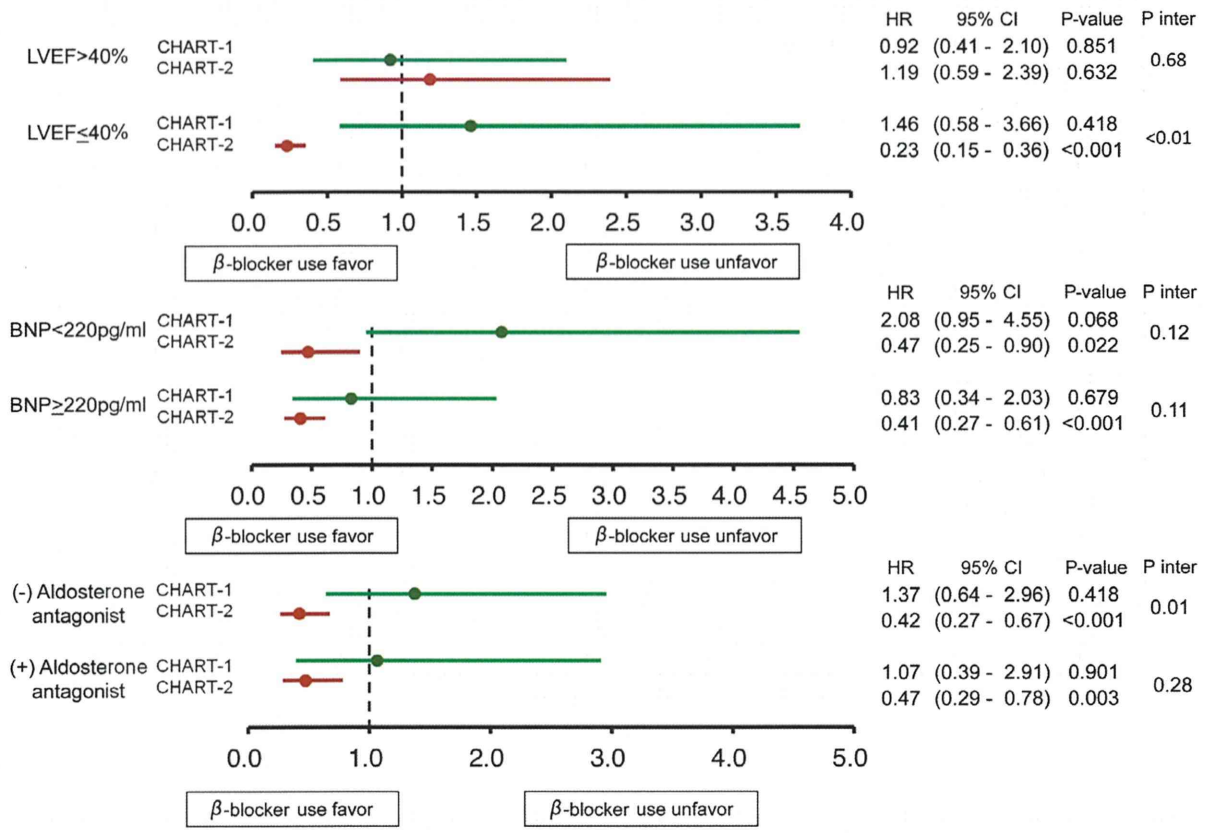

Figure 4. Inverse probability of treatment weighting analysis for each subgroup. BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

tendency for improved all-cause death (adjusted HR, 0.61; P=0.054) and the decreased incidence of cardiovascular death remained significant even after the adjustment (adjusted HR, 0.29; P<0.001). This finding, however, could be explained by the benefits of implementation of evidence-based medication, particularly, by that of β-blockers. In the present study, the use of β-blockers was markedly increased from 49% in CHART-1 to 81% in CHART-2, and the DCM patients treated with β-blockers had a better prognosis than those without them. Furthermore, the decrease in all-cause mortality was mainly associated with a decrease in cardiovascular death, specifically sudden death, supporting the notion that β-blockers were effective in improving the long-term prognosis of DCM patients in the present study. This is consistent with the previous reports that β-blockers improved LVEF and all-cause mortality in patients with CHF.[19–22] In addition, it is speculated that not only the prescription rates but also the dose of β-blockers was increased from the CHART-1 to the CHART-2 Studies, resulting in reduced mortality. Furthermore, it is conceivable that ICD/CRT-D treatment also played a significant role in preventing sudden cardiac death in the CHART-2 Study, although it is difficult to demonstrate its efficacy due to the small number of patients treated with ICD/CRT-D in the present study.

Subgroups With Improved Long-Term Prognosis

The present study demonstrated that the long-term prognosis of DCM patients was improved in several subgroups. In particular, the improvement was noted in patients with LVEF >40%, but not in those with LVEF ≤40%. It is difficult to explain the reason for this finding with regard to β-blocker use, because on IPTW analysis β-blockers improved prognosis over time from CHART-1 to CHART-2 in patients with LVEF ≤40% but not in those with LVEF >40%. This finding, however, is consistent with the previous findings that in-hospital mortality was improved over time between 2005 and 2010 in HF patients with preserved LVEF, but not in those with reduced LVEF,[23] and that HF patients with recovered LVEF had better prognosis than those with reduced LVEF or near-normal LVEF.[24,25] Furthermore, the present study also showed that the improvement was noted in the subgroup with BNP <220 pg/ml and that with aldosterone antagonist use. Interestingly, β-blocker use was associated with improved mortality in these subgroups, but not in those with BNP ≥220 pg/ml or those without aldosterone antagonist use, although the P-values for interaction were not significant. Thus, appropriate use of β-blockers might have played a role in the improvement of mortality in patients with BNP <220 pg/ml and in those with aldosterone antagonist use.

