]; Bhatia, reference [69]; CHART-1, reference [8]; CHART-2, reference [14]

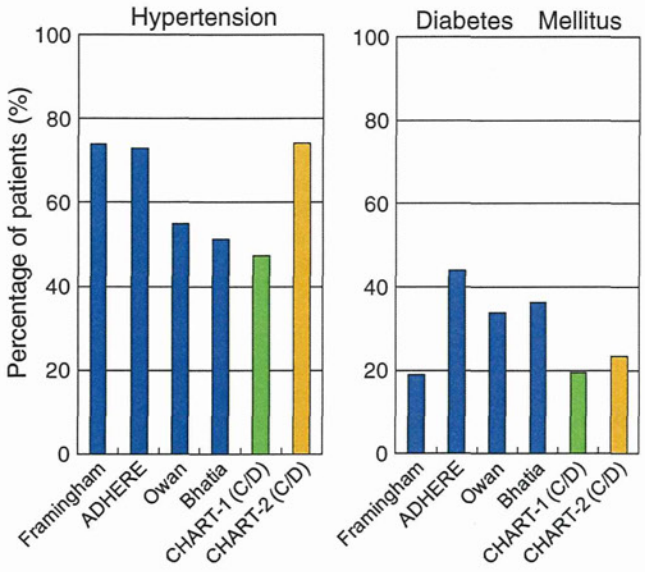

Fig. 15 Prevalence of hypertension and DM in Western patients and CHART patients [14]. Framingham, reference [65]; ADHERE, reference [66]; Owan, reference [68]; Bhatia, reference [69]; CHART-1, reference [8]; CHART-2, reference [14]

Primary results of the CHART-2 Study suggest that there has been a clear trend of increasing westernized etiology and risks among HF patients in Japan. Findings from the CHART-1 Study showed that HF patients with CAD had a poorer prognosis compared to those with non-ischemic cardiomyopathy [70]. Furthermore, it was predicted that the number of elderly HF patients will increase considerably in the near future and these patients showed a significantly increased rate of cardiovascular events and mortality [9].

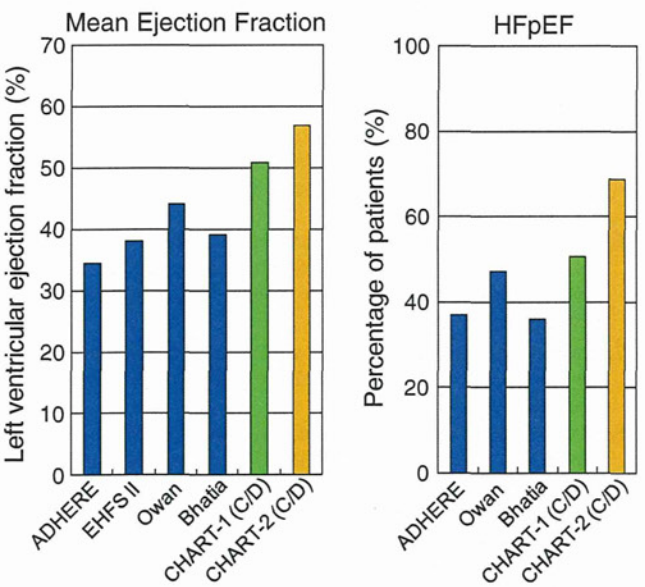

Fig. 16 EF and prevalence of HF patients with preserved EF in Western patients and CHART patients [14]. Framingham, reference [65]; ADHERE, reference [66]; Owan, reference [68]; Bhatia, reference [69]; CHART-1, reference [8]; CHART-2, reference [14]; HFpEF, heart failure patients with preserved ejection fraction

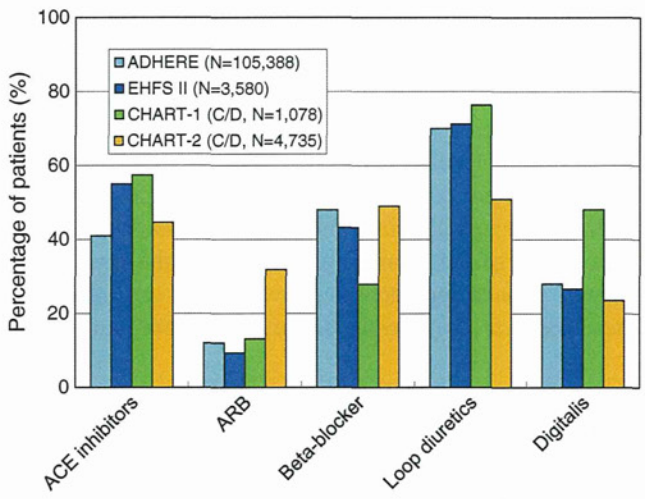

Fig. 17 Medication in patients with HF in Western patients and CHART patients [14]. ADHERE, reference [66]; EHFS II, reference [67]; CHART-1, reference [8]; CHART-2, reference [14]

The CHART-2 Study revealed that patients in stage B or with CAD had a higher prevalence of cardiovascular risks, elevated BNP level and possible under-treatment of risk control, even though these patients did not show any overt HF symptoms. These findings clearly suggested that patients in stage B or with CAD were significantly vulnerable to developing HF in the future. We have to make an accurate risk stratification of all patients in stage B or with CAD and urge aggressive treatment in such patients (as well as in patients in stage C or D) to improve the quality of life (QOL) and prognosis of all patients with CVD.

