地図と震度6以上、津波被害があった病院を除いた地図を作成し、平時と震災時の受け入れ外来患者数の差を算出した。

（倫理面への配慮）

本研究は、連結不可能匿名化された情報の二次利用であり、個人を特定する情報は含まれない。本研究は、国立循環器病研究センターの倫理委員会で承認された。

C. 研究結果

1) 死亡票に基づく循環器疾患死亡に関する分析

分析に用いた死亡票数を表1に示す。2008年~2012年における岩手県、宮城県、福島県の総死亡者数は320,348件であった。震災のあった2011年と他の年を比べると3県とも死亡者数は増加しており、特に宮城県では死亡者数の増加が大きかった（表1）。

月ごとの心筋梗塞による死亡率を図1に、脳卒中死亡率を図2に示す。いずれの年も冬に多く、夏に少ない傾向がみられるため、2011年の震災後4ヶ月までの各月の心筋梗塞・脳卒中死亡を過去3年の同月と比較した（表2）。心筋梗塞死亡は、震災後1ヶ月間において過去3年と比べて有意に増えていた（incident rate ratio [IRR]=1.39, 95% confidence interval [95%CI], 1.13 - 1.58）。脳卒中による死亡も同様に、震災後1ヶ月間の死亡は過去3年と比べて有意に増加していた（IRR=1.42, 95%CI, 1.29 - 1.57）。脳卒中による死亡増加は、震災後2ヶ月まで遷延していた。

2) 心筋梗塞と脳卒中死亡増加の地域集積性の検討

心筋梗塞と脳卒中の死亡増加の地域集積性の検定の結果を図3、図4に示す。2008年～2010年に比べて、2011年で心筋梗塞の死亡増加は、福島県の白河市から浅川町の地域で疾患集積性がみられた。一方、脳卒中による死亡の増加は、津波被害が大きかった大船渡市と陸前高田市で疾患集積性がみられた。また、白石市から相馬市にかけての内陸部でも集積性がみられた。

3) 心筋梗塞・脳卒中による死亡増加と関連する要因の探索的検討

震度や津波、放射線量と心筋梗塞・脳卒中による死亡増加の探索的な検討には、それぞれの被害地域にて層別したポワソン回帰分析を行った。その結果、震度は心筋梗塞、脳卒中とも震度が6以上の地域で死亡増加が大きかった。一方、津波に関しては、浸水がある地域では特に脳卒中による死亡が増加していた。放射線量については、1.0mSv以上での心筋梗塞、脳卒中による死亡増加はみられなかった（表4）。

被災による医療パワーへの影響をみるために作成した地図を図5に示す。平時受け入れ外来患者数の分布（a）と震災時に受け入れ可能と推定される外来患者数の分布（b）の差が被災により医療パワーが低下したと推定される地域（c）である。赤で表された地域が被災による医療パワーにもっとも影響があった地域であり、宮城県の栗原市と福島県のいわき市が大きな影響があったと推定された。

D. 考察

本研究は東日本大震災による循環器疾患への影響を、人口動態調査死亡票、医療施設調査、被害の情報（震度、津波、放射線量）、医療施設調査を用いて検討した。

震災後1ヶ月間の心筋梗塞、脳卒中による死亡は、過去3年の同時期に比べて有意に増加していた。大規模な震災の後に、心筋梗塞、脳卒中などの循環器疾患が増加することは国内外で報告されている。本調査では震災直後に心筋梗塞による死亡が短期間増加し、その後減少していた。これは、東日本大震災での宮城県の救急搬送データを用いて調査された循環器疾患発生と同じ傾向であった。阪神淡路大震災では8週間の間、心筋梗塞による死亡が増加していることが報告されている。今回の解析は、阪神淡路大震災で報告された研究に比べて、より大規模であること、被害状況は両者でことなることなどが関連している可能性がある。一方、震災後の脳卒中の死亡について経時的に記述した報告はなく、新たな知見であった。

震災後の心筋梗塞・脳卒中死亡増加の疾患集積性の検定では、心筋梗塞と脳卒中で集積した地域に違いが見られた。脳卒中に関しては、津波被害があった地域で死亡増加の集積性がみられた。津波の浸水地域で層別したポワソン回帰分析の結果においても、心筋梗塞死亡の増加よりも脳卒中死亡の増加が大きい結果が得られており、津波被害においては心筋梗塞よりも脳卒中に影響が大きい可能性がある。

医療パワーの検討において、被災による影響が大きいと推定された地域において、震災による心筋梗塞・脳卒中死亡の増加はみられなかった。日本は阪神淡路大震災後に、災害急性期に活動できる機動性を持ち、トレーニングを受けた医療チームである DMAT が発足されていることや、多くの医療ボランティアが入っていたことが、病院の被災による心筋梗塞・脳卒中死亡への影響を防いだ可能性がある。しかしながら、今回の研究ではそれについて検証することはできなかった。

