Clinical Characteristics and Long-Term Prognosis of Vasospastic Angina Patients Who Survived Out-of-Hospital Cardiac Arrest: Multicenter Registry Study of the Japanese Coronary Spasm Association

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Abstract:

Background- Coronary artery spasm plays an important role in the pathogenesis of ischemic heart disease; however, its role in sudden cardiac death remains to be fully elucidated. We examined the clinical characteristics and outcomes of patients with vasospastic angina (VSA) in our nationwide multicenter registry by the Japanese Coronary Spasm Association.

Methods and Results- Between September 2007 and December 2008, 1,429 patients with VSA (M/F, 1,090/339: median 66 years) were identified. They were characterized by a high prevalence of smoking and included 35 patients who survived out-of-hospital cardiac arrest (OHCA). The OHCA survivors, as compared with the remaining 1,394 non-OHCA patients, were characterized by younger age (median 58 vs. 66 years, P<0.001) and higher incidence of left anterior descending coronary artery spasm (72 vs. 53%, P<0.05). In the OHCA survivors, 14 patients underwent implantable cardioverter defibrillator (ICD) implantation while intensively treated with calcium channel blockers. Survival rate free from major adverse cardiac events (MACE) was significantly lower in the OHCA survivors compared with the non-OHCA patients (72 vs. 92% at 5 years, P<0.001), including appropriate ICD shocks for ventricular fibrillation in 2 patients. Multivariable analysis revealed that OHCA event was significantly correlated with MACE (hazard ratio, 3.25; 95% confidence interval, 1.39 to 7.61; P<0.01).

Conclusions- These results from the largest VSA cohort indicate that vasospasm patients who survived OHCA are high risk population. Further studies are needed to determine whether ICD therapy improves the patients' prognosis.

Key words; acetylcholine; angina; arrhythmia; prognosis; vasospasm

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem. Its estimated number is 300,000 to 400,000 per year in the United States.[1] A prospective study showed an incidence of 53/100,000 per year, with 25% of victims being younger than 65 years.[2] Causes of OHCA are strongly associated with coronary artery disease as evidenced at autopsy and the survival rate from OHCA still remains to be substantially improved.[1] Importantly, a significant number of OHCA cases remained unexplained if victims have no structural abnormalities (e.g. organic coronary stenosis) in the post-mortem analysis.[3] This finding strongly suggests that functional abnormalities of the coronary artery are also involved in the pathogenesis of OHCA.[4]

Recently, the prevalence of early access to emergency medical service, early bystander cardiopulmonary resuscitation and early defibrillation has been increasing with a resultant improvement of the survival rate from OHCA.[5-7] The progress of the chain of survival now opens the window to elucidate the underlying mechanisms of patients who survived OHCA. Coronary artery spasm plays an important role in the pathogenesis of a wide variety of ischemic heart disease, including sudden cardiac death, and thus could be one of the most important functional abnormalities of the coronary artery.[8-9, 10] However, little is known about the clinical characteristics including gender difference and long-term prognosis of patients with vasospastic angina (VSA) who survived OHCA, except for the previous single center studies with a small number of patients.[11, 12]

In the present study, we thus conducted the nationwide multicenter registry study with the large patient number by the Japanese Coronary Spasm Association to elucidate the clinical characteristics and long-term prognosis of VSA patients, especially those who survived OHCA.

Methods

The Japanese Coronary Spasm Association was founded in 2006 and currently 68 institutes participate. The present study was approved by the institutional review boards or ethics committees of all participating institutions.

Study Patients

All VSA patients were referred or admitted to the participating institutes and were originally diagnosed between April 1, 2003 and December 31, 2008. The registration was made between September 1, 2007 and December 31, 2008. In the present study, data collection was conducted in a retrospective fashion for patients seen before September 2007 and in a prospective manner for those seen after that date. The diagnosis of VSA was made based on the Guidelines for Diagnosis and Treatment of Patients with Vasopastic Angina of the Japanese Circulation Society.[13] The definition of VSA included an angina attack at rest and/or on effort, accompanied by a transient ECG ST-segment elevation or depression of more than 0.1 mV or a newly appearance of negative U wave in at least 2 related leads, and/or a total or subtotal coronary artery narrowing during the provocation test of coronary spasm, accompanied by chest pain and/or ischemic ECG changes mentioned above.

Data Collection

The demographic and clinical data were submitted to a central database, including age, gender, coronary risk factors, family history, type of angina episodes, circadian distribution of angina attacks, leads of ST-segment elevation or depression and arrhythmias during spontaneous or provoked angina attack, location of coronary spasm, device therapy such as implantable cardioverter defibrillator (ICD), medical therapy and its adherence. We defined

reduction and discontinuation of medication as having a gap in use of any medication and no use of medication, respectively. Hypertension, dyslipidemia and diabetes mellitus were diagnosed based on the guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society, and Japan Diabetes Society, respectively.[14-16] Significant coronary stenosis was defined as more than 50% of luminal narrowing of major coronary arteries evaluated by coronary angiography. OHCA was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[17]

Endpoints

The primary endpoint was major adverse cardiac events (MACE), including cardiac death, non-fatal myocardial infarction, hospitalization due to unstable angina pectoris and heart failure and appropriate ICD shocks during the follow-up period which began at the date of original VSA diagnosis. The secondary endpoint was all cause mortality. Cardiac death was defined as sudden death (i.e. death occurring unexpectedly without any apparent symptoms or within 1 hour of symptom onset, or non-witnessed death in the absence of any other possible cause) or death associated with acute myocardial infarction. Acute myocardial infarction was defined in patients with prolonged (>30 min) chest pain, associated with ST-segment changes and elevated levels of cardiac enzymes. Unstable angina pectoris was diagnosed if chest discomfort or pain became recurrent or worsening along with ischemic ECG changes. Heart failure was diagnosed if a patient showed signs of exertional dyspnea, orthopnea, rales in more than one-third of the lung fields, elevated jugular venous pressure or pulmonary congestion on chest X-ray related to cardiac dysfunction.

