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Original article

Long-term prognostic impact of the Great East Japan Earthquake in patients with cardiovascular disease – Report from the CHART-2 Study

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ABSTRACT

Background: We and others have previously reported that the Great East Japan Earthquake (GEJE) caused a significant but transient increase in cardiovascular diseases and deaths in the disaster area. However, it remains to be examined whether the GEJE had a long-term prognostic influence in large-scale cohort studies. This point is important when analyzing the data before and after the GEJE in the cohort studies in the disaster area.

Methods: We examined 8676 patients registered in our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (N = 10,219) between 2006 and 2010 and were alive after March 10, 2011.

Results: There were 48 GEJE-related deaths, causing a sharp and transient increase in all-cause death within a month after the GEJE. However, after excluding the GEJE-related deaths, the cubic polynomial spline smoothing showed no significant increase in all-cause death, heart failure admission, non-fetal acute myocardial infarction, or non-fetal stroke during the median 3-year follow-up after the GEJE. The extrapolation curves beyond the GEJE, which were obtained by the parametric survival models based on the survival data censored on the GEJE, were not significantly different from the Kaplan–Meier curves estimating the survival functions of deaths and cardiac events during the total follow-up period without considering the impacts of the GEJE. Furthermore, the multivariate Cox proportional hazard model applied to the matched cohort of the baseline data and the data after the GEJE showed no significant differences in the impacts of prognostic factors on all-cause mortality before and after the GEJE.

Conclusions: These results indicate that the GEJE had no significant long-term prognostic impact after the earthquake in cardiovascular patients in the disaster area.

Introduction

On March 11, 2011, the Great East Japan Earthquake (GEJE) hit the Tohoku district, the northeast part of Japan. With a magnitude of Richter scale 9.0, it was one of the top 5 largest earthquakes in the world since 1900 [1]. The GEJE caused huge damage, including 19,418 deaths, 2592 missing persons, and 400,305 destroyed houses as of March 8, 2016 [2], and also caused a significant increase in cardiovascular diseases (CVDs) and/or deaths [3–8]. We examined the impact of the GEJE on the occurrences of CVDs and pneumonia by comparing all ambulance records between 2008 and 2011 in Miyagi Prefecture, the center of the disaster area, showing that the occurrences of all types of CVDs and pneumonia were transiently increased in different time-courses after the earthquake [3]. We also reported that the weekly occurrences of several CVDs, including heart failure (HF), pulmonary thromboembolism, and infectious endocarditis, were sharply and transiently increased after the GEJE in patients admitted to the

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cardiology departments at 10 hospitals in the disaster area after the earthquake [4]. Others also reported an increase of out-of-hospital cardiac arrest in the first 4 weeks after the GEJE [6] and an increase in acute decompensated heart failure (ADHF) [7,8]. These lines of evidence suggest that the GEJE caused a rapid and transient increase in all types of CVD in the disaster area. However, it remains to be examined whether the GEJE had a long-term prognostic influence in the disaster area.

The CHART-2 Study is a multicenter, prospective observational cohort study to identify the clinical characteristics, treatments, and prognosis of patients with HF and those at high risk for HF [9–26]. We started the study in 2006 and were able to enroll a total of 10,219 patients aged ≥20 years until March, 2010, including patients with significant coronary artery disease (CAD) (Stage A) [27] ($N = 718$) and patients in Stages B–D [27] HF ($N = 9501$) [9]. On March 10, 2011, when we unexpectedly experienced the GEJE, we already had followed up the CHART-2 Study cohort for a median 3.1-years after the enrollment, and fortunately, after the earthquake, we were able to continue to follow them up without interruption. In other words, the GEJE gave us a unique opportunity to examine the short- and long-term effects of the earthquake on prognosis in patients with CVD registered in the CHART-2 Study.

In the present study, we thus examined whether the GEJE had a long-term prognostic impact after the earthquake in CVD patients in the disaster area in our CHART-2 Study.

Material and methods

The CHART-2 Study

The CHART-2 Study ($N = 10,219$) is a multicenter, prospective observational study, as previously described (NCT00418041, UMIN000000562) [9–26]. The CHART-2 Study was approved by the local ethics committees of each participating hospital and written informed consent was obtained from all patients [9–13]. Patients aged ≥20 years with significant CAD ($N = 868$, 8.5%) or HF in Stage B ($N = 4465$, 43.7%), C ($N = 4782$, 46.8%), or D ($N = 94$, 0.9%), as defined according to the American College of Cardiology Foundation/American Heart Association guidelines [27] were enrolled in the study from October 2006 to March 2010. Clinical information was recorded at the time of enrollment and has been thereafter updated annually by trained clinical research coordinators. To date, however, we have only used the data obtained before the GEJE in the previous reports [9–22,24–26] except for the one that examined the prognostic impact of post-traumatic stress disorder after the GEJE [23] since we have not yet known whether the GEJE had a long-term prognostic impact in the disaster area. Thus, this is the first analysis to compare the data before and after the GEJE in the CHART-2 Study.

Study design

The flow of the present study is shown in Fig. 1. Among the 10,219 patients enrolled in the CHART-2 Study, 10 were excluded because of missing data. The primary and secondary endpoints were recorded until September 30, 2014, and the annual inspection measurements were confirmed and fixed until 3 years after the enrollment. On March 11, 2011, the GEJE hit the northeast part of Japan. The number at risk at the time of the GEJE was 8676 patients with 3.6-year follow-up after the GEJE, and 48 deaths were caused by the GEJE until April 10, 2011 (earthquake- and tsunami-related death in 42, earthquake-related death in 3, and missing after the earthquake in 3). To compare the data after the enrollment and those after the GEJE with similar background, the study patients were randomly separated into the Group 1 ($N = 5104$) and the Group 2 ($N = 5105$), and then the subgroup patients with available data after the GEJE were selected from the Group 1 ($N = 1442$) and the Group 2 ($N = 1485$). Finally, the data at the enrollment (baseline) and the data after the GEJE (post-GEJE) were randomly matched for their covariates to compose the Group A ($N = 1131$ at baseline and $N = 1077$ for post-GEJE) and the Group B ($N = 1533$ at baseline and $N = 1380$ for post-GEJE) (Fig. 1). In the present study, tsunami areas were determined based on the location of the hospital at which each participant was registered; the hospitals defined as those in the tsunami area included the Ishinomaki municipal hospital, Iwate Prefectural Miyako hospital, Iwaki Kyoritsu hospital, Shizugawa Public hospital, Saito hospital, and Watanabe hospital.