Predictive, preventive, and personalized medicine in HF patients in Japan

Predictive, preventive, and personalized medicine is a new approach in managing chronic diseases. HF is one of the diseases that need this new philosophy to reduce prevalence and to improve long-term outcomes and QOL. Given the future increase in the number of HF patients in Japan, management must implement 5 main strategies at each stage of development and progression of HF. Firstly, there must be an accurate prediction of individuals at a higher risk of disease progression or development of HF using biomarkers and prognostic risks (e.g., BNP, EF, GFR, and other authorized risk factors). Secondly, effective prevention of disease progression through appropriate treatments based on evidence-based guidelines is necessary. Thirdly, optimally personalized treatments (especially in elderly individuals, who form the majority of HF patients) are

required. Fourthly, we need a lifelong approach for preventing the development of HF and caring for HF patients. CVD or HF usually needs a long time to develop; but, atherosclerosis starts to develop early in youth or even in childhood. Finally, the translation of genomic medicine (including gene expression, proteomics, metabolomics, molecular imaging) into a prospective personalized health plan is one of the promising strategies in the near future. Subsets of such approaches are available in cardiology, but these issues are beyond the scope of this contribution.

Conclusions and outlook

In Japan, a rapidly aging population and westernization of cardiovascular risks have led to an increase in the number of patients with CVD and HF. These trends may contribute in progression of CVD and further deteriorate the prognosis of such patients.

Given the progressive nature of the disease, an appropriate prospective approach is needed in the management of HF. Patients at a higher risk of developing HF must be predicted using biomarkers and other prognostic risk factors. Effective prevention of HF in Japan includes the strict control of westernized risks based on clinical guidelines to reduce the development of CAD, risk stratification of patients in stage B or those with CAD, and delaying the stage progression of CVD with personalized medical or surgical treatment. The number of elderly patients with CVD or HF has been increasing. Hence, we must urge lifelong risk management in the general population as well. In addition, we need further studies to clarify the pathophysiology of HF with preserved EF and to determine novel risks that exacerbate the severity of CVD and HF. Predictive, preventive, and personalized medicine must be appropriately applied in patients with CVD or HF as well as in those at future risk of such diseases.

Conflict of interest None.

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Prognostic Impact of Blood Urea Nitrogen Changes During Hospitalization in Patients With Acute Heart Failure Syndrome

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Background: Elevated blood urea nitrogen (BUN) observed in patients hospitalized for acute heart failure syndrome (AHFS) may represent increased neurohumoral activation. The purpose of this study was to examine the prognostic impact of BUN changes during hospitalization on the long-term prognosis of AHFS patients.

Methods and Results: The Tohoku Acute Heart Failure Registry (n=497) is a multicenter retrospective cohort study enrolling AHFS patients who were admitted in 2007. The 337 survivors (mean age, 76 years; 52% male) were divided into 3 groups according to tertiles of BUN change during hospitalization: Decreased (D-BUN, ΔBUN (BUN level at discharge–BUN level at hospitalization) ≤–1.63 mg/dl, n=112); Unchanged (U-BUN, ΔBUN –1.64 to 5.73 mg/dl, n=113); Increased (I-BUN, ΔBUN >5.73 mg/dl, n=112). The D-BUN group had higher prevalence of lowest glomerular filtration rate during hospitalization, whereas the I-BUN group had higher systolic blood pressure. During a median follow-up period of 2.3 years after discharge, the Kaplan-Meier curve showed that D-BUN and I-BUN had worse prognosis compared with U-BUN. Multivariable logistic model showed that all-cause death was more frequent in I-BUN (hazard ratio, 2.94; 95% confidence interval, 1.51–5.73; P<0.001). Subgroup analysis revealed that BUN increase during hospitalization was associated with all-cause death, regardless of renal function.

Conclusions: AHFS patients with a BUN increase during hospitalization have worse long-term prognosis, independent of renal function.

Key Words: Acute heart failure syndrome; Blood urea nitrogen; Neurohumoral activation; Renal dysfunction

The activation of neurohumoral factors, including the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAS) and arginine vasopressin (AVP), is considered as the central pathophysiology of heart failure (HF).[1] The elevated SNS and RAS activities in the kidney enhance urea absorption in the proximal tubules and flow-dependent urea absorption in the distal tubules.[1] Furthermore, increased AVP upregulates urea transporters in the inner medullary collecting duct.[1] Thus, an elevated blood urea nitrogen (BUN) level could be regarded as a surrogate marker for neurohumoral activation in HF patients.

Several studies have reported that elevated BUN levels are associated with adverse outcomes in HF patients, especially in those hospitalized because of acute HF syndrome (AHFS).[2–8] Using recursive partitioning of 33,046 AHFS patients with 39 variables, Fonarow et al revealed that the best single predictor for in-hospital death of AHFS patients at admission was high BUN level (≥43 mg/dl), followed by low systolic blood pressure (SBP, <115 mmHg) and high serum creatinine level (≥2.75 mg/dl).[2] In addition, it has been shown that elevated BUN level at admission can predict poor in-hospital and long-term outcomes after the onset of AHFS.[4–8] Accordingly, the BUN level at admission appears to be a useful predictor of survival of AHFS patients.

However, it is unclear whether BUN levels can predict the long-term outcomes of AHFS patients, especially after dis-

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charge. In the present study, we thus examined the prognostic implication of BUN level on long-term outcome after discharge in AHFS patients. We particularly focused on the effect of BUN changes during AHFS hospitalization, because evaluation of dynamic changes in the BUN level during hospitalization could be more informative as compared with one-point assessment at admission or discharge.

Methods

The present study was approved by the Ethical Committees of Tohoku University (No. 2009-366) and the other 3 collaborating hospitals. The Ethical Committees judged that informed consent from each patient was not required for the present study.

