Long-Term Prognosis in Recipients of Implantable Cardioverter-Defibrillators for Secondary Preventions in Taiwan – A Multicenter Registry Study

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Background: The use of an implantable cardioverter-defibrillator (ICD) has a proven capacity to prevent sudden cardiac death (SCD), and can also improve survival duration in well-selected patients. The goal of the present study was to investigate the long-term prognosis and predictors of mortalities among ICD recipients in Taiwan.

Methods: From 1998 to 2009, 238 consecutive patients who experienced SCDs or life-threatening ventricular tachyarrhythmias without correctable causes and received ICD implantations in 3 medical centers (Taipei, Taichung and Kaohsiung Veterans General Hospital) were enrolled in this study. The clinical endpoint was defined as the occurrence of all-cause mortality during the follow-up.

Results: The mean age of the patients was 63.0 ± 15.3 years, and 76.5% of them were male. Ischemic cardiomyopathy was the leading cause for the ICD implantations (39.1%). During the mean follow-up duration of 36.8 ± 29.8 months, there were 48 patients (20.2%) who died. Patients with structural heart diseases had a higher mortality rate than those without such diseases. Additionally, old age, low left ventricular ejection fraction (LVEF) and a history of diabetes mellitus (DM) were significant predictors of mortality. The optimal cutoff values for age (70 years) and LVEF (40%) in predicting mortality were further identified using the receiver operating characteristic curves.

Conclusions: Based on the ICD registry from 3 medical centers in Taiwan, the annual mortality rate was around 6.6% and was higher in those patients with structural heart diseases. We observed that old age, low LVEF and a history of DM were significant predictors of mortality.

Key Words: Implantable cardioverter-defibrillator • Mortality • Predictor • Taiwan

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INTRODUCTION

Sudden cardiac death (SCD) caused by ventricular tachyarrhythmias is a growing health concern in Taiwan and throughout the world, with an unpredictable course which can result in unfavorable medical consequences. Prevention of SCD using implantable cardioverter-defibrillator (ICD) implantation has been proven to enhance survival durations in well-selected patients.1-4 From 1996 through 2003, there was a 160% rise in the absolute number of new ICD implantations in the United States.5 Because the number of ICD implantations continues to grow, finding the most efficacious way to cor-
rectly identify patients at risk of mortality after procedures becomes an important issue. Several factors, such as age, left ventricular ejection fraction (LVEF), the presence of atrial fibrillation (AF) and diabetes mellitus (DM), were reported to be associated with a poor prognosis among recipients of ICDs. However, all of these publications originated in western countries and the data about long-term prognosis and predictors for ICD recipients in Taiwan were limited. Since the indications for ICD implantations in Taiwan were mainly limited to secondary prevention (which is significantly different from those results focusing on western countries), it remains uncertain whether the findings derived from Caucasians can be applied to Taiwanese patients. Therefore, the goal of the present study was to investigate the long-term prognosis and the predictors of mortalities among ICD recipients in Taiwan.

METHODS

Study population

From 1998 to 2009, a total of 238 consecutive patients who experienced SCDs or life-threatening ventricular tachyarrhythmias without correctable causes and received ICD implantations in 3 medical centers (Taipei Veterans General Hospital, Taichung Veterans General Hospital and Kaohsiung Veterans General Hospital) were enrolled in this study. Patient data, including baseline characteristics, clinical comorbidities, primary cardiac diagnosis, the use of anti-arrhythmia drugs and LVEF were registered and collected from these 3 sites. The study protocol was approved by the Institutional Review Board.

Implantation techniques

All patients received ICD implantations using transvenous lead systems with either single or dual chambers devices. The details of how such devices are implanted have been described in our previous work. In brief, the skin was prepared by using beta-iodine and alcohol solutions to sterilize the insertion site before the implantations occurred. Thereafter, local anesthesia was administered before any surgical incision was made. Leads were inserted transvenously through the cephalic or subclavian veins. Generators were positioned within the submuscular area of pectoralis major.

