JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 68, NO. 2, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.04.050

ORIGINAL INVESTIGATIONS

Prognosis of Variant Angina Manifesting as Aborted Sudden Cardiac Death

Jung-Min Ahn, MD,[a] Ki Hong Lee, MD,[b] Sang-Yong Yoo, MD,[c] Young-Rak Cho, MD,[d] Jon Suh, MD,[e] Eun-Seok Shin, MD,[f] Jae-Hwan Lee, MD,[g] Dong Il Shin, MD,[h] Sung-Hwan Kim, MD,[i] Sang Hong Baek, MD,[i] Ki Bae Seung, MD,[i] Chang-Wook Nam, MD,[j] Eun-Sun Jin, MD,[k] Se-Whan Lee, MD,[l] Jun-Hyok Oh, MD,[m] Jae Hyun Jang,[a] Hyung Wook Park, MD,[b] Nam Sik Yoon, MD,[b] Jeong Gwan Cho, MD,[b] Cheol Hyun Lee, MD,[a] Duk-Woo Park, MD,[a] Soo-Jin Kang, MD,[a] Seung-Whan Lee, MD,[m] Jun Kim, MD,[a] Young-Hak Kim, MD,[a] Ki-Byung Nam, MD,[a] Cheol Whan Lee, MD,[a] Kee-Joon Choi, MD,[a] Jae-Kwan Song, MD,[a] You-Ho Kim, MD,[a] Seong-Wook Park, MD,[a] Seung-Jung Park, MD[a]

ABSTRACT

BACKGROUND The long-term prognosis of patients with variant angina presenting with aborted sudden cardiac death (ASCD) is unknown.

OBJECTIVES The purpose of this study was to evaluate the long-term mortality and ventricular tachyarrhythmic events of variant angina with and without ASCD.

METHODS Between March 1996 and September 2014, 188 patients with variant angina with ASCD and 1,844 patients with variant angina without ASCD were retrospectively enrolled from 13 heart centers in South Korea. The primary endpoint was cardiac death.

RESULTS Predictors of ASCD manifestation included age (odd ratio [OR]: 0.980 by 1 year increase; 95% confidence interval [CI]: 0.96 to 1.00; $p = 0.013$), hypertension (OR: 0.51; 95% CI: 0.37 to 0.70; $p < 0.001$), hyperlipidemia (OR: 0.38; 95% CI: 0.25 to 0.58; $p < 0.001$), family history of sudden cardiac death (OR: 3.67; 95% CI: 1.27 to 10.6; $p = 0.016$), multivessel spasm (OR: 2.06; 95% CI: 1.33 to 3.19; $p = 0.001$), and left anterior descending artery spasm (OR: 1.40; 95% CI: 1.02 to 1.92; $p = 0.04$). Over a median follow-up of 7.5 years, the incidence of cardiac death was significantly higher in ASCD patients (24.1 per 1,000 patient-years vs. 2.7 per 1,000 patient-years; adjusted hazard ratio [HR]: 7.26; 95% CI: 4.21 to 12.5; $p < 0.001$). Death from any cause also occurred more frequently in ASCD patients (27.5 per 1,000 patient-years vs. 9.6 per 1,000 patient-years; adjusted HR: 3.00; 95% CI: 1.92 to 4.67; $p < 0.001$). The incidence rate of recurrent ventricular tachyarrhythmia in ASCD patients was 32.4 per 1,000 patient-years, and the composite of cardiac death and ventricular tachyarrhythmia was 44.9 per 1,000 patient-years. A total of 24 ASCD patients received implantable cardioverter-defibrillators (ICDs). There was a nonsignificant trend of a lower rate of cardiac death in patients with ICDs than those without ICDs ($p = 0.15$).

CONCLUSIONS The prognosis of patients with variant angina with ASCD was worse than other patients with variant angina. In addition, our findings supported ICDs in these high-risk patients as a secondary prevention because current multiple vasodilator therapy appeared to be less optimal. (J Am Coll Cardiol 2016;68:137–45) © 2016 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Heart Institute, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; [b]Chonnam National University Hospital, Gwangju, South Korea; [c]Department of Cardiology, University of Ulsan College of Medicine, Gangneung Asan Hospital, Gangneung, South Korea; [d]Department of Cardiology, Dong-A University Hospital, Busan, South Korea; [e]Department of Cardiology, Soonchunhyang University Hospital Bucheon, Bucheon, South Korea; [f]Ulsan University Hospital, Ulsan, South Korea; [g]Department of Cardiology, Chungnam National University Hospital, Daejeon, South Korea; [h]Department of Cardiovascular Medicine, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, South Korea; [i]Department of Cardiovascular Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [j]Keimyung University Dongsan Medical Center,

ABBREVIATIONS AND ACRONYMS

ASCD = aborted sudden cardiac arrest

CI = confidence interval

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IPTW = inverse-probability-of-treatment weighting

OR = odds ratio

Variant angina is characterized by chest pain at rest and transient ST-segment elevation on an electrocardiogram caused by dynamic coronary artery spasm (1). It usually has a favorable long-term prognosis because coronary artery spasms respond well to vasodilator therapy (2). However, coronary artery spasms might also have an important role in the pathogenesis of ventricular arrhythmia and subsequent cardiac arrest (3). The long-term prognosis of patients with variant angina who present with aborted sudden cardiac death (ASCD) is controversial. Previous studies have demonstrated a recurrence of lethal arrhythmic events and poor clinical outcomes (4–6). Other studies have reported favorable long-term outcomes (7–9). This uncertainty has led to variations in treatment, with some cardiologists favoring implantable cardioverter-defibrillators (ICDs) (10) and others believing that coronary spasms are reversible and can be controlled by intensive vasodilator treatment (11).

