Figure 3. Distribution of the elapsing time from onset to admission before and after the Great East Japan Earthquake (March 11, 2011) (**A,B**), and the in-hospital mortality by the elapsing time from onset to admission before and after the Earthquake (**C,D**). *P<0.05 between before and after the Earthquake.

PCI. P<0.05 was considered statistically significant. All statistical analyses were performed using the statistical software R. 2.15.2 (http://www.r-project.org/) (See **Supplementary File 1: Methods** for details).

Results

The total number of AMI patients in the study period (from January 11 to November 15) in 2008, 2009, 2010 and 2011 was 985, 972, 1038 and 942, respectively. The weekly occurrence of AMI in Miyagi prefecture did not differ significantly after the Great East Japan Earthquake of March 11, 2011 compared with the previous 3 years (**Figure S2**). The clinical characteristics and outcomes of AMI patients in 2008–2010 and 2011 are summarized in **Table 1**. Importantly, the emergency care of AMI was significantly improved in 2011 compared with the previous 3 years, as evidenced by shorter elapsing time from onset to admission, higher performance rate of primary PCI and lower in-hospital mortality despite higher CPK levels. The time-courses of in-hospital mortality according to sex, age, early (≤3h) and late (>3h) admission and ambulance use are shown in **Figure 1**. As compared with 2008–2010, significant improvement of in-hospital mortality was noted during the first 2 months after the Earthquake in 2011 (**Figure 1A**), particularly in male patients (**Figures 1B,C**), younger patients (<70 years) (**Figures 1D,E**) and those with early admission (≤3h) (**Figures 1F,G**), whereas the using an ambulance had no significant effects (**Figures 1H,I**).

To explore the factors involved in the improved in-hospital

mortality of AMI patients soon after the Earthquake, we performed time-course analyses of the clinical characteristics of AMI patients in 2011 compared with the previous 3 years. In accordance with the imprived in-hospital mortality, the time from onset to admission shortened significantly in 2011 compared with the previous 3 years (**Figures 2A,B**), whereas, the door-to-balloon time was comparable (**Figure 2C**). Accordingly, treatment delay, defined as the time from onset to reperfusion, was significantly improved during the first 2 months after the Earthquake (**Figure 2D**) despite no significant change in the ambulance use rate (**Figure 2E**). Performance rate of primary PCI was correspondingly also significantly increased (**Figure 2F**). In contrast, peak CPK levels (**Figure 2G**) and the prevalences of symptomatic heart failure (Killip class ≥2 on admission) (**Figure 2H**), females (**Figure 2I**) and elderly patients (≥70 years) (**Figure 2J**) were almost comparable between 2011 and the previous 3 years.

Furthermore, distribution of the elapsing time from AMI onset to admission showed that the proportion of patients with early admission (≤3h from onset) was significantly increased after the Earthquake (**Figures 3A,B**). We also found a significant reduction in the in-hospital mortality of these patients after the Earthquake (**Figures 3C,D**). Multivariate logistic regression analysis demonstrated that before the Earthquake, early admission was significantly associated with a higher incidence of in-hospital mortality but became insignificant after the Earthquake (**Figure 4**). As shown in **Table 2**, the patients with early admission during the first 2 months after the Earthquake were characterized by lower in-hospital mortality as-
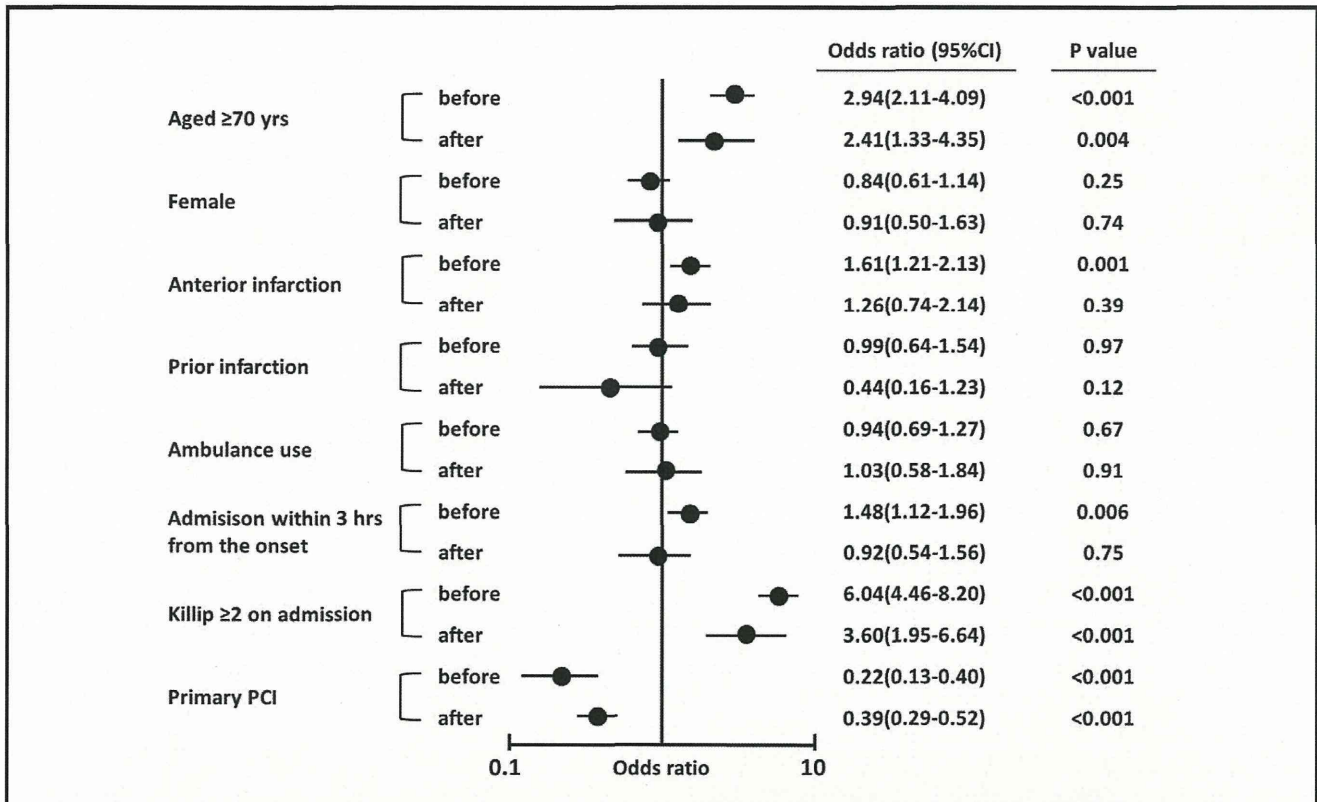
		Odds ratio (95%CI)	P value
Aged ≥70 yrs	before	2.94(2.11-4.09)	<0.001
	after	2.41(1.33-4.35)	0.004
Female	before	0.84(0.61-1.14)	0.25
	after	0.91(0.50-1.63)	0.74
Anterior infarction	before	1.61(1.21-2.13)	0.001
	after	1.26(0.74-2.14)	0.39
Prior infarction	before	0.99(0.64-1.54)	0.97
	after	0.44(0.16-1.23)	0.12
Ambulance use	before	0.94(0.69-1.27)	0.67
	after	1.03(0.58-1.84)	0.91
Admisison within 3 hrs from the onset	before	1.48(1.12-1.96)	0.006
	after	0.92(0.54-1.56)	0.75
Killip ≥2 on admission	before	6.04(4.46-8.20)	<0.001
	after	3.60(1.95-6.64)	<0.001
Primary PCI	before	0.22(0.13-0.40)	<0.001
	after	0.39(0.29-0.52)	<0.001