Increase in Lifestyle-Related Comorbidities

Another novel finding of the present study is that the prevalence of lifestyle-related comorbidities (eg, hypertension, dyslipidemia and diabetes mellitus) was increased from the

CHART-1 to the CHART-2 Study. The recent trend of westernization of clinical background in overall CHF patients in Japan has been previously reported,[7,9] and lifestyle-related diseases are emerging as comorbidities in DCM patients in Japan. Given that hypertension, dyslipidemia and diabetes are all recognized as coronary risk factors, this suggests that ischemic heart disease may stand out as one of the main causes of mortality and morbidity in DCM patients in the near future. Thus, more attention should be paid to the prevention of coronary artery disease through management of lifestyle-related comorbidities in current DCM practice.

Study Limitations

Several limitations should be mentioned for the present study. First, given that both the CHART-1 and CHART-2 Studies are prospective observational studies in the Tohoku district of Japan, we need to be cautious when extrapolating the present findings to other cohorts, particularly to those in other countries. Second, the diagnosis, evaluation, and management of DCM were made in each participating hospital, and thus there could be a selection and/or other bias in the present study. Finally, the number of the patients enrolled from the CHART-1 Study was relatively small, which might have limited the power to identify significant observations.

Conclusions

Three-year mortality of DCM patients has been significantly improved along with the implementation of evidence-based medication in Japan. Subgroup analysis, however, suggested that the improvement was concentrated in the subgroups with BNP <220 pg/ml, LVEF >40%, β-blocker use and aldosterone antagonist use.

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Disclosures

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Appendix. The CHART-2 Study Investigators

1. Executive Committee

Hiroaki Shimokawa (Chair), Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Mitsumasa Fukuchi, Kanichi Inoue, Atsushi Kato, Masafumi Sugi, Masatoshi Ohe, Tsuyoshi Shinozaki, Satoru Horiguchi, Hiroshi Kato.

2. Steering Committee

Kanichi Inoue, Tetsuya Hiramoto, Masahiko Ogata, Atsushi Kato, Shoichi Sato, Masafumi Sugi.

3. Collaborating Hospitals and Active Investigators by Prefecture

Aomori Prefecture

Shigeto Oyama (Towada City Hospital).

Iwate Prefecture

Eiji Nozaki, Akihiro Nakamura, Tohru Takahashi, Hideaki Endo, Shigehumi Fukui, Sota Nakajima (Iwate Prefectural Central Hospital). Makoto Nakagawa, Tetsuji Nozaki, Takuya Yagi (Iwate Prefectural Isawa Hospital).

Akita Prefecture

Satoru Horiguchi, Etsuko Fushimi, Yoshinao Sugai, Satoru Takeda, Kouhei Fukahori, Kentaro Aizawa (Hiraka General Hospital).

Yamagata Prefecture

Masatoshi Ohe, Takurou Tashima, Katsuhiko Sakurai, Tadashi Kobayashi (Kojirakawa Shiseido Hospital). Toshikazu Goto, Motoyuki Matsui, Yoshiaki Tamada, Tomoyasu Yahagi, Akio Fukui, Katsuaki Takahashi, Yoku Kikuchi (Yamagata Prefectural Central Hospital).

Miyagi Prefecture

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Fukushima Prefecture

Masafumi Sugi, Yoshito Yamamoto, Sunao Toda, Yutaka Minatoya, Yusuke Takagi, Yuhi Hasebe, Taro Nihei (Iwaki Kyouritsu Hospital). Koji Fukuda (Watanabe Hospital).

4. Head Office and Coordinating Center

Yasuhiko Sakata, Yoshihiro Fukumoto, Jun Takahashi, Satoshi Miyata, Kotaro Nochioka, Masanobu Miura, Soichiro Tadaki, Ryoichi Ushigome, Takeshi Yamauchi, Kenjiro Sato, Kanako Tsuji, Takeo Onose, Ruri Abe, Chiharu Saga, Junko Suenaga, Yoko Yamada, Junko Kimura, Hiromi Ogino, Izumi Oikawa, Sanae Watanabe, Madoka Saga, Miki Washio, Keiko Nagasawa, Sachiko Nagasawa, Sachie Kotaka, Wakiko Komatsu, Reiko Hashimoto, Yasuko Ikeno, Tomoyuki Suzuki, Hiroko Hamada.

Supplementary Files

Supplementary File 1

Figure S1. Change in survival rate between CHART-1 and CHART-2 for (**A**) left ventricular ejection fraction (LVEF) > or ≤40%, (**B**) brain natriuretic peptide (BNP) < or ≥220 pg/ml, (**C**) presence of β-blockers and (**D**) presence of aldosterone antagonist.

