ORIGINAL RESEARCH ARTICLE

# Clinical impact of heart rate change in patients with acute heart failure in the early phase

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## Abstract

**Aims**   Patients with acute heart failure (AHF) often present with an increased heart rate (HR), and the HR changes dramatically after initial treatment for AHF. However, the HR change after admission and the relationship between HR change in the early phase and prognosis have not been fully elucidated.
**Methods and results**   From a multicentre AHF registry, we retrospectively evaluated 1527 consecutive patients admitted with AHF. HR change (%) was calculated by [HR (at admission) − HR (24 h after admission)] × 100/HR (at admission). The median HR change was 15.1% (range, 2.0–28.4%). The HR decreased most in the first 24 h and then gradually thereafter [admission: 98 (81–117) b.p.m., 24 h: 80 (70–92) b.p.m., 48 h: 78 (68–90) b.p.m., and 72 h: 77 (67–88) b.p.m.]. In Kaplan–Meier analysis, the cumulative event-free rates in the composite endpoint of death and rehospitalization due to AHF showed better according to larger HR change (*P* = 0.012, log rank). Cox proportional hazards analysis showed that HR change was a prognostic factor for composite endpoint adjusted by age and sex [hazard ratio, 0.995; 95% confidence interval (CI), 0.991–0.998; *P* = 0.006]. HR change was associated with outcome adjusted by age and sex in patients with sinus rhythm (hazard ratio, 0.993; 95% CI, 0.988–0.999; *P* = 0.015), but not in patients with atrial fibrillation (hazard ratio, 0.996; 95% CI, 0.990–1.002; *P* = 0.15).
**Conclusions**   A decrease in HR in the first 24 h after admission indicates better prognosis in patients with AHF, although the prognostic influence may differ between patients with sinus rhythm and those with atrial fibrillation.

## Introduction

Hospitalization of patients with acute heart failure (AHF) is a life-threatening condition and an increasing major public health problem.[1–3] Patients with AHF often present with an increased heart rate (HR), reflecting increased sympathetic and neurohumoral factors.[4] Several studies have evaluated the prognostic value of HR admission and HR change during hospitalization in patients with AHF. One study showed that higher HR at admission was associated with lower mortality in patients with AHF, while those discharged with controlled HR also had survival advantage.[5] That is, patients presenting

with tachycardia and discharged with a controlled HR had better outcomes. In contrast, another study revealed that HR reduction during hospitalization for HF was not associated with better prognosis in patients with sinus rhythm.[6] However, these studies evaluated the HR change at admission and discharge, and no conclusion has been reached as yet. Several guidelines emphasize the importance of earlier stabilization for haemodynamic abnormalities,[7] and HR often changes dramatically after initial treatment for AHF in clinical practice. Therefore, early HR change just after admission may reflect successful treatment and may be associated with outcome. However, in patients with AHF, the relationship

between HR change in the early phase and prognosis has not been fully elucidated. Thus, the aim of this study was to evaluate the HR change after admission and the prognostic value of HR change in the early phase in patients with AHF as well as the differences between the sinus rhythm and atrial fibrillation (AF) groups.

# Methods

## Study design and population

We analysed data from a multicentre retrospective registry of consecutive patients hospitalized for AHF from January 2012 to March 2019. This registry consisted of data gathered from the following three centres: Nagoya University Hospital, Nagoya Ekisaikai Hospital, and Ichinomiya Municipal Hospital. Patients who met the modified Framingham criteria were included.[8] The exclusion criteria were as follows: (i) an age <20 years; (ii) history of cardiac transplantation; (iii) treatment with chronic peritoneal dialysis or haemodialysis; (iv) concomitant hepatic cirrhosis; (v) acute myocarditis; (vi) acute coronary syndrome requiring emergency or urgent revascularization; and (vii) life expectancy <6 months due to non-cardiac disease such as end-stage cancer, as determined by the enrolling clinical investigator. In addition, patients with pacemaker rhythm and severe bradycardia requiring temporary pacing, ventricular tachycardia, or paroxysmal supraventricular tachycardia were excluded from the analysis because their HRs were strongly defined by either the arrhythmia itself or a pacemaker. We excluded patients without HR records at admission or 24 h after admission.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Nagoya University Hospital (approval number: 2019-0521) and Nagoya Ekisaikai Hospital (approval number: 2018-039) and Ichinomiya Municipal Hospital (approval number: 1250). Informed consent was not required from patients, and an opt-out method for participant recruitment was employed to avoid the delay in treatment and bias in results that might have occurred if written informed consent was obtained from all patients.