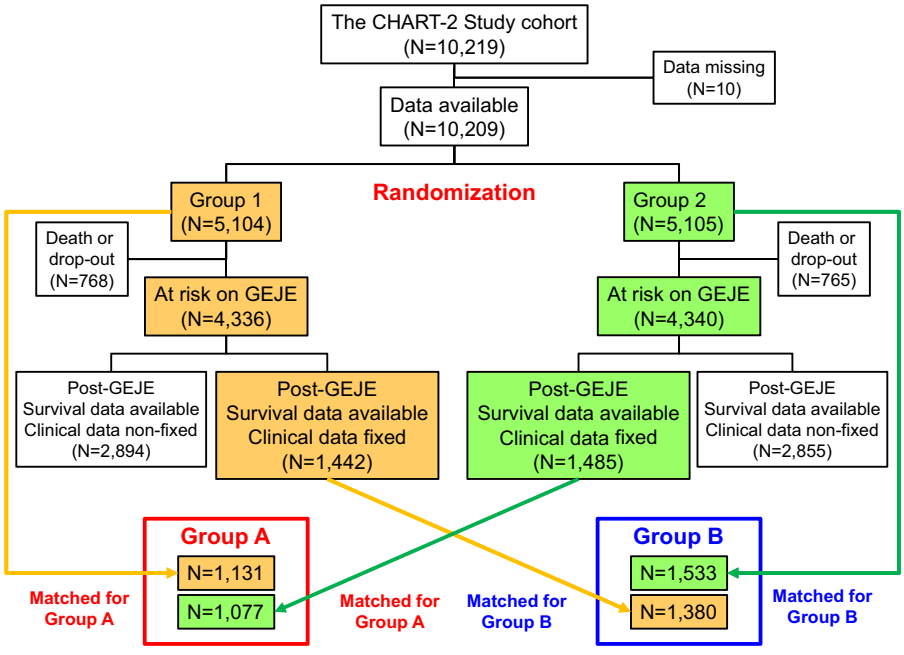

Fig. 1. Study flow. GEJE, Great East Japan Earthquake.

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Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with inter-quartile range (IQR) as appropriate, and were compared by the Welch's *t*-test. Categorical variables were expressed as numeral with percentage, and were compared by the Fisher's exact test. Incident rates (1000 person-years) of cardiac events from the baseline were estimated, and smoothed by cubic polynomial splines with and without the dummy variable of the time period from March 11 to April 10, 2011 to de-noise and extract their trend.

Survival functions of the outcomes were estimated using the Kaplan–Meier product limit estimator, and between-group differences were compared by the log-rank test. To examine whether the GEJE influenced the incidence of death and other CV events, we compared the Kaplan–Meier curves with 95% confidence bands based on data during the total follow-up period with the extrapolation curves by the parametric survival models with Weibull distribution based on the survival data censored on March 10, 2011. The simultaneous confidence band of the Kaplan–Meier curve was estimated using the "OIsurv" package [28] of the R software [29].

To examine the possible prognostic impacts of the GEJE, the incidences of deaths and other cardiac events were compared between the baseline and post-GEJE in both Group A and Group B. For this comparison, we matched the baseline and the post-GEJE data for their covariates, including the following variables: age, sex, height, body weight, etiologies of CHF, including ischemic heart disease (IHD), hypertension, valvular heart disease, dilated cardiomyopathy and hypertrophic cardiomyopathy, history of hypertension, diabetes mellitus, dyslipidemia, and admission for HF, malignant disease, brain disorder, systolic blood pressure, heart rate, logarithm of B-type natriuretic peptide, creatinine, hemoglobin, left ventricular ejection fraction (LVEF), and medical treatment, including beta-blockers, renin–angiotensin system (RAS) inhibitors, statins, loop diuretics, and calcium channel blockers. First, the total cohort was randomly separated into the Groups 1 and 2 (Fig. 1). Next, the standardized differences of the above covariates between the baseline data of randomly selected 10 samples in one group and the data after the GEJE of 10 samples in another group were calculated, and the sum of standardized differences was obtained. Then, consecutive samples were randomly chosen from the Groups 1 and 2, and the standardized differences were re-evaluated. Once the sum of squared standardized differences was reduced, the chosen samples were kept in the matched data, otherwise removed. Finally, the matched data of the Groups A and B were obtained after at least 2000 iterations (Fig. 1). In the survival time analysis, each procedure was applied to the Group A and the Group B, and the results of both groups were compared.

Risk factors for the survival outcomes were estimated utilizing univariate and multivariate Cox proportional hazard models with 3-year survival rate. To explore the independent prognostic factors of cardiac events, first, the univariate Cox proportional hazard model was applied to the individual covariates for the subgroup beginning from the baseline and that from the GEJE. Second, the multivariate model was fit using the variables with the *p*-values of the independent model <0.2. Finally, the optimal set of the prognostic factors was obtained as the union of the covariates selected in each subgroup by the stepwise backward elimination procedure. To examine whether the prognostic impacts of the GEJE were concentrated in specific subgroups, we compared the incidence of all-cause death, CV death, non-CV death, HF

Table 1
Patient characteristics.