SEE PAGE 146

Therefore, to overcome mixed evidence from anecdotal reports hampered by the limited number of patients and short follow-up periods, and to provide clinically relevant information in long-term appropriate management for this high-risk subset, a large multicenter cohort study with long-term follow-up was of paramount importance. In this study, we hypothesized that patients presenting with ASCD would have worse long-term prognosis, which would be irreversible to optimal vasodilator therapy only. To test our hypothesis, we first evaluated the long-term risk of mortality and ventricular tachyarrhythmic events in patients with variant angina with ASCD compared with those without ASCD. Second, we compared cardiac mortality between patients who received ICDs or did not in ASCD patients.

METHODS

STUDY DESIGN AND PATIENTS. This is a retrospective observational cohort study that discusses the characteristics of patients with variant angina with ASCD or without ASCD from 13 major heart centers in South Korea. The diagnosis of variant angina was made based on the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society (12). In addition, all patients with variant angina with ASCD who met the following criteria were included: (1) patients who experienced out-of-hospital cardiac arrest due to documented ventricular fibrillation, sustained rapid ventricular tachycardia, or pulseless electrical activity; (2) patients who were successfully resuscitated from cardiac arrest; (3) patients who had variant angina, which was defined by spontaneous coronary spasm with ST-segment elevation (≥0.1 mV) on the coronary angiogram and/or documented coronary spasm on an ergonovine provocation coronary angiogram; and (4) patients who did not have organic heart disease, including significant coronary artery stenosis or any other condition known to be associated with sudden cardiac arrest. To definitely rule out significant coronary artery disease, all ASCD patients underwent coronary angiography, and when the coronary angiogram showed a normal coronary artery, patients underwent an ergonovine provocation test. In addition, we excluded patients (n = 3) with poor neurological outcomes (defined as cerebral performance category scale ≥3) (13).

The non-ASCD group consisted of patients who had positive coronary artery spasm provocation tests due to typical or atypical angina-like chest pain suspected of being variant angina. In general, angina at rest in the early morning or at night was the hallmark feature that prompted the provocation test. Ergonovine provocation coronary angiography or echocardiography were used as provocation tests and were performed according to standard methods, which are described in the Online Appendix (12,14). The definitions of positive results were total or subtotal (>90% luminal diameter narrowing) occlusion in ergonovine provocation coronary angiography and new development of regional wall motion abnormalities on the ergonovine provocation echocardiogram. The local ethics committee at each hospital approved the use of the clinical data for this study.

TREATMENT. All patients who were enrolled in the present study received medical treatment, including calcium-channel blockers, long-acting nitrates, or

Daegu, South Korea; [k]Kyung Hee University Hospital, Gangdong, Seoul, South Korea; [l]Department of Cardiology, Soonchunhyang University Hospital Cheonan, Cheonan, South Korea; and the [m]Pusan National University Hospital, Busan, South Korea. This study was supported by funds from the CardioVascular Research Foundation, Seoul, South Korea. Drs. Ahn and Lee contributed equally to this article. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 29, 2016; revised manuscript received March 31, 2016, accepted April 12, 2016.

other vasodilators during follow-up. Selection of medical treatment for variant angina was at the discretion of each attending physician. In general, the dose of vasodilators was titrated up to relieve chest pain, and drug compliance was emphasized.

The decision for implantation of ICDs was at physicians' or patients' discretion after discussing the advantages and disadvantages of ICD therapy due to the lack of robust evidence favoring ICD therapy over intensive medical treatment. All patients who received an ICD had the documented shockable rhythm. A single- or dual-chamber ICD was implanted according to available clinical practice guideline recommendations. ICD programming was adjusted based on the individual clinical history and availability of new clinical evidence for device programming in secondary prevention patients (15–17). Patients who received ICD therapy were followed up every 3 to 6 months for clinical review, device interrogation, and capacitor reform, or in the event of symptom onset or device discharge.

STUDY OUTCOMES AND FOLLOW-UP. The primary endpoint in this study was cardiac death. The secondary endpoint was death from any cause. Cardiac death was defined as any death due to proximate cardiac cause, including cardiac arrest, myocardial infarction, low-output failure, or fatal arrhythmia. As another major secondary endpoint, death from arrhythmia and the recurrence of ventricular tachyarrhythmia were evaluated in ASCD patients. Definite or probable deaths from arrhythmia followed the definitions of the Cardiac Arrhythmia Pilot Study (18), described in the Online Appendix. Appropriate ICD treatment was defined as device-administered antitachycardia or defibrillation treatment for ventricular tachyarrhythmia that had not terminated spontaneously.

Medical records and telephone interviews were used to determine the occurrence of clinical events in all patients. The date of the last contact or review of the medical record was used to calculate follow-up time. All outcomes of interest were carefully verified and adjudicated by independent clinicians (K.H.L., J.K.) based on the source document, with disagreements between physicians resolved by consensus. In addition, the vital status of all patients was cross-checked using the unique identification numbers in the Korean Health System.

DATA COLLECTION. All baseline characteristics and outcome data were collected using a dedicated case report form by specialized personnel at each center. Monitoring and verification of registry data were performed in participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea) (19).