Post-implantation follow up

Patients were followed-up in the pacemaker outpatient clinic of the hospital at the interval of 2 weeks after implantation and then every 3 months to evaluate the ICD functions. Routine assessments, including free-run of electrocardiogram, retrieval of pacing parameter settings, high voltage impedance, and the sensing and pacing thresholds of leads were performed exclusively. If any therapy was noted, each episode was stored to the disc and printed out for further analysis. Patients were reminded to contact the clinic regarding any problem with the devices, such as being shocked, recurrent syncope or other cardiovascular conditions.

Interpretations of events and clinical endpoint

Stored intracardiac electrograms were analyzed to classify arrhythmias responsible for precipitating defibrillator discharges. Defibrillator discharges (shocks or pacing) were considered appropriate when triggered by ventricular fibrillation (VF) or rapid ventricular tachycardia (VT) (rate > 200 beats per minute) documented by stored electrographic or cycle length data. Interventions were considered inappropriate when triggered by heart rate exceeding the programmed threshold, as a consequence of either supraventricular arrhythmias, sinus tachycardia, or device malfunction documented by ICD interrogation. The clinical endpoint was defined as the occurrence of all-cause mortality during the follow-up.

Statistical analysis

Differences between continuous values were assessed using an unpaired 2-tailed t test for normally distributed continuous variables, the Mann-Whitney test for skewed variables, and the chi-square test for nominal variables. A Cox regression analysis was used to identify factors associated with mortalities. Variables selected to be tested in the multivariate analysis were those with a p value < 0.05 in univariate models. The optimal cut-off value of the continuous variable in the prediction of mortalities was identified using the receiver operating characteristic (ROC) curve. The mortality-free survival curve was plotted via the Kaplan-Meier method with the statistical significance examined by the log-rank test. All statistical significances were set at p < 0.05 and
all statistical analyses were carried out by SPSS 17.0 (SPSS Inc. USA).

RESULTS

Baseline characteristics and primary cardiac diagnosis

The baseline characteristics of the study population were shown in Table 1. The mean age of the patients was 63.0 ± 15.3 years (range, 16-87 years), and 76.5% of them were male. Congestive heart failure was the most prevalent underlying disease (53.8%), followed by hypertension (49.2%). The mean LVEF was 40.3 ± 13.3%, and 66.8% of the study population received ICD implantations with dual-chamber systems. The primary cardiac diagnoses responsible for the SCDs or ventricular tachyarrhythmias and subsequent ICD implantations were shown in Figure 1. Ischemic cardiomyopathy was the leading cause for the ICD implantations (39.1%), followed by idiopathic VT/VF (20.2%), dilated cardiomyopathy (17.6%), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (8.0%), hypertrophic cardiomyopathy (5.9%), Brugada syndrome (4.2%), long QT syndrome (2.9%) and other causes (2.1%). Patients with other causes (n = 5) include amyloidosis (n = 2), post-myocarditis (n = 1), catecholaminergic polymorphic ventricular tachycardia (n = 1) and noncompaction cardiomyopathy (n = 1).

Incidence of mortality

During the mean follow-up duration of 36.8 ± 29.8 months, there were 48 patients (20.2%) who died with the annual rate of around 6.6%. The baseline characteristics of patients with and without mortalities were shown in Table 1. Non-survivors were older and had more comorbidities, including DM, congestive heart failure and previous coronary artery bypass graft (CABG) surgery, and a lower LVEF compared to survivors. The percentage of the use of dual chamber system was higher in survivors than in non-survivors. The mortality rates of different groups of patients based on their primary cardiac diagnoses were shown in Figure 2. Patients with structural heart diseases had a higher mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 238)</th>
<th>Survivors (n = 190)</th>
<th>Non-survivors (n = 48)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.0 ± 15.3</td>
<td>61.0 ± 15.2</td>
<td>71.2 ± 13.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>76.5%</td>
<td>74.7%</td>
<td>83.3%</td>
<td>0.210</td>
</tr>
<tr>
<td>Smoking</td>
<td>34.0%</td>
<td>33.7%</td>
<td>35.4%</td>
<td>0.821</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49.2%</td>
<td>47.9%</td>
<td>54.2%</td>
<td>0.437</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24.4%</td>
<td>21.6%</td>
<td>35.4%</td>
<td>0.046</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>53.8%</td>
<td>45.8%</td>
<td>85.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous CABG surgery</td>
<td>15.1%</td>
<td>11.6%</td>
<td>29.2%</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>39.1%</td>
<td>37.4%</td>
<td>45.8%</td>
<td>0.283</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10.1%</td>
<td>8.9%</td>
<td>14.6%</td>
<td>0.184</td>
</tr>
<tr>
<td>Use of AADs</td>
<td>73.9%</td>
<td>72.6%</td>
<td>79.2%</td>
<td>0.357</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>40.3 ± 13.3</td>
<td>42.5 ± 12.6</td>
<td>31.3 ± 11.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dual chamber system</td>
<td>66.8%</td>
<td>72.1%</td>
<td>45.8%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

