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## G. 知的所有権の取得状況

### 1. 特許取得

特に無し

### 2. 実用新案登録

特に無し

### 3. その他

特に無し

# Ⅲ．研究成果の刊行に関する一覧表

| 文献番号 | 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
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# Ⅳ. 研究成果の刊行物・別刷

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# Usefulness of Combined Risk Stratification With Heart Rate and Systolic Blood Pressure in the Management of Chronic Heart Failure

## – A Report From the CHART-2 Study –

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***Background:*** The appropriate target ranges of heart rate (HR) and systolic blood pressure (SBP) for the management of chronic heart failure (CHF) patients remain to be elucidated in a large-scale cohort study.

***Methods and Results:*** We examined 3,029 consecutive CHF patients with sinus rhythm (SR) (mean age, 67.9 years) registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study (CHART-2; NCT00418041). There were 357 deaths (11.8%) during the median follow-up of 3.1 years. We first performed the classification and regression tree analysis for mortality, identifying SBP <89 mmHg, HR >70 beats/min and SBP <115 mmHg as the primary, secondary and tertiary discriminators, respectively. According to these, we divided the patients into low- (n=1,131), middle- (n=1,624) and high-risk (n=274) groups with mortality risk <10%, 10–20% and >20%, respectively. The low-risk group was characterized by SBP >115 mmHg and HR <70 beats/min and the high-risk group by SBP <89 mmHg regardless of HR values or SBP 89–115 mmHg and HR >76 beats/min. Multivariate Cox regression analysis revealed that the hazard ratio of all-cause death for low-, middle- and high-risk groups was 1.00 (reference), 1.48 (95% confidence interval (CI): 1.10–1.99, P=0.009) and 2.44 (95% CI 1.66–3.58, P<0.001), respectively. Subgroup analysis revealed that age ≥70 years, diabetes, or reduced left ventricular function had higher hazard ratios in the high-risk group.

***Conclusions:*** The results demonstrate the usefulness of combined risk stratification of HR and SBP in CHF patients with SR.

**Key Words:** CHART-2; Chronic heart failure; Heart rate; Prognosis; Systolic blood pressure

Elevated resting heart rate (HR) is an independent risk factor for mortality not only in the general population[1,2] but also in patients with coronary artery disease (CAD)[3] and those with chronic heart failure (CHF).[4] Furthermore, HR reduction is also associated with improvement in the prognosis of patients after myocardial infarction[5] and those with CHF.[6,7] According to the European Society of Cardiology (ESC) guidelines, HR should be controlled to less than 70 beats/min in CHF patients with reduced left ventricular ejection fraction (LVEF).[8] Thus, the management of HR is an important therapeutic strategy in CHF management. High systolic blood pressure (SBP) is also an adverse prognostic marker in both the general population[9] and patients with cardiovascular diseases.[10,11] However, increased SBP is associated with reduced mortality in CHF patients,[12] a phenomenon known as "reverse epidemiology".[13]

In the management of CHF, β-blockers are widely used because they have been shown to reduce mortality, particularly in patients with reduced LVEF.[14,15] However, physicians often hesitate to use β-blockers for CHF patients with reduced LVEF and lower SBP, because the drugs may further decrease SBP and HR. Indeed, in real-world practice, only a small percentage of CHF patients receive target doses of β-blockers despite

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**Table 1. Baseline Characteristics of the Patients With Chronic Heart Failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study**