STATISTICAL ANALYSIS. Baseline patient characteristics are represented as number (percentage) for categorical variables and mean ± SD for continuous variables. Differences between groups were analyzed using the Student *t* test or Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. Differences in the adjusted risk of study outcomes were investigated using multivariable Cox proportional hazards regression. The proportional hazards assumption was confirmed by examination of log (–log [survival]) curves and testing of partial (Schoenfeld) residuals (20). No relevant violations were found. Final models are provided in Online Table 1. We also performed additional adjustments for differences in baseline patient characteristics with propensity score matching (21,22) and weighted Cox proportional hazards regression models with inverse-probability-of-treatment weighting (IPTW) (23,24). In the matched cohorts, survival curves were constructed with Kaplan-Meier estimates and compared using methods described previously (22). Multivariate logistic regression analysis was used to determine the independent factors associated with ASCD. In addition, multivariate Cox proportional hazards regression analysis was used to identify predictors of long-term mortality (death from any cause and cardiac death) in the overall cohort.

All reported p values are 2-sided, and p values <0.05 were considered statistically significant. SAS software (version 9.1, SAS Institute, Cary, North Carolina) and the R programming language (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

RESULTS

STUDY PATIENTS. Between March 1996 and September 2014, 188 patients with variant angina with ASCD and 1,844 patients with variant angina without ASCD were retrospectively enrolled from 13 heart centers in South Korea. **Table 1** summarizes the baseline patient characteristics. The mean age of ASCD patients was 52.8 ± 9.9 years, and 76% were men. Diagnosis of coronary spasm was based on a positive ergonovine provocation coronary angiogram in 134 patients (71.3%) and a spontaneous coronary artery spasm with ST-segment elevation in 54 patients (28.7%). The initial rhythm was ventricular tachyarrhythmia in 137 patients (72.9%) and pulseless electrical activity in 51 patients (27.1%). An ICD was implanted in 24 patients (12.8%). For

TABLE 1 Baseline Characteristics of the Patients Presenting With or Without Aborted Sudden Cardiac Death

	With ASCD (n = 188)	Without ASCD (n = 1,844)	p Value
Age, yrs	52.8 ± 9.9	55.3 ± 9.5	0.001
Male	143 (76.1)	1,427 (77.4)	0.68
Hypertension	64 (34.0)	914 (49.5)	<0.001
Diabetes	15 (8.0)	190 (10.3)	0.31
Smoking	103 (54.8)	900 (48.8)	0.12
Hyperlipidemia	27 (14.4)	560 (30.4)	<0.001
Family history of sudden cardiac death	5 (2.7)	16 (0.9)	0.021
Angina attack			<0.001
None or atypical chest pain	32 (17.0)	101 (5.5)	
Rest chest pain	127 (67.6)	1,484 (80.5)	
Effort chest pain	20 (10.6)	142 (7.7)	
Rest and effort chest pain	9 (4.8)	117 (6.3)	
ST-segment change during angina attack			<0.001
ST-segment elevation	102 (54.3)	509 (27.6)	
ST-segment depression	53 (18.6)	237 (12.9)	
Location of spasm			
Left anterior descending artery	107 (56.9)	838 (45.4)	0.003
Left circumflex artery	31 (16.5)	334 (18.1)	0.58
Right coronary artery	95 (50.5)	867 (47.0)	0.34
Multivessel spasm	32 (17.0)	171 (9.3)	0.001
Ejection fraction, %	60.6 ± 9.9	62.5 ± 5.4	0.01
Medication at discharge			
Aspirin	96 (51.1)	665 (36.1)	<0.001
Statin	94 (50.0)	890 (48.3)	0.65
Beta blocker	40 (21.3)	256 (13.9)	0.006
Calcium-channel blocker			
Any	177 (94.1)	1817 (98.5)	<0.001
Diltiazem	154 (81.9)	1739 (94.3)	<0.001
Verapamil	7 (3.7)	45 (2.4)	0.29
Dihydrophyridine	66 (35. 1)	691 (37.5)	0.52
Long-acting nitrate	148 (78.7)	1,431 (77.6)	0.73
Nicorandil	96 (50.5)	196 (10.6)	<0.001
Cilostazol	11 (5.9)	88 (4.8)	0.51
No. of type of vasodilator	2.6 ± 0.9	2.3 ± 0.8	<0.001

Values are mean ± SD or n (%).
ASCD = aborted sudden cardiac death.

non-ASCD patients, coronary spasm was documented by ergonovine provocation echocardiogram (n = 1,020) and ergonovine provocation coronary angiogram (n = 824). Overall, ASCD patients were younger (52.8 ± 9.9 years vs. 55.3 ± 9.5 years; p = 0.001); they had more frequent multivessel spasms (17.0% vs. 9.3%; p = 0.001), had a lower incidence of hypertension (34.0% vs. 49.5%; p < 0.001), hyperlipidemia (14.4% vs. 30.4%; p < 0.001), and family history of sudden cardiac death (2.7% vs. 0.9%; p = 0.021), and took more vasodilators than non-ASCD patients (2.6 ± 0.9 vs. 2.3 ± 0.8; p < 0.001) (Table 1). Among the ASCD patients who experienced clinical events of cardiac death and ventricular tachyarrhythmia, all but 2 patients received at least 2 vasodilator therapies (Online Table 2).