0.1   Odds ratio   10

Figure 4. Multivariate adjusted odds ratio and 95% confidence intervals (CI) for in-hospital mortality of patients with acute myocardial infarction patients before and after the Earthquake. PCI, percutaneous coronary intervention.

Table 2. Clinical Characteristics and Outcome of Patients With Early Admission (≤3h From Onset) in 2008–2010 and 2011*

	2 months before March 11			2 months after March 11		
	2008–2010 (n=243)	2011 (n=96)	P value	2008–2010 (n=216)	2011 (n=101)	P value
Age [median (IQR)], years	68 (57–78)	69 (55–79)	0.62	70 (60–79)	72 (61–82)	0.44
Female (%)	26.1	29.2	0.56	24.0	19.8	0.41
Anterior infarction (%)	50.8	41.7	0.13	42.7	54.5	0.05
Prior infarction (%)	10.7	8.3	0.51	11.6	8.9	0.48
Ambulance use (%), (n)	72.8 (177)	79.2 (76)	0.23	69.9 (151)	66.3 (67)	0.52
Killip ≥2 on admission (%)	13.2	14.6	0.73	16.2	6.9	0.02
Primary PCI (%)	83.1	81.3	0.68	76.4	89.1	0.008
Peak CPK [median (IQR)], IU/L	1,622 (618–3,003)	1,653 (615–2,886)	0.80	1,386 (590–3,058)	1,634 (712–3,389)	0.28
Door-to-balloon time [median (IQR)], min†	62 (45–109)	58 (40–92)	0.61	67 (43–113)	68 (45–110)	0.90
In-hospital mortality (%), (n)	12.3 (30)	10.4 (10)	0.62	14.8 (32)	5.9 (6)	0.02

*Only patients with data available on onset time (n=459 in 2008–2010 and n=197 in 2011). †Only patients who received primary PCI with data available on door-to-balloon time (n=276 in 2008–2010 and n=165 in 2011).
Abbreviations as in Table 1.

sociated with lower prevalence of heart failure with Killip class ≥2 on admission and higher performance rate of primary PCI, compared with those in 2008–2010. In contrast, the clinical characteristics of the patients with late admission (>3h) did not significantly change after the Earthquake (Table 3).

Although the tsunami directly and severely damaged the seacoast area, there was no regional difference between the seacoast area and inland areas in the factors relevant to the emergency care of AMI (Table 4), suggesting that the emergency medical system of AMI was fairly maintained throughout Miyagi prefecture soon after the Earthquake.