Characteristics	Overall (*N* = 10,209)	Group 1 (*N* = 5104)	Group 2 (*N* = 5105)	*p*-Value*
Age, years	68.3 ± 12.1	68.3 ± 12.0	68.2 ± 12.2	0.917
Female, *N* (%)	3099 (30.4)	1564 (30.6)	1535 (30.1)	0.533
Height, cm	159.9 ± 9.4	159.8 ± 9.5	160.0 ± 9.4	0.394
Body weight, kg	61.7 ± 12.2	61.5 ± 12.1	61.8 ± 12.3	0.162
Etiology, *N* (%)				
Ischemic heart disease	5694 (55.8)	2870 (56.2)	2824 (55.3)	0.359
Hypertensive heart disease	558 (5.5)	270 (5.3)	288 (5.6)	0.459
Valvular heart disease	867 (8.5)	428 (8.4)	439 (8.6)	0.723
Dilated cardiomyopathy	765 (7.5)	371 (7.3)	394 (7.7)	0.408
Hypertrophic cardiomyopathy	355 (3.5)	185 (3.6)	170 (3.3)	0.418
Risk factors, *N* (%)				
Hypertension	9109 (89.2)	4542 (89.0)	4139 (89.5)	0.463
Diabetes mellitus	3419 (33.5)	1723 (33.8)	1696 (33.2)	0.571
Dyslipidemia	8366 (81.9)	4227 (82.3)	4139 (81.1)	0.024
Previous history, *N* (%)				
Admission for heart failure	2590 (25.4)	1278 (25.0)	1312 (25.7)	0.453
Malignant disease	1366 (13.4)	698 (13.7)	668 (13.1)	0.383
Stroke	1957 (19.2)	793 (19.1)	984 (19.3)	0.801
Hemodynamics and LV function				
Systolic BP, mmHg	128.3 ± 18.5	128.5 ± 18.5	128.2 ± 18.6	0.335
Heart rate, bpm	71.0 ± 14.1	70.9 ± 13.8	71.0 ± 14.3	0.778
LVEF, %	60.9 ± 14.1	60.9 ± 14.0	61.1 ± 14.1	0.368
Laboratory findings				
logBNP, log(pg/ml)	4.2 ± 1.3	4.2 ± 1.3	4.2 ± 1.3	0.682
Creatinine, mg/dl	1.0 ± 0.7	1.0 ± 0.8	1.0 ± 0.7	0.156
Hemoglobin, g/dl	13.4 ± 1.9	13.4 ± 1.8	13.4 ± 1.9	0.622
Medications, *N* (%)				
Beta-blockers	4141 (40.6)	2097 (41.1)	2022 (43.5)	0.285
RAS inhibitors	6627 (64.9)	3312 (64.9)	3315 (64.9)	0.967
Statins	4240 (41.5)	2130 (41.7)	2110 (41.3)	0.688
Loop diuretics	3071 (30.1)	1508 (29.5)	1563 (30.6)	0.244
Calcium channel blockers	4654 (45.6)	2328 (45.6)	2326 (45.6)	0.968

BNP, brain natriuretic peptide; BP, blood pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; RAS, renin–angiotensin system.
* *p*-Value for comparison between Group 1 and Group 2.

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admission, non-fatal acute myocardial infarction (AMI) and non-fatal stroke in the subgroups that were further divided by age (70 years), sex, presence or absence of IHD, estimated glomerular filtration rate (60 mL/min/1.73 m^2), LVEF (50%), and tsunami area between the baseline and post-GEJE periods. In this subgroup analysis, the prognostic impacts of the GEJE were considered as present only when the comparison in the univariate Cox proportional hazard model was concertedly significant in both Groups A and B. The two-sided $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed using the statistical computing software R version 3.3.0 [29].

Results

Patient characteristics

The clinical characteristics at the time of enrollment in the CHART-2 Study for overall, Group 1 and Group 2 patients are shown in Table 1. There were no differences in these baseline characteristics except for the history of dyslipidemia between the Groups 1 and 2. Table 2 shows the characteristics of the patients in the Groups A and B. In both groups, the baseline and post-GEJE data were well balanced without significant differences between the covariates, but with small absolute values of the standardized differences <0.1.

Incident rates of cardiac events

The incident rates per person-months of cardiac events are shown in Fig. 2A. The smoothed curves with the dummy variable of time period from March 11, 2011 to April 10, 2011 are presented by red lines while the smoothed curves without the dummy are shown by black lines with dotted lines of 95% prediction intervals. As for all-cause death and non-cardiovascular death, incident rates per person-months after the GEJE were significantly different from the trend without the dummy variable for the one-month period after the GEJE. In all other cases, including HF admission, non-fatal AMI, or non-fatal stroke, the instantaneous impacts of the GEJE after March 11, 2011 were not significant (Fig. 2A). Furthermore, the increase in deaths within one month after the GEJE disappeared when the follow-up was censored on March 10, 2011 for the patients with GEJE-related death (Fig. 2B).

Comparison of survival curves and its extrapolation

The Kaplan–Meier curves with 95% simultaneous confidence band of the cardiac events were compared with the curve based on extrapolation of the corresponding survival function based on the survival data censored on March 11, 2011 (Fig. 3). For the case of AMI, 95% pointwise confidence band was adopted for technical reasons due to the limited number of AMI events. In all cases, the curve based on extrapolated survival function was not significantly different from the Kaplan–Meier curves (Fig. 3).

Survival functions of cardiac events

Fig. 4 shows the Kaplan–Meier estimates of the survival functions for cardiac events between the matched subgroups in Group A (Fig. 4A) and Group B (Fig. 4B), comparing the data when starting from the baseline and when starting from the GEJE (Fig. 1).