| | All patients (n=3,029) | Low-risk group (n=1,131) | Middle-risk group (n=1,624) | High-risk group (n=274) | P value for 3 groups |
|---|---|---|---|---|---|
| **Age (years)** | 67.9±12.8 | 69.0±11.8 | 67.4±13.1 | 66.9±14.6 | 0.002 |
| **Male (%)** | 70.1 | 73.4 | 68.4 | 66.1 | 0.006 |
| **History of admission for HF (%)** | 47.1 | 42.1 | 48.3 | 60.2 | <0.001 |
| **Etiology** | | | | | |
| Ischemic heart disease (%) | 58.8 | 60.9 | 58.9 | 48.9 | 0.001 |
| Cardiomyopathy (%) | 16.8 | 16.1 | 15.8 | 25.5 | <0.001 |
| Valvular heart disease (%) | 17.1 | 16.3 | 17.7 | 17.2 | 0.63 |
| Hypertensive heart disease (%) | 10.1 | 11.8 | 9.8 | 5.1 | 0.004 |
| **Comorbidities (%)** | | | | | |
| Hypertension | 78.7 | 85.5 | 76.8 | 61.3 | <0.001 |
| Diabetes | 28.3 | 28.6 | 27.8 | 29.6 | 0.78 |
| Hyperuricemia | 42.1 | 42.5 | 41.1 | 46.0 | 0.29 |
| Cerebrovascular disease | 15.9 | 15.8 | 16.4 | 13.1 | 0.4 |
| PAF | 7.8 | 7.8 | 7.8 | 6.2 | 0.64 |
| **Clinical status** | | | | | |
| NYHA class III or IV (%) | 9.9 | 7.8 | 10.2 | 17.2 | <0.001 |
| Body mass index (kg/m$^2$) | 23.7±4.7 | 24.2±4.3 | 23.7±4.8 | 22.0±5.5 | <0.001 |
| SBP (mmHg) | 128±19 | 135±14 | 127±19 | 103±10 | <0.001 |
| DBP (mmHg) | 73±12 | 74±10 | 73±13 | 64±10 | <0.001 |
| HR (beats/min) | 71±14 | 60±6 | 76±13 | 86±11 | <0.001 |
| **Measurements** | | | | | |
| LVEF (%) | 57.4±15.7 | 60.7±14.1 | 56.2±15.7 | 52.3±10.5 | <0.001 |
| LVDd (mm) | 51.8±9.1 | 51.4±8.2 | 52.1±9.5 | 52.3±10.5 | 0.12 |
| Hemoglobin (g/dl) | 13.2±2.1 | 13.3±2.2 | 13.2±2.0 | 12.9±2.8 | 0.02 |
| Blood urea nitrogen (mg/dl) | 19.6±10.7 | 19.3±10.9 | 19.4±9.8 | 21.5±13.7 | 0.007 |
| Serum creatinine (mg/dl) | 1.1±0.9 | 1.0±0.6 | 1.1±1.0 | 1.2±1.1 | 0.008 |
| Serum sodium (mEq/L) | 141±2.8 | 141±2.7 | 141±2.7 | 140±3.3 | <0.001 |
| Serum potassium (mEq/L) | 4.4±0.8 | 4.4±0.4 | 4.4±0.4 | 4.5±0.5 | 0.04 |
| Brain natriuretic peptide (pg/ml) | 76.3 | 70.7 | 73.2 | 135 | <0.001 |
| **Medications** | | | | | |
| ACE inhibitor (%) | 44.1 | 42.4 | 44.3 | 50.0 | 0.07 |
| ARB (%) | 32.5 | 34.9 | 31.7 | 27.4 | 0.03 |
| β-blocker (%) | 47.5 | 50.3 | 45.9 | 46.0 | 0.06 |
| Loop diuretics (%) | 39.8 | 32.4 | 42.4 | 54.4 | <0.001 |
| Aldosterone inhibitor (%) | 20.4 | 15.2 | 20.8 | 39.1 | <0.001 |
| Digitalis (%) | 12.1 | 9.5 | 13.1 | 17.2 | <0.001 |

Results of continuous values are presented as mean±SD. BNP levels are presented as medians.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; SBP, systolic blood pressure.

being recommended in guidelines, especially those with lower SBP.[16,17] Furthermore, the appropriate target ranges of HR and SBP for the management of CHF have been studied separately[4,6,7] and the usefulness of combined risk stratification with HR and SBP remains to be examined in a large-scale cohort study.