Discussion

The novel findings of the present study are that emergency care of AMI improved soon after the Great East Japan Earthquake as compared with ordinary times, for which a shorter elapsing time from onset to admission and a higher perfor-

Table 3. Clinical Characteristics and Outcome of Patients With Late Admission (>3 Hours From the Onset) in 2008–2010 and 2011*

	2 months before March 11			2 months after March 11		
	2008–2010 (n=296)	2011 (n=77)	P value	2008–2010 (n=261)	2011 (n=63)	P value
Age [median (IQR)], years	73 (63–81)	75 (64–84)	0.02	72 (61–80)	70 (63–78)	0.44
Female (%)	29.4	35.1	0.34	25.0	23.8	0.85
Anterior infarction (%)	45.6	48.1	0.70	48.5	36.5	0.09
Prior infarction (%)	6.1	7.8	0.59	12.3	7.9	0.33
Ambulance use (%), (n)	69.6 (206)	53.2 (41)	0.007	57.9 (151)	68.3 (43)	0.13
Killip ≥2 on admission (%)	12.2	6.5	0.16	14.2	12.7	0.76
Primary PCI (%)	77.7	85.7	0.12	77.4	82.5	0.37
Peak CPK [median (IQR)], IU/L	1,396 (616–2,691)	1,267 (600–2,624)	0.62	1,451 (702–2,812)	1,481 (876–3,228)	0.84
Door-to-balloon time [median (IQR)], min†	65 (45–102)	73 (50–108)	0.91	84 (55–123)	80 (50–120)	0.51
In-hospital mortality (%), (n)	8.1 (24)	6.5 (5)	0.64	11.5 (30)	9.5 (6)	0.66

*Only patients with data available on onset time (n=557 in 2008–2010 and n=140 in 2011). †Only patients who received primary PCI (n=294 in 2008–2010 and n=106 in 2011).
Abbreviations as in Table 1.

Table 4. Differences in the Clinical Characteristics and Outcomes of AMI Patients in the Inland and Seacoast Areas*

	2 months before 11 March			2 months after 11 March		
	Inland (n=146)	Seacoast (n=33)	P value	Inland (n=136)	Seacoast (n=31)	P value
Age [median (IQR)], years	70 (58–81)	70 (61–81)	0.91	69 (60–79)	76 (65–85)	0.009
Female (%)	31.5	27.3	0.63	20.6	25.8	0.52
Anterior infarction (%)	44.5	45.5	0.92	46.3	58.1	0.24
Prior infarction (%)	6.8	12.1	0.31	9.6	3.2	0.25
Ambulance use (%), (n)	67.8 (99)	57.6 (19)	0.26	69.1 (94)	58.1 (18)	0.24
Time elapsing from onset to admission [median (IQR)], min†	156 (60–516)	189 (74–458)	0.68	150 (66–402)	90 (60–312)	0.23
Killip ≥2 on admission (%)	12.3	6.1	0.30	8.8	12.9	0.72
Primary PCI (%)	82.2	87.9	0.43	87.5	83.9	0.59
Peak CPK [median (IQR)], IU/L	1,325 (740–2,470)	1,618 (413–3,336)	0.84	1,597 (755–3,521)	1,316 (670–2,689)	0.60
Door-to-balloon time [median (IQR)], min‡	65 (45–94)	80 (38–128)	0.78	71 (50–120)	78 (45–106)	0.65
In-hospital mortality (%), (n)	9.6 (14)	6.1 (2)	0.64	7.4 (10)	6.5 (2)	0.86

*Patients were divided into 2 groups according to transferred hospital located within 5 km of the sea (seacoast area, n=64) or not (inland area, n=282). †Only patients with data available on onset time (n=278 in the inland area and n=63 in the seacoast area). ‡Only patients who received primary PCI with data available on door-to-balloon time (n=220 in the inland area and n=55 in the seacoast area).
Abbreviations as in Table 1.

mance rate of primary PCI may be involved. To the best of our knowledge, this is the first report demonstrating that the emergency care of AMI can be improved through improved chain of survival, especially earlier admission from onset, following a natural disaster in a large community.

Occurrence of AMI After the Great East Japan Earthquake

The present study demonstrated that the occurrence of AMI per se did not significantly increase after the Earthquake, a finding consistent with our recent report.[14] In contrast, it has been reported that the occurrence of AMI increased after previous earthquakes that occurred in the early morning, such as the Northridge earthquake in 1994 (Los Angeles, CA, USA), and the Hanshin-Awaji earthquake in 1995 (Kobe, Japan).[22,23] This discrepancy might be attributable, at least in part, to the type of earthquake (ocean-trench earthquake in the present study vs. inland ones in the previous studies) and when the earthquake occurred (afternoon in the present study vs. early morning in the previous studies). AMI would be more likely to occur if an extreme emotional stress following abrupt awak-

ening by an earthquake is superimposed, as in the previous studies, whereas it was reported that the incidence of AMI did not significantly increase after earthquakes in the afternoon such as the Loma Prieta earthquake in 1989 (San Francisco, CA, USA) and the Niigata-Chuetsu earthquake in 2004 (Niigata, Japan).[24,25] In addition, the discrepancy could also be explained by differences in subject numbers and study period, as the present study had a large study population and a longer study period compared with previous studies.[22,23] We also had the advantage of being able to compare the data after the Earthquake with historical data from the previous 3 years.

Increased Rate of Performing Primary PCI After the Great East Japan Earthquake

During the first 2 months after the Earthquake, in-hospital mortality of AMI patients was significantly improved in Miyagi prefecture, associated with a shorter elapsing time from onset to admission and higher performance rate of primary PCI, as compared with the previous 3 years. Previous clinical studies have demonstrated that coronary reperfusion therapies, includ-

ing primary PCI, effectively reduce infarct size and improve the clinical outcomes of AMI patients.[1,3] In the Miyagi AMI Registry Study, the use of primary PCI has dramatically increased since the 1990s and more than 80% of AMI patients underwent the therapy in recent years.[2] In the present study, the performance rate of primary PCI was approximately 85% in 2011 and during the first 2 months after the Earthquake, it was significantly higher compared with the previous 3 years.