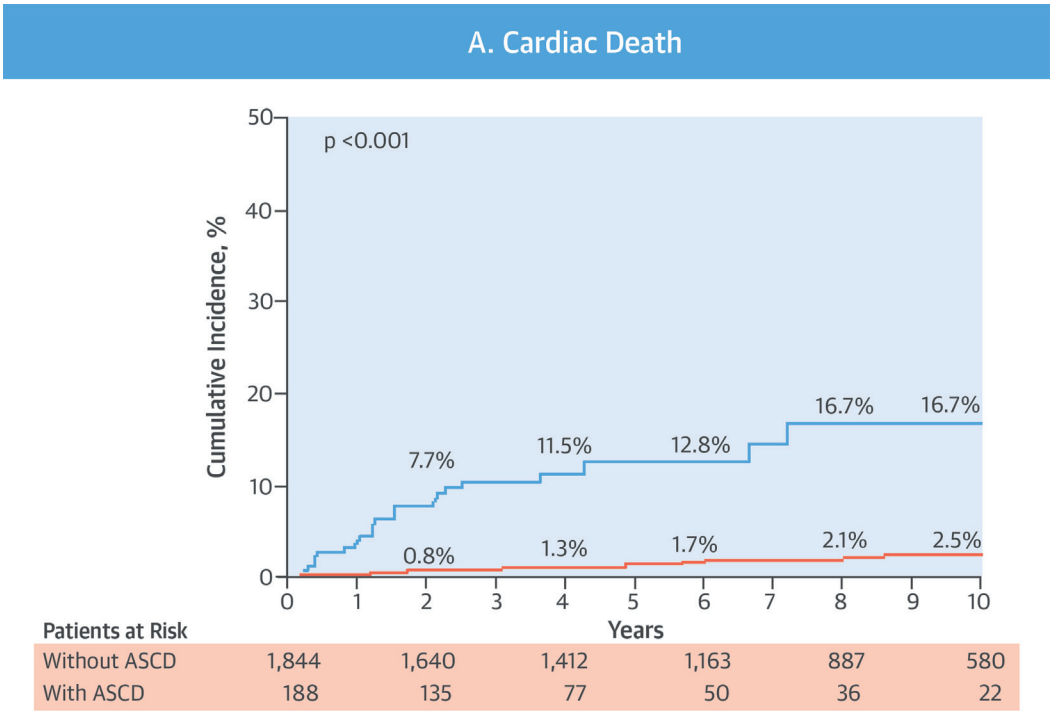
Multivariate binary logistic regression analysis identified independent factors associated with ASCD. They included age (odd ratio [OR]: 0.980 by 1 year increase; 95% confidence interval [CI]: 0.96 to 1.00; p = 0.013), hypertension (OR: 0.51; 95% CI: 0.37 to 0.70; p < 0.001), hyperlipidemia (OR: 0.38; 95% CI: 0.25 to 0.58; p < 0.001), family history of sudden cardiac death (OR: 3.67; 95% CI: 1.27 to 10.6; p = 0.016), multivessel spasm (OR: 2.06; 95% CI: 1.33 to 3.19; p = 0.001), and left anterior descending coronary artery spasm (OR: 1.40; 95% CI: 1.02 to 1.92; p = 0.04).

OUTCOMES. Over a median follow-up of 7.5 years (interquartile range: 4.0 to 11.8 years), cardiac death occurred in 21 ASCD patients and in 42 patients non-ASCD patients (Central Illustration). The incidence rate of cardiac death was significantly higher in ASCD patients (24.1 per 1,000 patient-years vs. 2.7 per 1,000 patient-years; adjusted hazard ratio [HR]: 7.26; 95% CI: 4.21 to 12.5; p < 0.001) (Table 2). All but 1 cardiac death in ASCD patients were adjudicated as arrhythmic death. Death from any cause occurred in 24 ASCD patients and in 145 non-ASCD patients (Central Illustration). The incidence rate of death from any cause was significantly higher in ASCD patients than non-ASCD patients (27.5 per 1,000 patient-years vs. 9.6 per 1,000 patient-years; adjusted HR: 3.00; 95% CI: 1.92 to 4.67; p < 0.001) (Table 2). In addition, propensity score matching was used to assemble a cohort of patients with similar baseline characteristics. After matching, baseline characteristics were balanced between 172 pairs (Online Table 3). Patients with ASCD, compared with those without ASCD, had a higher risk of cardiac death (HR: 9.81; 95% CI: 3.02 to 31.8; p < 0.001) (Figure 1A) and death from any cause (HR: 4.09; 95% CI: 2.28 to 10.5; p < 0.001) (Figure 1B). The results after adjustment by IPTW was consistent (Table 2).