## Heart rate measurements and heart rate change

The admission HR was defined as the first HR recorded in the emergency or outpatient department before any acute HF medications. The HR at 24, 48, and 72 h after admission was obtained from the HR measured by electrocardiogram monitoring. We focused not on HR itself but on HR change in the first 24 h. We defined HR change (%) as follows: HR change = [HR (at admission) − HR (at 24 h after admission)] × 100⁄HR (at admission).

## Study outcomes

The outcome of this study was a composite of all-cause death and readmission for heart failure within 1 year.

## Statistical analysis

Continuous data are presented as medians with inter-quartile ranges and were compared using the Mann–Whitney $U$ test or Wilcoxon signed-rank test, and Kruskal–Wallis test (all continuous variables showed non-normal distribution). The Friedman test was used to compare the HR between different time phases. In our study, age was analysed as a per year continuous variable. Categorical data are presented as percentages and were analysed using the $\chi^2$ test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to determine cumulative probabilities of composite outcome throughout the follow-up period. The cumulative event rates were compared using the log-rank test. To evaluate the prognostic value of HR change for composite outcome, univariate and multivariate Cox proportional hazard analyses were performed adjusted by age and sex (Model 1) and adjusted by age, sex, body mass index, systolic blood pressure at admission, ischaemic aetiology, hypertension, diabetes mellitus, beta-blocker at admission, albumin, creatinine, sodium, haemoglobin, logarithm brain natriuretic peptide, left ventricular ejection fraction, use of inotropes, and use of negative chronotropic agents (Model 2). Negative chronotropic agents, including diltiazem, landiolol, digoxin, and amiodarone, and also inotropes affect the HR change. To eliminate this effect, we performed Cox proportional hazards analysis in patients without negative chronotropic agents or inotropes in the 24 h after admission as sensitivity analyses. We also assessed the hazard ratio across the spectrum of HR change for composite outcome, using restricted cubic splines, with three knots placed at the 10th, 50th, and 90th percentiles. Furthermore, we divided the patients into 12 groups according to tertile of HR at admission and quartile of HR change, and hazard ratio was evaluated as reference of the group with higher tertile of baseline HR and fourth quartile of HR change. $P$ values <0.05 were considered statistically significant for all tests. Statistical analyses were performed using R Version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and STATA Version 16.1 software (College Station, TX).

# Results

## Study groups and patients' characteristics

During the study period, 1870 patients with AHF were admitted to the three participating hospitals. Of these, 343

patients were excluded for the following reasons: 199 patients with pacemaker rhythm and severe bradycardia requiring temporary pacing, ventricular tachycardia, or paroxysmal supraventricular tachycardia and 144 patients without adequate records regarding HR. Finally, 1527 patients were taken forward for final analysis. Among the 1527 patients, 962 (63.0%) had sinus rhythm and 565 (37.0%) had AF.

Among the 1527 patients, the median HR change was 15.1%. Patients were divided into four groups according to the quartile of HR change: first quartile, HR change <2.0%; second quartile, $2.0 \leq$ HR change < 15.1%; third quartile, $15.1 \leq$ HR change < 28.4%; and fourth quartile, $28.4\% \leq$ HR change. The median age of the patients was 79 (70–85) years, and 866 patients (56.7%) were male. The patients' background data by HR change are presented in *Table 1*. In larger HR change group, the patients tended to be younger and have a higher frequency of New York Heart Association Class III or IV, higher systolic blood pressure and HR at admission,

less frequent use of mineralocorticoid receptor antagonists, and lower levels of serum blood urea nitrogen and serum creatinine. As for the treatment after admission, the group with large changes in HR used non-invasive ventilation more frequently and negative chronotropic agents, including diltiazem, landiolol, and digoxin, more frequently.

We divided the patients into two groups according to the rhythm at admission (sinus rhythm group and AF group) and, similarly, divided the HR change into quartiles in each group, respectively (Supporting Information, *Tables S1* and *S2*). We also divided the patients into three groups according to the baseline HR at admission (Supporting Information, *Table S3*).