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RAPID COMMUNICATION

Predictors and Prognostic Impact of Post-Traumatic Stress Disorder After the Great East Japan Earthquake in Patients With Cardiovascular Disease

– Report From the CHART-2 Study –

Takeo Onose, MD; Kotaro Nochioka, MD, PhD; Yasuhiko Sakata, MD, PhD; Masanobu Miura, MD, PhD; Soichiro Tadaki, MD; Ryoichi Ushigome, MD; Takeshi Yamauchi, MD; Kenjiro Sato, MD; Kanako Tsuji, MD; Ruri Abe, MD; Satoshi Miyata, PhD; Jun Takahashi, MD, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators

Background: We examined the prevalence, predictors and prognostic impact of post-traumatic stress disorder (PTSD) after the Great East Japan Earthquake in patients with cardiovascular disease (CVD) in the CHART-2 study.

Methods and Results: The prevalence of PTSD was 14.7% at 6 months after the Earthquake. Female sex, experiencing the Tsunami, property loss, poverty, and insomnia medication use were associated with PTSD. The patients with PTSD more frequently experienced a composite of death, acute myocardial infarction, stroke and heart failure (18.5% vs. 15.0%, P=0.035).

Conclusions: PTSD was frequent in CVD patients after the Earthquake and had an adverse prognostic impact. (*Circ J* 2015; **79:** 664–667)

Key Words: Cardiovascular disease; Great East Japan Earthquake; Post-traumatic stress disorder

In March 2011, the Great East Japan Earthquake, followed by a devastating tsunami and Fukushima-Daiichi nuclear power plant explosion, destroyed 370,780 houses and killed 15,785 people in the Tohoku District of Japan.[1–3] Our observational study, the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2),[4–6] which enrolled 10,219 patients with cardiovascular disease (CVD) in the disaster area, has provided a unique opportunity to examine the prognostic impact of disaster-related mental stress in survivors with CVD.

Methods

The CHART-2 study is a multicenter observational study of Japanese patients with CVD (Identifier: NCT00418041).[4–6] Briefly, the study enrolled 10,219 consecutive Japanese patients older than 20 years with heart failure (HF) in Stages B/C/D or those with coronary artery disease (Stage A) between October 2006 and March 2010. Stages of HF were defined according to the ACC/AHA guidelines.[7] Information on medical history and baseline demographics, including medication and echocardiographic data, was collected at the time of enrollment and thereafter annually by clinical research coordinators. The CHART-2 study was approved by the local ethics committees and written informed consent was provided by all patients. In September 2011, we sent a self-administered questionnaire including the Japanese version of the Impact of Event Scale-Revised (IES-R-J, Cronbach's Alpha; 0.95)[8] to 8,823 patients registered in the CHART-2 study. The IES-R-J score ranges from 0 to 88, and post-traumatic stress disorder (PTSD) is defined as a score ≥25.[8] The primary endpoint was a composite of all-cause mortality and hospitalization for acute myocardial infarction, angina pectoris, stroke and HF. The present study was approved by the ethics committee of each participating hospital. All analyses were performed using R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

By December 2011, we obtained 3,620 valid responses, among which 534 (14.7%) patients were diagnosed as having PTSD.

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Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

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Table. Baseline Characteristics of the Patients

	PTSD		P value
	Yes (n=534)	No (n=3,086)	
Age at questionnaire, mean (SD), years	68.2 (10.9)	66.6 (11.4)	0.002
Female sex, n (%)	205 (38.4)	756 (24.5)	<0.001
Height, mean (SD), cm	159.2 (8.9)	161.5 (8.9)	<0.001
Body weight, mean (SD), kg	61.4 (12.3)	63.2 (11.6)	0.002
Body mass index, mean (SD), kg/m^2	24.1 (4.2)	23.9 (4.2)	0.417
SBP, mean (SD), mmHg	127.5 (18.2)	128.1 (17.1)	0.504
DBP, mean (SD), mmHg	72.8 (11.5)	74.2 (11.5)	0.01
Heart rate, mean (SD), beats/min	69.5 (13.5)	70.2 (13.7)	0.253
Current or past smoking, n (%)	222 (44.6)	1,446 (49.4)	0.047
Echocardiography and laboratory findings			
LVEF, mean (SD), %	62.2 (14.1)	62.0 (13.8)	0.84
LVEF <50%	100 (20.0)	560 (19.1)	0.624
Left atrial dimension, mean (SD), mm	40.3 (8.4)	40.4 (7.8)	0.86
Hemoglobin, mean (SD), g/dl	13.4 (2.1)	13.7 (1.8)	<0.001
Total protein, mean (SD), g/dl	7.3 (2.8)	7.2 (0.6)	0.305
Albumin, mean (SD), g/dl	4.2 (0.4)	4.2 (0.4)	0.348
Total cholesterol, mean (SD), mg/dl	184.8 (35.5)	184.7 (34.8)	0.963
HbA1c, mean (SD), %	5.8 (11.5)	5.9 (2.5)	0.712
eGFR, mean (SD), ml·min^{-1}·1.73m^{-2}	64.6 (28.3)	65.8 (22.8)	0.383
BNP, median (25th, 75th percentiles), pg/ml	59.2 (24.5, 129.6)	50.4 (21.6, 119.8)	0.025
Medical history, n (%)			
Heart failure in Stage C/D	234 (43.8)	1,272 (41.2)	0.274
Hypertension	394 (73.8)	2,348 (76.1)	0.251
Diabetes mellitus	127 (23.8)	756 (24.5)	0.744
Dyslipidemia	385 (72.1)	2,386 (77.3)	0.009
Hemodialysis	5 (0.9)	23 (0.7)	0.594
Stroke	94 (17.6)	434 (14.1)	0.039
Atrial fibrillation	138 (26.0)	716 (23.3)	0.184
Cancer	49 (9.2)	313 (10.1)	0.601
COPD	9 (4.6)	35 (2.8)	0.175
Ischemic heart disease	272 (50.9)	1,764 (57.2)	0.008
Valvular heart disease	96 (18.0)	502 (16.3)	0.344
Cardiomyopathy	67 (12.5)	422 (13.7)	0.537
Medications, n (%)			
ACEI or ARB	335 (62.7)	1,967 (63.7)	0.661
Loop diuretics	133 (24.9)	632 (20.5)	0.025
Aldosterone antagonists	67 (12.5)	346 (11.2)	0.376
Calcium-channel blockers	242 (45.3)	1,422 (46.1)	0.778
Digitalis	72 (13.5)	407 (13.2)	0.836
β-blockers	209 (39.1)	1,293 (41.9)	0.235
Past or current insomnia medication use	194 (36.3)	171 (5.5)	<0.001
Disaster experience, n (%)			
No effect from the Earthquake	60 (11.2)	733 (23.8)	<0.001
Tsunami evacuation or being trapped	82 (15.4)	144 (4.7)	<0.001
Own hospitalization	43 (8.1)	65 (2.1)	<0.001
Hospitalization of close relatives	102 (19.1)	223 (7.2)	<0.001
Major property loss	238 (44.6)	857 (27.8)	<0.001
Economic poverty	69 (12.9)	96 (3.1)	<0.001
Change of residence	58 (10.9)	102 (3.3)	<0.001
Unemployment or job change	22 (4.1)	43 (1.4)	<0.001