In the present study, we addressed this important clinical issue in a registry, namely the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (n=10,219) (NCT 00418041).[18]

## Methods

### Population and Inclusion Criteria

Details of the design, purpose, and basic characteristics of the CHART-2 Study have been described previously (NCT00418041).[18] Briefly, eligible patients were aged ≥20 years with significant CAD or in stages B, C and D as defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults.[19] Patients were classified as having HF by experienced cardiologists of 24 participating hospitals, using the criteria of the Framingham Heart Study.[20] The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively enrolled after written informed consent was obtained. The CHART-2 Study was started in October 2006 and the entry period was successfully closed in March 2010 with 10,219 patients registered from the participating hospitals. All data and events will be surveyed at least once each year until September 2018.

In the CHART-2 Study, each patient's resting HR was measured by ECG after a 2–3-min rest while supine. SBP was mea-

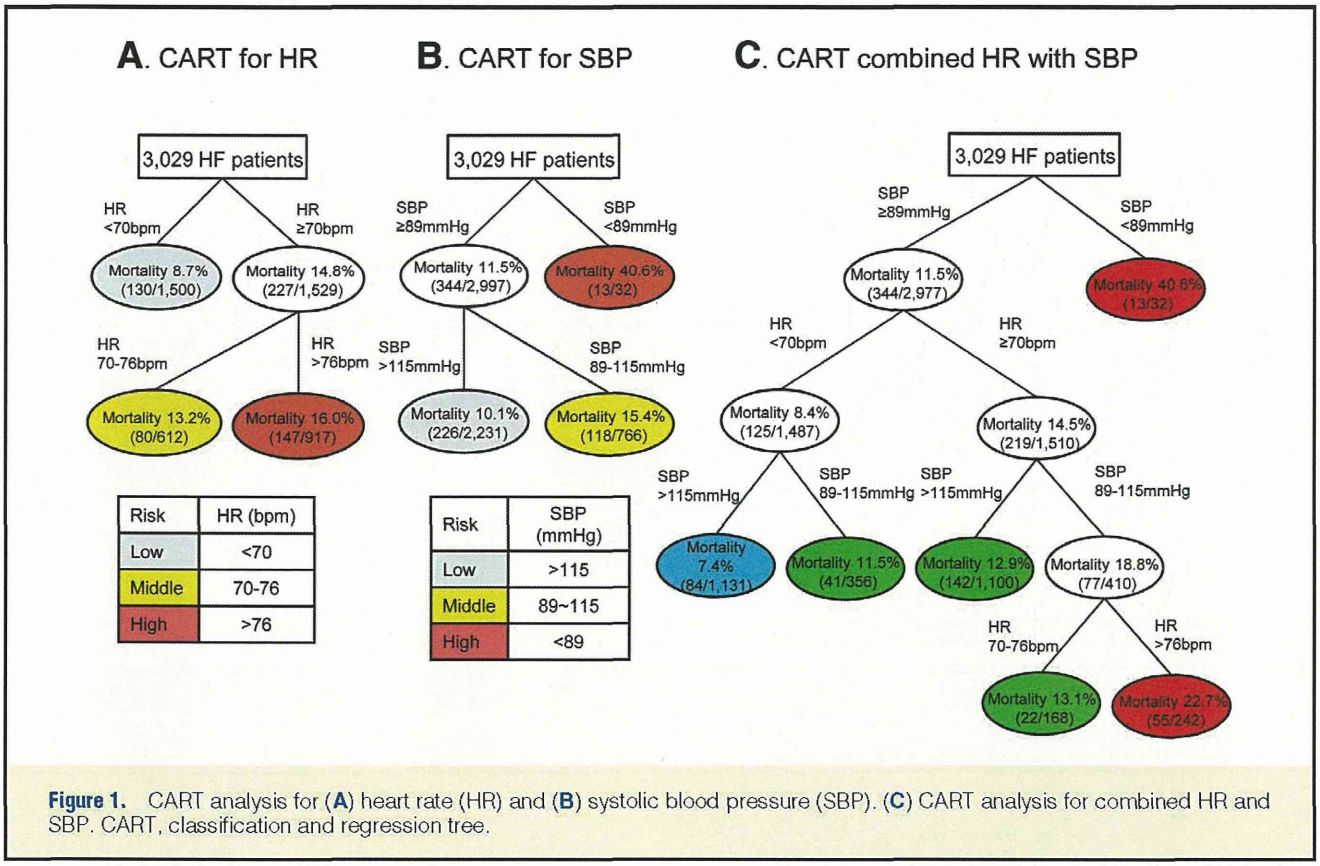


**Figure 1.** CART analysis for (**A**) heart rate (HR) and (**B**) systolic blood pressure (SBP). (**C**) CART analysis for combined HR and SBP. CART, classification and regression tree.

sured while seated after a 2–3-min rest. In the present study, we excluded asymptomatic patients in stage B (n=5,484) and patients with a pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy (n=486). We also excluded patients with chronic atrial fibrillation (n=1,079), those without sufficient data (n=89), and those who could not be followed up (n=53). Finally, 3,029 CHF patients in sinus rhythm (SR) at baseline were included in the present study. Among them, 236 patients had a history of paroxysmal atrial fibrillation (PAF).

### Follow-up Survey and Study Outcomes

We conducted the second survey of survival in November 2011 and the median follow-up period of the study population was 3.1 years. The outcome of this study was all-cause death.