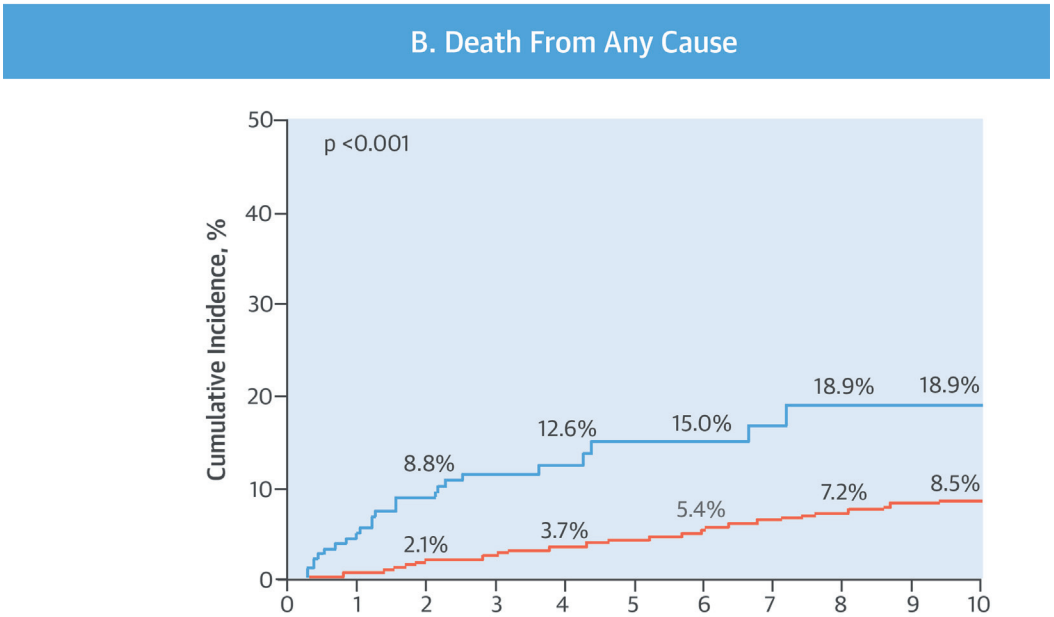
We also evaluated independent predictors of mortality in our cohort. These included ASCD (HR: 2.89; 95% CI: 1.85 to 4.52; p < 0.001), diabetes (HR: 2.16; 95% CI: 1.43 to 3.27; p < 0.001), age (HR: 1.06 by 1 year increase; 95% CI: 1.04 to 1.07; p < 0.001), and statins (HR: 0.53; 95% CI: 0.38 to 0.75; p < 0.001) for death from any cause, and ASCD (HR: 5.92; 95% CI: 3.19 to 11.0; p < 0.001), nitrates (HR: 2.60; 95% CI: 1.03 to 6.56; p = 0.043), aspirin (HR: 1.82; 95% CI: 1.06 to 3.11; p = 0.029), statins (HR: 0.32; 95% CI: 0.17 to 0.59; p < 0.001), and hypertension (HR: 0.43; 95% CI: 0.23 to 0.80; p = 0.008) for cardiac death.

Recurrent ventricular tachyarrhythmia occurred in 26 ASCD patients (25 ventricular fibrillation and 1 ventricular tachycardia). The incidence rate of recurrent ventricular tachycardia was 32.4 per 1,000 patient-years (Figure 2A). Recurrent myocardial

CENTRAL ILLUSTRATION **Mortality of Patients With Variant Angina Presenting With or Without ASCD in the Overall Cohort**



Patients at Risk						
Without ASCD	1,844	1,640	1,412	1,163	887	580
With ASCD	188	135	77	50	36	22



Patients at Risk						
Without ASCD	1,844	1,649	1,412	1,163	887	580
With ASCD	188	138	77	50	36	22

With ASCD Without ASCD

Ahn, J.-M. et al. J Am Coll Cardiol. 2016;68(2):137–45.

(A) Cumulative incidences of the primary endpoint of cardiac death and **(B)** death from any cause. The illustrated event rates are Kaplan-Meier estimates. The p value was calculated using log-rank test on the basis of all available follow-up data. ASCD = aborted sudden cardiac death.

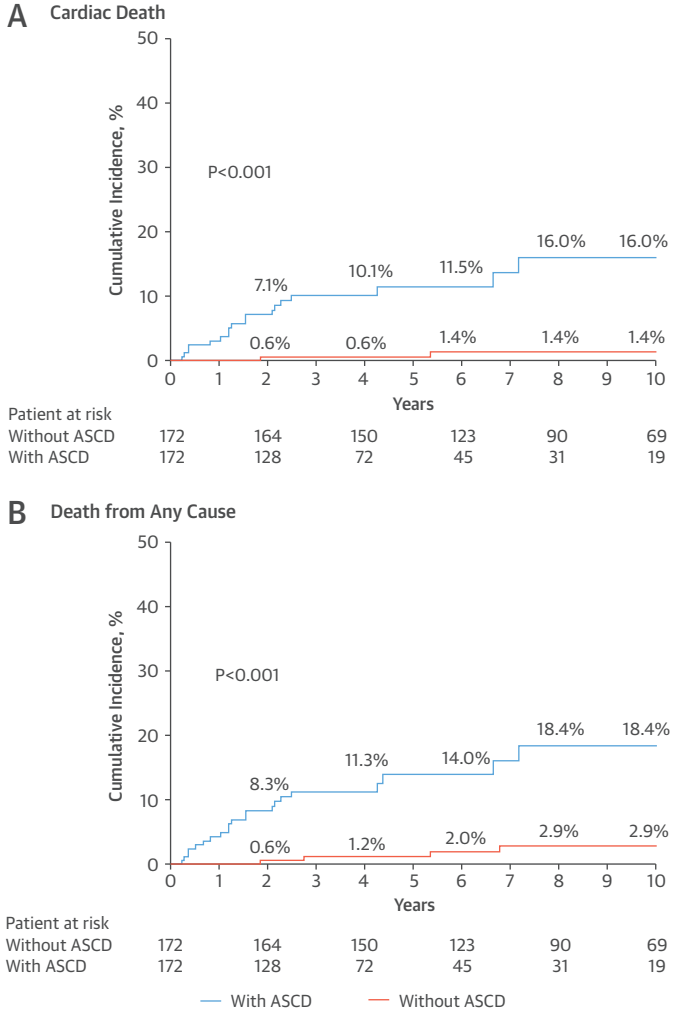
TABLE 2 Events in Patients With or Without Aborted Sudden Cardiac Death

Events	With ASCD (n = 188) Incidence Rate Per 1,000 Person-Yrs	Without ASCD (n = 1,844) Incidence Rate Per 1,000 Person-Yrs	Crude HR (95% CI)*	Adjusted HR (95% CI)* Multivariate	Adjusted HR (95% CI)* Propensity Matching	Adjusted HR (95% CI)* IPTW
Cardiac death	24.1	2.7	7.77 (4.56–13.2)	7.26 (4.21–12.5)	9.81 (3.02–31.8)	7.85 (3.58–17.2)
Death from any cause	27.5	9.6	2.82 (1.82–4.36)	3.00 (1.92–4.67)	4.09 (2.28–10.5)	2.99 (1.45–6.18)
Ventricular tachyarrhythmia	32.4					
Cardiac death or ventricular tachyarrhythmia	44.9					

*All $p < 0.01$.

