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.
**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).

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...
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
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) (Figure 2A) and death from any cause (HR: 4.09; 95% CI: 2.28 to 10.5; p < 0.001) (Figure 2B). The results after adjustment by IPTW was consistent (Table 2).
(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.
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 ICDs.

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).

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

<table>
<thead>
<tr>
<th>Events</th>
<th>Incidence Rate Per 1,000 Person-Yrs</th>
<th>Crude HR (95% CI)*</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>24.1</td>
<td>7.77 (4.56–13.2)</td>
<td>7.26 (4.21–12.5)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>27.5</td>
<td>2.82 (1.82–4.36)</td>
<td>3.00 (1.92–4.67)</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmia</td>
<td>32.4</td>
<td>9.81 (3.02–31.8)</td>
<td>9.81 (3.02–31.8)</td>
</tr>
<tr>
<td>Cardiac death or ventricular tachyarrhythmia</td>
<td>44.9</td>
<td>7.85 (3.58–17.2)</td>
<td>7.85 (3.58–17.2)</td>
</tr>
</tbody>
</table>

*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 Moeeschberger (22) on the basis of all available follow-up data. ASCD = aborted sudden cardiac death.
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). Non-adherence 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 tachyarrhythmia 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).
Mortality of Patients Receiving and Not Receiving ICDs

**FIGURE 3**

<table>
<thead>
<tr>
<th>Years</th>
<th>Patient at risk</th>
<th>ICD (-)</th>
<th>ICD (+)</th>
<th>Appropriate ICD treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>164</td>
<td>24</td>
<td>19</td>
<td>78</td>
</tr>
<tr>
<td>1</td>
<td>112</td>
<td>24</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>16</td>
<td>19.3%</td>
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<td>3</td>
<td>38</td>
<td>13</td>
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<td>6</td>
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<td>7</td>
<td>19</td>
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</table>

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.

**REFERENCES**


**PER 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.


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

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