Table 2A
Patient characteristics in Group A.

Characteristics	Group A			
	Enrollment (*N* = 1131)	Post-GEJE (*N* = 1077)	*p*-Value	Stand diff, %
Age, years	68.7 ± 11.2	69.4 ± 12.2	0.150	−0.061
Female, *N* (%)	320 (28.3)	313 (29.1)	0.707	−0.017
Height, cm	160.2 ± 9.1	160.2 ± 9.6	0.958	0.002
Body weight, kg	62.3 ± 11.8	62.5 ± 12.8	0.750	−0.014
Etiology, *N* (%)				
Ischemic heart disease	698 (61.7)	651 (60.4)	0.541	0.026
Hypertensive heart disease	63 (5.6)	67 (6.2)	0.528	−0.028
Valvular heart disease	0 (0)	1 (0.1)	0.488	−0.043
Dilated cardiomyopathy	81 (7.2)	84 (7.8)	0.572	−0.024
Hypertrophic cardiomyopathy	47 (4.2)	40 (3.7)	0.662	0.023
Risk factors, *N* (%)				
Hypertension	1028 (90.9)	985 (91.5)	0.653	−0.02
Diabetes mellitus	421 (37.2)	422 (39.2)	0.358	−0.04
Dyslipidemia	1020 (90.2)	985 (91.5)	0.304	−0.044
Previous history, *N* (%)				
Admission for heart failure	259 (22.9)	257 (23.9)	0.615	−0.023
Malignant disease	147 (13.0)	150 (13.9)	0.533	−0.027
Stroke	219 (19.4)	208 (19.3)	1.000	0.001
Hemodynamics and LV function				
Systolic BP, mmHg	127.7 ± 17.3	127.5 ± 17.5	0.796	0.011
Heart rate, bpm	70.3 ± 13.8	69.7 ± 13.8	0.320	0.043
Laboratory findings				
logBNP, log(pg/ml)	4.1 ± 1.3	4.0 ± 1.2	0.184	0.061
Creatinine, mg/dl	1.0 ± 0.7	1.01 ± 0.9	0.417	−0.035
Hemoglobin, g/dl	13.4 ± 1.8	13.5 ± 1.9	0.820	−0.010
LVEF, %	61.1 ± 13.8	61.5 ± 12.7	0.431	−0.036
Medications, *N* (%)				
Beta-blockers	479 (42.4)	466 (43.3)	0.667	−0.019
RAS inhibitors	720 (63.7)	684 (63.5)	0.965	0.003
Statins	536 (47.4)	530 (49.2)	0.395	−0.036
Loop diuretics	291 (25.7)	260 (24.1)	0.403	0.037
Calcium channel blockers	558 (49.3)	518 (48.1)	0.580	0.025

BNP, brain natriuretic peptide; BP, blood pressure; GEJE, the Great East Japan Earthquake; LV, left ventricle; LVEF, left ventricular ejection fraction; RAS, renin–angiotensin system; Stand diff, standardized difference.

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Table 2B
Patient characteristics in Group B.

Characteristics	Group B			
	Enrollment (*N* = 1533)	Post-GEJE (*N* = 1380)	*p*-Value	Stand diff, %
Age, years	69.0 ± 11.3	69.7 ± 12.2	0.095	−0.062
Female, *N* (%)	471 (30.7)	438 (31.7)	0.575	−0.022
Height, cm	159.9 ± 9.3	160.1 ± 9.8	0.478	−0.028
Body weight, kg	62.0 ± 12.0	62.3 ± 13.7	0.589	−0.021
Etiology, *N* (%)				
Ischemic heart disease	857 (55.9)	731 (53.0)	0.118	0.059
Hypertensive heart disease	91 (5.9)	86 (6.2)	0.756	−0.012
Valvular heart disease	131 (8.5)	120 (8.7)	0.895	−0.005
Dilated cardiomyopathy	102 (6.7)	86 (6.2)	0.651	0.017
Hypertrophic cardiomyopathy	52 (3.4)	49 (3.6)	0.84	−0.009
Risk factors, *N* (%)				
Hypertension	1401 (91.4)	1269 (92.0)	0.592	−0.021
Diabetes mellitus	558 (36.4)	506 (36.7)	0.908	−0.006
Dyslipidemia	1348 (87.9)	1236 (89.6)	0.178	−0.052
Previous history, *N* (%)				
Admission for heart failure	366 (23.9)	341 (24.7)	0.604	−0.019
Malignant disease	235 (15.3)	222 (16.1)	0.575	−0.021
Stroke	302 (19.7)	270 (19.6)	0.963	0.003
Hemodynamics and LV function				
Systolic BP, mmHg	127.6 ± 17.6	127.3 ± 17.4	0.601	0.020
Heart rate, bpm	69.4 ± 12.9	68.9 ± 13.6	0.348	0.036
Laboratory findings				
logBNP, log(pg/ml)	4.1 ± 1.2	4.0 ± 1.2	0.168	0.056
Creatinine, mg/dl	1.0 ± 0.8	1.0 ± 0.9	0.460	−0.028
Hemoglobin, g/dl	13.4 ± 1.9	13.4 ± 1.9	0.667	0.016
LVEF, %	61.5 ± 13.6	62.2 ± 12.2	0.137	−0.058
Medications, *N* (%)				
Beta-blockers	635 (41.4)	595 (43.1)	0.367	−0.034
RAS inhibitors	962 (62.8)	849 (61.5)	0.515	0.025
Statins	691 (45.1)	633 (45.9)	0.682	−0.016
Loop diuretics	407 (26.5)	345 (25.0)	0.351	0.035
Calcium channel blockers	720 (47.0)	644 (46.7)	0.882	0.006

BNP, brain natriuretic peptide; BP, blood pressure; GEJE, the Great East Japan Earthquake; LV, left ventricle; LVEF, left ventricular ejection fraction; RAS, renin–angiotensin system; Stand diff., standardized difference.