Statistics

Continuous variables are presented as medians and interquartile ranges and categorical

variables as percentages. Group comparisons were performed with Mann-Whitney test for continuous variables, Fisher's exact test for categorical variables and log-rank test for survival curves. Survival free from death and MACE were analyzed by the Kaplan-Meier method. Multivariable analysis of correlated factors of MACE was performed with a Cox proportional hazard model. Variables depicted by univariable analysis to be correlated with MACE and well-known predictive variables were subjected to the forced entry method. The proportional hazards assumption was examined with the log minus log plot. Hazard ratio (HR) and 95% confidence interval (CI) were also calculated. A value of $P<0.05$ was considered to be statistically significant.

Results

Clinical Characteristics of Patients with VSA

Among a total of 1,528 VSA patients registered from 47 institutes, 99 patients were excluded because they did not meet the diagnostic criteria (n=7) or the inclusion criteria (n=92). Finally, 1,429 patients were studied (Supplemental Figure 1). The clinical characteristics of those patients are summarized in Table 1. Among the coronary risk factors, smoking was observed most frequently (~60%), especially in male patients. The prevalence of family history of ischemic heart diseases, previous myocardial infarction and the existence of organic coronary stenosis was relatively low (~10%). When compared with the female patients, the male patients were characterized by younger age, higher incidences of previous myocardial infarction, organic coronary stenosis, angina attack with ST-segment elevation and lower incidence of family history of ischemic heart diseases. In contrast, no sex difference was noted in the prevalence of arrhythmia during spontaneous attacks, including OHCA (Table 1). Among the 1,317 patients in whom ECG was recorded during

spontaneous attack, significant ST-segment elevation and depression was documented in 272 and 121 patients, respectively.

Among the registered patients except 169 patients (12%, not recorded), angina attacks occurred exclusively at rest in 634 patients (44%), whereas it occurred predominantly at rest but was also induced by effort in 513 patients (36%). In 113 patients (8%), angina attacks were induced only by effort. In 658 patients, typical circadian pattern was identified mostly from midnight to early morning as follows; from 0 am to 4 am (n=160), 4 am to 8 am (n=377), 8 am to noon (n=122), noon to 4 pm (n=36), 4 pm to 8 pm (n=40) and 8 pm to 12 pm (n=66).

Provocation test was performed during coronary angiography in 1,244 patients with either acetylcholine (n=713, 57.3%), ergonovine (n=497, 40.0%), both of them (n=23, 1.8%) or others (e.g., hyperventilation) (n=11, 0.9%). The prevalence of arrhythmic events during provocation test (n=85, 6.8%) was similar with that during spontaneous attack (n=107, 7.5%) (Supplemental Table 1).

Medical Treatments

In the present study, 1,331 patients (93%) were treated with CCBs, either CCBs alone (48%) or combination of CCBs, and long-acting nitrates including nicorandil (45%). Most of the patients (n=1162, 81%) were treated with one type of CCB; delayed- or modified-release formulations of first generation of CCBs in 814 and the second and third generation of CCBs with longer plasma half-lives in 348.[18] Anti-platelet agents were used in 669 patients (47%). However, the use of β-blockers was limited to 61 patients (4%) in the present study.

Prognostic Factors of MACE by Multivariate Analysis

During the median follow-up period of 32 months (interquartile range 17 to 46 months), 19 patients (1.3%) died, where 6 patients had cardiac death. MACE occurred in 85 patients

(5.9%), including myocardial infarction (n=9), hospitalization due to unstable angina (n=68) and heart failure (n=4) and appropriate ICD shocks (n=2). Overall 5-year survival rate free from all cause death or MACE was 98% and 91%, respectively (Figure 1). Especially, 5-year survival rate free from non-fatal myocardial infarction was high (99%).

Multivariable analysis demonstrated that in addition to the established prognostic factors (smoking, spontaneous attack with ST-segment elevation, multivessel spasm and significant organic stenosis in major coronary arteries), history of OHCA was significantly correlated with MACE (Table 2). Even when the analysis was limited to the patient without significant coronary stenosis, the survival curve (Supplemental Figure 2) and the correlated factors were unchanged (Supplemental Table 2).

Importantly, the rate of cardiac death and non-fatal myocardial infarction in patients in whom medications were reduced or discontinued (8%, 2 out of 25 patients) was 10-fold higher than that in the patients with continued medications (0.7%, 10 out of 1,404 patients, P=0.017).

VSA Patients Who Survived Out-of-Hospital Cardiac Arrest due to Coronary Artery Spasm

The present study included 35 VSA patients who survived OHCA as their first manifestation of clinical events in 14 institutes, 7 of which had the emergency care department. In these 7 hospitals, coronary artery spasm was documented in 22 patients (6.0%) out of 365 patients resuscitated from OHCA of cardiac origin between April 1, 2003, and December 31, 2008. The OHCA survivors with VSA were characterized by younger age and higher incidence of coronary spasm in the left anterior descending coronary artery as compared with the remaining non-OHCA patients (Table 3). However, the prevalence of significant coronary stenosis was comparable between the 2 groups. Appropriate ICD shocks for VF were

documented in 2 out of the 14 patients with ICD implantation during intensive medical treatment. Sudden cardiac death occurred in one patient without ICD who terminated medication himself before the fatal event. Hospitalization was needed due to non-fatal myocardial infarction (n=1) and unstable angina pectoris (n=3). Despite the comparable incidence of all cause mortality (Figure 2A), event-free survival was significantly lower in the OHCA survivors as compared with the non-OHCA patients (72 vs. 92% at 5 years, P<0.001) (Figure 2B). In subgroup analysis between OHCA survivors who did (n=5) and did not (n=30) have later adverse events, left ventricular ejection fraction and the prevalence of significant coronary stenosis was comparable (Supplemental Table 3).