本研究は、既存のデータベースを用いて震災の影響を推定しているため、いくつかの限界がある。第一に、循環器疾患による死亡の把握に、人口動態調査死亡票を用いていることである。死亡票は、該当者の住民票がある市町村の保健所にて作成されるため、実際には転居していても住民票が移されていなければ、住民票に記載されている市区町村における死亡として集計される。そのため、震災後の一時的な避難による移動、その後の原発避難者特例法などによる住民票を異動しない避難者などの数が正確に把握できない。一方、死亡票を用いて津波被害による直接の死亡を除く住民の数を分母とした場合の死亡割合が推定できるという利点がある。第二に震災による医療パワーへの影響に関する分析では、被災の影響があった病院を震度と津波より推定したが、実際の被災状況は調査できていない。

上記のような限界はあるものの東日本大震災後の循環器疾患に関する情報を収

集し実態を把握したことは、今後の災害対策を考える上で貴重な資料となると考える。

E. 結論

心筋梗塞による死亡は東日本大震災後1ヶ月間、脳卒中死亡は震災後2ヶ月間まで増加がみられた。

震災後の心筋梗塞と脳卒中死亡増加には疾患集積性がみられた。震度は心筋梗塞死亡、津波被害は脳卒中死亡と関連している可能性が示唆された。また、被災による医療パワーの低下は心筋梗塞、脳卒中死亡に影響は与えていない可能性が示された。

F. 研究発表

1. 論文発表

   特になし

2. 学会発表

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G. 知的財産権の出願・登録状況

（予定を含む.）

1. 特許取得

   特になし

2. 実用新案登録

   特になし

3. その他

   特になし

表 1　人口動態調査死亡票 2008 年から 2012 年の 3 県の死亡者数

	被災地 3 県			
年	岩手県	宮城県	福島県	合計
2008	15,042	20,722	21,617	57,381
2009	15,434	20,873	21,602	57,909
2010	15,784	21,984	22,804	60,572
2011	**22,362**	**34,052**	**26,150**	**82,564**
2012	16,168	22,287	23,467	61,922

表 2　東日本大震災後 4 ヶ月の心筋梗塞と脳卒中の死亡増加

	心筋梗塞			脳卒中		
	IRR	95%CI	*p* value	IRR	95%CI	*p* value
Mar 11 - Apr 10	**1.34**	**(1.13 - 1.58)**	**0.001**	**1.42**	**(1.29 - 1.57)**	**<0.001**
Apr 11 - May 10	0.96	(0.78 -1.14)	0.521	**1.14**	**(1.03 - 1.27)**	**0.014**
May 11 - Jun 10	0.88	(0.72 - 1.07)	0.194	1.07	(0.96 - 1.20)	0.236
Jun 11 - Jul 10	0.95	(0.77 - 1.18)	0.640	1.03	(0.92 - 1.16)	0.576

・過去 3 年間の同月の心筋梗塞および脳卒中の死亡数を reference とした Poisson 回帰分析

・IRR: Incident rate ratio, 95%CI: 95% confidential interval

表 3　被害別の東日本大震災後 1 ヶ月の心筋梗塞、脳卒中死亡

		心筋梗塞			脳卒中		
		IRR	95%CI	*p* value	IRR	95%CI	*p* value
震度	6 未満	1.3	(1.1-1.5)	0.008	1.4	(1.2-1.5)	<0.001
	6 以上	1.6	(1.1-2.4)	0.014	1.7	(1.4-2.1)	<0.001
津波	浸水なし	1.3	(1.1-1.6)	0.010	1.2	(1.1-1.4)	0.004
	浸水あり	1.4	(1.1-1.8)	0.021	1.8	(1.6-2.2)	<0.001
放射線	1.0 未満	1.3	(1.1-1.6)	0.001	1.4	(1.3-1.6)	<0.001
	1.0 以上	1.3	(0.9-2.0)	0.206	1.3	(0.8-1.8)	0.183