AHFS Patients and Inclusion Criteria

The Tohoku Acute Heart Failure Registry (n=497) is a multicenter retrospective cohort study, enrolling AHFS patients who were admitted to the 4 participating hospitals. We included consecutive AHFS patients aged ≥20 years who were admitted to the hospitals in 2007. We excluded AHFS patients with acute coronary syndrome, primary pulmonary arterial hypertension or pericardial disease. AHFS was defined as a gradual or rapid change in the signs and symptoms of HF that necessitated urgent hospitalization, diagnosed by experienced cardiologists, based on the criteria of the Framingham Heart Study.[9] Medical records were reviewed by trained clinical research coordinators and the patients' data were collected for the present registry using a pre-fixed registration form. The baseline data included demographic information, medical history, clinical signs and symptoms of HF, and initial treatment at admission. Clinical signs and treatments were surveyed at 24–72 h after hospitalization and at discharge. The primary outcome of the present study was all-cause mortality after discharge. Data acquisition was performed from November 2009 to February 2011. Finally, 497 AHFS patients from the 4 participating hospitals were registered.

In the present analysis, we excluded some patients for the following reasons: hospitalization for myocarditis (n=1) or takotsubo cardiomyopathy (n=3); requiring hemodialysis (n=5); insufficient data (n=58). Furthermore, we excluded the patients who did not receive intravenous diuretics (n=43), because intravenous diuretics strongly influence fluid volume status, which may be associated with BUN change during AHFS hospitalization. Additionally, we excluded patients who died during hospitalization (n=50). In total, 337 AHFS survivors were included in the present study. The outcome of the present study was all-cause death. To evaluate the prognostic impact of BUN changes during hospitalization in AHFS patients, we divided the subjects into 3 groups based on the tertile of BUN change during hospitalization: 112 patients whose BUN levels decreased (ΔBUN ≤–1.63, D-BUN group); 113 whose BUN levels were unchanged (ΔBUN, –1.64 to 5.73, U-BUN group); 112 whose BUN levels increased during hospitalization (ΔBUN >5.73, I-BUN group). ΔBUN was defined as BUN level at discharge–BUN level at admission.

BUN Level

BUN level was measured in each participating hospital on admission, at 24–72 h after hospitalization and at discharge.

Renal Function

Estimated glomerular filtration rate (eGFR, $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was calculated at the time of hospitalization using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient.[10] Worsening renal function (WRF) was defined as an increase in serum creatinine at discharge of >0.3 mg/dl compared with that at admission, based on previous reports.[11–14]

Statistical Analysis

Comparisons among the 3 groups were performed by ANOVA test. Continuous data are described as mean±standard deviation (SD). Kaplan-Meier curves were plotted to evaluate the association between the BUN changes during hospitalization and all-cause death.

We constructed unadjusted (model a) and adjusted (models b and c) logistic regression models to evaluate the association between BUN changes and outcome. In model (b), we included the following covariates at admission that could influence both the outcome and the BUN changes during hospitalization: age, sex, history of HF hospitalization, SBP, heart rate (HR), hemoglobin level, serum sodium (Na), serum potassium (K), eGFR, comorbidities (diabetes mellitus, history of coronary artery disease (CAD), malignant tumor and cerebrovascular disease), left ventricular ejection fraction (LVEF) and use of inotropes. In model (c), we included the following covariates that could influence BUN changes and prognosis during hospitalization: age, sex, diabetes mellitus, histories of CAD, cerebrovascular disease, and malignant tumor, LVEF, changes in SBP (ΔSBP), HR (ΔHR), serum sodium (ΔNa), serum potassium (ΔK), serum creatinine (ΔCre) and hemoglobin (ΔHb), medical treatment (β-blockers, RAS inhibitors, loop diuretics and aldosterone antagonists) and number of days spent fasting after hospitalization.

We also performed multivariable logistic analysis to compare the prognostic effect of one-point BUN or creatinine level at admission or at discharge, and the change in BUN levels during hospitalization (ΔBUN) and WRF. We adjusted the baseline characteristics that included in model (b). Furthermore, we performed the multivariable logistic regression analysis to determine the predictors of BUN increase during hospitalization in the I-BUN group. We included the following covariates at admission that potentially influence BUN increases during hospitalization: age, sex, New York Heart Association class, history of HF hospitalization, clinical scenario (CS) status, HR, eGFR, diabetes mellitus, histories of CAD, malignant tumor and cerebrovascular disease, LVEF and previous treatment (β-blockers, RAS inhibitors, diuretics, and spironolactone). To examine whether renal function influences the prognostic impact of BUN changes during hospitalization, we examined the influence of BUN and creatinine levels at admission and WRF during hospitalization on BUN changes during hospitalization.

Numerical data are expressed as mean±SD. All statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc, Chicago, IL, USA) and statistical significance was defined as a 2-sided P-value <0.05.

Results

Baseline Characteristics of AHFS Patients

Mean age was 76.0±12.0 years and male patients accounted for 51.9%. The prevalence of de novo AHFS and Nohria profile C were 70.6% and 19.6%, respectively. CAD was observed in 27.9% and mean LVEF and eGFR at admission were 45.5±16.2% and 46.2±25.8 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$, respectively. The mean period of hospitalization was 30.4±19.4 days. Carperitide was given to 89% of the study patients after admis-