CI = confidence interval; HR = hazard ratio; IPTW = inverse probability-of-treatment weight; other abbreviation as in Table 1.

FIGURE 1 Mortality of Patients With Variant Angina Presenting With or Without ASCD in Matched Cohort



(A) Cumulative incidences of the primary endpoint of cardiac death and **(B)** death from any cause. The illustrated event rates are Kaplan-Meier estimates. The p value was calculated using methods described by Klein and Moeschberger (22) on the basis of all available follow-up data. ASCD = aborted sudden cardiac death.

infarction occurred in 8 patients. The composite of cardiac death and ventricular tachyarrhythmia occurred in 36 patients at a rate of 44.9 per 1,000 patient-years (Figure 2B). A total of 24 ASCD patients received ICDs and had more vasodilator treatment (Online Table 4). Of those, 6 patients experienced ventricular fibrillations, and 5 patients received appropriate treatment, but 1 patient died due to intractable ventricular fibrillation. During follow-up, there was a nonsignificant trend of a lower rate of cardiac death in patients with ICDs than those without ICDs (p = 0.15) (p = 0.15) (Figure 3).

DISCUSSION

In our present study, we found that patients with variant angina with ASCD had higher rates of cardiac death and death from any cause than non-ASCD patients, despite successful resuscitation and treatment with multiple vasodilator therapies. ASCD patients also had a high recurrence rate of ventricular tachyarrhythmia (32.4 per 1,000 patient-years). ASCD patients who underwent ICD implantation frequently received appropriate ICD treatment and had a nonsignificant trend of a lower rate of cardiac death compared with patients without ICD implantation.

Prognostic data on patients with variant angina presenting with ASCD has been scarce and limited in size and duration of follow-up. Furthermore, these reports have shown conflicting results. One case series that followed 8 patients with ventricular fibrillation and refractory variant angina showed that all patients had recurrence of ventricular tachyarrhythmia during follow-up (6). However, another series of 7 patients who presented with sudden cardiac death from coronary vasospasms had a favorable prognosis over a mean 4.8-year follow-up, except for 1 patient with recurrent cardiac arrest (7). More recently, an observational study of 35 survivors of

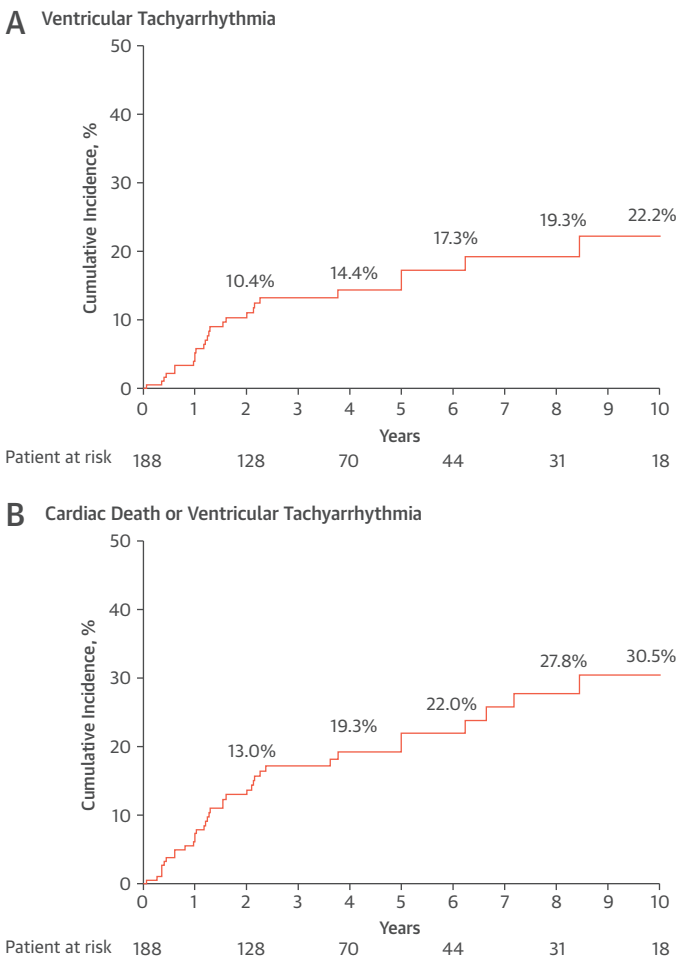
cardiac arrest from a group of 1,429 patients with variant angina reported 2 ICD shock treatments and 1 sudden cardiac death over a mean 2.7-year follow-up (5). However, another observational study of 17 patients who recovered from cardiac arrest reported no cardiac events over a mean 5.6-year follow-up (9). Our present multicenter study had one of the largest cohorts reported to date and had a long follow-up period, which provided relevant clinical insight on the prognosis of this population. The outcomes of these high-risk patients was unfavorable despite multiple vasodilator treatments.