Both Kaplan–Meier curves, either when starting from the baseline or from the GEJE, were superimposable in both Group A (Fig. 4A) and Group B (Fig. 4A), indicating that the GEJE had no significant impacts on the mortality and other CV events. Furthermore, the subgroup analysis showed that the prognostic impacts of the GEJE were insignificant in the subgroups divided by age, sex, IHD, chronic kidney disease (CKD), or LVEF levels (eTables 1 and 2). In addition, tsunami areas were not associated with an increased incidence of deaths or CV events (eTable 3).

Independent prognostic factors of cardiac events

Table 3 shows the results of the multivariate Cox proportional hazard analyses for the matched cohorts (Groups A and B). In both Groups A and B, the similar covariates were selected for the baseline and post-GEJE. Furthermore, these variables had comparable impacts on all-cause death between the baseline and post-GEJE in Groups A and B, indicating that the GEJE had no significant impact on the prognostic factors.

Discussion

The major finding of the present study is that the GEJE had no significant long-term prognostic impact after the earthquake in CVD patients in the disaster area. In the present study, although there was a sharp and transient increase in all-cause death shortly after the GEJE, after excluding the GEJE-related deaths, the increase in all-cause death was not significant during the median 3-year follow-up. Furthermore, the background-matched cohorts showed no difference in prognosis or prognostic factors before and after the GEJE.

Increase in all-cause death shortly after the GEJE

In the present study, we found a sharp and transient increase in all-cause death shortly after the earthquake. Although the precise underlying mechanisms for the increases remain to be fully elucidated, the increases in CVD and/or CV deaths have been previously reported after earthquakes [3–8,30–41]. Kloner et al. analyzed all deaths in the entire population of the Los Angeles County, CA, USA, before, during, and after the Northridge Earthquake in 1995, showing an increase in death due to coronary artery disease, but not due to other cardiac causes, followed by a decrease in death overcompensating for the excess of death [30]. Leor et al. reviewed the records of the Department of Coroner of the Los Angeles County, demonstrating that in the Northridge Earthquake in 1995, the number of sudden deaths from cardiac causes sharply increased only on the day and thereafter decreased to the level below the baseline value [31]. In the Athens earthquake in Greece in 1994, an excess of deaths from cardiac and external causes, but no excess of deaths from cancer and little excess of deaths from other causes, was reported shortly after the earthquake [32]. Also in the GEJE, Kitamura et al. reported that the risk of out-of-hospital cardiac arrest was significantly increased especially in the first week after the earthquake [6].

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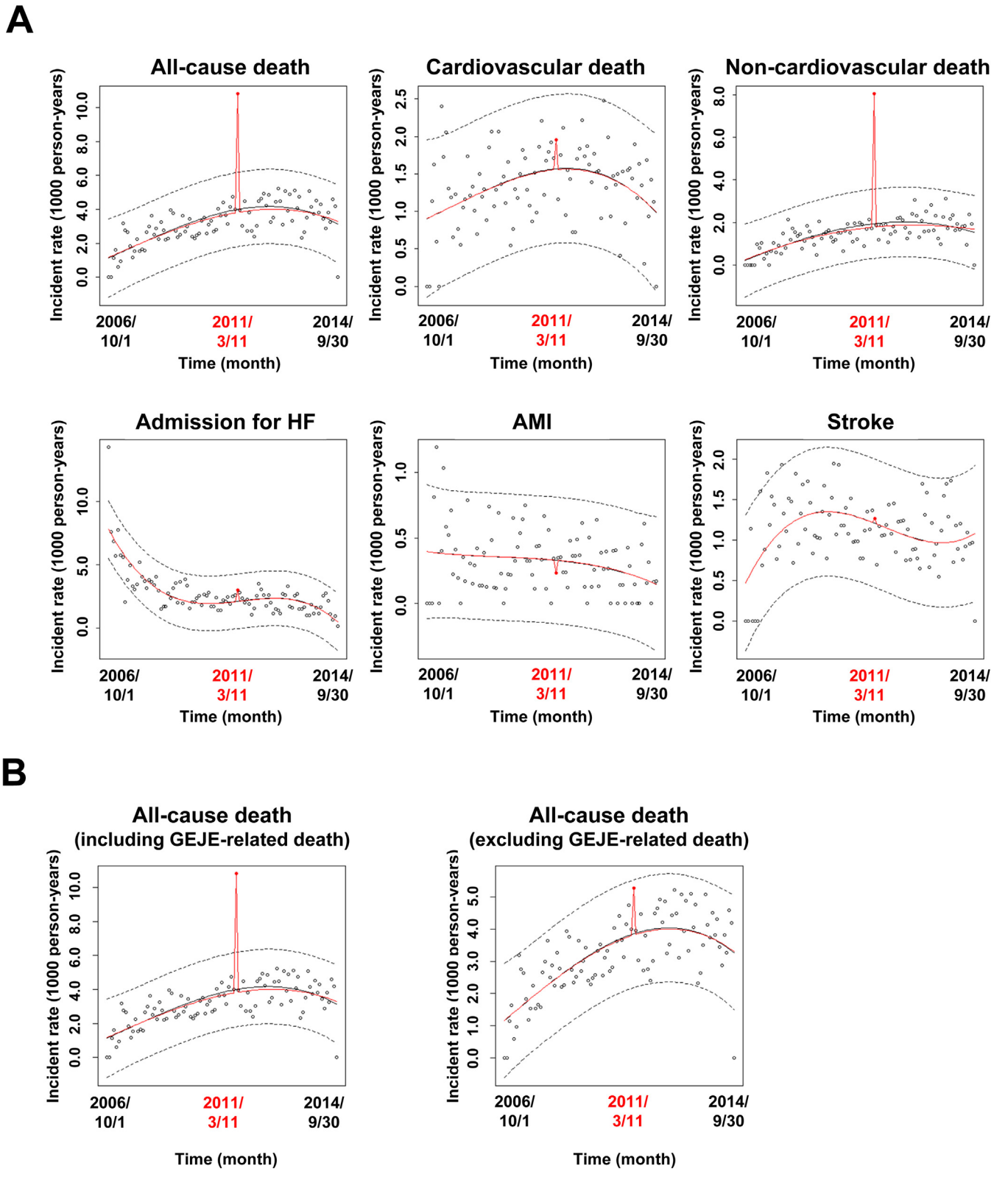