Discussion

To the best of our knowledge, the present multicenter study with 1,429 patients is the largest cohort of VSA, where the patients were registered based on the standardized criteria by the Japanese Circulation Society.[13] The present study also is characterized by the fact that ~400 VSA cases with documented spontaneous attacks were included, which enhances the scientific level of the study. In the present study, we were able to demonstrate that VSA patients who survived OHCA are particularly high-risk population even in the current era with long-acting CCBs.

VSA Patients Who Survived OHCA as a High-Risk Population

In 2000's, early initiation of cardiopulmonary resuscitation and the widespread use of defibrillation programs have saved many patients with OHCA, making subsequent care of these patients more important than ever.[19] Accumulating evidence indicates that cardiac arrest in the absence of organic heart disease is more common than previously expected.[20]

In the autopsy studies in patients with sudden cardiac death, the prevalence of no significant coronary stenosis was higher in Japanese (26%) than in European populations (4%),[21, 22] indicating the potential importance of functional coronary abnormalities in the pathogenesis of sudden cardiac death in Japanese. In the present study, coronary spasm was documented in 6% of the patients resuscitated from OHCA of cardiac origin. The prevalence of vasospasm in OHCA patients appeared to be doubled in comparison with that (3%) reported in the previous study participating 4 French emergency units.[20] Because the racial differences may affect the diagnostic and therapeutic strategies (e.g. use of the provocation test), the study with Japanese patients should provide important information for better understanding of the pathogenesis of VSA.

In the present study, the incidence of OHCA in VSA patients was 2.4%, which is 50-fold higher than that (0.05%) in the general Japanese population,[23] indicating that VSA patients, especially those who survived OHCA, are high-risk population. As shown in Figure 2B, event-free survival rate in the OHCA survivors was much lower than in the non-OHCA patients. The event of OHCA and worse clinical outcome may not be coincidental but could be explained in part by severe myocardial ischemia due to left anterior descending artery spasm (Table 3).[24]

The multivariable analysis also demonstrated that prior history of OHCA events was a novel and significant correlated factor of MACE in VSA patients (Table 2). While life-threatening arrhythmias may be related to increased disease activity of coronary spasm,[25, 26] a potential involvement of an arrhythmic substrate in association with ventricular repolarization abnormalities has been suggested in the previous study.[27, 28] In patients with variant angina complicated by cardiac arrest, the prevalence of QT dispersion was significantly higher compared with uncomplicated patients.[27] We also have recently reported that OHCA survivors with coronary spasm demonstrated concomitant idiopathic VF,

indicating heterogeneity of the underlying mechanisms.[28]

The association of potentially lethal ischemia-induced ventricular arrhythmias may justify the use of an ICD.[29] Meisel et al. reported both the efficacy and limitation of ICD therapy in patients with refractory variant angina.[12] In their 7 patients with variant angina complicated by VF, appropriate ICD shocks were documented in 4 patients, but one patient died of electromechanical dissociation even under intensive medical treatment with CCBs. However, in the previous studies with a small number of patients (n=6~7), the prognosis was favorable in survivors of cardiac arrest due to coronary spasm who did not receive ICD.[10, 11] It remains to be examined in a future multicenter study whether ICD therapy can improve the prognosis of OHCA survivors with coronary spasm.

Importance of Continued Medical Treatment for VSA

Following withdrawal of CCB, silent myocardial ischemia with fatal arrhythmias[30] and a rebound phenomenon of the spasm[31, 32] could occur. In the present study, Fisher's exact test also demonstrated that the incidence of cardiac death and non-fatal myocardial infarction was significantly increased in patients in whom medications were reduced or discontinued. These findings indicate that medications should not be withdrawn carelessly even if symptomatic attacks seem to be controlled. Although CCBs remain the main stay of the current clinical practice, it has been reported that 6-month CCBs therapy did not completely normalize coronary vasoconstricting responses to acetylcholine despite the absence of symptomatic angina.[33] Even after 1-year CCB therapy, myocardial fatty acid metabolic images assessed using ^{123}I-15-(p-iodophenyl) -3-R,S-methyl pentadecanoic acid have been reported to appear abnormal in VSA patients.[34] These findings suggest that there are also limitations of these classes of drug. Recently, the accumulating evidence demonstrated that small GTPase RhoA and its downstream effector Rho-kinase play a central role by increased

Ca^{2+} sensitivity of vascular smooth muscle cells in the molecular mechanism of coronary vasospasm in animal models and VSA patients.[35] The inhibition of Rho-kinase with fasudil has been reported to result in the disappearance of coronary vasospastic activity[36] and is a novel therapeutic option that could target specific abnormalities with a resultant remission of VSA.

Changing Characteristics of VSA Patients

In association with the epidemics of obesity and metabolic syndrome, the general population has been rapidly growing older and the westernization of lifestyle has been progressing, especially in Japan.[37] Thus, the present nationwide multicenter registry study also focuses on the clinical characteristics and outcomes of VSA patients in the current era of 2000's.

Coronary spasm was most frequently noted in middle-aged male, who otherwise did not exhibit coronary risk factors except for higher prevalence of smoking. In male VSA patients (Table 1), the prevalence of smoking still remains high (~70%). The lower incidence of previous myocardial infarction and of organic coronary disease were comparable with the previous report on the clinical characteristics of Japanese patients as compared with Caucasian patients.[38]

Several prognostic studies with a few hundreds of patients were performed in 1980's. Yasue et al. reported that 5-year survival rate free from death or myocardial infarction was 97% and 83% in 245 patients.[39] In general, as reported in the previous comparative study,[38] the prognosis was much worse in Western population than in Japanese population.[26, 40] In the current era, the clinical outcome of VSA patients appears to be further improved in 2000's as compared with 1980'.[26, 38-40]

Limitations of the Study

Several limitations should be mentioned for the present study. First, the present study is a retrospective observational study and thus the association found in the present study is not necessarily causal. In order to address this important issue, we have recently started prospective studies by our Japanese Coronary Spasm Association. Second, the follow-up period was variable and it is highly possible that many arrhythmic events were missed during the periods of time that the patients were not being monitored. Third, complex composite primary endpoint, including ICD shocks, was used in the present study. Appropriate ICD shocks are not certainly a surrogate for sudden cardiac death. Fourth, management decisions were left to the discretion of each attending physician. Fifth, there is no sufficient information available about the date of reduction or discontinuation of medications and thus this variable was not included in the present Cox proportional hazard model. However, despite these limitations, the present findings should merit emphasis for better understanding of the pathogenesis and the long-term prognosis of VSA in the current era.