The high rate of adverse cardiac events in ASCD patients has several possible explanations. First, these patients had more frequent multivessel spasms involving the left anterior descending artery; therefore, a single episode of spasm resulted in the induction of more severe myocardial ischemia. Second, even optimal medical treatments sometimes fail to eliminate all risk of episodes of spasm and subsequent ventricular tachyarrhythmia recurrence. Previous studies have described coronary artery spasms and ventricular arrhythmias even in patients who underwent symptomatic remission following medical treatment (3,25). Nonadherence to long-term medication is also common in patients with cardiovascular disease (26). In addition, medical treatment could not cure the fundamental mechanism causing the coronary spasms, although it usually relieved the coronary spasms well. Third, the myocardium of these patients might be more sensitive to ischemia or other stimuli, which resulted in a high rate of recurrent ventricular tachyarrhythmia (3). Fourth, a myocardial scar formed by ischemia at the time of the initial arrest might provide a reentry circuit for recurrence. Finally, coronary spasms might be an unrelated condition, and other electrophysiological disorders that were not evident initially but were diagnosed later might be a cause of cardiac arrest (27–29).

Current guidelines recommend ICD therapy in patients who are survivors of cardiac arrest caused by ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after they undergo evaluation to define the cause of the event and to exclude any completely reversible causes (30). However, it has not been determined if coronary spasms that lead to cardiac arrest are reversible, mainly due to a lack of prognostic data. In our present analyses, we observed a high recurrence rate of lethal ventricular arrhythmias despite optimal medical treatment (4). In addition, the rate of cardiac death or ventricular tachyarrhythmia was approximately 3% per year, similar to the annual risk of the control group in an ICD trial (31). Finally, in our cohort, ICD implantation was associated with reduced cardiac mortality, although statistical significance was not achieved, which was likely due to the small sample size. Therefore, our findings suggest that ICD implantation might prevent future cardiac events in addition to optimal medical treatment, although this hypothesis requires further prospective clinical trials.

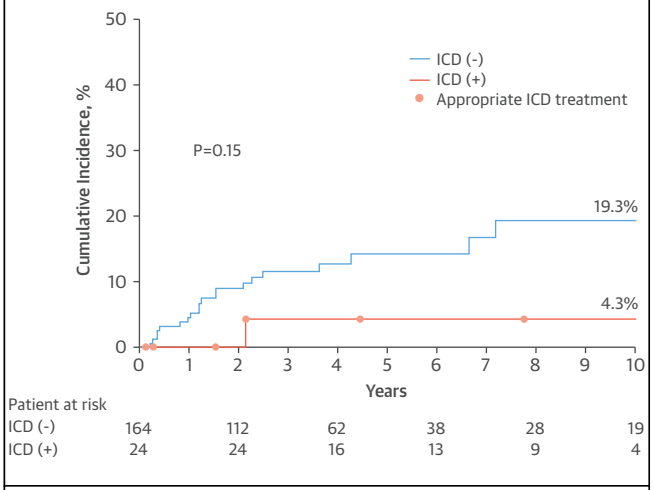
In this large registry, we confirmed the favorable long-term prognosis of patients with variant angina without ASCD, and our event rates were consistent with previous studies. The 10-year survival rate in patients with variant angina has been reported to be 93% (2). Another large Japanese registry reported a 98% survival rate after 5 years (5).

FIGURE 2 Clinical Outcomes of Patients Presenting With ASCD



(A) Cumulative incidences of the ventricular tachyarrhythmia and the **(B)** composite of cardiac death or ventricular tachyarrhythmia. The illustrated event rates are Kaplan-Meier estimates. Abbreviation as in Figure 1.

FIGURE 3 Mortality of Patients Receiving and Not Receiving ICDs



Cumulative incidences of cardiac death. Event rates shown are Kaplan-Meier estimates. The p value was calculated using the log-rank test on the basis of all available follow-up data. ICD = implantable cardioverter defibrillator.

STUDY LIMITATIONS. First, it was retrospective and observational, which has inherent limitations. Second, we described a detailed prescription of medical treatment in ASCD patients who had clinical events. However, we did not have accurate information about their response to medical treatment and compliance. However, all study investigators had sufficient experiences in the management of variant angina due to its high prevalence in South Korea. Generally, doses of vasodilators were titrated up to relieve chest pain. Compared with other registries, our patients received more intensive vasodilator therapies, particularly ASCD patients (32). In addition, physicians always emphasized the importance of compliance of vasodilator therapy with patients. Therefore, the high clinical event rate in ASCD patients may not be related with a less sufficient dose of medical treatment or poor medical compliance. Third, all of our patient subjects were Korean, an ethnicity with a high prevalence of variant angina. However, there is no evidence to date that the prognosis of patients with variant angina that present with ASCD differs by ethnicity (31). Nevertheless, external validation of our present findings in another study population is necessary.

CONCLUSIONS

The prognosis of patients with variant angina with ASCD was worse than other patients with variant angina, and current multiple vasodilator therapy appeared to be suboptimal. Therefore, ICD implantation, together with multiple vasodilator therapy, might be necessary as a secondary prevention treatment, although this strategy should be tested in a future large and prospective clinical trial.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Kee-Joon Choi, Department of Cardiology, Heart Institute, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul, 138-736, South Korea. E-mail: kjchoi@amc.seoul.kr. OR Dr. Seung-Jung Park, Heart Institute, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong Songpa-gu, Seoul 138-736, South Korea. E-mail: sjpark@amc.seoul.kr.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with variant angina presenting with aborted sudden arrhythmic death face a worse prognosis than those without this type of presentation. Therapy with multiple vasodilator drugs is not sufficiently protective.