Table 1. Baseline Characteristics of the Study Patients

Groups	D-BUN	U-BUN	I-BUN	P value
ΔBUN (mg/dl) (median, 95% CI)	−7.8 (−13.8 to −9.5)	1.8 (1.4 to 2.2)	15.5 (13.4 to 17.6)	
n	112	113	112	
Age (years)	76.7±11.9	73.7±13	77.6±10.6	0.04
Male (%)	58	51.3	46.4	0.22
History of HF hospitalization (%)	30.4	24.8	33	0.38
History of malignant tumor (%)	17	13.3	14.3	0.72
Ischemic HF (%)	28.3	28.6	26.8	0.28
Comorbidities (%)				
Hypertension	69.6	70.8	67.9	0.89
Diabetes	43.8	36.3	33	0.24
Atrial fibrillation	50	61.9	50	0.19
Cerebrovascular disease	22.3	18.6	21.4	0.77
Clinical status at admission				
NYHA class III and IV (%)	99.1	93.8	98.3	0.09
Nohria profile C (%)	33.9	12.4	12.5	<0.001
Clinical scenario 1 (%)	52.7	49.6	62.5	0.13
SBP (mmHg)	142.4±36.4	146.2±33.9	153.3±37	0.07
DBP (mmHg)	81.3±26.1	84.3±21.8	86.1±22	0.3
HR (beats/min)	94.2±27.9	101.2±15.8	70.7±13.8	0.17
Clinical variables at admission				
LVEF (%)	45.6±16	45.2±16.5	45.9±16.2	0.96
Hemoglobin (g/dl)	11.6±2.5	12.4±2.2	11.4±2.2	0.006
BUN (mg/dl)	34.8±17.4	21.1±10.6	24.4±12.9	<0.001
Serum Cre (mg/dl)	1.4±0.9	1±0.6	1.2±0.8	0.001
Serum sodium (mEq/L)	139.5±4.4	141±3.9	140.8±4	0.02
Serum potassium (mEq/L)	4.4±0.4	4.2±0.5	4.1±0.7	<0.001
eGFR ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	38.8±18.9	53.6±27.1	46.3±28.4	<0.001
BNP (pg/ml)	1,360±1,662	939±709	1,177±1,167	0.06
Treatment at admission (%)				
Diuretics	58	50.4	54.5	0.52
Carperitide	88	90.9	90.8	0.81
Nitrates	18.8	17.7	17.9	0.98
Dopamine	8.9	8	1.8	0.06
Dobutamine	14.3	8	3.6	0.02
PDE III inhibitor	10.7	5.3	12.5	0.16
Calcium-channel blocker	9.8	9.7	9.8	1
Fasting period (days)	1.9±1.9	1.4±0.7	1.6±0.9	0.02
Length of hospital stay (days)	32.5±20.3	29±20.6	29.6±17.5	0.36

Numerical data are expressed as mean±SD.
D, decreased; BUN, blood urea nitrogen; U, unchanged; I, increased; CI, confidence interval; HF, heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; Cre, creatinine; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; PDE, phosphodiesterase.

sion. Furthermore, intravenous furosemide and intensive respiratory management were given to 54.3% and 10.1% of the study patients, respectively.

The mean BUN levels (mg/dl) at admission and discharge were 26.7±15.1 and 28.6±16.2, respectively. We divided the study subjects into 3 groups based on the tertile of the ΔBUN values as mentioned earlier (**Table 1**). The BUN levels at 24–72h after admission was not significantly increased as compared with those at admission in all groups (**Figure 1A**). The U-BUN group was characterized by younger age and had the highest eGFR and lowest brain natriuretic peptide (BNP) level. The D-BUN group was characterized by higher prevalence of Nohria profile C, the highest BNP level and the lowest eGFR at admission. Furthermore, patients in the D-BUN group were more frequently treated with inotropes (dopamine or dobutamine) at admission. In contrast, the I-BUN group was characterized by older age and had higher SBP at admission and lower hemoglobin level. The fasting period was longer in the I-BUN group than in the U-BUN group (**Table 1**).

Changes in Clinical Variables During Hospitalization

The changes in BUN level and other clinical variables during hospitalization in each group are shown in **Table 2** and **Figure 1**. The mean interval of BUN measurements was 25.7±23.6 days and was comparable among the 3 groups (21.9±18.8, 27.4±19.8 and 27.8±30.4 days in the U-BUN, D-BUN and

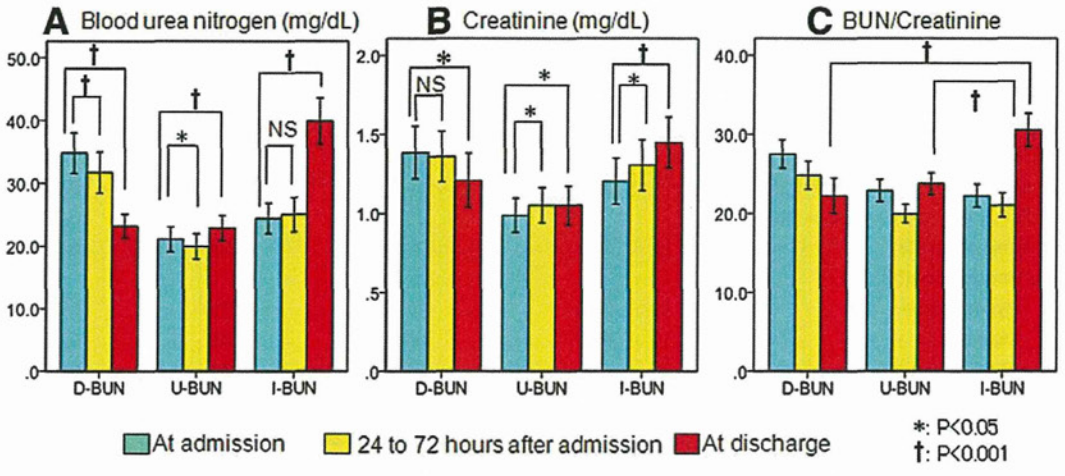

Figure 1. (**A**) Changes in BUN levels during hospitalization for AHFS. (**B**) Changes in creatinine level during hospitalization. (**C**) Changes in BUN/creatinine ratio during hospitalization. AHFS, acute heart failure syndrome; BUN, blood urea nitrogen.