Conclusions

The present multicenter study by the Japanese Coronary Spasm Association describes the largest cohort of patients with vasospastic angina and cohort who have survived cardiac arrest. Especially, VSA patients who survived OHCA are a high-risk population and the importance of continued medications should be emphasized.

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Conflict of Interest Disclosures: None.

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Table 1. Demographic Characteristics of VSA Patients

	Overall	Men	Women	P value
No. of patients, n (%)	1,429 (100)	1,090 (76)	339 (24)	< 0.001
Age, median (IQR), y	66 (58, 73)	66 (58, 72)	69 (60, 75)	< 0.001
Coronary risk factor, n (%)				
Hypertension	666 (47)	511 (47)	155 (46)	0.38
Dyslipidemia	647 (45)	481 (44)	166 (49)	0.07
Diabetes mellitus	233 (16)	186 (17)	47 (14)	0.09
Smoking	848 (59)	781 (72)	67 (20)	< 0.001
Family history of IHD, n (%)	168 (12)	118 (11)	50 (15)	0.033
Previous MI, n (%)	91 (6)	81 (7)	10 (3)	0.003
Organic stenosis >50%, n (%)	201 (14)	170 (16)	31 (9)	0.001
ST segment change during spontaneous attack, n (%)				
ST elevation	272 (19)	234 (21)	38 (11)	< 0.001
ST depression	121 (8)	83 (8)	38 (11)	0.027
Arrhythmic event during spontaneous attack, n (%)				
PVC	14 (1)	12 (1)	2 (1)	0.32
VT/VF	17 (1)	14 (2)	3 (1)	0.40
AV block	21 (1)	19 (2)	2 (1)	0.09
Bradycardia / Sinus pause	28 (2)	20 (2)	8 (2)	0.34
Out-of-hospital cardiac arrest †	35 (2)	30 (3)	5 (1)	0.13

† Twenty-six patients (male/female, 23/3 patients) were also complicated by non-fatal VT/VF.
AV, atrioventricular; IHD, ischemic heart disease; IQR, interquartile range; MI, myocardial infarction; PVC, premature ventricular contraction; VF, ventricular fibrillation; VSA, vasospastic angina; VT, ventricular tachycardia.

Table 2. Correlated factors for Major Adverse Cardiac Events in VSA Patients

	Univariable analysis			Multivariable analysis *		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97 - 1.01	0.38			
Men	1.07	0.64 - 1.79	0.79			
Hypertension	0.90	0.58 - 1.38	0.62			
Dyslipidemia	1.17	0.76 - 1.79	0.48			
Diabetes mellitus	1.57	0.94 - 2.61	0.09	1.39	0.82 – 2.34	0.22
Smoking	1.96	1.21 - 3.19	0.006	1.67	1.02 - 2.73	0.041
Family history of IHD	1.10	0.58 - 2.06	0.78			
Previous MI	2.19	1.10 - 4.38	0.026	1.39	0.64 - 3.02	0.41
Significant organic stenosis	2.28	1.39 - 3.73	0.001	2.04	1.21 - 3.44	0.008
ST elevation during spontaneous attack	1.62	1.01 - 2.60	0.045	1.77	1.09 - 2.87	0.022
VT/VF during spontaneous attack †	1.00	0.14 - 7.18	1.00			
History of OHCA	3.98	1.73 - 9.13	0.001	3.25	1.39 - 7.61	0.007
LAD spasm	1.15	0.75 - 1.77	0.51			
LCx spasm	0.92	0.55 – 1.53	0.74			
RCA spasm	1.17	0.76 - 1.78	0.48			
Multivessel spasm	1.45	0.93 - 2.26	0.10	1.62	1.03 - 2.56	0.037
Administration of β-blockers	2.34	1.08 - 5.06	0.032	1.56	0.64 - 3.79	0.33

* Analysis was performed on 8 variables including diabetes mellitus, smoking, previous MI, significant organic stenosis, ST elevation during spontaneous attack, history of OHCA, multivessel spasm and administration of β-blockers.
† Patients complicated by OHCA were not included.
CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; OHCA; out-of-hospital cardiac arrest; RCA, right coronary artery; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3. Demographic Characteristics and Angiographic Findings of VSA Patients with and Those without Out-of-Hospital Cardiac Arrest

	OHCA (n=35)	Non-OHCA (n=1,394)	P value
Age, median (IQR), y	58 (44, 65)	66 (58, 73)	< 0.001
Men, n (%)	30 (86)	1,060 (76)	0.13
Coronary risk factor, n (%)			
Hypertension	13 (37)	653 (47)	0.17
Dyslipidemia	7 (20)	640 (46)	0.002
Diabetes mellitus	4 (11)	229 (16)	0.30
Smoking	24 (69)	824 (59)	0.17
Family history of IHD, n (%)	3 (9)	165 (12)	0.40
Family history of sudden death, n (%)	0 (0)	19 (1)	0.62
Previous MI, n (%)	5 (14)	86 (6)	0.07
Organic stenosis >50%, n (%)	5 (14)	196 (14)	0.56
LAD	4 (11)	112 (8)	0.32
LCx	1 (3)	62 (4)	0.54
RCA	2 (6)	69 (5)	0.53
ST-segment changes during spontaneous attack, n (%)			
ST elevation	6 (17)	266 (19)	0.49
ST depression	5 (14)	116 (8)	0.17
Spasm-positive arteries, n (%) †			
LAD	23 (72)	643 (53)	0.025
LCx	11 (34)	306 (25)	0.17
RCA	17 (53)	676 (56)	0.45
Multi-vessel	13 (41)	361 (30)	0.13