・過去 3 年間の同月の心筋梗塞および脳卒中の死亡数を reference とした Poisson 回帰分析

・IRR: Incident rate ratio, 95%CI: 95% confidential interval

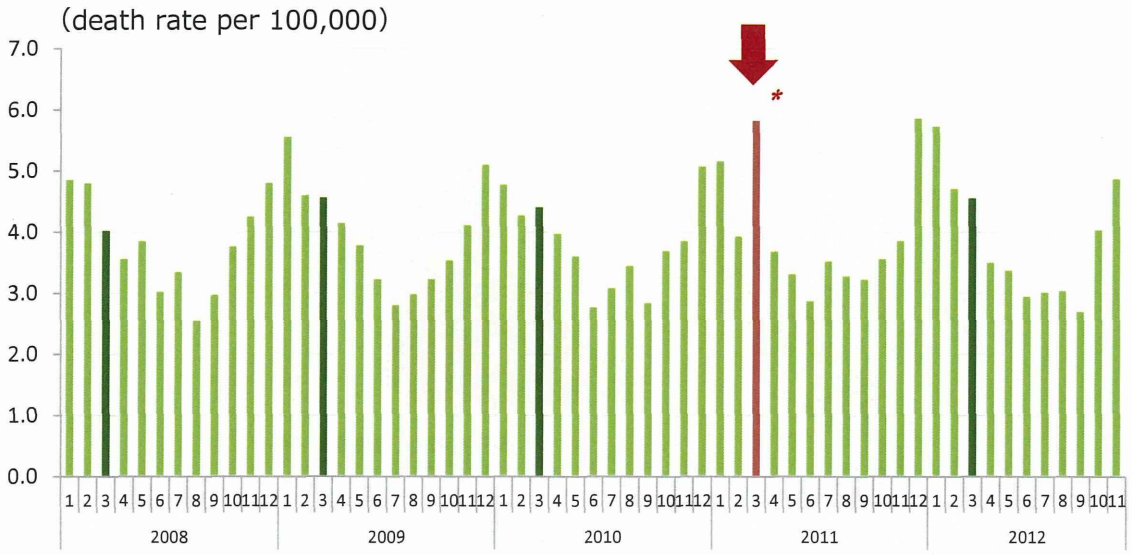

図 1　岩手、宮城、福島県の心筋梗塞による月別死亡数

・過去 3 年間の同月の心筋梗塞および脳卒中の死亡数を reference とした Poisson 回帰分析

・* p=0.001

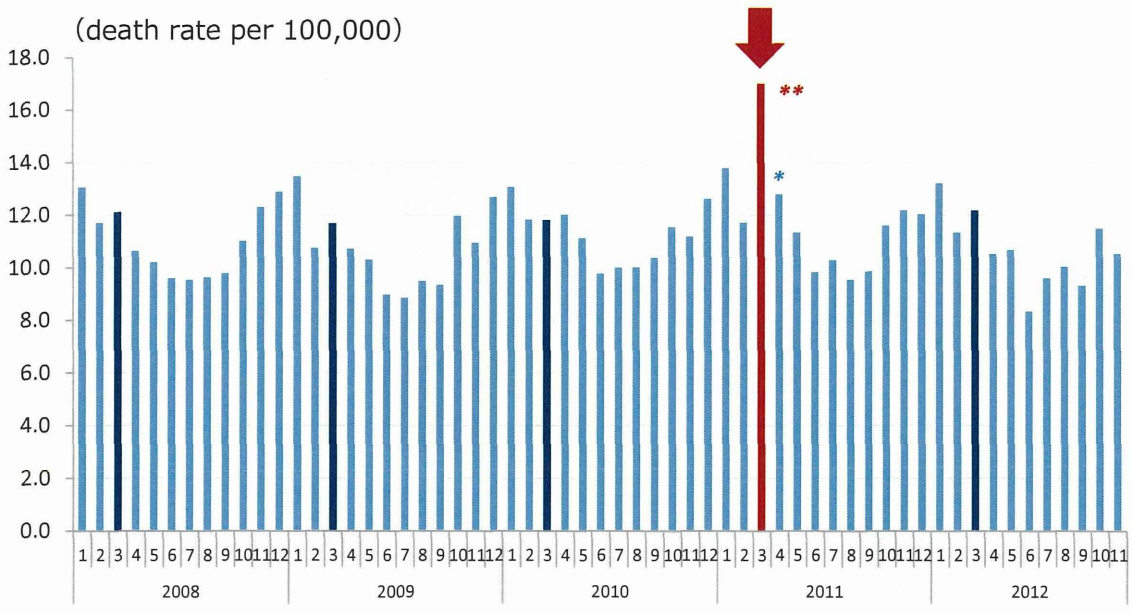

図 2　岩手、宮城、福島県の脳卒中（脳梗塞、脳出血）による月別死亡数

・過去 3 年間の同月の心筋梗塞および脳卒中の死亡数を reference とした Poisson 回帰分析

・** p<0.001, * p=0.014

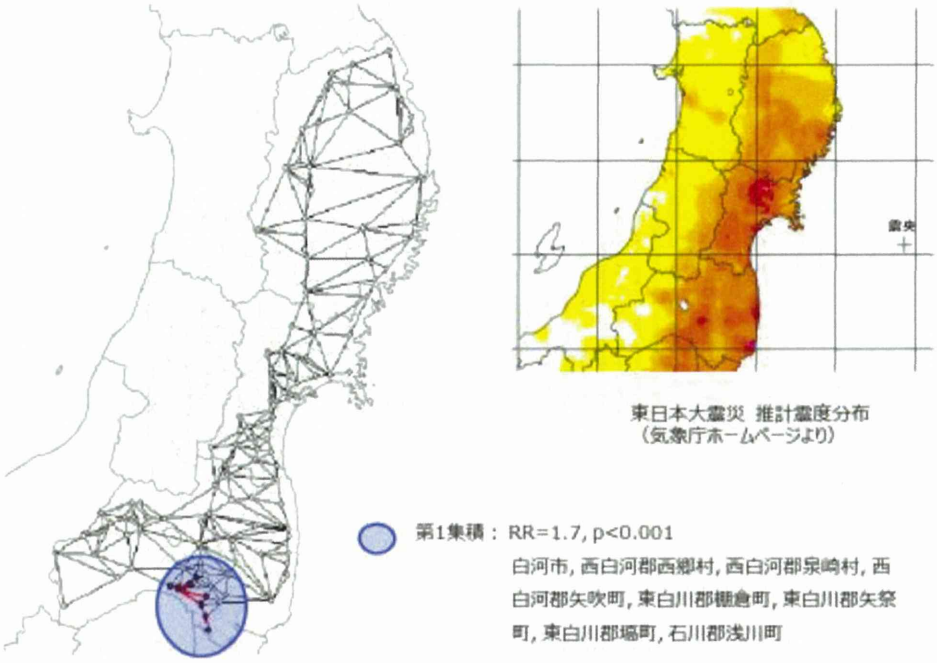

図 3　地域の疾患集積性の検定：震災後 1 年間の心筋梗塞死亡増加

・RR: Relative risk

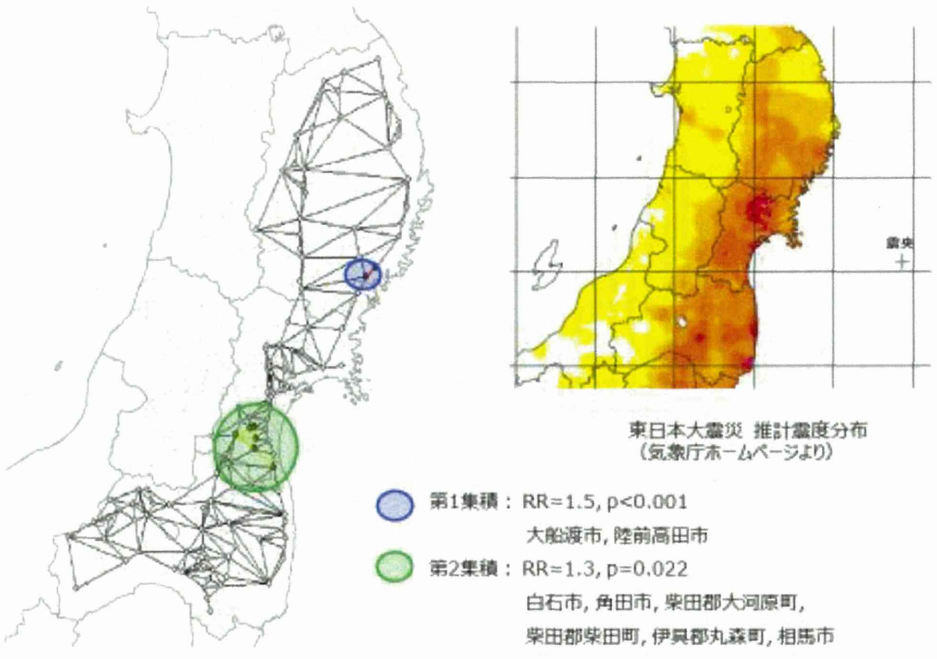

図 4　地域の疾患集積性の検定：震災後 1 年間の脳卒中死亡増加

・RR: Relative risk

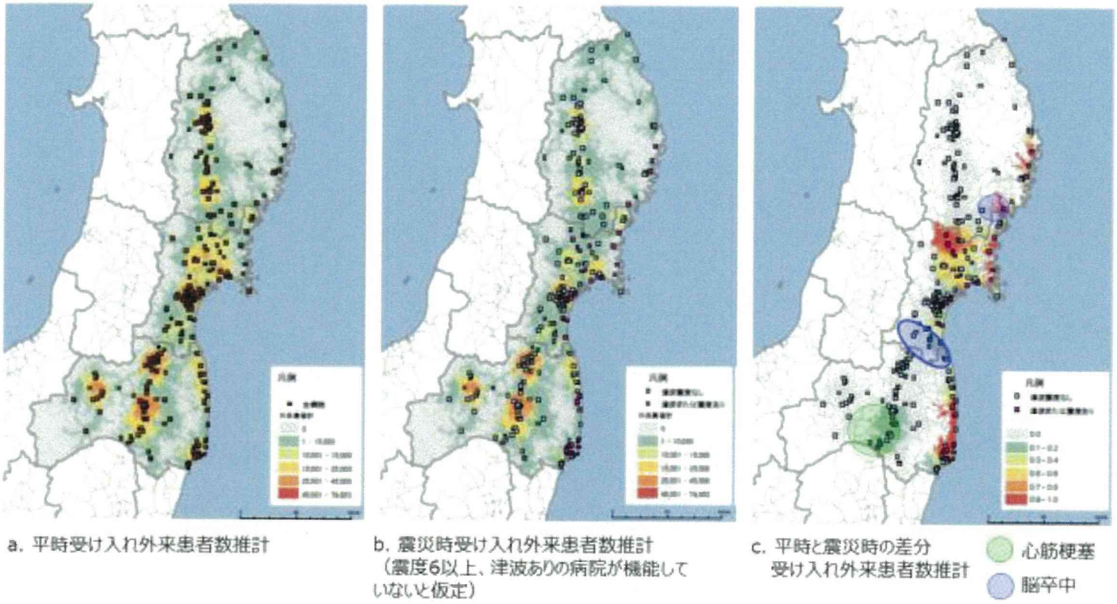

図５　被災による医療パワーへの影響

・C の地図上にある円で囲まれた地域は、心筋梗塞・脳卒中による死亡増加に集積がみられた地域を表す

厚生労働科学研究費補助金（循環器疾患・糖尿病等生活習慣病対策総合研究事業
（循環器疾患・糖尿病等生活習慣病対策実用化研究事業））
分担研究報告書