## Heart rate course

The course of HR after admission is shown in *Figure 1*. HR decreased most within the first 24 h [at admission: 98 (81–117)

**Table 1** Baseline patient characteristics at admission and within 24 h treatment

| | First quartile (*n* = 379) HR change <2.0% | Second quartile (*n* = 384) 2.0% ≤ HR change < 15.1% | Third quartile (*n* = 381) 15.1% ≤ HR change < 28.4% | Fourth quartile (*n* = 383) 28.4% ≤ HR change | *P* value |
|---|---|---|---|---|---|
| Age (years) | 81 (74–87) | 80 (68–86) | 77 (68–84) | 78 (69–84) | <0.001 |
| Male, *n* (%) | 207 (54.6) | 218 (56.8) | 224 (58.8) | 217 (56.7) | 0.72 |
| Body mass index (kg/m$^2$) | 22.1 (19.9–24.9) | 22.6 (19.9–25.6) | 22.8 (19.9–25.5) | 21.6 (19.3–24.7) | 0.010 |
| NYHA Classes III and IV, *n* (%) | 306 (80.7) | 326 (84.9) | 334 (87.7) | 348 (90.9) | <0.001 |
| Systolic blood pressure (mmHg) | 131 (115–153) | 139 (120–160) | 148 (128–172) | 165 (134–195) | <0.001 |
| Heart rate (b.p.m.) | 79 (68–90) | 89 (77–103) | 101 (90–117) | 123 (110–144) | <0.001 |
| Atrial fibrillation rhythm, *n* (%) | 144 (38.0) | 102 (26.6) | 139 (36.5) | 180 (47.0) | <0.001 |
| Ischaemic aetiology, *n* (%) | 103 (27.2) | 99 (25.8) | 123 (32.3) | 91 (23.8) | 0.058 |
| History of HF hospitalization, *n* (%) | 129 (34.1) | 146 (38.0) | 120 (31.5) | 113 (29.5) | 0.070 |
| Co-morbidities | | | | | |
|   Hypertension, *n* (%) | 218 (57.5) | 237 (61.7) | 218 (57.2) | 242 (63.2) | 0.23 |
|   Diabetes mellitus, *n* (%) | 105 (27.7) | 122 (31.8) | 124 (32.5) | 115 (30.0) | 0.46 |
| Oral medication before admission | | | | | |
|   ACE-I/ARB, *n* (%) | 161 (42.5) | 156 (40.6) | 151 (39.6) | 156 (40.7) | 0.88 |
|   Beta-blocker, *n* (%) | 136 (35.9) | 155 (40.4) | 111 (29.1) | 131 (34.2) | 0.012 |
|   MRA, *n* (%) | 103 (27.2) | 87 (22.7) | 74 (19.4) | 67 (17.5) | 0.008 |
| Laboratory data | | | | | |
|   Albumin (g/dL) | 3.4 (3.1–3.8) | 3.4 (3.0–3.8) | 3.5 (3.1–3.9) | 3.5 (3.1–3.9) | 0.051 |
|   BUN (mg/dL) | 23.2 (17.0–31.2) | 22.9 (16.1–31.6) | 21.0 (16.0–29.4) | 20.1 (15.5–27.0) | 0.002 |
|   Creatinine (mg/dL) | 1.06 (0.83–1.46) | 1.08 (0.84–1.55) | 0.98 (0.79–1.30) | 0.97 (0.78–1.30) | <0.001 |
|   Sodium (mEq/L) | 140 (137–142) | 140 (137–142) | 140 (138–142) | 140 (138–142) | 0.27 |
|   Haemoglobin (g/dL) | 11.4 (9.8–12.9) | 11.2 (9.9–13.3) | 11.9 (10.3–13.7) | 12.2 (10.6–13.8) | <0.001 |
|   BNP (pg/mL) | 638 (339–1117) | 795 (413–1508) | 629 (373–1216) | 630 (358–1046) | 0.008 |
|   CRP (mg/dL) | 0.65 (0.21–2.91) | 0.77 (0.30–2.22) | 0.87 (0.25–2.26) | 0.70 (0.22–2.70) | 0.85 |
| LVEF (%) | 45 (30–59) | 39 (26–54) | 38 (27–53) | 38 (28–53) | 0.007 |
| Treatment within 24 h | | | | | |
|   NIV, *n* (%) | 39 (10.3) | 63 (16.4) | 107 (28.1) | 175 (45.7) | <0.001 |
|   Endotracheal intubation, *n* (%) | 10 (2.6) | 6 (1.6) | 11 (2.9) | 14 (3.7) | 0.32 |
|   Inotropes, *n* (%) | 47 (12.4) | 60 (15.6) | 37 (9.7) | 42 (11.0) | 0.10 |
|   Diltiazem, *n* (%) | 15 (4.0) | 23 (5.9) | 49 (12.9) | 74 (19.3) | <0.001 |
|   Landiolol, *n* (%) | 5 (1.3) | 8 (2.1) | 10 (2.6) | 24 (6.3) | <0.001 |
|   Digitalis, *n* (%) | 7 (1.8) | 4 (1.0) | 8 (2.1) | 17 (4.4) | 0.009 |
|   Amiodarone, *n* (%) | 6 (1.6) | 11 (2.9) | 12 (3.1) | 15 (3.9) | 0.18 |
| HR change (%) | −6.6 (−17.2- -1.5) | 8.5 (5.6–12.1) | 22.7 (19.2–25.6) | 38.5 (33.8–34.5) | <0.001 |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NIV, non-invasive ventilation; NYHA, New York Heart Association.
Values are presented as number (%) or median (lower quartiles–upper quartiles).