Table 2. Changes in Clinical Variables During Hospitalization and Medications at Discharge

	D-BUN (n=112)	U-BUN (n=113)	I-BUN (n=112)	P value
Changes in clinical variables during hospitalization				
Interval of measurement (days)	27.4±19.7	21.9±18.8	27.8±30.3	0.11
ΔSBP (mmHg)	−26±31.7	−32.7±29.8	−36.8±31.9	0.04
ΔHR (beats/min)	−24.9±28.7	−32.5±31.6	−29.6±27.5	0.16
ΔBUN (mg/dl)	−11.7±11.5	1.8±2	15.5±11.3	<0.001
25% increase in BUN (%)	0	13.3	94.6	<0.001
ΔCre (mg/dl)	−0.2±0.7	0.1±0.2	0.3±0.4	<0.001
0.3mg/dl increase in Cre (%)	5.4	9.7	32.1	<0.001
ΔSerum sodium (mEq/L)	0.7±5.1	−0.6±4.2	−1.2±4.9	0.01
ΔSerum potassium (mEq/L)	−0.1±0.8	0.3±0.6	0.4±0.8	<0.001
ΔHemoglobin (g/dl)	0±1.6	0±1.5	−0.3±1.5	0.27
Oral medications at admission				
Diuretics (%)	58	47.8	50	0.27
Spironolactone (%)	22.3	14.2	21.4	0.23
ACEIs (%)	24.1	22.1	29.5	0.42
ARBs (%)	25.9	25.7	26.8	0.98
β-blockers (%)	21.4	31.9	20.5	0.09
Oral medications at discharge				
Diuretics (%)	85.7	82.3	90.2	0.23
Furosemide dose (mg/day)	35.2±21.1	32.5±17.0	33.7±17.6	0.68
Spironolactone (%)	39.3	40.7	51.8	0.12
ACEIs (%)	50.9	61.1	58.9	0.27
ARBs (%)	31.3	22.1	32.1	0.18
β-blockers (%)	50.9	62.8	50.9	0.12

Numerical data are expressed as mean±SD.
ΔSBP, SBP at discharge–SBP at hospitalization; ΔHR, HR at discharge–HR at hospitalization; ΔBUN, BUN at discharge–BUN at hospitalization; ΔCre, Cre at hospitalization–Cre at discharge; Δserum sodium (Na), Na at discharge–Na at hospitalization; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations as in Table 1.

I-BUN groups, respectively, P=0.11, **Figure 1A**). In the I-BUN group, ≥25% increase in BUN level was noted in 94.6% and WRF in 32.1% of the patients (**Figure 1B**). Furthermore, the I-BUN group had the largest BUN/creatinine ratio at discharge among the 3 groups (**Figure 1C**). In the U-BUN group, ≥25% increase in BUN was noted only in 13.3% and the prevalence of WRF was lower than in the I-BUN group. In the I-BUN group, the changes in SBP, serum Na level and serum K level were the largest among the 3 groups.

Medications at Discharge

Among the 3 groups, there was no significant difference in medications at either admission or discharge, although the I-BUN group tended to have more diuretics and spironolactone and the U-BUN group more angiotensin-converting enzyme inhibitors and β-blockers (Table 2). There was no difference in the furosemide dose at discharge among the 3 groups.

Prognostic Impact of BUN Changes During Hospitalization of AHFS Patients

During the median follow-up period of 2.3 years after discharge, 120 patients (35.6%) died. Figure 2 shows the Kaplan-Meier survival curves for all-cause death. The D-BUN and I-BUN groups had worse prognosis compared with the U-BUN group. Furthermore, 3-year mortality rate of the I-BUN group was approximately 150% higher compared with the D-BUN group.

Table 3 shows the results of multivariable logistic regression models for all-cause death. In the unadjusted model (a), as compared with the U-BUN group (reference), both the D-BUN and I-BUN groups showed 181% and 277% increase, respectively, in the risk for all-cause death (P=0.049 and P<0.001, respectively). In model (b), as compared with the U-BUN group (reference), the hazard ratio (95% confidence interval [CI]) for all-cause death of the D-BUN and I-BUN groups was 1.09 (0.54–2.21) and 2.94 (1.51–5.73), respectively. In model (c), the hazard ratio (95% CI) for all-cause death in groups D-BUN and I-BUN was 0.93 (0.43–2.01) and 4.27 (2.14–8.52), respectively, as compared with the U-BUN group (reference). Furthermore, the I-BUN group also had significantly higher hazard ratios for all-cause death as compared with the D-BUN group in both model (b) and (c) (hazard ratio 2.78, 95% CI 1.36–5.68, P=0.002; hazard ratio 4.19, 1.77–9.91, P=0.001, respectively).

Figure 3A shows the results of multivariable logistic models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge, and BUN increase and WRF during hospitalization for all-cause death. BUN increase during hospitalization had the highest heart rate for all-cause death compared with BUN and creatinine levels both at admission and at discharge. Figure 3B shows that BUN increase was significantly associated with