Such a higher performance rate of primary PCI may have substantially contributed to the better prognosis of AMI patients in 2011.

Improved Chain of Survival of AMI After the Great East Japan Earthquake

In addition to the increased performance rate of primary PCI, the elapsing time from symptom onset of AMI to reperfusion therapy (ie, the chain of survival) is another important factor in the clinical outcome of AMI patients.[4-6] This treatment delay is divided into 2 major components: (1) the time from onset to the first contact by a patient with emergency care (patient delay) and (2) from the first contact with emergency care to first balloon dilatation (system delay)[4] (Figure S2A). Although previous trials have succeeded in improving the system delay,[26,27] no attempt has been made regarding the patient delay.[7,8] In the present study, we found that the time from onset to admission was significantly shortened after the Earthquake and that the trend continued throughout the year of 2011. Before the Earthquake, patients with early admission had a significantly higher mortality despite their younger age compared with those with late admission (Table S1). These paradoxical findings were consistent with a recent report from Japan[28] that indicated patients with signs of left ventricular failure have a significantly shorter patient delay.[29] Indeed, a multivariate analysis also showed that early admission correlated with worse in-hospital mortality before the Earthquake, suggesting that the severity of AMI in those patients were high (eg, complicated with cardiac arrest or cardiogenic shock). In contrast, after the Earthquake, the patients with early admission had a better in-hospital outcome, associated with a lower prevalence of symptomatic heart failure, despite peak CPK levels comparable to those before the Earthquake. These findings indicate that after the Earthquake, AMI patients were transferred to hospitals earlier regardless of the severity of the disorder. As demonstrated in previous studies,[1,30] it is probably the earlier admission and less severe condition on admission that were associated with the higher performance rate of primary PCI after the Earthquake than in ordinary times (Figure S2B). In contrast, the ambulance use rate was unchanged before and after the Earthquake. Thus, it is highly possible that the patient delay was reduced with a resultant favorable prognosis soon after the Earthquake. Indeed, a recent study also emphasized that efforts to minimize patient delay are recommended to improve clinical outcomes in AMI patients because the benefit of a short door-to-balloon time was limited only to patients with early admission.[31] The present study also demonstrates that in-hospital mortality in the acute phase of AMI was improved after the Earthquake, together with the increased rate of early admission and unchanged door-to-balloon time as compared with ordinary times (Figure S2B). Additionally, based on the fact that the Niigata-Chuetsu earthquake significantly increased long-term mortality from AMI,[32] we have to recognize the need for long-term prevention of AMI in the future.

It remains to be elucidated why patients with AMI presented earlier after the Earthquake. Disaster-related mental and physical stresses are known to activate the sympathetic nervous system and enhance the activity of key molecules associated with coronary artery vasomotion such as Rho/Rho-kinase.[13,16] It is possible that those activated pathways reduce the threshold level of ischemia-related symptoms. Furthermore, disasters can cause various manifestations of psychological distress in survivors, including feelings of tension and anxiety, concentration difficulty, hostility and rage, sleep problems and intrusion/avoidance of disaster-related memories.[33,34] It has been reported that exposure to extreme stressors may enhance an individual's reactivity to subsequent stressors. That process is termed "stress sensitization", in which an organism responds more strongly to a variety of stimuli after exposure to a potentially threatening or noxious stimulus.[35-37] In the present critical situation caused by the Earthquake, tsunami and subsequent aftershocks, many residents in Miyagi prefecture would have experienced stress sensitization. Generally, the human instinct to survive is the most powerful drive and the fight-or-flight reaction, which is the best-known expression of our survival instinct, is triggered when we perceive a situation as a threat to our existence.[38-40] Thus, it is highly possible that in the present disaster, stress sensitization and enhanced survival instincts made the AMI patients more sensitive to their health or physical disorder with resultant earlier admission than in ordinary times.

However, it is important to note that a previous study of a community intervention targeting mass media and patient education failed to improve appropriate action for AMI symptoms.[7] In the present study, we also found no difference in door-to-balloon time that would reflect the system delay before and after the Earthquake, suggesting that the medical system itself functioned as well as in ordinary times, despite the fact that the Earthquake damaged infrastructure and caused shortages of medicines. We also found no difference in the ambulance use rate, elapsing time from onset to admission, performance rate of primary PCI or in-hospital mortality between the inland and seacoast areas, which suggests that the emergency medical system was well maintained throughout the prefecture during the disaster period.

Study Limitations

First, although almost all AMI patients were transferred to participating hospitals in Miyagi prefecture, not all patients may have been registered in the registry, especially during the disaster period. Second, as shown by several previous studies, including our own recent reports, the occurrence of cardiopulmonary arrest significantly increases after large earthquakes.[11,41] Thus, it is conceivable that patients who died from AMI-related cardiopulmonary arrest were not included in the present study and the incidence of AMI after the Earthquake could be underestimated. However, we found that the emergency care of AMI worked better soon after the Great East Japan Earthquake than in ordinary times. Third, there was no detailed angiographic data in our database. Thus, we were unable to determine the subtypes of MI based on the universal definition[42] or the incidence of takotsubo cardiomyopathy misdiagnosed as AMI. In addition, because we have no data available on the prevalence of pre-infarction angina and glucose levels on admission, both of which have been shown to be associated with the prognosis of AMI patients,[43,44] we were unable to examine how those prognostic factors had been affected by the Earthquake. Fourth, since the present study was observational in nature, the precise mechanisms of the improvement in the emergency care of AMI, especially that of the improved time from onset to admission, remain to be fully elucidated.