**Figure 1** Heart rate course after admission (A) in all patients, (B) in the sinus rhythm group, and (C) in the atrial fibrillation (AF) group.
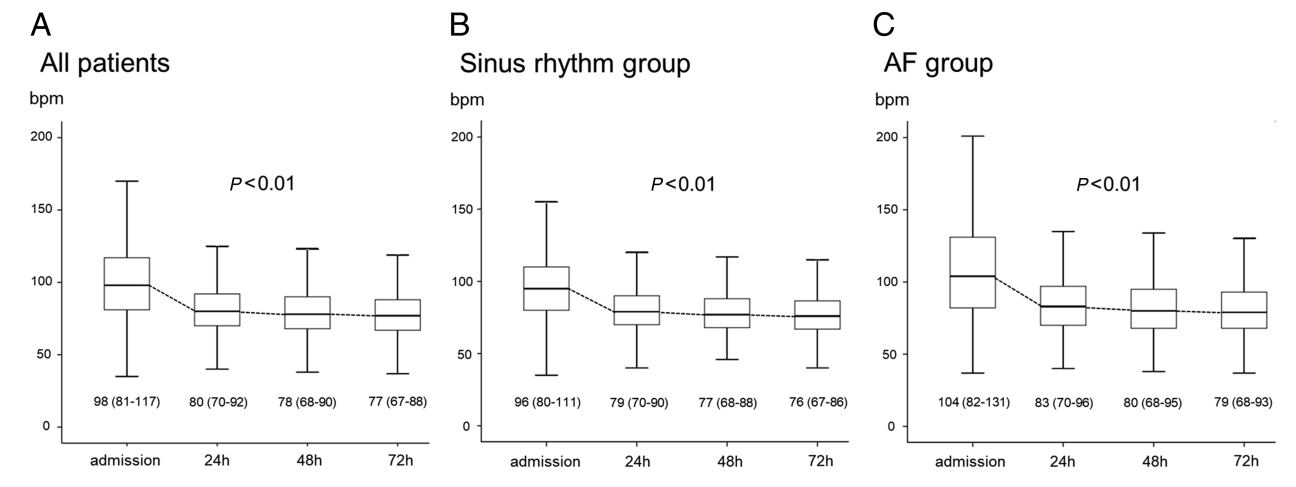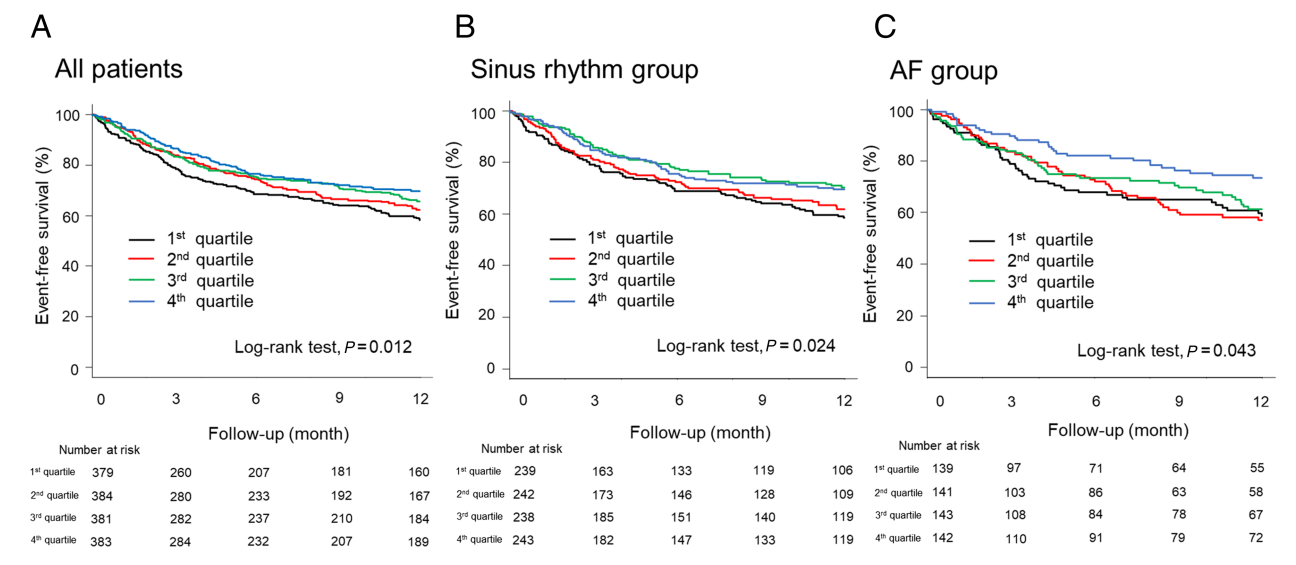