Comparisons between groups were performed by the Welch's t-test for continuous variables, and by the Fisher's exact test for dichotomous variables. All analyses were performed using R version 3.0.3. P<0.05 was considered to be statistically significant. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

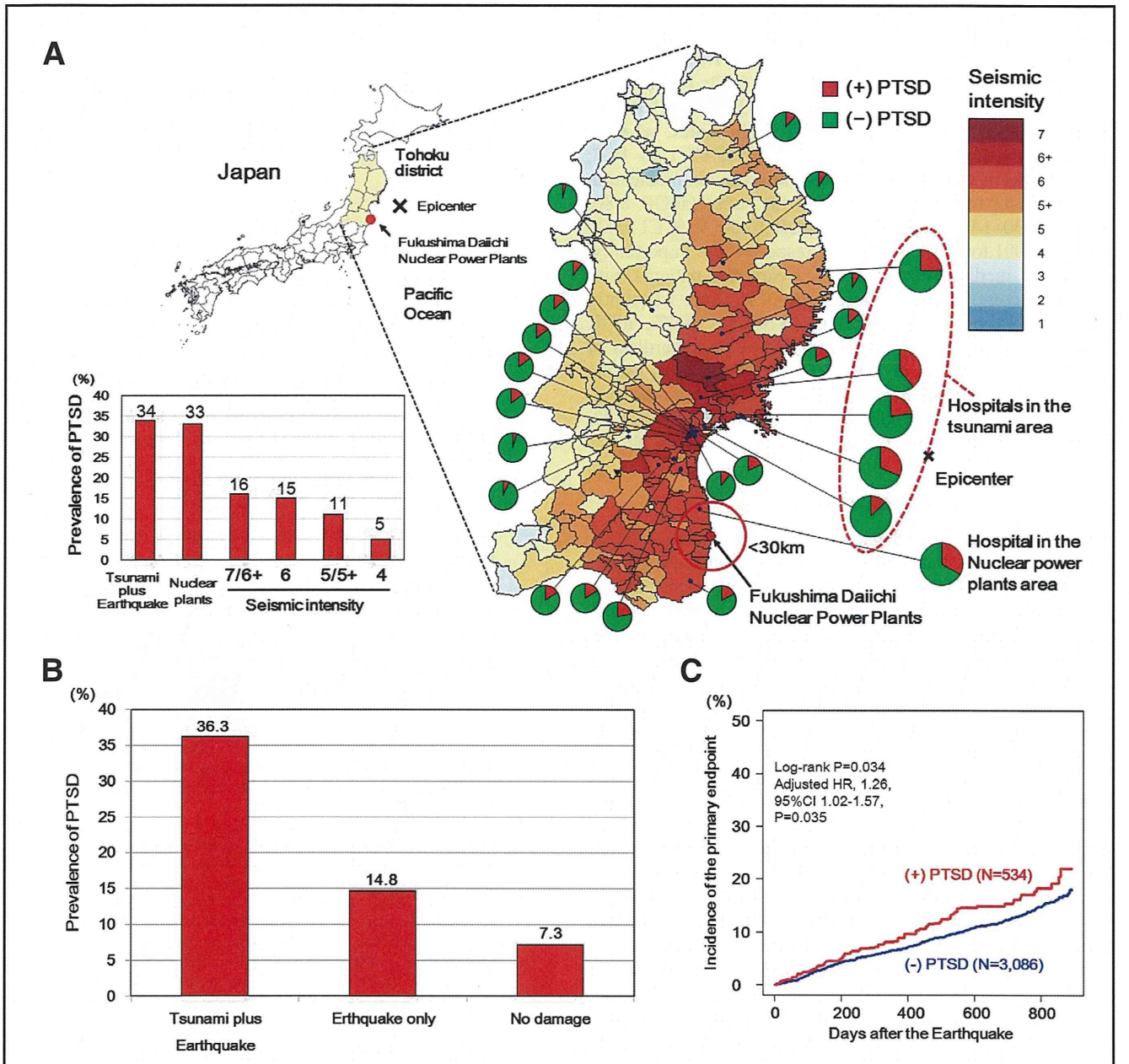

Figure. (**A**) Location of the epicenter of the Great East Japan Earthquake, the Fukushima-Daiichi nuclear power plants, and the study sites, and the proportions of patients with post-traumatic stress disorder (PTSD). (**B**) The questionnaire-based prevalence of PTSD in patients who experienced the Tsunami plus Earthquake, the Earthquake alone, or neither. (**C**) Kaplan-Meyer survival curves for the primary endpoint. Adjusted hazard ratio (HR) was determined by a stepwise Cox proportional hazard model with the following variables: PTSD, disaster-related experience, age, sex, systolic blood pressure, diastolic blood pressure, heart rate, body mass index, HF stage, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of cancer, stroke, HF hospitalization, ischemic heart disease, valvular heart disease, left ventricular ejection fraction, B-type natriuretic peptide level, and use of renin-angiotensin system inhibitors, β-blockers, loop diuretics and calcium-channel blockers.

The patients with PTSD were characterized by female sex, higher age, lower diastolic blood pressure, lower prevalence of ischemic heart disease, higher prevalence of stroke and, particularly, a higher frequency of a past or current history of insomnia medication use (**Table**). The prevalence of PTSD was highest in the hospitals in the area directly affected by the Tsunami or within close proximity (<30km) to the Fukushima-Daiichi nuclear power plant, and decreased in association with the reduction in seismic intensity (**Figure A**). The patients who experienced the Tsunami had the highest prevalence of PTSD (**Figure B**). Multivariate logistic regression analysis revealed that PTSD was significantly associated with several factors, including female sex (adjusted odds ratio (adOR) 1.27; 95% confidence interval (CI) 1.02–1.57; P=0.02), dyslipidemia (adOR 0.58; 95% CI 0.38–0.93; P=0.02), past or current insomnia medication use (adOR 8.57; 95% CI 5.76–12.76; P<0.001), experiencing the Tsunami (adOR 1.95; 95% CI 1.00–3.67; P=0.04), major property loss (adOR 1.65; 95% CI