Conclusions

Emergency care of AMI patients worked better soon after the Great East Japan Earthquake than in ordinary times, for which several factors, including shorter elapsing time from onset to admission and higher performance rate of PCI, may be involved.

Disclosures

Conflict of interest: None declared.

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Appendix

Participating Hospitals and Investigators of the Miyagi AMI Registry Study

Hospitals in the Seacoast Area

Ishinomaki Medical Association; Ishinomaki Municipal Hospital, Akai K, MD; Ishinomaki Red-cross Hospital, Sukegawa H, MD; Kesen-numa Hospital, Ogata K, MD; Miyagi Eastern Cardiovascular Institute, Kikuchi Y, MD; Miyagi Social Insurance Hospital, Hanadate Y, MD; Saito Hospital, Otsuka K, MD; Saka General Hospital, Watanabe K, MD; Sen-en General Hospital, Hashiguchi R, MD; Shiogama City Hospital, Goto J, MD; Tohoku Pharmaceutical University Hospital, Katahira Y, MD.

Hospitals in the Inland Area

Fukaya Hospital, Akiho H, MD; Hikarigaoka Spellman Hospital, Shimura S, MD; JR Sendai Hospital, Honda H, MD; Katta General Hospital, Kanno H, MD; Kurihara Central Hospital, Akai K, MD; Labour Welfare Corporation Tohoku Rosai Hospital, Kato H, MD; Marumori National Health Insurance Hospital, Otomo M, MD; Miyagi Cancer Center, Owada N, MD; Miyagi Cardiovascular and Respiratory Center, Komaru T, MD; Mori Hospital, Mori A, MD; Nagamachi Hospital, Mitobe H, MD; Nishitaga National Hospital, Kitaoka S, MD; NTT EAST Tohoku Hospital, Yamada A, MD; Oizumi Memorial Hospital, Koiwa Y, MD; Osaki Citizen Hospital, Hiramoto T, MD; Sendai Cardiovascular Center, Fujii S, MD; Sendai City Hospital, Yagi T, MD; Sendai Kosei Hospital, Meguro T, MD; Sendai Medical Center, Shinozaki T, MD; Sendai Open Hospital Sendai City Medical Center, Kato A, MD; Sendai Public Health Insurance Hospital, Oikawa Y, MD; Sendai Red-cross Hospital, Sugimura A, MD; Sendai Tokushukai Hospital, Fukuchi M, MD; Shichigashuku National Health Insurance Clinic, Nagashima T, MD; South Miyagi Medical Center, Inoue K, MD; Tohoku Kosai Hospital, Suzuki S, MD; Tohoku University Hospital, Department of Cardiovascular Medicine, Shimokawa H, MD; Department of Cardiovascular Surgery, Saiki Y, MD; Department of Medical Engineering and Cardiology, Institute of Development, Aging and Cancer, Yanbe T, MD; Tome Citizen Hospital, Izuma M, MD; Toyama Clinic on Tome City, Ishii M, MD.

Supplementary Files

Supplementary File 1.

Methods.

Figure S1. Emergency care of acute myocardial infarction and the involvement of the 3 delays in treatment response.

Figure S2. Weekly occurrence of acute myocardial infarction in 2011 and 2008–2010.

Figure S3. (A) Shortened delay from onset to admission and unchanged door-to-balloon time in the present study. (B) Factors involved in the improved outcome of patients with acute myocardial infarction patients after the Great East Japan Earthquake.

Table S1. Differences between patients with early (≤3 h) and late admission (>3 h) after onset of acute myocardial infarction

Please find supplementary file(s);
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Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 Study

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Aims	It is still controversial whether elevated baseline heart rate (HR) is associated with higher mortality in patients with heart failure (HF) with preserved ejection fraction (HFpEF). We compared the impacts of baseline HR on mortality in patients with HFpEF and those with HF with reduced ejection fraction (HFrEF).
Methods and results	We enrolled consecutive 2688 patients in Stage C or D HF with sinus rhythm from our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study ($n = 10\ 219$). The prognostic impact of HR increase was compared between the two groups, defined as left ventricular ejection fraction of $\leq 50\%$ (HFrEF) and $> 50\%$ (HFpEF). Cox regression analysis revealed that elevated baseline HR was associated with increased all-cause mortality in both groups [hazard ratio for the highest tertile (HH) 1.77 in HFrEF, $P = 0.008$; HH1.82 in HFpEF, $P = 0.001$]. However, as for mode of death, elevated HR was associated with cardiovascular (CV) death in HFpEF (HH 2.17, $P = 0.012$), but the association was modest in HFrEF (HH1.49, $P = 0.14$): in particular, impact on HF death was different between HFpEF (HH 3.79, $P = 0.020$) and HFrEF (HH 1.07, $P = 0.864$). In contrast, the prognostic impact of baseline HR on non-CV death was noted only in patients with HFrEF. β-Blocker therapy was associated with reduced HF mortality in HFrEF (hazard ratio 0.49, $P = 0.038$) but not in HFpEF (hazard ratio 0.64, $P = 0.321$).
Conclusions	Elevated HR was associated with increased CV death in HFpEF compared with HFrEF, although its impact on all-cause mortality was comparable between the two groups.
Keywords	Heart failure • Heart rate • Prognosis