Fig. 2. (A) Incident rates of all-cause death, cardiovascular death, non-cardiovascular death, admission for heart failure (HF), acute myocardial infarction (AMI), and stroke from the baseline. (B) Incident rate of all-cause death from the baseline with (left) and without (right) disaster-related deaths. Red line, polynomial spline with dummy of the month from the Great East Japan Earthquake (GEJE); black line, polynomial spline without dummy of the month from the GEJE; dotted lines, 95% prediction interval of spline.

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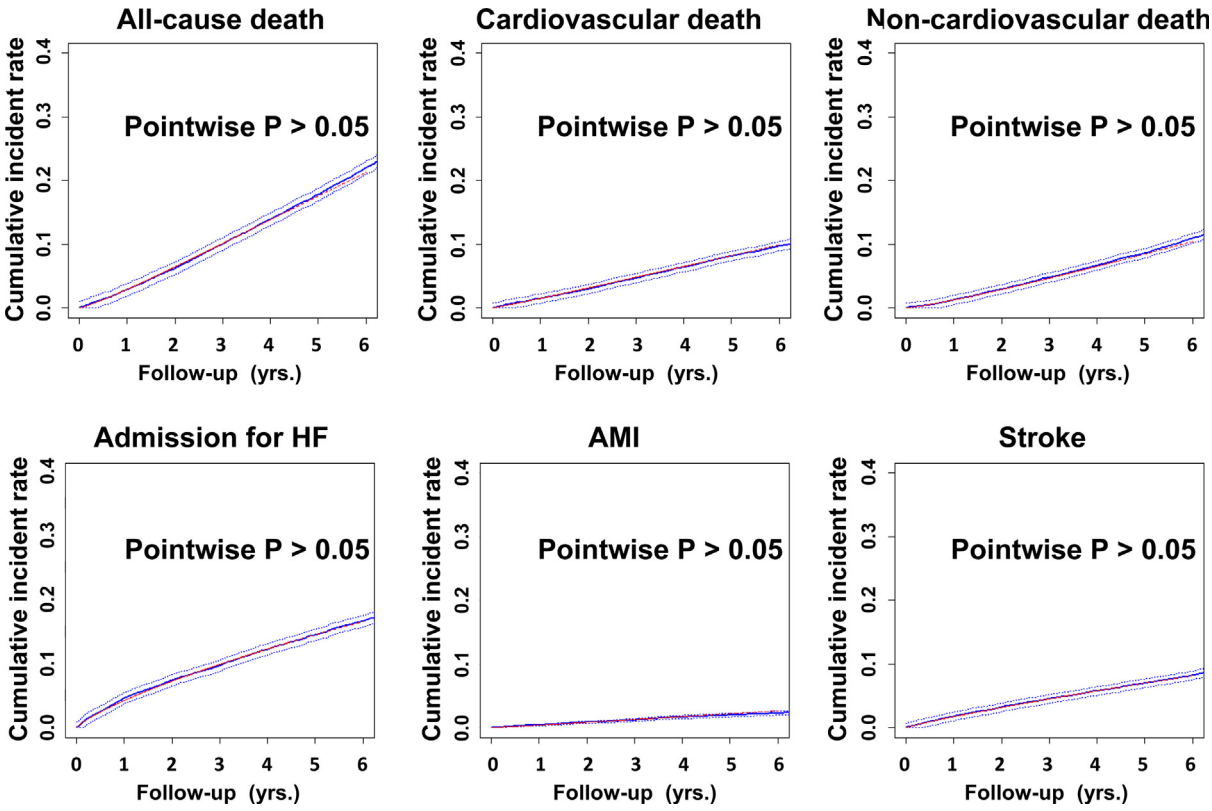

Fig. 3. Cumulative incident rate of cardiovascular events. Blue line, Kaplan–Meier curve with the whole data; blue dotted lines, 95% confidence band of Kaplan–Meier curves; red line, Kaplan–Meier curve with the data censored on GEJE; red dashed line, extrapolation of survival functions. AMI, acute myocardial infarction; HF, heart failure; GEJE, Great East Japan Earthquake.

Lack of long-term increase in CVD after the GEJE

The present study suggests that the increase in deaths shortly after the GEJE was most likely due to an increase in the GEJE-related deaths, but not due to that in CV deaths. It was noteworthy that not only all-cause death, but also HF admission, non-fatal AMI, or non-fatal stroke did not significantly increase during the median 3.6-year follow-up period after the GEJE in the present study. Furthermore, these observations were corroborated by the fact that the impacts of prognostic factors were comparable before and after the GEJE in both datasets with matched clinical backgrounds. This finding was novel as it is inconsistent with those from the previous reports demonstrating the mid- to long-term adverse impacts of the earthquakes on the incidence of CVD and/or CV deaths [3–8,33–41]. We have previously reported increases in CVD, including HF, acute coronary syndrome (ACS), stroke, cardiopulmonary arrest, tachyarrhythmia, pulmonary thromboembolism, and infectious endocarditis after the GEJE by reviewing the ambulance records [3], hospital records [4], and records of implanted cardiac devices [5]. Kario et al. reported that in the Awaji Island near the epicenter of the Great Hanshin-Awaji Earthquake (GHAE) in Japan, the incidences of coronary artery disease and stroke were increased by 1.5- and 1.9-times, respectively, during the 3-month period after the earthquake [33,34] and others also reported an increase in AMI [35,36] and an increased standardized mortality ratio of AMI [37] sustained for weeks after the GHAE. Although Takegami et al. reported that the adverse impacts of the GHAE on CVD mortality was sustained for months after the earthquake but was rather diminished after the GEJE [38], the reasons for the lack of long-term increase in CVD after the GEJE remain to be elucidated.