1.14–2.38; P<0.01) and economic poverty after the Earthquake (adOR 3.22; 95% CI 1.73–5.91; P<0.001). Interestingly, dyslipidemia (adOR 0.52; 95% CI 0.31–0.92; P=0.02), major property loss (adOR 1.78; 95% CI 1.15–2.72; P<0.01) and economic poverty (adOR 4.64; 95% CI 2.33–9.12; P<0.001) were more likely associated with PTSD in males, whereas experiencing the Tsunami (adOR 4.40; 95% CI 1.26–14.7; P=0.02) was in females. Past or current insomnia medication use had comparable effect between the sexes (adOR 8.80; 95% CI 5.30–14.1; P<0.001, and adOR 10.00; 95% CI 5.00–20.4; P<0.001 for male and female, respectively). Importantly, during the median follow-up of 2 years, the patients with PTSD, as compared with those without it, more frequently experienced the primary endpoint (18.5% vs. 15.0%, adOR 1.26; 95% CI 1.02–1.57, P=0.035) (**Figure C**), regardless of age, sex, HF etiology or stage. Corporeal damages by the Tsunami and/or by the Earthquake did not influence the incidence of the primary endpoint (adOR 0.99; 95% CI 0.80–1.23, P=0.93) regardless of the presence or absence of PTSD.

Discussion

To the best of our knowledge, this is the first study demonstrating the prevalence, predictors and adverse prognostic impact of psychological stress caused by a major earthquake. Although the overall prevalence of PTSD (11.4%) was comparable with that reported in the general population after major disasters,[9,10] the present study demonstrates for the first time that the intensity of the Earthquake, experiencing the Tsunami and proximity to the nuclear power plants were independently associated with the incidence of PTSD. PTSD was more frequently observed in females than in males,[11] and furthermore, sex differences were suggested in the mechanisms of PTSD after the Earthquake; dyslipidemia, major property loss and economic poverty were mainly associated with PTSD in males, whereas the Tsunami experience was the main factor for females. Thus, corporeal and spiritual losses differently influence mental disorders in males and females after a major natural disaster. In contrast, the prognostic effect of the Earthquake was comparable between the sexes in patients with PTSD.

In conclusion, PTSD was frequently noted in CVD patients at 6 months after the Great East Japan Earthquake and associated with subsequent adverse prognostic impact. Furthermore, the present study demonstrates the importance of a sex-based approach to preventing PTSD after major disasters when victims experience several types of stress.[12] Further studies are needed to generalize the present findings to other cohorts.