Introduction

Elevated baseline heart rate (HR) could be a reflection of activated sympathetic nervous system, a negative force-frequency response of failing myocardium and worsening myocardial ischaemia.[1–3] Furthermore, increased heart rate was associated with increased systemic inflammation and endothelial dysfunction.[4] Thus, it is widely considered to be a predictor of poor prognosis in patients with heart failure (HF). Indeed, unfavourable prognostic impact of elevated baseline HR has been repeatedly noted in patients with HF with reduced ejection fraction (HFrEF).[5–8] For instance, in addition to β-blocker, HR reduction with ivabradine has been reported as effective for patients with HFrEF.[9] In the European Society of Cardiology guidelines, ivabradine is recommended to

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reduce the risk of HF hospitalization in symptomatic (NYHA class II–IV) patients in sinus rhythm with an EF $\leq$ 35% and a heart rate remaining $\geq$ 70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).[10] However, it is still controversial whether elevated baseline HR is associated with poor prognosis in patients with HF with preserved ejection fraction (HFpEF).[11–13] This is possibly because these previous findings regarding the association between baseline HR and prognosis of HFpEF were derived from *post hoc* analysis of randomized control trials[11,13] or from an observational study with a relatively small sample size,[12] and thus likely involved selection bias. Furthermore, even in the positive studies,[11,12] it has not been elucidated which modes of deaths or cardiac events were particularly associated with elevated HR in HFpEF. Thus, it has been awaited to address the prognostic impacts of elevated HR in patients with HFpEF in more detail, using a large-scale prospective observational cohort.

In the present study, we thus examined the prognostic impact of baseline HR in HFpEF in our prospective observational multicentre cohort study, named the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study, where we successfully enrolled consecutive 10 219 patients in Stage B, C, and D HF.[14–16] The aim of the present study was to compare the impact of elevated HR on clinical outcomes between HFpEF and HFrEF, especially on cardiovascular (CV) death and HF death.

Methods

Design of the present study

The CHART-2 Study is a prospective observational multicenter cohort study, as previously reported in detail (NCT00418041).[14] Among 4735 stage C/D patients in the CHART-2 Study (*n* = 10 219),[14–16] 2863 in sinus rhythm without history of paroxysmal atrial fibrillation or implantable cardiac device were enrolled in the present study. They were divided into the two groups according to the baseline left ventricular ejection fraction (LVEF) of $\leq$ 50% (HFrEF) or > 50% (HFpEF) in the present study.[17] The prognostic impact of elevated baseline HR was examined by calculating relative risks in the highest and second highest tertiles of baseline HR compared with the lowest tertile. We also examined whether β-blocker therapy could affect the relationship between HR increase and prognostic endpoints between the HFrEF and the HFpEF groups. Furthermore, we explored optimal cut-off points of HR to split risk of mortality endpoints using the classification and regression tree (CART) method.[18,19]

Statistical analysis

The outcomes of all-cause death, CV death and non-CV death were estimated by Kaplan–Meier curve and log-rank test in both groups. The impact of each tertile defined by baseline HR for the endpoints was examined using the univariate and multivariate Cox proportional hazard model. The covariates for the multivariate analysis included gender, age, body mass index, systolic blood pressure (SBP), LV diastolic diameter (LVDd), LVEF, haemoglobin level, estimated glomerular filtration ratio, malignant diseases, β-blocker, RASI, enrolment location (inpatient or outpatient) and HR categories. The association between β-blockers and outcomes was assessed using univariate and

multivariate Cox proportional hazard models with the same covariates except β-blocker use. Statistical analysis was performed using IBM SPSS Statistics 19 software (IBM, Armonk, NY, USA) and R software (version 2.5). To determine the optimal cut-off points of HR to split CV and non-CV mortality for overall, HFrEF and HFpEF patients, respectively, an open-source adaptation of the CART algorithm from R software was used.

Methods are mentioned in more detail in the Supplementary material online, Appendix S1.

Results

Baseline characteristics

Among the 2863 Stage-C/D HF patients in sinus rhythm enrolled in the present study, we finally analysed 2688 (93.9%) patients in whom both HR and LVEF data were available (mean age 67.5 $\pm$ 13.0 years, male 70%, and median follow-up period of 3.13 years). *Table 1* shows baseline characteristics of the patients in the HFrEF and HFpEF groups. The number of patients in the HFpEF group was twice that in the HFrEF group. The HFpEF group was characterized by more females, older age, higher SBP, lower HR and NYHA functional class, higher prevalence of hypertension and valvular heart disease, and lower serum brain natriuretic peptide levels. The prevalence of β-blocker use was significantly lower in the HFpEF group than in the HFrEF group (40% vs. 65%, *P* < 0.001). Supplementary material online, Table S1, shows the baseline characteristics of tertiles of baseline HR for both groups. Although almost all backgrounds except β-blocker use were comparable among the tertiles in the HFrEF group, the tertiles in the HFpEF group showed statistically significant trends in LVDd, LVEF value, ischaemic heart disease, prevalence of female sex and loop diuretics use, in addition to β-blocker use.