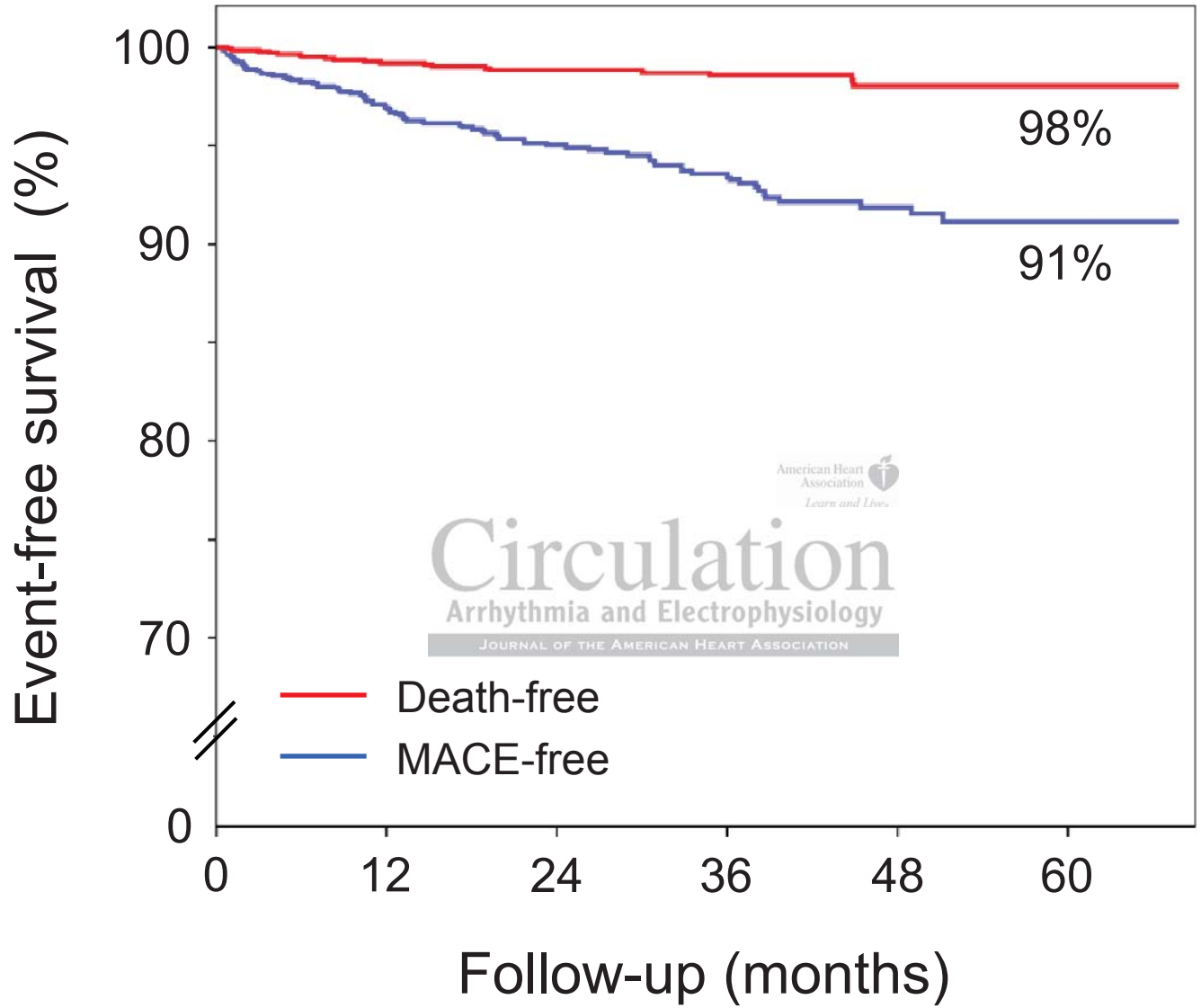
† Data analyzing 1,244 patients (32 OHCA survivors and 1,212 non-OHCA patients) who underwent vasospasm provocation test.

IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; OHCA, out-of-hospital cardiac arrest; RCA, right coronary artery.

Figure Legends:

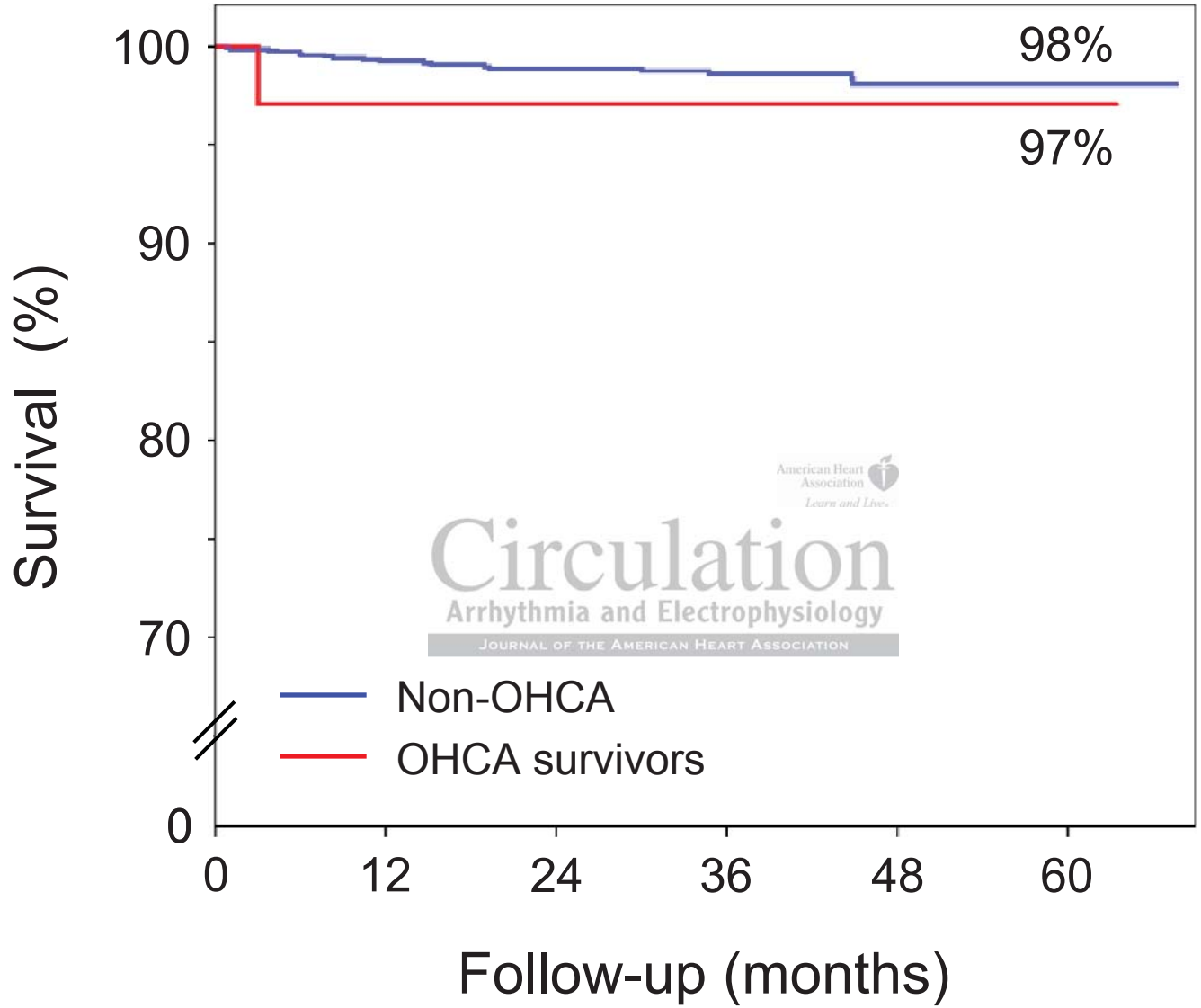
Figure 1. Kaplan-Meier curve for survival (red-line) and major adverse cardiac events (MACE) (blue-line) in VSA patients

Figure 2. Kaplan-Meier curve for all cause of death and major adverse cardiac events in VSA patients **(A)** The survival rate was comparable between the VSA patients who survived OHCA (red line, n=35) and those without OHCA (blue line, n=1,394) (P=0.30). **(B)** Major cardiac events (MACE)-free survival was significantly worse in the VSA patients who survived OHCA (red line, n=35) compared with those without OHCA (blue line, n=1,394) (P<0.001). MACE include cardiac death, non-fatal myocardial infarction, hospitalization due to heart failure and unstable angina pectoris and appropriate implantable cardioverter defibrillator shocks.