**Figure 2** Kaplan–Meier analysis for the composite outcome among the four groups (first to fourth quartiles of the heart rate change) (A) in all patients, (B) in the sinus rhythm group, and (C) in the atrial fibrillation (AF) group.



b.p.m.; 24 h: 80 (70–92) b.p.m.]. After 24 h, the HR gradually decreased, but this change was not large [48 h: 78 (68–90) b. p.m.; 72 h: 77 (67–88) b.p.m.]. Similar results were obtained in both the sinus rhythm group and the AF group.

## Outcome

Of all patients, composite outcomes were observed in 468 patients (30.6%). Kaplan–Meier survival analysis demonstrated that the event-free rate for the composite outcome decreased progressively with lower values of the HR change quartile (log rank, $P = 0.012$) (*Figure 2*), and these tendencies were similar in both the sinus rhythm group and the AF group (sinus rhythm group: log rank, $P = 0.024$; AF group: log rank, $P = 0.043$). In Kaplan–Meier survival analysis of the relationship between baseline HR and composite outcomes, the lower the HR at admission, the worse the prognosis. And this result was same in both the sinus rhythm group and the AF group (Supporting Information, *Figure S1*).

The univariate and multivariate Cox proportional hazard analyses for composite outcomes are summarized in *Table 2*. In the univariate analysis, HR change was associated with composite outcome (hazard ratio, 0.993; 95% confidence interval, 0.980–0.997; $P < 0.001$). In the multivariate analysis adjusted by age and sex (Model 1), HR change was a prognostic factor for composite outcome (hazard ratio, 0.995; 95% confidence interval, 0.991–0.998; $P = 0.006$). However, when adjusted by multiple variables (Model 2),

**Table 2** Cox proportional hazards regression analysis

| | All patients | | | Sinus rhythm group | | | AF group | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value |
| Univariate | | | | | | | | | |
| HR change | 0.993 | 0.980–0.997 | <0.001 | 0.992 | 0.987–0.998 | 0.004 | 0.994 | 0.988–0.999 | 0.027 |
| HR at admission | 0.992 | 0.989–0.996 | <0.001 | 0.992 | 0.986–0.997 | 0.002 | 0.992 | 0.987–0.996 | <0.001 |
| Model 1 | | | | | | | | | |
| HR change[a] | 0.995 | 0.991–0.998 | 0.006 | 0.993 | 0.988–0.999 | 0.015 | 0.996 | 0.990–1.002 | 0.15 |
| HR at admission[a] | 0.995 | 0.991–0.998 | 0.004 | 0.996 | 0.990–1.001 | 0.10 | 0.994 | 0.989–0.999 | 0.011 |
| Model 2 | | | | | | | | | |
| HR change[b] | 0.999 | 0.994–1.004 | 0.62 | 0.998 | 0.990–1.005 | 0.50 | 0.999 | 0.992–1.007 | 0.84 |
| HR at admission[b] | 0.997 | 0.993–1.002 | 0.28 | 0.997 | 0.990–1.004 | 0.39 | 0.997 | 0.990–1.003 | 0.32 |