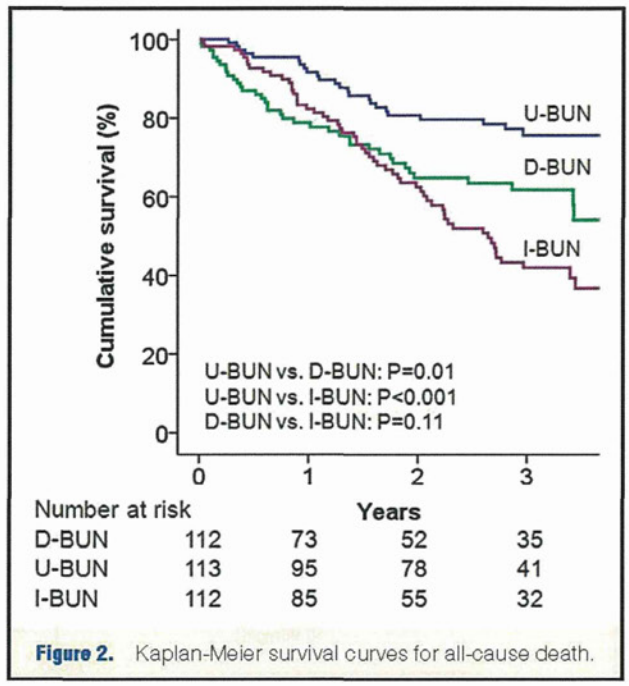

Figure 2. Kaplan-Meier survival curves for all-cause death.

all-cause death, regardless of serum BUN or creatinine level at admission. Furthermore, the prognostic impact of BUN increase during hospitalization for all-cause death was insignificant in AHFS patients with WRF, whereas it was significant in those without WRF.

Predictors of BUN Increase During Hospitalization

In the I-BUN group, the prevalence of patients with ≥25% increase in BUN level during hospitalization was 94.6%. Among the covariates, only SBP at admission was associated with the increase in BUN level during hospitalization (Table 4). The analysis also showed that CS1 (SBP >140 mmHg) was associated with 81% increase in the prevalence of the BUN increase compared with CS >1 (hazard ratio 1.81, 95% CI 1.05–3.12, P=0.03). Importantly, β-blocker use before hospi-

Table 3. Logistic Regression Models for All-Cause Death

Hazard ratio categories	All-cause death	U-BUN (reference)	D-BUN	I-BUN
No. of events (%)		25 (22.1)	38 (33.9)	57 (50.9)
No. of events/100 person-year		11.7	14.1	25.2
Unadjusted				
Hazard ratio		1.00	1.81	2.77
95% CI			1.00–3.27	1.73–4.44
P value	<0.001		0.049	<0.001
Baseline adjusted				
Hazard ratio		1.00	1.09	2.94
95% CI			0.54–2.21	1.51–5.73
P value	<0.001		0.81	0.002
Adjusted by the covariates including the change in clinical status				
Hazard ratio		1.00	0.93	4.26
95% CI			0.43–2.01	2.14–8.52
P value	<0.001		0.76	<0.001

See text for explanations of hazard ratio categories. Abbreviations as in Table 1.

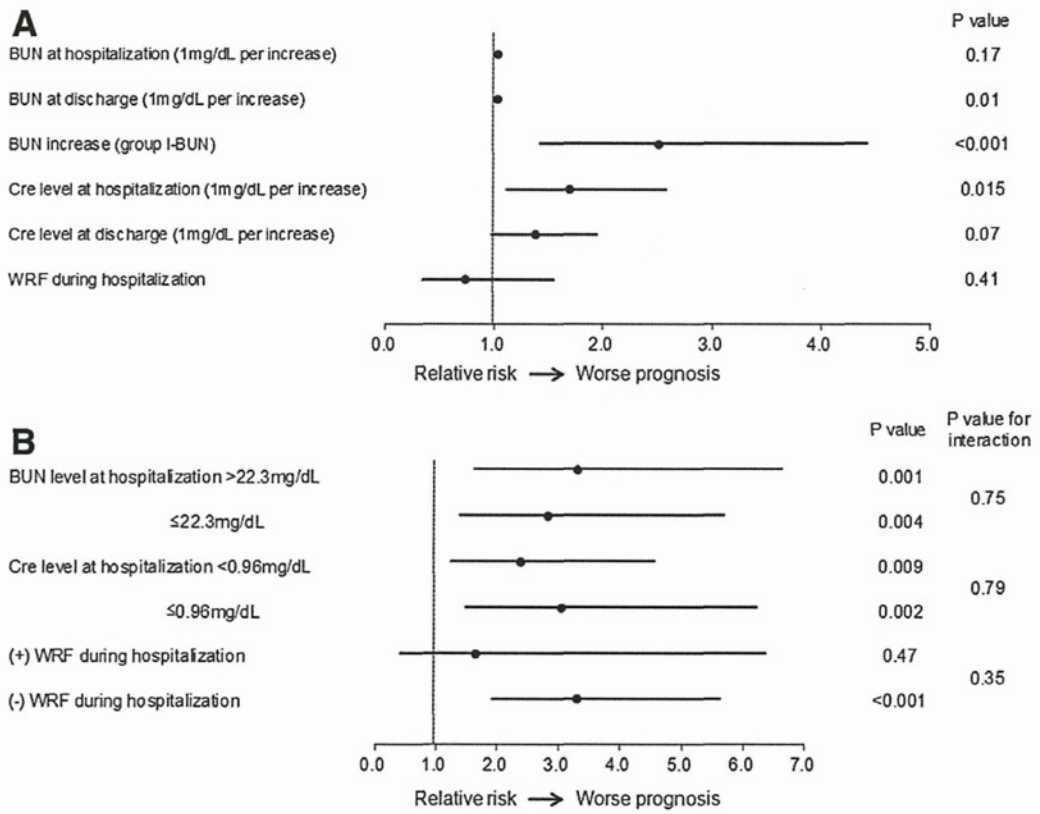

Figure 3. Multivariable logistic analysis. (**A**) Models to compare the prognostic impact of BUN and creatinine levels at admission, BUN and creatinine levels at discharge and BUN increase and WRF during hospitalization for all-cause death. (**B**) Subgroup analysis of prognostic value of BUN increase according to serum BUN and creatinine levels at admission and WRF during hospitalization. BUN, blood urea nitrogen; WRF, worsening renal function.