大規模災害における循環器病診療の体制と手法の確立に関する多施設共同研究
（Ｈ２６－循環器等（生習）－一般－009）

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研究分担者　小川　久雄　国立循環器病研究センター　副院長

研究要旨：今後、南海トラフ大地震や東京直下型地震の発生が予想されていることから、災害時循環器疾患への対策としてチェックリストを作成し、災害(非)拠点病院での実態調査を行った。

A．研究目的

災害時循環器疾患への対策としてチェックリストを作成し、災害(非)拠点病院での実態調査を行うこと。

B．研究方法

チェックリスト作成に際しては平成24年度厚生労働科学研究「東日本大震災における疾病構造と死因に関する研究」報報告書「BCP(business continuity plan)の考え方に基づいた病院災害対応計画作作成の手引き」、「災害時循環器疾患の管理・予防に関するガイドライン」（日本循環器学会・日本心臓病学会・日本高血圧学会合同作成）を参考にした。（倫理面への配慮）臨床研究に関する倫理指針を遵守する。

C．研究結果

災害時循環器疾患チェックリストに関するアンケート調査を平成26年12月に36施設（災害拠点病院：23施設，64%）を対象に実施した。調査内容16項目 102チェックリストについて全体の達成率は61％であった。内訳は　体制・整備関連68%、環境整備関連60%、訓練関連75%、患者教育関連21%であった。病院タイプ別では東北地方；拠点69% vs 非拠点51%、近畿地方；拠点59% vs 非拠点63% であった。

D．考察

今回のアンケート調査対象は東北地方と近畿地方の施設に限定されていることに関連している可能性はあるが、阪神淡路大震災と東日本大震災の経験から、この地域の対策が進んでいるものと思われた。

E．結論

災害時循環器疾患チェックリストに関するアンケート調査を実施することにより、現状を把握することができた。災害拠点施設と非災害拠点施設との違いや地域差等を検証しより有効な対策を今後講じていく必要がある。

F．研究発表

1.　論文発表

なし

2.　学会発表

なし

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Ⅲ.研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

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Ⅳ.研究成果の刊行物・別刷

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

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 –

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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* 20■■; ■■: ■■■■–■■■■)

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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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}·1.73 m^{-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.