AF, atrial fibrillation; CI, confidence interval; HR, heart rate.
[a]Adjusted by age and sex.
[b]Adjusted for age, sex, body mass index, systolic blood pressure at admission, ischaemic aetiology, hypertension, diabetes mellitus, beta-blocker at admission, albumin, creatinine, sodium, haemoglobin, logarithm brain natriuretic peptide, left ventricular ejection fraction, use of inotropes, and use of negative chronotropic agents.

**Figure 3** Distribution of the heart rate (HR) change and its relationship with outcome. The hazard ratio across the spectrum of HR change for composite outcome was assessed.
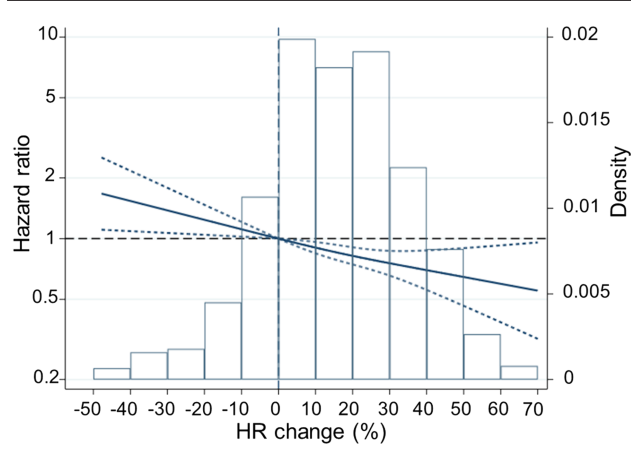


HR change was not an independent prognostic factor for outcome (hazard ratio, 0.998; 95% confidence interval, 0.993–1.000; *P* = 0.46). In the sinus rhythm group, HR change was associated with outcome in both the univariate and multivariate analyses (Model 1), but not in the multivariate analysis (Model 1) in the AF group. Similar to HR change, baseline HR was a prognostic factor in univariate analysis and Model 1, but not in Model 2, in the all patients. Contrary to HR change, in Model 1, baseline HR was a prognostic factor in AF group, but not in sinus rhythm group (*Table 2*). *Figure 3* shows the distribution of HR change and its relationship with the outcome. The hazard ratio tended to decrease as the HR change increased. In the analysis of dividing the patients into 12 groups according to HR at admission and HR change, higher tertile of baseline HR and fourth quartile of HR change (reference) had the lowest hazard ratio (*Figure 4*). The lower the tertile in baseline HR and the first quartile in HR, the worse is the outcome.

**Figure 4** Comparison of hazard ratio for composite outcome, dividing the patients into 12 groups according to heart rate (HR) at admission and HR change.
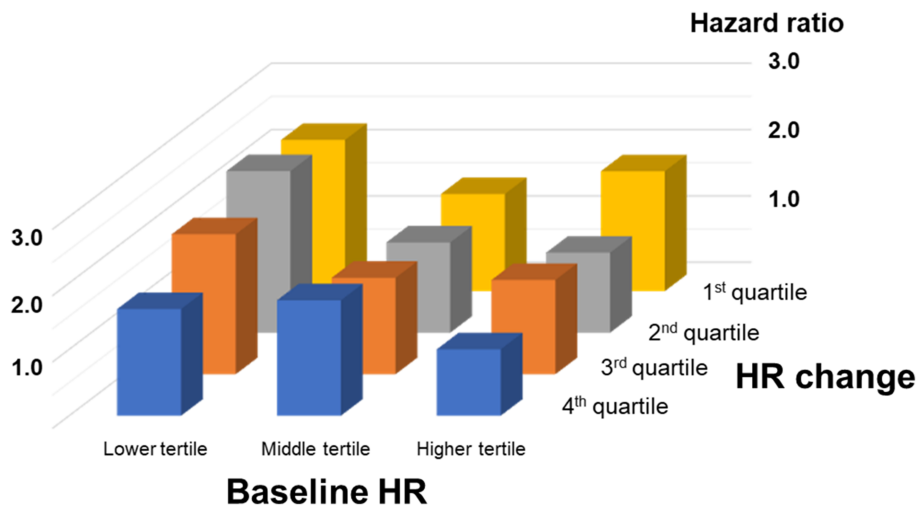
## Sensitivity analysis