Mechanisms for the lack of CVD increase after the GEJE

The lack of increase in CVD after GEJE could be explained by the characteristics of the CHART-2 Study as a secondary prevention cohort. The CHART-2 Study enrolled CV patients treated by cardiologists at hospitals, and thus most of the patients in the CHART-2 Study had been treated with medications; 45.6%, 40.6%, 64.9%, and 41.5% of the patients had been treated with anti-platelets, beta-blockers, renin–angiotensin system inhibitors and statins at the time of enrollment, respectively. Activation of the sympathetic nervous system and the renin–angiotensin system by an earthquake could play important roles in the development of CVD and CV deaths [42]. Indeed, Yamauchi et al. reported that the incidence of ADHF was increased after the GEJE in association with high blood pressure, interruption of drugs, inflammation, malnutrition, and fluid retention [7]. Thus, treatment with anti-platelets, beta-blockers, renin–angiotensin system inhibitors, and/or statins before the GEJE could have been beneficial to prevent the development of CVD and CV deaths after the GEJE in the present study. In this regard, further implementation of evidence-based medications should be recommended for patients with CVD in order to prevent unexpected CV events related to natural disasters.

Unmeasured prognostic factors possibly influenced by the GEJE

In the present study, the subgroup analysis showed no adverse impacts of the GEJE in any specific subgroup divided by age, sex, IHD, CKD, or LVEF. However, it is possible that the GEJE had prognostic impacts in specific subgroups in the CHART-2 Study population, which were not examined in the present study. Indeed, we have recently reported that post-traumatic stress disorder

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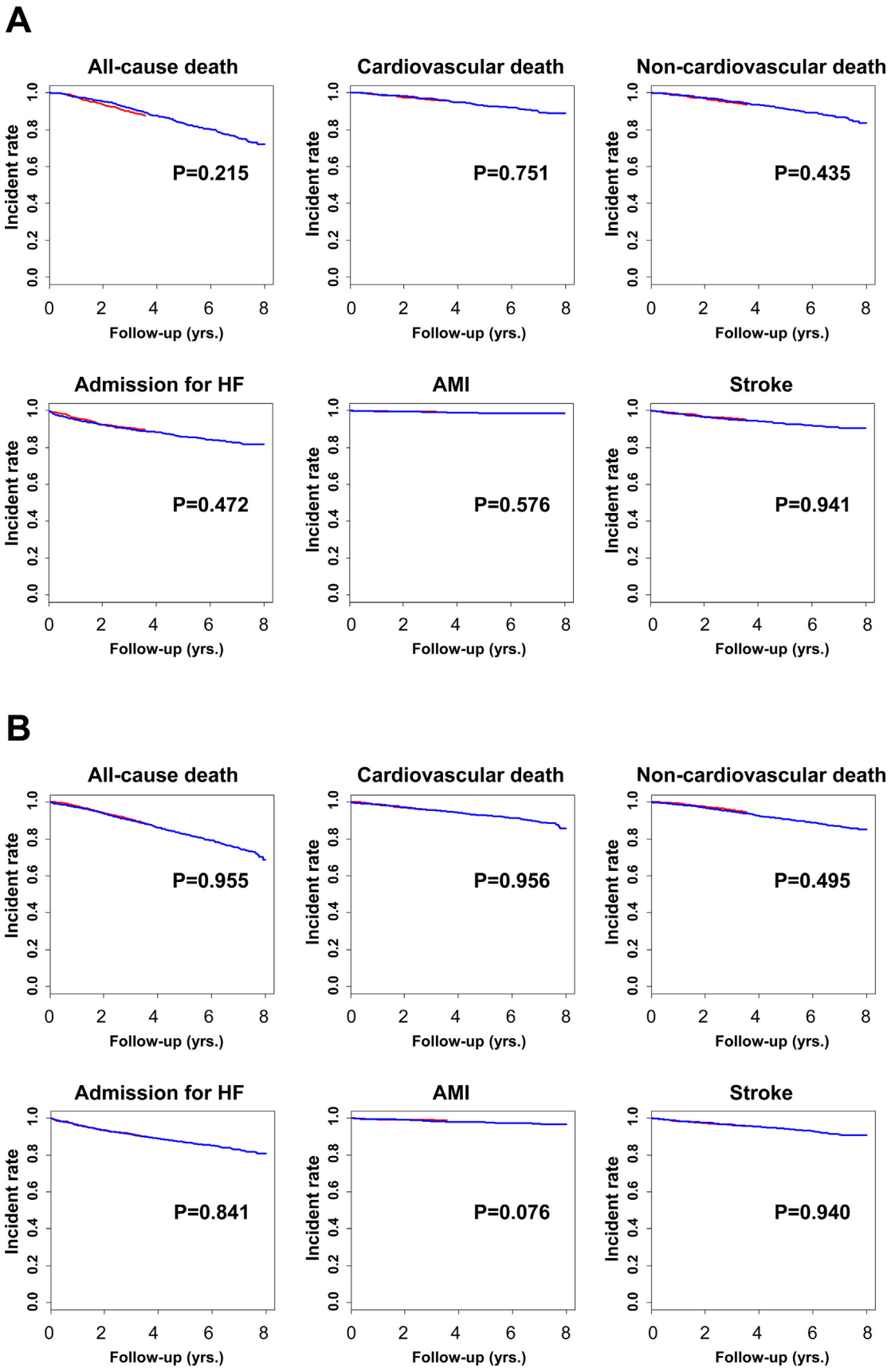

Fig. 4. Incident rates of all-cause death, cardiovascular death, non-cardiovascular death, admission for heart failure (HF), acute myocardial infarction (AMI) and stroke in the Great East Japan Earthquake (GEJE) in Group A (A) and Group B (B). Blue line, Kaplan–Meier curve with the matched data from the baseline; red line, Kaplan–Meier curve with the matched data from GEJE.