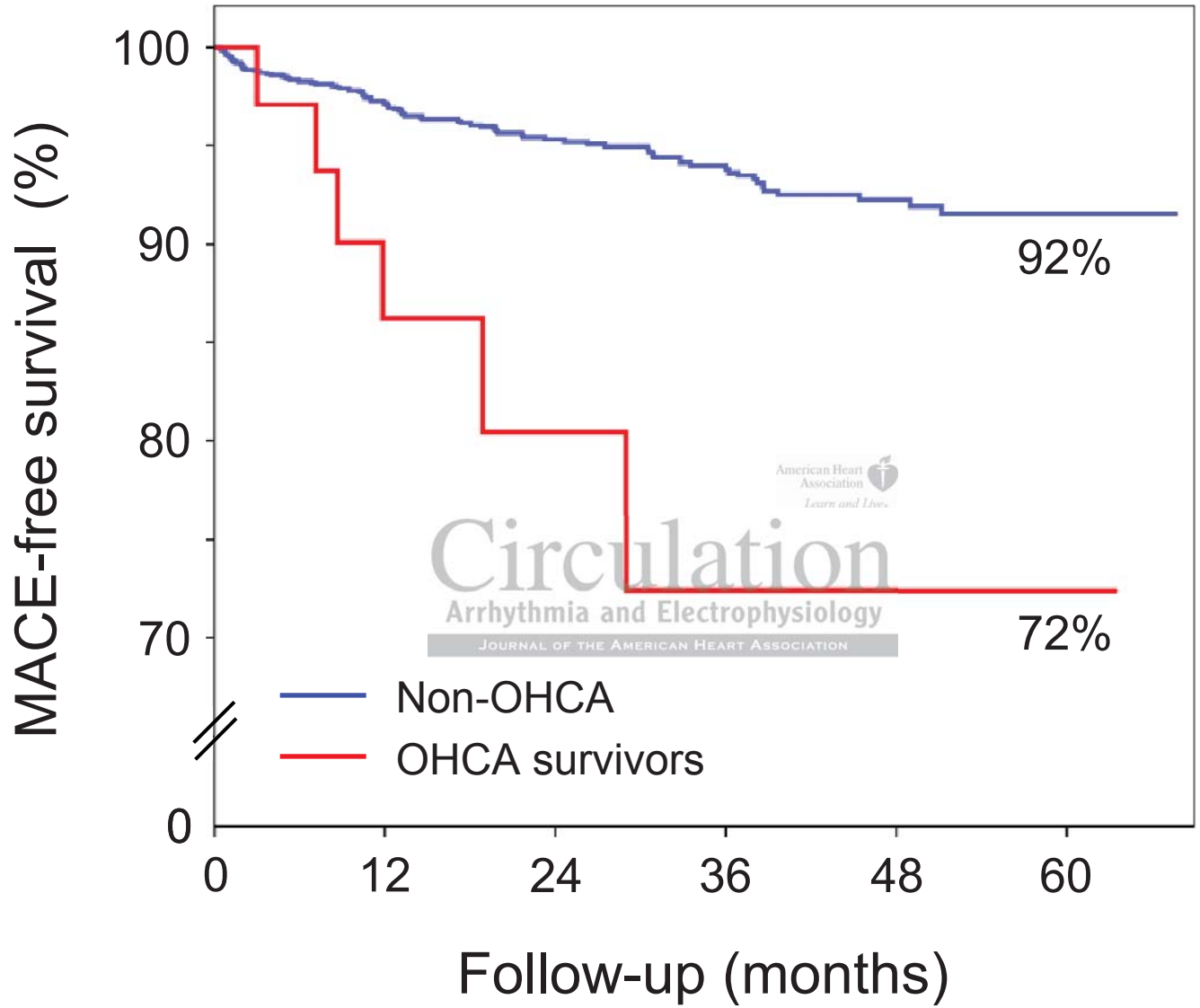
No. at risk

Death-free	1429	1230	880	629	316	59
MACE-free	1429	1200	841	587	302	57



No. at risk

Non-OHCA	1394	1206	866	618	313	57
OHCA survivors	35	24	14	11	3	2



No. at risk

Non-OHCA	1394	1178	828	578	299	55
OHCA survivors	35	22	13	9	3	2

Clinical Characteristics and Long-Term Prognosis of Vasospastic Angina Patients Who Survived Out-of-Hospital Cardiac Arrest: Multicenter Registry Study of the Japanese Coronary Spasm Association

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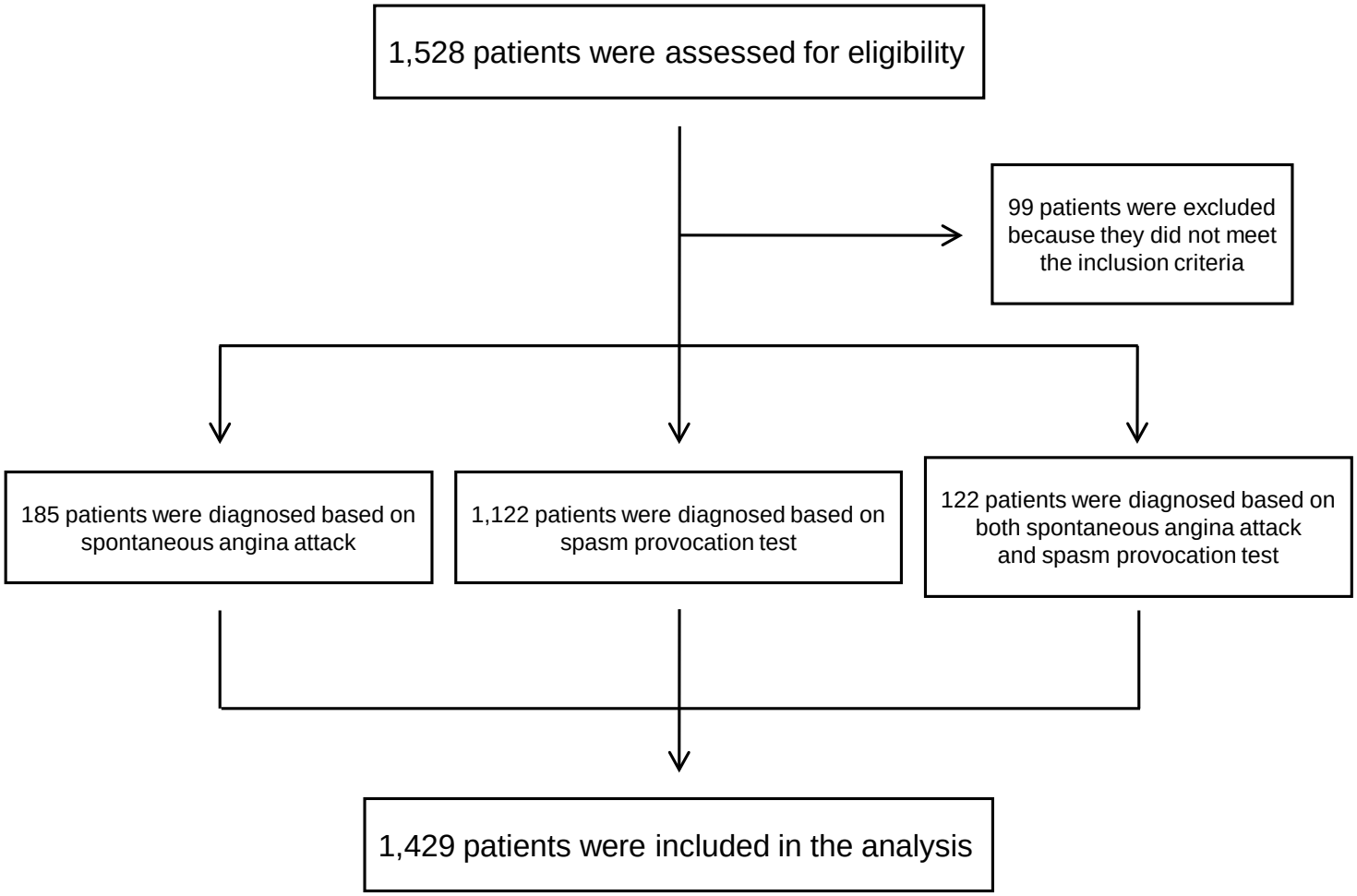
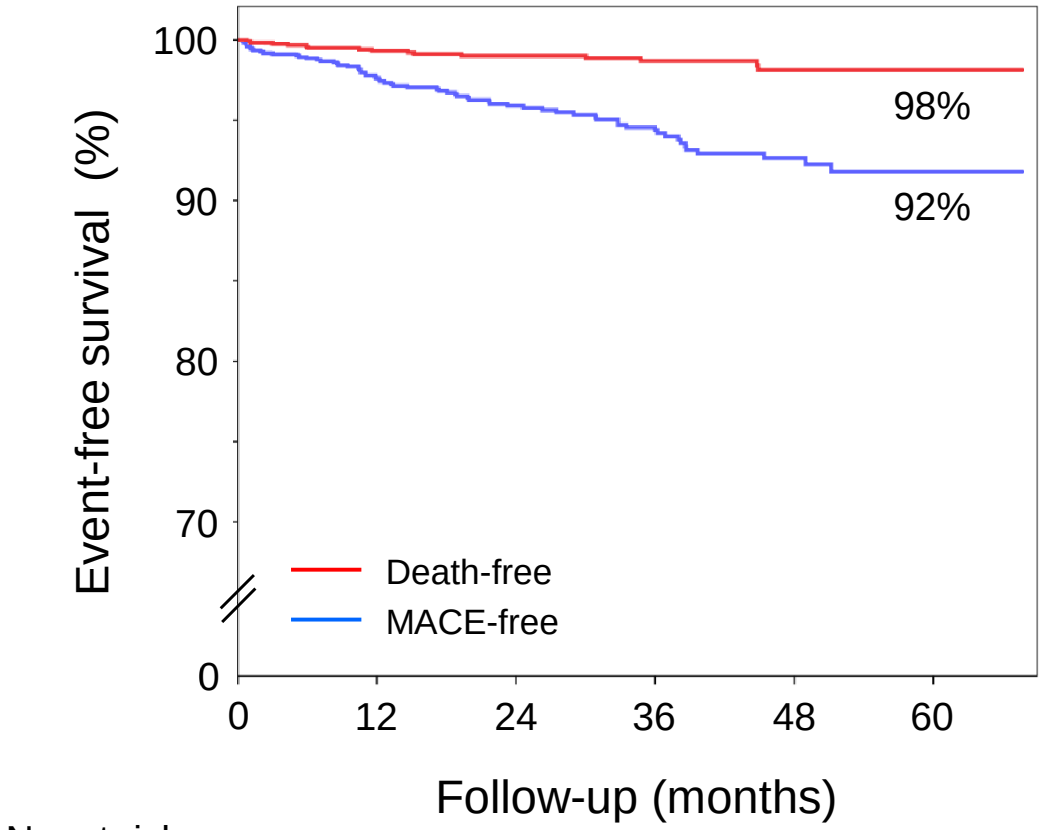
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Patient flow diagram