Cox proportional hazards analyses were performed as sensitivity analyses in patients without negative chronotropic agents or inotropes in 24 h of admission. In patients without negative chronotropic agents (Supporting Information, *Table S4*), HR change was associated with composite outcome in the univariate analysis (hazard ratio, 0.995; 95% confidence interval, 0.990–0.999; *P* = 0.015) and in Model 1 (hazard ratio, 0.996; 95% confidence interval, 0.991–0.999; *P* = 0.044). However, in Model 2, HR change was not a prognostic factor for composite outcome (hazard ratio, 0.999; 95% confidence interval, 0.994–1.005; *P* = 0.75). In the AF group, HR change was not a prognostic factor even in the univariate analysis and Model 1. In patients without inotropes (Supporting Information, *Table S5*), HR change was associated with outcome in the univariate analysis (hazard ratio, 0.993; 95% confidence interval, 0.988–0.997; *P* < 0.001) and in Model 1 (hazard ratio, 0.995; 95% confidence interval, 0.991–0.999; *P* = 0.015). However, in Model 2, HR change was not a prognostic factor for composite outcome (hazard ratio, 0.998; 95% confidence interval, 0.993–1.004; *P* = 0.51). In the sinus rhythm group, HR change was a prognostic factor in the univariate analysis and Model 1; however, it was not in Model 1 in the AF group.

## Discussion

The present study has three important findings. First, the HR significantly decreased within 24 h of admission but did not change dramatically after 24 h in patients with AHF. Second, the HR change in the 24 h following admission was associated with adverse outcomes in patients with AHF. Third, the association of HR change with prognosis may be different in patients with sinus rhythm and AF, and the HR change may not have clinical value in AF.

There is an increasing interest in the role of HR not only in patients with chronic HF but also in patients admitted for AHF.[9] In patients with HF, increased HR is a featured haemodynamic abnormal finding that is well known to be related to poor outcome.[10] The mechanism in which increased HR is associated with poor outcome can be explained by several mechanisms: sympathetic overactivity, increased myocardial oxygen consumption, reduced diastolic filling times, and compromised coronary perfusion with myocardial ischaemia.[11,12] AHF registries in Europe showed that patients admitted with AHF have a higher basal HR than those with chronic HF.[13,14] In patients with AHF, HR is more strongly affected by sympathetic and haemodynamic status.[15] Low cardiac output and hypoperfusion of multiple organs activate the sympathetic nerve system, resulting in HR elevation as an attempt to compensate for haemodynamic dysfunction and to restore cardiac output.[16,17] Increased respiratory work and respiratory distress due to acute cardiogenic pulmonary oedema also lead to further sympathetic overactivity.[18] Considering these mechanisms, a large HR reduction in response to initial treatment is thought to lead to significant improvement in these abnormal conditions, leading to our main result that patients with the largest HR changes had better outcomes.

Although several papers have discussed the prognosis of AHF in relation to HR change between admission and discharge, we should pay attention to the fact that HR at discharge can be defined depending not only on the sympathetic and neurohumoral response to AHF management but also on these suppression by beta-blockers, which are commonly prescribed for the management of chronic heart failure.[19,20] The ability to predict prognosis earlier than at discharge has the advantage of providing strategic information to clinicians in earlier timing of AHF. In addition, as the HR difference between 24 and 72 h was not large, we focused on the HR 24 h after admission. A previous report by Lancellotti *et al*. also evaluated the association between HR at 24–36 h after admission and outcome.[21] They found that higher HR at 24–36 h was related to higher in-hospital mortality and that the best cut-off value was 91 b.p.m. from receiver operating characteristic curves. In our study, we focused on not the HR itself but the HR change in early phase. HR change can be expressed by the absolute value of the difference between HR at admission and HR 24 h later or by the ratio of the difference in HR between the two time phases. It was considered that the absolute value of the HR change was largely influenced by baseline HR. In the current study, we adopted HR change as a percentage in order to reduce this influence as much as possible.