Table 4. Predictors of BUN Increase During Hospitalization for AHFS

	Hazard ratio	95% CI	P value
Male (vs. female)	1.23	0.66–2.02	0.61
Age (per 1-year older)	1.01	0.99–1.04	0.34
Ischemic HF	1.02	0.56–1.86	0.96
Past history			
HF hospitalization	0.77	0.42–1.39	0.96
Diabetes	0.87	0.51–1.5	0.62
Malignant tumor	0.74	0.36–1.52	0.41
Cerebrovascular disease	0.87	0.45–1.67	0.67
Previous medications			
ACEIs	1.68	0.89–3.18	0.11
ARBs	0.85	0.45–1.6	0.62
Diuretics	1.19	0.66–2.15	0.56
β-blockers	0.51	0.26–0.99	0.047
Clinical condition at admission			
CS 1 (vs. CS 2 & 3)	1.81	1.05–3.12	0.03
HR (per 1 beat/min increase)	1	0.99–1.01	1
NYHA class III and IV (vs. class II)	1.81	0.19–16.9	0.6
SpO2 (per 1% decrease)	1.01	0.96–1.06	0.79
Hemoglobin (per 1 g/dl increase)	0.92	0.8–1.05	0.21
LVEF (per 1% increase)	1	0.98–1.01	0.56
eGFR (per 1 ml·min^{-1}· 1.73 m^{-2} increase)	0.99	0.7–1.42	0.97

AHFS, acute heart failure syndrome. Other abbreviations as in Tables 1,3.

talization was associated with 49% decrease in the incidence of the BUN increase during hospitalization (hazard ratio 0.51, 95% CI 0.26–0.99, P=0.047) (**Table 4**).

Discussion

The novel findings of the present study were that AHFS patients with increased BUN levels during hospitalization had worse long-term prognosis after discharge, regardless of renal function, and that the BUN increase during hospitalization was a strong predictor of the long-term prognosis of post-AHFS patients. Thus, the present study suggests that more attention should be paid to BUN changes during hospitalization for risk stratification of post-AHFS patients, regardless of creatinine-based measures of renal function.

Prognostic Importance of BUN Increase During AHFS Hospitalization

Elevated BUN level at admission is well known to be associated with increased in-hospital mortality and adverse outcomes after discharge.[2,4–8] However, the BUN level during hospitalization for AHFS often fluctuates dynamically because it is widely influenced not only by neurohumoral factors but also by several biological parameters, including fluid volume balance, nutritional status, and hemodynamics.[15] Therefore, it is clinically important to evaluate BUN changes during hospitalization to predict the prognosis of AHFS patients. In the present study, we found that the patients with increased BUN levels during hospitalization (I-BUN group) had the worse prognosis compared with those with unchanged BUN levels (U-BUN group) or decreased BUN levels (D-BUN group). Singh et al reported that BUN level at admission was more important than subsequent in-hospital fluctuations of BUN in terms of predicting short-term and long-term risk.[16] However, the length of the hospital stay in their study was shorter than in ours (5.3±6.4 vs. 30.4±19.4 days), which could explain the discrepancy in the results of the 2 studies.

We did not have enough data to examine the association between BUN increase and neurohumoral factors (eg, RAS activities). However, it has been reported that a higher BUN level is associated with a greater degree of elevation of neurohumoral activation.[17] Therefore, in the present study a BUN increase during AHFS hospitalization may have reflected activated neurohumoral systems.

Our results also demonstrated that the prognosis of the D-BUN group was relatively better than that of the I-BUN group, although the D-BUN group had worse clinical profiles characterized by higher prevalence of Nohria profile C, use of inotropes and lower eGFR at admission. Thus, it is suggested that even if AHFS patients have elevated BUN levels and a more severe clinical status at admission, their long-term prognosis could be improved if their BUN levels are decreased during hospitalization with intensive medical treatment.

WRF and BUN Increase During Hospitalization

It has been reported that WRF is a complication in approximately one-third of AHFS patients and is associated with poor prognosis.[11–14,18] In the present study, the I-BUN group had a higher prevalence of WRF, suggesting a close association between WRF and BUN increase during hospitalization. However, it is noteworthy that the effect of BUN increase during hospitalization (ie, I-BUN group) was associated with the worst long-term survival, regardless of the presence or absence of WRF. Indeed, the present study showed that an increase in BUN level had a higher hazard ratio in patients without WRF than in those with WRF (**Figure 3B**). Thus, evaluation of BUN increase during hospitalization, regardless of WRF, could be important for appropriate risk stratification of AHFS patients.

Predictors for BUN Increase During AHFS Hospitalization

The present results showed that higher SBP at admission was significantly associated with BUN increase during hospitalization. In previous reports, higher SBP at admission was found to be a risk factor for WRF,[14] but AHFS patients with higher SBP, who were often classified as CS1, have significantly decreased mortality compared with those with normal or lower SBP.[19] Thus, caution should be paid to AHFS patients with higher SBP at admission, because they are likely to develop BUN increase during subsequent hospitalization, which may increase the risk of death after discharge. In the present study, SBP at 24–72h after admission was almost same level among the 3 groups. However, the change in SBP during the 24–72h after admission was –43.9±35.8 vs. –29.4±31.2mmHg in the patients with WRF and those without WRF, respectively (P=0.03). Considering that early SBP drop may cause WRF in AHFS patients,[20] reduction in SBP should be achieved carefully in AHFS patients with higher SBP in order to prevent WRF and BUN increase during hospitalization.