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Conflict of Interest

H.S. received lecture fees from Bayer Yakuhin, Ltd (Osaka, Japan), Daiichi Sankyo Co, Ltd (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan). The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by the unrestricted research grants from Daiichi Sankyo Co, Ltd (Tokyo, Japan), Bayer Yakuhin, Ltd (Osaka, Japan), Kyowa Hakko Kirin Co, Ltd (Tokyo, Japan), Kowa Pharmaceutical Co, Ltd (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co, Ltd (Osaka, Japan), and Nippon Boehringer Ingelheim Co, Ltd (Tokyo, Japan).

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Supplementary Files

Supplementary File 1

Appendix S1. The CHART-2 Study Investigators

Please find supplementary file(s);
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ORIGINAL ARTICLE
Heart Failure

Prognostic Impact of Statin Use in Patients With Heart Failure and Preserved Ejection Fraction

– A Report From the CHART-2 Study –

Kotaro Nochioka, MD, PhD; Yasuhiko Sakata, MD, PhD; Satoshi Miyata, PhD; Masanobu Miura, MD, PhD; Tsuyoshi Takada, MD, PhD; Soichiro Tadaki, MD; Ryoichi Ushigome, MD; Takeshi Yamauchi, MD; Jun Takahashi, MD, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators'

Background: The effectiveness of statins remains to be examined in patients with heart failure (HF) with preserved ejection fraction (EF).

Methods and Results: Among 4,544 consecutive HF patients registered in the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2) between 2006 and 2010, 3,124 had EF ≥50% (HFpEF; mean age 69 years; male 65%) and 1,420 had EF <50% (HF with reduced EF (HFrEF); mean age 67 years; male 75%). The median follow-up was 3.4 years. The 3-year mortality in HFpEF patients was lower in patients receiving statins [8.7% vs. 14.5%, adjusted hazard ratio (HR) 0.74; 95% confidence interval (CI), 0.58–0.94; P<0.001], which was confirmed in the propensity score-matched cohort (HR, 0.72; 95% CI, 0.49–0.99; P=0.044). The inverse probability of treatment weighted further confirmed that statin use was associated with reduced incidence of all-cause death (HR, 0.71; 95% CI, 0.62–0.82, P<0.001) and noncardiovascular death (HR, 0.53; 95% CI, 0.43–0.66, P<0.001), specifically reduction of sudden death (HR, 0.59; 95% CI, 0.36–0.98, P=0.041) and infection death (HR, 0.53; 95% CI, 0.35–0.77, P=0.001) in HFpEF. In the HFrEF cohort, statin use was not associated with mortality (HR, 0.87; 95% CI, 0.73–1.04, P=0.12), suggesting a lack of statin benefit in HFrEF patients.

Conclusions: These results suggest that statin use is associated with improved mortality rates in HFpEF patients, mainly attributable to reductions in sudden death and noncardiovascular death. (*Circ J* 2015; **79:** 574–582)

Key Words: Heart failure; Lipids; Noncardiovascular death; Statins; Sudden death

Heart failure (HF) is a progressive disorder with high mortality and morbidity,[1] and its prevalence has been rapidly increasing worldwide.[2] Particularly, the obvious increase in the prevalence of HF with preserved ejection fraction (HFpEF) is now a serious healthcare problem all over the world.[3] To date, however, no pharmacological strategy has been established for the treatment of HFpEF patients.[4–8]

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Unlike in patients with HF with reduced ejection fraction (HFrEF), previous randomized clinical trials with cardioprotective drugs, including angiotensin-converting enzyme inhibitors (ACEIs),[4] angiotensin II receptor blockers (ARBs),[5,6] aldosterone antagonists[7] and β-blockers,[8] have failed to show the effectiveness of these drugs in HFpEF patients, which could be at least in part explained by differences in the characteristics of HFrEF and HFpEF patients. Indeed, as compared with HFrEF, HFpEF is characterized by higher age, higher prevalence of female sex, hypertension, and left ventricular diastolic dysfunction associated with myocardial hypertrophy and fibrosis, and lower incidence of cardiovascular death, but comparable all-cause death.[9–11]

Statins [3-hydroxy-3-methylgulutaryl coenzyme A reductase inhibitors] are cholesterol-lowering drugs with pleiotropic properties, such as antiinflammatory,[12] antihypertrophic,[13] antifibrotic and antioxidant effects,[14,15] all of which could be theoretically beneficial for the management of HF. However, previous

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Department of Cardiovascular Medicine and Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
The Guest Editor for this article was Hiroyuki Tsutsui, MD.
Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp
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clinical trials have failed to show beneficial effects of statins in HFrEF patients,[16–18] but the prognostic effect of statins in HFpEF patients remains to be elucidated. Therefore, in the present study, we aimed to examine whether statin use is associated with better clinical outcomes in HFpEF patients, using the database of the Chronic Heart Failure Registry and Analysis in the Tohoku district-2 (CHART-2), a multicenter prospective observational study of cardiovascular diseases (CVD) in Japan.[19–22]

Methods

Data Sources

The CHART-2 Study is a registry of Japanese patients with CVD.[19–22] Between October 2006 and March 2010, 10,219 consecutive Japanese patients older than 20 years with ACC/AHA stages B–D of HF[23] or coronary artery disease (CAD) were enrolled in both in- and outpatient settings.[19] The ACC/AHA stages B–D of HF were defined as follows: Stage B, structural heart disease but without signs or symptoms of HF; Stage C, structural heart disease with prior or current symptoms of HF; Stage D, refractory HF requiring specialized interventions.[23] The diagnosis of HF was based on the Framingham criteria.[24] Written informed consent was provided by all patients before enrollment.[19] Information on medical history and baseline demographics, including medications and echocardiographic data, was collected at the time of enrollment by the clinical research coordinators. Follow-up was at least twice yearly by review of medical records, surveys and telephone interviews conducted by clinical research coordinators. The CHART-2 Study was approved by the local ethics committees of the 24 participating hospitals (1 university hospital, 23 general hospitals) and registered in ClinicalTrials.gov (Identifier: NCT00418041).