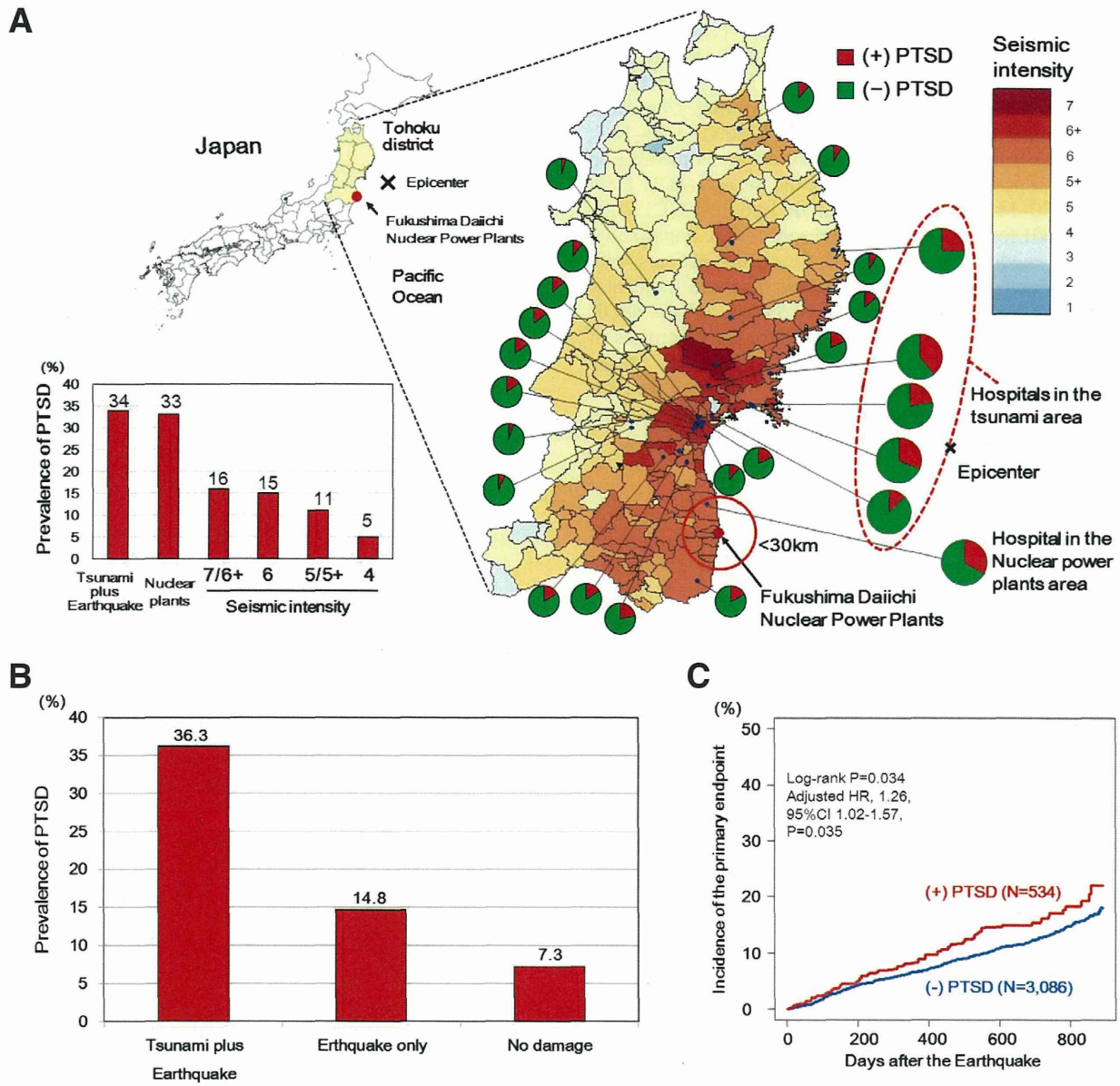

Figure. (**A**) Location of the epicenter of the Great East Japan Earthquake, the Fukushima-Daiichi nuclear power plants, and the study sites, and the proportions of patients with post-traumatic stress disorder (PTSD). (**B**) The questionnaire-based prevalence of PTSD in patients who experienced the 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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CLINICAL PAPER

Heart failure/cardiomyopathy

Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial

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We examined whether an additive treatment with an angiotensin receptor blocker, olmesartan, reduces the mortality and morbidity in hypertensive patients with chronic heart failure (CHF) treated with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, or both. In this prospective, randomized, open-label, blinded endpoint study, a total of 1147 hypertensive patients with symptomatic CHF (mean age 66 years, 75% male) were randomized to the addition of olmesartan ($n = 578$) to baseline therapy vs. control ($n = 569$). The primary endpoint was a composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospitalization for worsening heart failure. During a median follow-up of 4.4 years, the primary endpoint occurred in 192 patients (33.2%) in the olmesartan group and in 166 patients (29.2%) in the control group [hazard ratio (HR) 1.18; 95% confidence interval (CI), 0.96–1.46, $P = 0.112$], while renal dysfunction developed more frequently in the olmesartan group (16.8 vs. 10.7%, HR 1.64; 95% CI 1.19–2.26, $P = 0.003$). Subgroup analysis revealed that addition of olmesartan to combination of ACE inhibitors and β-blockers was associated with increased incidence of the primary endpoint (38.1 vs. 28.2%, HR 1.47; 95%

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CI 1.11–1.95, $P = 0.006$), all-cause death (19.4 vs. 13.5%, HR 1.50; 95% CI 1.01–2.23, $P = 0.046$), and renal dysfunction (21.1 vs. 12.5%, HR 1.85; 95% CI 1.24–2.76, $P = 0.003$). Additive use of olmesartan did not improve clinical outcomes but worsened renal function in hypertensive CHF patients treated with evidence-based medications. Particularly, the triple combination therapy with olmesartan, ACE inhibitors and β-blockers was associated with increased adverse cardiac events. This study is registered at clinicaltrials.gov-NCT00417222.