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Table 3A
All-cause death in the multivariate Cox proportional hazard model (Group A).

Characteristics	Baseline			Post-GEJE		
	Baseline HR	95% CI	*p*-Value	Post-GEJE HR	95% CI	*p*-Value
Age, years	1.04	1.01–1.08	0.015	1.04	1.01–1.08	<0.001
Height, cm	0.98	0.94–1.03	0.361	1.02	0.97–1.07	0.399
Body weight, kg	1.00	0.97–1.03	0.903	0.93	0.90–0.97	<0.001
Heart rate, bpm	1.02	1.00–1.03	0.051	1.00	0.98–1.02	0.821
Log BNP, log(pg/ml)	1.31	1.04–1.64	0.022	1.33	1.01–1.74	0.042
Hemoglobin, g/dl	0.83	0.72–0.96	0.014	0.89	0.77–1.03	0.127
LVEF, %	0.99	0.97–1.01	0.369	0.98	0.96–1.00	0.045
Admission for HF	2.15	1.25–3.71	0.006	1.75	0.92–3.33	0.087
Diabetes mellitus	1.21	0.74–1.96	0.446	1.67	0.96–2.89	0.068
Malignant disease	1.45	0.83–2.54	0.195	1.68	0.90–3.13	0.106
Stroke	1.51	0.89–2.57	0.129	1.60	0.87–2.95	0.129
Beta-blockers	0.60	0.35–1.03	0.062	0.67	0.37–1.20	0.181
Female sex	0.31	0.13–0.70	0.005	0.31	0.14–0.73	0.007
Hypertensive heart disease	0.93	0.70–1.23	0.606	0.26	0.06–1.08	0.063

BNP, brain natriuretic peptide; GEJE, the Great East Japan Earthquake; HF, heart failure; LVEF, left ventricular ejection fraction.

Table 3B
All-cause death in the multivariate Cox proportional hazard model (Group B).

Characteristics	Baseline			Post-GEJE		
	Baseline HR	95% CI	*p*-Value	Post-GEJE HR	95% CI	*p*-Value
Age, years	1.06	1.03–1.09	<0.001	1.02	0.99–1.05	0.129
Height, cm	1.04	1.01–1.07	0.010	1.05	1.02–1.09	0.002
Body weight, kg	0.97	0.95–0.99	0.008	0.98	0.95–1.01	0.132
Systolic BP, mmHg	0.99	0.98–1.00	0.057	1.00	0.99–1.02	0.731
Heart rate, bpm	1.02	1.00–1.03	0.018	1.02	1.00–1.03	0.026
Log BNP, log(pg/ml)	1.57	1.28–1.91	<0.001	2.08	1.62–2.68	<0.001
Creatinine, mg/dl	1.15	1.01–1.31	0.041	0.96	0.77–1.19	0.699
Hemoglobin, g/dl	0.83	0.74–0.92	<0.001	0.87	0.75–1.01	0.063
Admission for HF	1.58	1.03–2.44	0.038	2.03	1.21–3.43	0.008
Malignant disease	1.71	1.17–2.52	0.006	2.89	1.67–4.99	<0.001
Beta-blockers	0.57	0.39–0.84	0.005	0.88	0.53–1.47	0.633
Stroke	1.34	0.91–1.99	0.144	1.72	1.01–2.95	0.046
Loop diuretics	1.14	0.75–1.74	0.547	1.37	0.82–2.31	0.233

BNP, brain natriuretic peptide; BP, blood pressure; GEJE, the Great East Japan Earthquake; HF, heart failure; LVEF, left ventricular ejection fraction.

(PTSD) was frequent (14.6%) in CVD patients 6 months after the GEJE and had an adverse prognostic impact thereafter [23]. In this analysis, PTSD was significantly associated with female sex, tsunami experience, property loss, poverty, and insomnia medication use [23]. However, in the present study, it was difficult to assess the direct impacts of PTSD on the incidence of deaths or CV events due to the lack of precise information. In addition, there is a possibility that PTSD was just more frequently observed in patients with increased disease severity requiring insomnia medication use, warranting a need to address the actual cause–effect relationship between PTSD and poor prognosis. Thus, it remains to be examined whether other prognostic factors (e.g. PTSD) that were not addressed in the present study have any long-term impacts in the GEJE.

Study limitations

Several limitations should be mentioned for the present study. First, the GEJE delayed confirmation of data accuracy and reliability for the annual measurements of the covariates in the CHART-2 Study, resulting in the limited number of patients with available data after the GEJE as of September 30, 2014. Thus, further confirmation study with more available data should be done in the near future. Second, since the follow-up period of the primary and secondary endpoints was terminated on September 30, 2014 in the present study, it is difficult to analyze the data for longer-term survival. This point also remains to be addressed in future studies.

Conclusions

In the present study, we were able to demonstrate that the GEJE had no significant long-term prognostic impact after the earthquake in CVD patients in the disaster area.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2016.10.018.

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