Study Sample

Of 10,219 patients, 4,736 had a history of or current symptoms of HF (Stage C/D).[19] After exclusion of 192 patients lacking EF data, we enrolled 3,124 patients with HFpEF (EF ≥50%, mean [SD] age 69.4 [12.2] years; male 65%) and 1,420 patients with HFrEF (EF <50%, mean [SD] age 67.4 [12.4] years; male 75%) in the present study (**Figure S1**).

Study Outcomes and Definitions

The study endpoints were death, mode of death and hospitalization for worsening HF. All events and mode of death were reviewed and assigned by consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association (**Appendix S1**) after reviewing case reports, death certificates, and hospital records provided by the investigators. Cardiovascular death was defined as death attributed to car-

Table 1. Baseline Characteristics of the Total and Matched Cohorts of Patients With HFpEF

	Total cohort (n=3,124)			Matched cohort (n=1,252)		
	Statin use		P value	Statin use		P value
	Yes (n=1,163)	No (n=1,961)		Yes (n=626)	No (n=626)	
Age, mean (SD), years	69.0 (11.0)	69.7 (12.9)	0.108	69.4 (11.2)	70.0 (11.9)	0.362
Male sex, n (%)	785 (67.5)	1,256 (64.0)	0.052	410 (65.5)	421 (67)	0.550
BP, mean (SD), mmHg						
Systolic	131 (18)	127 (19)	<0.001	129 (17)	130 (19)	0.360
Diastolic	74 (12)	72 (12)	<0.001	73 (12)	74 (12)	0.652
Heart rate, mean (SD), beats/min	71 (14)	72 (15)	0.008	72 (14)	71 (14)	0.163
Body mass index (SD), kg/m²	24.7 (3.6)	23.5 (3.8)	<0.001	24.2 (3.6)	24.2 (4.1)	0.884
NYHA classification, n (%)			<0.001			0.877
I	365 (30.4)	465 (23.7)		147 (23.5)	159 (35.4)	
II	723 (62.2)	1,286 (65.6)		422 (67.4)	409 (65.3)	
III	82 (7.1)	196 (10)		53 (8.5)	54 (8.6)	
IV	4 (0.3)	14 (0.7)		4 (0.6)	4 (0.6)	
Current or past smoker, n (%)	527 (45.3)	801 (40.8)	0.015	281 (44.9)	290 (46.3)	0.650
Medical history, n (%)						
Hospitalization for HF	488 (42.0)	994 (50.7)	<0.001	281 (44.9)	273 (43.6)	0.690
Hypertension	989 (85.0)	1,505 (76.7)	<0.001	518 (82.7)	505 (80.7)	0.380
Diabetes mellitus	393 (33.8)	409 (20.9)	<0.001	181 (28.9)	163 (26.0)	0.282
Dyslipidemia	1,158 (99.6)	1,073 (54.7)	<0.001	624 (99.7)	361 (57.7)	<0.001
Atrial fibrillation	243 (20.9)	848 (43.2)	<0.001	200 (31.9)	186 (29.7)	0.426
Stroke	217 (18.7)	338 (17.2)	0.033	113 (18.1)	119 (19.0)	0.716
Cancer	117 (10.1)	261 (13.3)	0.008	74 (11.6)	71 (11.3)	0.860
Previous MI	579 (49.8)	364 (18.6)	<0.001	212 (33.9)	211 (33.7)	1.000
Coronary artery disease	832 (71.5)	591 (30.8)	<0.001	344 (55.0)	307 (49.0)	0.042
Coronary artery angiography	505 (43.4)	360 (18.4)	<0.001	209 (33.4)	190 (30.4)	0.374
1-vessel disease	231 (19.9)	208 (10.6)	<0.001	110 (17.6)	106 (16.9)	0.764
2-vessel disease	174 (15.0)	103 (5.3)	<0.001	72 (11.5)	58 (9.3)	0.391
3-vessel disease	100 (8.6)	49 (2.5)	<0.001	27 (4.3)	26 (4.2)	1.000
Valvular dysfunction	212 (18.2)	673 (34.3)	<0.001	167 (26.7)	160 (25.6)	0.700
Hypertrophic cardiomyopathy	87 (7.5)	272 (13.9)	<0.001	67 (10.7)	77 (12.3)	0.425

(**Table 1** continued the next page.)