Impact of HR increase on clinical outcomes

During the follow-up period of median 3.13 years, 133 (15.0%) and 176 (9.8%) all-cause deaths, 79 (8.9%) and 76 (4.2%) CV deaths, 42 (4.7%) and 32 (1.8%) deaths for heart failure, 164 (18.5%) and 122 (6.8%) admission for heart failure, 42 (4.7%) and 86 (4.8%) non-CV deaths were noted in the HFrEF and HFpEF groups, respectively. There were 26 deaths due to unknown origins. The actual number of events and event rate in tertiles are shown in Supplementary material online, Table S2. The Kaplan–Meier curves and multivariate Cox regression analyses revealed that the higher HR tertile had more increased risk of all-cause death in both the HFrEF and HFpEF groups (*Figures 1A,B* and 2). As for CV and HF death, a significant relationship between HR and mortality was noted in the HFpEF group (hazard ratios of the highest HR tertile 2.17, 95% CI 1.19–3.99, *P* = 0.012 for CV death and 3.79, 95% CI 1.24–11.62, *P* = 0.020 for HF death). In contrast, in the HFrEF group, elevated HR was not significantly associated with increased risk of CV mortality and HF mortality (hazard ratios of the highest HR tertile 1.49, 95% CI 0.87–2.54, *P* = 0.143 for CV death; and 1.07, 95% CI 0.50–2.27, *P* = 0.864 for HF death) (*Figures 1C,D* and 2). Furthermore, a significant relationship between HR and non-CV

Table 1 Baseline characteristics of two groups defined by baseline LVEF

	Total n = 2688 (100%)	HFrEF n = 885 (32%)	HFpEF n = 1803 (67%)	P-value
Patients' characteristics				
Male sex	1874 (70%)	654 (74%)	1220 (68%)	0.001
Age (years)	67.5 ± 13	66.6 ± 13.0	67.9 ± 13.0	0.020
BMI	24.0 ± 3.9	23.5 ± 4.0	24.3 ± 3.8	< 0.001
Systolic BP (mmHg)	127.9 ± 19.0	123.3 ± 19.8	130.2 ± 18.2	< 0.001
Heart rate (bpm)	71.1 ± 13.5	72.9 ± 13.7	70.2 ± 13.3	< 0.001
LVDd (mm)	52.0 ± 9.2	58.6 ± 9.1	48.7 ± 7.3	< 0.001
LVEF (%)	57.2 ± 15.6	38.8 ± 8.8	66.2 ± 8.9	< 0.001
NYHA				< 0.001
I	702 (26%)	154 (17%)	548 (31%)	
II	1701 (64%)	605 (69%)	1096 (61%)	
III	254 (9%)	111 (13%)	143 (8%)	
IV	18 (1%)	11 (1%)	7 (0%)	
Medical history				
Hypertension	2109 (78%)	637 (72%)	1472 (82%)	< 0.001
Diabetes mellitus	758 (28%)	258 (29%)	500 (28%)	0.466
Dyslipidaemia	2079 (77%)	695 (79%)	1384 (77%)	0.327
Stroke	420 (16%)	122 (14%)	298 (17%)	0.070
Malignant disease	280 (10%)	92 (10%)	188 (10%)	1.000
Ischaemic heart disease	1594 (59%)	517 (58%)	1077 (60%)	0.531
Cardiomyopathy	469 (17%)	267 (30%)	202 (11%)	0.000
Valvular heart disease	472 (18%)	89 (10%)	383 (21%)	< 0.001
Laboratory data				
Haemoglobin (g/dL)	13.2 ± 2.0	13.2 ± 2.0	13.2 ± 1.9	0.667
Albumin (mg/dL)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.005
LDL-C (mg/dL)	105.4 ± 30.7	105.6 ± 31.3	105.3 ± 30.4	0.840
eGFR (mL/min/1.73 m^2)	62.8 ± 25.3	60.7 ± 22.6	63.8 ± 26.5	0.002
BNP [pg/mL, median (IQR)]	71 (29–186)	135 (53–316)	53 (22–131)	< 0.001
Medication				
β-Blockers	1292 (48%)	575 (65%)	717 (40%)	< 0.001
RASI	1966 (73%)	706 (80%)	1260 (70%)	< 0.001
Loop diuretics	1073 (40%)	506 (57%)	567 (31%)	< 0.001
Aldosterone antagonists	548 (20%)	303 (34%)	245 (14%)	< 0.001
Statins	1240 (46%)	407 (46%)	833 (46%)	0.934

BMI, body mass index; BP, blood pressure; LVDd, left ventricular diastolic diameter; LDL-C, low-density lipoprotein-cholesterol; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; RASI, renin–angiotensin system inhibitors.

mortality was noted in the HFrEF group (hazard ratio of the highest HR tertile 2.33, 95% CI 1.09–4.97, P = 0.029), but not in the HFpEF group (Figure 2). Hazard ratio for HF admission tended to increase according to HR increment in the HFpEF group but not in the HFrEF group (Figure 2). The prognostic impact of baseline HR on CV and HF mortality were more evident in the HFpEF than in the HFrEF group, whereas such an impact on non-CV death was noted only in the HFrEF group (Figure 2).

β-Blocker use and prognostic impact of HR

When the baseline characteristics were examined according to LVEF and use of β-blockers, the patients treated with β-blockers were younger and had lower HR compared with those treated