### Statistical Analysis

In the present study, we performed classification and regression tree (CART) analysis[21] in order to identify the HR and SBP that would classify HF patients for all-cause death. CART analysis is an empirical, statistical technique based on recursive partitioning of the data space to predict the response.[21] The models are obtained by binary splitting of the data by the value of predictors, and the split variable and split-point are automatically selected from possible predictor values to achieve the best fit. Then, 1 or both "child nodes" are split into 2 or more regions recursively, and the process continues until some stopping rule is applied. Finally, the result of this process is represented as a binary decision tree.

First, we performed CART analysis for both HR and SBP to identify low-, middle-, and high-risk values of HR and SBP. Second, using these risk values of HR and SBP, we performed CART analysis by crossing over the risk values of HR and SBP. Then, we divided the study subjects into 3 risk groups according to the CART analysis and mortality rate: low-, middle-, and high-risk groups. We developed Kaplan-Meier curves and Cox proportional hazard models to compare the risk for all-cause death among the 3 groups. We constructed the following 3 Cox proportional hazard models; (a) unadjusted, (b) age- and sex-adjusted and (c) fully adjusted for clinical status, comorbidities and medications. We included the following covariates, which potentially influence the outcomes: age; sex; NYHA class; history of HF admission and malignant tumor; ischemic etiology of HF; LVEF; body mass index (BMI); serum sodium, serum potassium, serum creatinine, blood urea nitrogen (BUN) concentrations; comorbidities (anemia defined as hemoglobin <12 g/dl in females and <13 g/dl in males, diabetes mellitus, hyperuricemia and cerebrovascular disease); and medications ($\beta$-blockers, renin-angiotensin system inhibitors, calcium-channel blockers, loop diuretics, aldosterone antagonists and digitalis). We also performed subgroup analyses based on sex, age (<median or ≥median), history of PAF, LVEF (<50% or ≥50%), history of diabetes, cause of HF (ischemic or non-ischemic), and $\beta$-blocker therapy. Comparisons among the 3 groups were performed by chi-square test. Continuous data are described as mean±standard deviation and discrete-valued data as %.

The statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc, Chicago, IL, USA) and R 2.15.2.[22] Statistical significance was defined as a 2-sided P-value less than 0.05.

## Results

### Baseline Characteristics of All Study Subjects (Table 1)

Mean age was 67.9±12.8 years, and male patients accounted for 70.1% and ischemic HF for 58.8% of the study population. Mean