Supplemental Figure 2. Kaplan-Meier curve for survival (red-line) and major adverse cardiac events (MACE) (blue-line) in a total of 1,228 VSA patients without significant coronary stenosis.



No. at risk

Death-free	1228	1070	772	557	279	52
MACE-free	1228	1049	744	524	267	50

Supplemental Table 1. Arrhythmic Events during Provocation Tests (n=1,244)

	No. of patients, n (%)
PVC	13 (1.0)
VT/VF	40 (3.2)
AV block	8 (0.6)
Bradycardia/Sinus pause	28 (2.3)
Total	85 (6.8)

AV, atrioventricular; PVC, premature ventricular contraction;
VF, ventricular fibrillation; VT, ventricular tachycardia, including both sustained and non-sustained VT.

Supplemental Table 2. Factors Correlated for Major Adverse Cardiac Events in VSA Patients without Significant Organic Stenosis (n=1,228)

	Univariable analysis			Multivariable analysis *		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97 - 1.01	0.36			
Men	0.97	0.55 - 1.70	0.91			
Hypertension	0.90	0.55 - 1.48	0.68			
Dyslipidemia	1.18	0.72 - 1.92	0.52			
Diabetes mellitus	1.39	0.74 - 2.61	0.30			
Smoking	2.35	1.32 - 4.19	0.004	2.12	1.18 - 3.80	0.012
Family history of IHD	1.35	0.69 - 2.64	0.39			
Previous MI	2.90	1.32 - 6.35	0.008	2.21	0.95 - 5.15	0.07
ST elevation during spontaneous attack	1.33	0.76 - 2.35	0.32	1.35	0.75 - 2.43	0.32
VT/VF during spontaneous attack †	1.25	0.17 - 9.04	0.82			
History of OHCA	4.85	1.94 - 12.11	0.001	4.22	1.67 - 10.63	0.002
LAD spasm	1.20	0.73 - 1.96	0.47			
LCx spasm	0.84	0.47 - 1.53	0.57			
RCA spasm	1.26	0.77 - 2.05	0.37			
Multivessel spasm	1.51	0.91 - 2.49	0.11	1.45	0.87 – 2.41	0.16
Administration of β-blockers	2.24	0.81 - 6.16	0.12	1.87	0.62 - 5.63	0.27

* Analysis was performed on 6 variables including smoking, previous MI, ST elevation during spontaneous attack, history of OHCA, multivessel spasm and administration of β-blockers.

† Patients complicated by OHCA were not included.

CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; OHCA; out-of-hospital cardiac arrest; RCA, right coronary artery; VF, ventricular fibrillation; VT, ventricular tachycardia.

Supplemental Table 3. Left Ventricular Function and the Prevalence of Organic Coronary Stenosis in OHCA Survivors with and without MACE after Discharge

	OHCA survivors (n=35)		P value
	(+) MACE (n=5)	(-) MACE (n=30)	
LVEF, median (IQR), %	60 (58, 69)	65 (56, 69)	0.83
LVEF <50%, n (%)	0 (0)	4 (14)	0.45
Organic stenosis >50%, n (%)	1 (17)	4 (14)	0.63
LAD	0 (0)	4 (14)	0.45
LCx	0 (0)	1 (3)	0.83
RCA	1 (17)	1 (3)	0.32

IQR, interquartile range; LVEF, left ventricular ejection fraction.

Appendix 1

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