AADs, antiarrhythmic drugs (amiodarone or mexiletine); CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.
rate (28% for ischemic cardiomyopathy, 21.4% for dilated cardiomyopathy, 21.4% for hypertrophic cardiomyopathy) than those without structural heart diseases. Among the group with other uncommon etiologies (n = 5) as mentioned above, patients with amyloidosis (n = 2) and history of myocarditis (n = 1) all died during the follow-up period.

**Predictors of mortality**

The results of Cox regression analysis in predicting mortality were shown in Table 2. Age, DM, congestive heart failure, previous CABG surgery and LVEF were significant predictors of mortality in the univariate model. After the adjustment in the multivariate analysis, age, DM and LVEF remained as independent factors in predicting mortalities. At the cutoff value of 70 years identified by the ROC curve (Figure 3A), Kaplan-Meier survival analysis showed that patients older than 70 years old had a higher mortality rate than those younger than 70 years old (32.0% versus 11.1%, p value < 0.001) (Figure 3B). The ROC curve of LVEF in predicting mortalities was shown in Figure 4A. At the cutoff value of 40%, Kaplan-Meier survival analysis showed that patients with a LVEF higher than 40% had a favorable outcome more frequently than those with a LVEF lower than 40% (33.3% versus 6.8%, p value < 0.001) (Figure 4B).

**Incidence and causes of inappropriate shock**

There were 34 patients (14.3%) suffering from inappropriate shocks during the study period. Among these patients, AF (n = 11) and sinus tachycardia (n = 10) accounted for 61.8% of the causes (Figure 5). Other etiologies in-

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**Table 2. Cox regression analysis for predictors of mortality of ICD implantations**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.055</td>
<td>1.028-1.082</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.122</td>
<td>0.521-2.414</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.029</td>
<td>0.566-1.870</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.427</td>
<td>0.807-2.525</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.336</td>
<td>1.286-4.243</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.942</td>
<td>2.214-11.029</td>
</tr>
<tr>
<td>Previous CABG surgery</td>
<td>2.608</td>
<td>1.395-4.877</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1.449</td>
<td>0.819-2.567</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.647</td>
<td>0.737-3.681</td>
</tr>
<tr>
<td>Use of AADs</td>
<td>1.339</td>
<td>0.666-2.690</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.941</td>
<td>0.919-0.964</td>
</tr>
<tr>
<td>Dual chamber system</td>
<td>0.980</td>
<td>0.526-1.826</td>
</tr>
</tbody>
</table>

* The multivariate analysis included variables whose p values were < 0.05 in univariate models.

AADs, antiarrhythmic drugs (amiodarone or mexiletine); CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

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**Figure 2. Mortality rates of patients with different etiologies of ICD implantations.** Patients with structural heart diseases had a higher mortality rate (28% for ischemic cardiomyopathy, 21.4% for dilated cardiomyopathy, 21.4% for hypertrophic cardiomyopathy) than those without structural heart diseases. Among the group with other uncommon etiologies (n = 5), patients with amyloidosis (n = 2) and history of myocarditis (n = 1) died during the follow-up period. * The group includes patients with amyloidosis (n = 2), post-myocarditis (n = 1), catecholaminergic polymorphic ventricular tachycardia (n = 1) and noncompaction cardiomyopathy (n = 1). ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.
cluded T wave oversensing (n = 8; 23.5%) and insulation break of leads with electrical interference or myopotentials (n = 5; 14.7%). The relationship between the occurrences of inappropriate shocks and mortality did not reach a statistical significance with a hazard ratio of 2.191 (95% confidence interval = 0.676-7.097, p value = 0.191).