	Total cohort (n=3,124)			Matched cohort (n=1,252)		
	Statin use		P value	Statin use		P value
	Yes (n=1,163)	No (n=1,961)		Yes (n=626)	No (n= 626)	
Laboratory data						
LDL-C, mg/dl	99 (27)	110 (31)	<0.001	101 (28)	113 (29)	<0.001
HDL-C, mg/dl	52 (15)	53 (16)	0.266	53 (15)	52 (15)	0.213
Triglyceride, mg/dl	134 (73)	124 (82)	0.001	136 (79)	128 (84)	0.109
Hemoglobin, g/dl	13.3 (2.1)	13.0 (2.0)	<0.001	13.2 (1.9)	13.2 (1.9)	0.937
BNP (IQR), pg/dl	76 (28–145)	116 (45–197)	<0.001	83 (32–155)	102 (37–159)	0.626
Potassium, mEq/L	4.4 (0.4)	4.4 (0.5)	0.036	4.3 (0.4)	4.4 (0.5)	0.829
eGFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	61 (28)	62 (22)	0.310	61 (34)	62 (21)	0.752
CRP (IQR), mg/dl	0.2 (0.1–0.8)	0.3 (0.1–0.8)	0.018	0.2 (0.1–0.8)	0.3 (0.1–0.8)	0.098
LVEF, %	66 (9)	65 (9)	0.223	65 (9)	65 (9)	0.851
LAD, mm	41 (8)	43 (10)	<0.001	42 (9)	42 (9)	0.543
Medications, n (%)						
Loop diuretics	373 (32.1)	892 (45.5)	<0.001	246 (39.3)	221 (35.3)	0.161
ACEI or ARB	857 (73.7)	1,310 (66.8)	<0.001	440 (70.3)	454 (72.5)	0.416
β-blocker	533 (45.8)	772 (39.4)	<0.001	278 (44.4)	268 (42.8)	0.608
Aldosterone antagonist	174 (15.0)	426 (21.7)	<0.001	113 (18.1)	103 (16.5)	0.501
Calcium-channel blocker	590 (50.7)	810 (41.3)	<0.001	291 (46.5)	304 (48.6)	0.497
Antiplatelet or anticoagulant	1,048 (90.1)	1,437 (73.3)	<0.001	523 (83.5)	520 (83.1)	0.880
Other lipid-lowering medicine	43 (3.7)	78 (4.0)	0.774	28 (4.5)	21 (3.4)	0.382
Intervention history, n (%)						
PCI	625 (53.7)	360 (18.4)	<0.001	217 (34.7)	227 (36.3)	0.595
CABG	179 (15.4)	111 (5.7)	<0.001	61 (9.7)	47 (7.5)	0.190
ICD	11 (0.9)	27 (1.4)	0.316	6 (1.0)	6 (1.0)	1.000
CRTD	1 (0.1)	10 (0.5)	0.063	0	2 (0.3)	0.500

Values are expressed as n (%) unless otherwise indicated. The majority of variables were used for derivation of the propensity score. The following covariates were not included for derivation of the propensity score: diastolic BP; dyslipidemia; LDL-C, HDL-C, triglyceride and CRP levels; other lipid-lowering medicine, ICD, and CRTD.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CRP, C-reactive protein; CRTD, cardiac resynchronization therapy defibrillator; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure and preserved ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation.

diovascular origins. Noncardiovascular death was defined as death from noncardiovascular causes. For the mode of death, only the main mode was recorded. Hospitalization for worsening HF was defined as documentation of worsening HF requiring hospitalization. A patient admitted for worsening HF had to show signs and symptoms of HF and to require treatment with intravenous diuretics.

Statistical Analysis

Descriptive statistics, including mean±SD, median and frequencies for continuous and categorical data, are presented for all patients and by statin treatment category. The Wilcoxon rank sum and Pearson's chi-square test were used to compare the characteristics of patients with and without statin therapy.

To reduce confounding effects related to differences in the patient's background between those with and those without statin use, 3 propensity score (PS) methods were used in combination with Cox regression modeling. For the calculation of PS, we used a logistic regression model in which the treatment status of statins was regressed for the following 31 baseline characteristics: age, male sex, blood pressure, heart rate, body mass index, NYHA classification, smoking status (current and past smoker or nonsmoker), history of hospitalization for HF, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, stroke, cancer, previous myocardial infraction (MI), CAD (3-vessel disease), hypertrophic cardiomyopathy, hemoglobin, B-type natriuretic peptide, potassium, estimated glomerular filtration rate, LVEF, left atrial dimension, loop diuretics, ACEI or ARB, β-blocker, aldosterone antagonist, calcium-channel blocker, antiplatelet or anticoagulant, percutaneous coronary intervention and coronary artery bypass grafting.[9,11,25,26] Missing data for 31 variables were handled by estimating the variables for each missing variable based on the pattern for all available observations. Area under the curve (AUC) to show the performance of the PS for statin use was 0.78 [95% confidence interval (CI), 0.77–0.80]. Using the PS, patients were matched for 1:1 optimal match with a <0.001 caliper and no replacement. The distribution of PS in the total and matched cohorts is shown in **Figure S2**. Kaplan-Meier curves were plotted to evaluate the association between statin use and all-cause death or hospitalization for worsening HF in the total cohort using the log-rank test and PS-matched cohort using the PS-stratified Cox analysis. To reduce confounding in the time-to-event observational data, the inverse probability of treatment weighted (IPTW) method was used.[27] Using the same 31 variables for the PS calculation, case-weight estimation was done with a logistic regression model to predict the inverse probability of statin use. Finally, in order to examine the clinical effect of statins in the total cohort, we constructed 5 Cox proportional hazard models: unadjusted, age- and sex-adjusted, PS-