Keywords Heart failure • Hypertension • Angiotensin II receptor blocker • Olmesartan

Introduction

In patients with heart failure (HF) with reduced ejection fraction (EF) (HFrEF), inhibition of renin–angiotensin system (RAS) by angiotensin-converting enzyme (ACE) inhibitors is generally recommended to improve mortality and morbidity in the clinical guidelines.[1,2] Angiotensin receptor blockers (ARBs) are considered as reasonable alternatives of ACE inhibitors since they improve outcomes in patients with HFrEF and intolerance of ACE inhibitors.[3] However, it is still controversial whether the additive use of ARBs to evidence-based medications is beneficial in patients with HFrEF, particularly in the subset of those who have a history of hypertension.[4–6] Furthermore, unlike in HFrEF patients, beneficial impacts of RAS inhibitors (ACE inhibitors or ARBs) or β-blockers have not been shown in the randomized clinical trials in patients with HF with preserved EF (HFpEF),[7–10] and thus neither RAS inhibitors nor β-blockers are recommended for the treatment of HFpEF in the clinical guidelines.[1,2] In case of hypertensive patients with HFpEF, however, RAS inhibitors and/or β-blockers could be used as anti-hypertensive medication,[1,2] but the supplemental benefit of ARBs in combination with anti-hypertensive medications has not been examined.

These lines of evidence suggest a need to elucidate whether additive use of ARB is beneficial or not in the general practice of hypertensive chronic heart failure (CHF) patients treated with ACE inhibitors and/or β-blockers. In the supplemental benefit of ARB in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial, we thus aimed to examine whether a supplemental use of olmesartan provides beneficial impacts in patients with a broad spectrum of HF, who are treated with conventional therapies, namely with ACE inhibitors and/or β-blockers.[11]

Methods

Study design

The SUPPORT trial was a prospective, randomized, open-label blinded endpoint study,[11] which was conducted according to the ethical principles described in Declaration of Helsinki. The study protocol was approved by the institutional ethics committees of the 17 participating institutions in the Tohoku District of Japan (Appendix). The primary objective of the study was to examine whether an additive treatment with an ARB, olmesartan, reduces the mortality and morbidity of hypertensive patients with stable CHF (NCT00417222). The inclusion criteria were designed to enroll hypertensive patients aged 20–79 with symptomatic CHF but in stable condition and were treated with ACE inhibitors and/or β-blockers, while the exclusion criteria were designed to exclude patients with substantive confounding medical conditions or an inability to meaningfully participate in the SUPPORT trial (*Table 1*). Finally, a total of 1147 symptomatic CHF patients with a history of hypertension who met the inclusion and exclusion criteria and gave written informed consent for the trial were assigned to either the olmesartan or the control group according to a 1:1 ratio of olmesartan to control, through stratification by participating institute, sex and age between October 2006 and March 2010. The patients were followed up until the study ended on 31 March 2013 (*Figure 1*). If contact could not be made at the end of the study, data of these patients were censored at the date when they were known to be alive last. Olmesartan was initiated at a dose of 5–10 mg/day, and then up titrated to 40 mg/day, if tolerable, in the olmesartan group, while no ARB use was allowed in the control group. The diagnosis of HF was made based on the criteria of the Framingham study[12] by an attending physician at each hospital. All physicians were encouraged to control blood pressure of the patients in each group according to the recommendations in the JNC7.[13] The primary endpoint was the composite of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and worsening HF requiring hospitalization, while secondary endpoints consisted of the modes of death, hospitalization for cardiovascular reasons, surrogate markers for HF and development of cardiovascular disease, atrial fibrillation, diabetes, and renal dysfunction (see Supplementary material online, *Table S1*).

Table 1 Inclusion and exclusion criteria

Inclusion criteria
• NYHA Classes II to IV CHF
• History of hypertension or treated with anti-hypertensive medications
• Aged 20 or older and <80 years at the entry
• Stable with angiotensin-converting enzyme inhibitors and/or β-blockers
• Not treated with angiotensin II receptor blockers
Exclusion criteria
• Patients who have renal dysfunction (serum creatinine ≥3.0 mg/dL) or those who are under chronic haemodialysis
• Drug hypersensitivity to olmesartan
• Severe liver dysfunction
• History of angioedema
• History of malignant tumour or life-threatening illness of poor prognosis
• Pregnant or possibly pregnant patients
• Cardiovascular surgery within 6 months prior to the date of the entry
• Acute myocardial infarction within 6 months prior to the date of the entry
• Percutaneous coronary intervention with or without stent implantation within 6 months prior to the date of the entry.

Other patients deemed unsuitable as subjects of the study by physician in charge.