The clinical impact of baseline HR at admission has already been reported in several studies[22,23]; however, the results were controversial. The sub-analysis in this study showed that the group with higher HR at admission had a better prognosis. In addition, we identified that the smaller HR change tended to relate to poor outcome in all baseline HR groups (*Figure 4*).

Comprehensive inpatient monitoring is crucial for optimal management of patients with AHF. According to the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology, several tools are available for monitoring patients with AHF, each of which can play a role at different times throughout the course of treatment.[24] In addition to chest radiography, echocardiography, and laboratory assessments, including cardiac biomarkers and lactate, HR was recommended as a monitoring indicator. HR has the advantage of being easy, non-invasive, and repeatedly collected in daily practice. Our study suggests that a decrease in HR reflects successful initial treatment, and therefore, HR can be considered as a useful monitoring indicator for the early treatment of AHF. Although the HR change was not significantly associated with outcome in multivariate

analysis (Model 2), we believe that there is a large merit in predicting prognosis with simple parameters 'HR changes', rather than using numerous variables in the early stages of hospitalization.

Sensitivity analysis showed that HR change was not significantly associated with outcome in patients with AF, after excluding patients who had been treated with negative chronotropic agents within 24 h. This result indicates that the association of HR change with prognosis may be different in patients with sinus rhythm and AF, and HR change may not have clinical value in AF. However, we have to take into account the fact that patients with negative chronotropic agents generally demonstrate large HR changes, and exclusion of distorted patient populations might have resulted in no significant association between HR change and prognosis in AF patients. Moreover, we cannot deny that HR change induced by the use of negative chronotropic agents for AF tachycardia led to improved prognosis because patients with negative chronotropic agents showed better outcomes than those without (log rank, *P* = 0.002) (Supporting Information, *Figure S2*).

## Study limitations

This study has some limitations. First, given that we excluded patients with pacemaker rhythm and severe bradycardia requiring temporary pacing, ventricular tachycardia, or paroxysmal supraventricular tachycardia, our results do not pertain to all patients with AHF. Second, this was an observational study, so we cannot determine whether HR would be a useful therapeutic target; in other words, we were unable to establish whether decreasing the HR strategy would improve the prognosis. In the acute setting, beta-blockers may worsen the haemodynamics due to their negative inotropic effects. On the other hand, ivabradine has no negative inotropic effect and is reported to suppress dobutamine-induced tachycardia and ventricular arrhythmias,[25,26] suggesting possibility of advantage in lowering HR without less adverse effects. Third, cases with altered rhythm after admission cannot be considered; therefore, we were unable to clarify the clinical significance of HR change in cases with AF rhythm on admission and sinus rhythm at 24 h. Fourth, we did not have data about the dosages of inotropes and negative chronotropic agents, and beta-blocker discontinuation. Finally, HR is affected by various diseases other than cardiovascular disease. We were unable to evaluate thyroid function in all patients in the acute phase, and we were unable to completely exclude the presence of patients with hypothyroidism or hyperthyroidism. Similarly, although there was no significant difference in C-reactive protein levels between the quartiles, it is possible that inflammatory conditions influenced the HR change.

## Conclusion

A decrease in HR in the 24 h after admission indicates better prognosis in patients with AHF. The association of HR change with prognosis is different in patients with sinus rhythm and AF, and HR change may have more significant clinical value in patients with sinus rhythm than in those with AF.

## Conflict of interest

## Funding

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Kaplan-Meier analysis for the composite outcome among the three groups (first to third tertile of the HR at

admission) (A) in all patients, (B) in the sinus rhythm group, and (C) in the AF group.

**Figure S2.** Kaplan-Meier analysis for the composite outcome in patients with AF, with or without negative chronotropic agents within 24 hours of admission.

**Table S1.** Baseline patient characteristics at admission and within 24 hours treatment in sinus rhythm group.

**Table S2.** Baseline patient characteristics at admission and within 24 hours treatment in AF group.

**Table S3.** Baseline patient characteristics at admission and within 24 hours treatment in all patients when divided into tertile of heart rate at admission.

**Table S4.** Cox proportional hazards regression analysis excluding patients who have been treated with negative chronotropic agents within 24 hours after admission.

**Table S5.** Cox proportional hazards regression analysis excluding patients who have been treated with inotropes within 24 hours after admission.

# References

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