TRANSLATIONAL OUTLOOK: Further studies are needed to explore additional avenues of therapy and clarify the role of implanted defibrillators in patients with variant angina who survive cardiac arrest.

REFERENCES

1. Stern S, Bayes de Luna A. Coronary artery spasm: a 2009 update. Circulation 2009;119:2531–4.

2. Yasue H, Takizawa A, Nagao M, et al. Long-term prognosis for patients with variant angina and influential factors. Circulation 1988;78:1–9.

3. Myerburg RJ, Kessler KM, Mallon SM, et al. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary-artery spasm. N Engl J Med 1992;326:1451–5.

4. Matsue Y, Suzuki M, Nishizaki M, et al. Clinical implications of an implantable cardioverter-defibrillator in patients with vasospastic angina and lethal ventricular arrhythmia. J Am Coll Cardiol 2012;60:908–13.

5. Takagi Y, Yasuda S, Tsunoda R, et al. 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. Circ Arrhythm Electrophysiol 2011;4:295–302.

6. Meisel SR, Mazur A, Chetboun I, et al. Usefulness of implantable cardioverter-defibrillators in refractory variant angina pectoris complicated by ventricular fibrillation in patients with angiographically normal coronary arteries. Am J Cardiol 2002;89:1114–6.

7. Chevalier P, Dacosta A, Defaye P, et al. Arrhythmic cardiac arrest due to isolated coronary artery spasm: long-term outcome of seven resuscitated patients. J Am Coll Cardiol 1998;31:57–61.

8. Meune C, Joly LM, Chiche JD, et al. Diagnosis and management of out-of-hospital cardiac arrest secondary to coronary artery spasm. Resuscitation 2003;58:145–52.

9. Yamashina Y, Yagi T, Namekawa A, et al. Favorable outcomes of patients with vasospastic angina associated with cardiac arrest. J Cardiol 2014;63:41–5.

10. Eschalier R, Souteyrand G, Jean F, et al. Should an implanted defibrillator be considered in patients with vasospastic angina? Arch Cardiovasc Dis 2014;107:42–7.

11. Morikawa Y, Mizuno Y, Yasue H. Letter by Morikawa et al regarding article, "coronary artery spasm: a 2009 update." Circulation 2010;121:e16; author reply e19.

12. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 2014;78:2779–801.

13. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–4.

14. Shin DI, Baek SH, Her SH, et al. The 24-month prognosis of patients with positive or intermediate results in the intracoronary ergonovine provocation test. J Am Coll Cardiol Intv 2015;8:914–23.

15. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. J Am Coll Cardiol 2008;52:541–50.

16. Gasparini M, Proclemer A, Klersy C, et al. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. JAMA 2013;309:1903–11.

17. Conte G, Caputo ML, Regoli F, et al. True idiopathic ventricular fibrillation in out-of-hospital cardiac arrest survivors in the Swiss Canton Ticino: prevalence, clinical features, and long-term follow-up. Europace 2016 Feb 17 [E-pub ahead of print].

18. Greene HL, Richardson DW, Barker AH, et al. Classification of deaths after myocardial infarction as arrhythmic or nonarrhythmic (the Cardiac Arrhythmia Pilot Study). Am J Cardiol 1989;63:1–6.

19. Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015;372:1204–12.

20. Cain KC, Lange NT. Approximate case influence for the proportional hazards regression model with censored data. Biometrics 1984;40:493–9.

21. Therneau TM GP. Modeling survival data: extending the Cox model. New York, NY: Springer-Verlag, 2000.

22. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York, NY: Springer-Verlag, 1997.

23. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.

24. Kim YH, Park DW, Lee SW, et al. Long-term safety and effectiveness of unprotected left main coronary stenting with drug-eluting stents compared with bare-metal stents. Circulation 2009;120:400–7.

25. Seo SM, Kim PJ, Shin DI, et al. Persistent coronary artery spasm documented by follow-up coronary angiography in patients with symptomatic remission of variant angina. Heart Vessels 2013;28:301–7.

26. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009;119:3028–35.

27. Lee KH, Park HW, Cho JG, et al. Predictors of recurrent sudden cardiac death in patients associated with coronary vasospasm. Int J Cardiol 2014;172:460–1.

28. Oh CM, Oh J, Shin DH, et al. Early repolarization pattern predicts cardiac death and fatal arrhythmia in patients with vasospastic angina. Int J Cardiol 2013;167:1181–7.

29. Parchure N, Batchvarov V, Malik M, et al. Increased QT dispersion in patients with Prinzmetal's variant angina and cardiac arrest. Cardiovasc Res 2001;50:379–85.

30. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1–62.

31. Mitchell LB. Use of the implantable cardioverter-defibrillator in patients with coronary artery spasm as the apparent cause of spontaneous life-threatening ventricular tachycardia or ventricular fibrillation: crossing the spasm sudden death chasm. J Am Coll Cardiol 2012;60:914–6.

32. Takahashi J, Nihei T, Takagi Y, et al. Prognostic impact of chronic nitrate therapy in patients with vasospastic angina: multicentre registry study of the Japanese Coronary Spasm Association. Eur Heart J 2015;36:228–37.

KEY WORDS angina, cardiac arrest, coronary spasm, vasospastic angina, ventricular tachyarrhythmic

APPENDIX For supplemental methods and tables, please see the online version of this article.