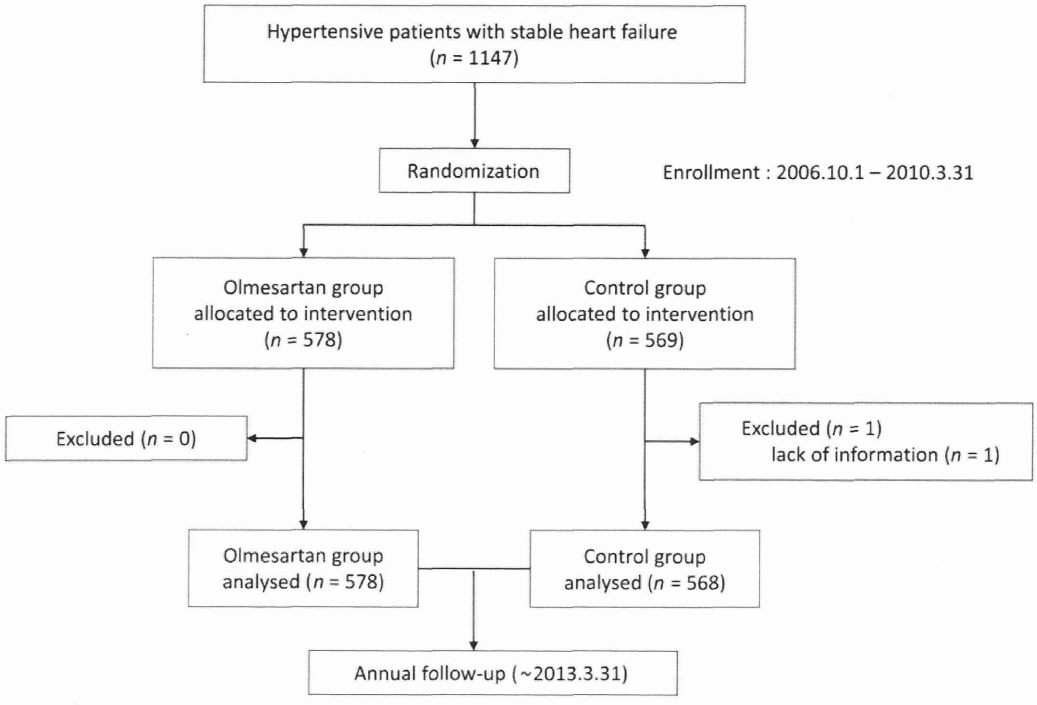

Figure 1 Trial profile.

Interim analysis and data monitoring

Meetings of the Data Safety Monitoring Board, which is independent of the study committees, were held twice a year throughout the trial period to monitor the study safety until the end of the trial. Interim analyses were conducted at the end of and 2 years after the end of the registration period, namely March 2010 and September 2011, to evaluate the primary endpoint and the safety for the continuation of the trial.

Statistical analysis

All analyses were performed according to a predefined statistical analysis plan. Y.S., S.M., and H.S. had a full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. The primary and secondary endpoints were analysed based on the time to the first occurrence, according to the intention-to-treat principle, including all patients of lost to follow-up censored at the day of the last contact. Survival curves were estimated using the Kaplan–Meier procedure and compared with a two-sided log-rank test. Based on the results of the CHART-1 Study,[14,15] we assumed that the annual incidence of the primary composite endpoint would be ~12% in the SUPPORT trial and thus 480 patients would be required on the condition of 3-year follow-up for each arm to provide 80% power to detect 30% risk reduction by olmesartan, using a two-sided significance level of 0.05 by the log-rank test.[11] Considering that ~15% of cases would be lost during follow-up or unsuitable for analysis, we estimated that >565 patients in each group (control and olmesartan) would be needed to complete the trial.

The *P*-value of the interim analysis was 0.005 while the *P*-value of the final analysis was 0.048. The effects of olmesartan were examined using Cox proportional hazards models. Subgroup analyses were performed according to baseline medication and other baseline characteristics and clinical parameters. Continuous variables are presented as means ± standard deviations except brain natriuretic peptide (BNP). Brain natriuretic peptide levels are presented as medians and interquartile ranges. Categorical variables were presented as numerals and percentages. Group comparisons were made with the Mann–Whitney test for continuous variables, and the χ^2-test without continuity correction for categorical variables. All statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM, Somers, NY, USA) and R 3.0.2 (R Foundation for Statistical Computing, Vienna. http://www.R-project.org/). A two-sided probability values of <0.05 and *P*-values for interaction <0.1 were considered to be statistically significant.

Results

Patient characteristics

Baseline characteristics were comparable between the olmesartan and the control groups (*Table 2*). The mean age was 66 and 75% of the patients were male. Functional class of HF was in NYHA Class II in 93% and Class III in 7%, and underlying heart disease included ischaemic heart disease in 48% and dilated cardiomyopathy in 21%. Mean systolic/diastolic blood pressure was 128/74 mmHg, and mean left ventricular ejection fraction (LVEF) was 54%. At the time of randomization, ACE inhibitors and β-blockers were prescribed in 81 and 72% of the patients, respectively.

Drug adherence and blood pressure

At the time of randomization, systolic/diastolic blood pressure was 128.7/74.8 ± 18.2/12.2 and 127.1/73.8 ± 18.1/11.7 mmHg in the