AHFS Treatment to Prevent BUN Increase

In the present study, β-blockers use before admission was inversely associated with BUN increase during hospitalization (eg, 49% decrease in the I-BUN group). However, de novo AHFS accounted for approximately 70% of AHFS patients and only 24.6% patients had been treated with β-blocker(s) before admission. Considering the renal protective effects of β-blockers[21] their use before hospitalization for AHFS may be important to prevent BUN increase during hospitalization. Indeed, the ACC/AHA Guidelines recommend that β-blocker therapy should be started at the earlier stage of cardiovascular disease.[22] Thus, the present results may support the notion that β-blocker initiation at the earlier stage of HF could reduce the incidence of BUN increase through inhibition of SNS and RAS activation.

Study Limitations

Several limitations should be mentioned. First, this study was a retrospective observational study in Japan, so caution is needed when interpreting the present results in comparison with other cohorts. For example, the median hospital stay for AHFS in the present study (24.0 days) was much longer than in Western countries.[23,24] However, the present study suggests the importance of re-evaluating the BUN level, at a 1-month interval, for risk stratification of the patients. Second, the BUN measurement was not performed at a central laboratory. Third, the lack of assessment of pulmonary congestion or volume overload during hospitalization was a major limitation. Fourth, we did not have enough data on nutrition status (eg, serum albumin and body mass index), which may affect the BUN changes during hospitalization. However, we performed logistic analysis adjusted for fasting period, which may influence nutritional status, and found no influence of fasting. Finally, we excluded the patients who died during hospitalization, which might have influenced the present results.

Conclusions

AHFS patients with increased BUN levels during hospitalization have worse long-term prognosis after discharge, regard-

less of creatinine-based measures of renal function. Although it has been established that a higher BUN level at admission is associated with poor in-hospital prognosis, the present study provides further insights into the importance of BUN changes during hospitalization for risk stratification of AHFS patients.

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Disclosures

Conflict of Interest: None.

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—— 目　　次 ——

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

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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

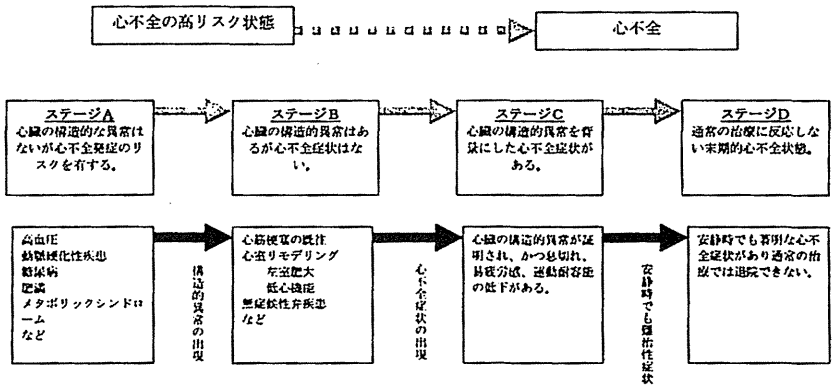

図1. 慢性心不全のステージ分類（AHA/ACCガイドラインより）[4]

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

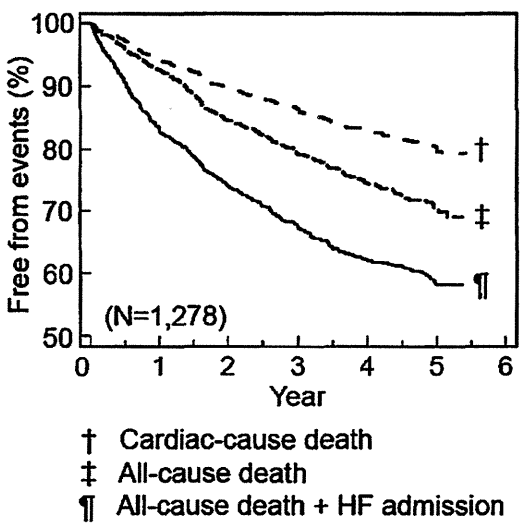

図2. 日本人心不全患者の予後[5]
HF, heart failure

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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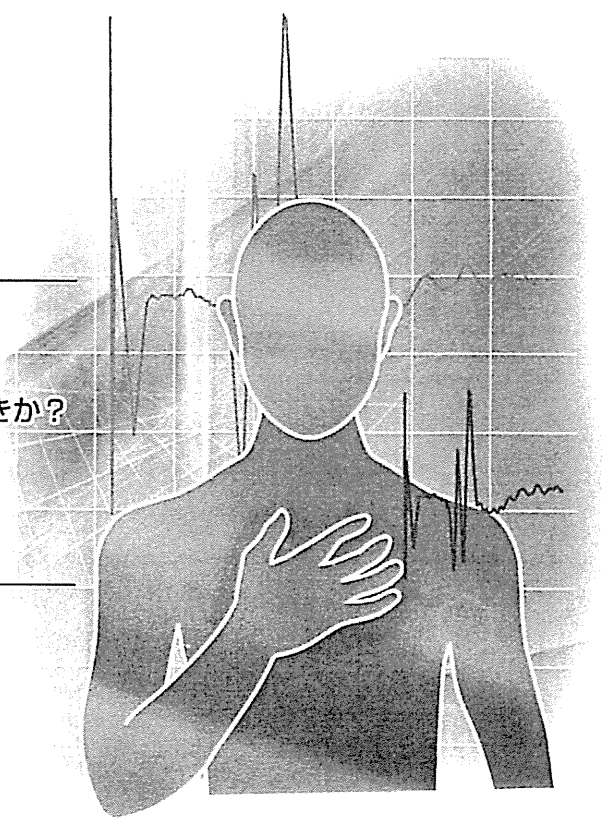
徹底ガイド

心不全 Q&A

―プレホスピタルから 慢性期まで―

特集編集　佐藤　直樹



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