without β-blockers in both the HFrEF and the HFpEF groups (Supplementary material online, Table S3). SBP was lower in the patients with β-blockers compared with those without β-blockers in the HFrEF group (121.4 ± 19.6 vs. 126.8 ± 19.7 mmHg), but not in the HFpEF group (130.3 ± 18.4 vs. 130.1 ± 18.1 mmHg). Importantly, both univariate and multivariate Cox regression analyses revealed that use of β-blockers was significantly associated with a reduction in HF death in the HFrEF but not in the HFpEF group (Table 2). Risk reduction by β-blockers for all-cause death, CV death and HF death were observed in the HFrEF patients but not in the HFpEF patients (Table 2). In contrast, use of β-blockers was not associated with reduced risk of admission for HF in either group. The association of mortality with HR categories was notable for all-cause death and CV death only in patients with HFpEF and treated without β-blockers.
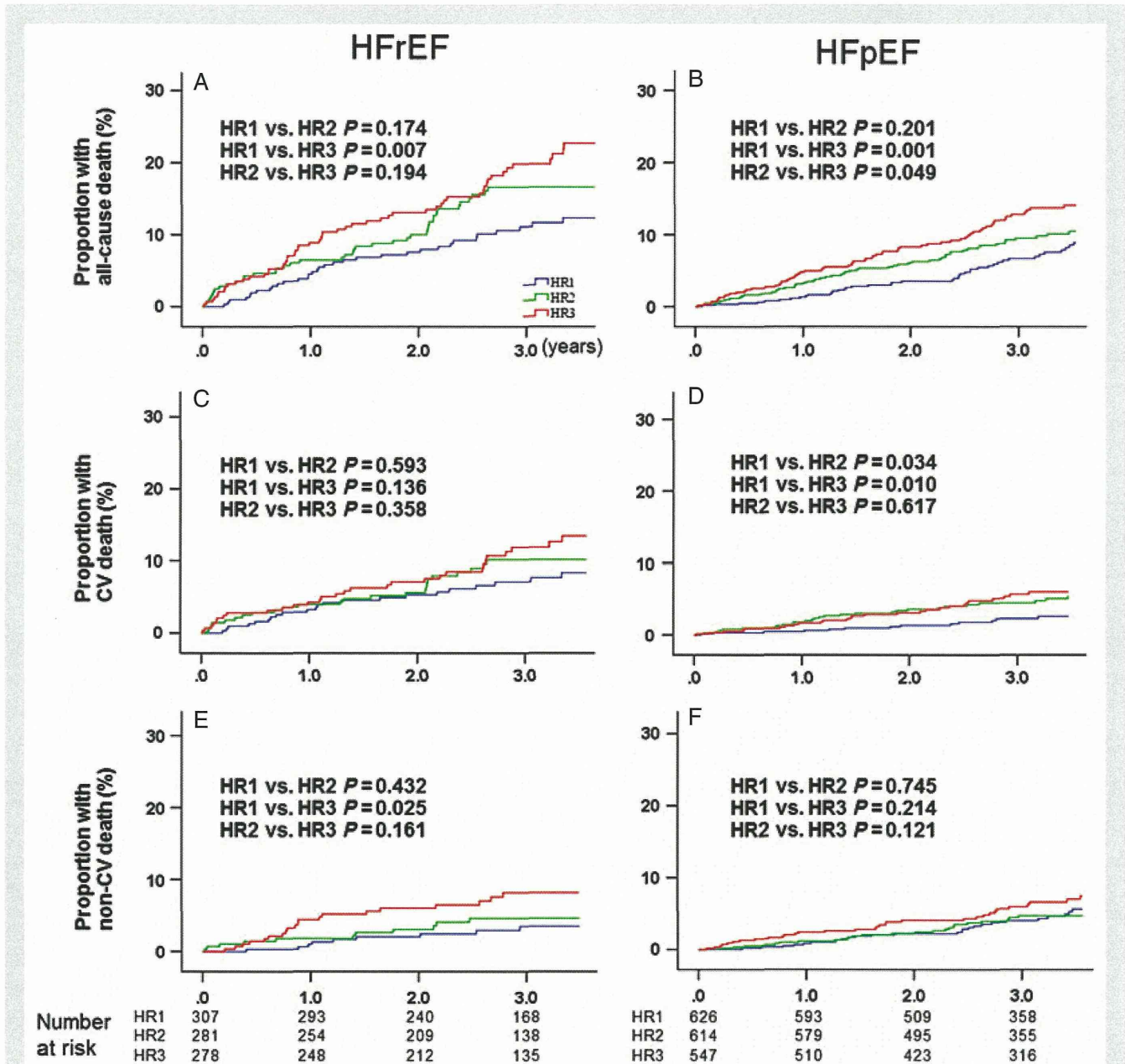
Figure 1 Kaplan–Meier curves for outcomes in HFrEF and HFpEF. Kaplan–Meier curves for all-cause death of HFrEF (A) and HFpEF (B), CV death of HFrEF (C) and HFpEF (D), and non-CV death of HFrEF (E) and HFpEF (F).

Cut-off value of HR for CV death

We attempted to search cut-off values of HR to split both HFrEF and HFpEF patients for CV death based on CART analysis (Table 3). CART analysis suggested that the primary cut-off value in baseline HR to discern a high-risk population for CV death were 63.5, 69.5, and 63.5 bpm in the overall, HFrEF, and HFpEF patients, respectively, and that those for non-CV death were all 71.5 bpm (Table 3). A total of 1683 (62.6%), 511 (57.7%), and 1172 (65.0%) patients had HR equal to or more than the cut-off values with hazard ratios of 1.85 (95% CI 1.26–2.73, P = 0.002), 1.60 (1.00–2.55, P = 0.051),

and 2.04 (1.17–3.53, P = 0.012) for CV death in the overall, HFrEF, and HFpEF patients, respectively (Table 3).

Discussion

In the present study, we examined the difference in the prognostic impact of HR status between the HFpEF and HFrEF groups in the CHART-2 study, the largest-scale prospective observational study for patients in Stage B, C, and D HF in Japan.[14–16] The present study is the first to report an association in detail between elevated HR and modes of death in HFpEF in comparison with those