DISCUSSION

Main findings

In this study, we investigated the prognosis and risk factors of mortalities for patients receiving ICD implantations. The main findings were as follows: (1) Ischemic cardiomyopathy was the most common primary cardiac diagnosis among ICD recipients; (2) The annual mortality rate was around 6.6%, and was higher in patients with structural heart diseases; and (3) Age, DM and LVEF were independent predictors of mortalities for patients receiving ICD implantations.

Prognosis and predictors of mortalities

Several studies from western countries have reported the predictors of mortality among ICD recipients. In the observational cohort study performed by Kremer et al. which enrolled 2717 ICD patients (mean age = 64.6 ± 14.5 years old, male = 77.2%, primary prevention = 74.7%) from 3 medical centers in the United States, peripheral arterial diseases, age ≥ 70 years, creatinine ≥ 2.0 mg/dl, and LVEF ≤ 20% were recognized as significant predictors of 1-year mortality. Stein et al. also tried to identify important factors associated with a poor prog-
nosis in 1703 patients receiving ICD implantations, and demonstrated that a history of AF, DM, low body mass index, low mean arterial pressure, and poor functional status significantly predicted the occurrences of mortalities at 1 year. In the present study which enrolled patients receiving ICD implantations for secondary preventions and underwent a long-term follow up, several factors, including the history of diabetes, an increasing age and a low LVEF, were identified as independent predictors of mortality which were consistent with that reported from the studies mentioned above. Since the most common etiology responsible for the implantations of ICDs in our study was ischemic heart disease, it is reasonable that DM, an important factor involved in the process of atherosclerosis and regarded as a coronary heart disease risk equivalent, was strongly associated with mortality.

The optimal cutoff values of age (70 years) and LVEF (40%) in predicting mortality were reported in the present study. For patients who were younger than 70 years old, had a LVEF larger than 40% and had no diabetes, the mortality was as low as 2.8%. On the contrary, the mortality rate was very high (38.9%) for diabetic patients who were older than 70 years of age and had a LVEF smaller than 40%. Previous studies have demonstrated that implanting devices in patients who are too sick to benefit from the intervention is not cost-effective. Clinical physicians should pay more attention to these high-risk patients, and more aggressive treatments of underlying diseases may be considered to improve the survivals.

**Comparisons with previous studies in Taiwan**

There were only 2 previous studies reporting the status of ICD implantations in Taiwan. Tsai et al. studied 92 patients receiving ICD implantations from 1995-2001 at 12 hospitals, and demonstrated that older age was the only factor associated with poor survival. Chen et al. reported data about 46 patients at a single-center from 1996 to 2006, and showed that left ventricular function is a major determinant affecting the outcome in ICD recipients. Compared to these previous studies, the present investigation enrolled a larger number of patients and may greatly strengthen the statistical power. Besides, patients enrolled in the present study were almost equally from the north (n = 80), middle (n = 86) and south (n = 72) parts of Taiwan and may be more able to represent the real condition in Taiwan.

**Study limitations**

There were several limitations of the present study. First, all study subjects received ICD implantations for the purposes of secondary preventions due to the rules of the National Health Insurance system in Taiwan. Whether the results presented here can be applied to ICD recipients for primary preventions remained uncertain. Second, the present study was a retrospective registry survey, and therefore some detailed data, such as body mass index and renal function, were not available. We were also not able to clarify the causes of deaths clearly. Third, although we analyzed the data of patients receiving ICD implantations in 3 medical centers, the case number was still limited. This may explain why we only found a trend suggesting that inappropriate shock may be a risk factor of mortality without reaching a statistical significance. Based on the limitations mentioned above, a prospective study enrolling ICD recipients from all hospitals in Taiwan is necessary to help us further understand the prognosis of Taiwanese patients receiving ICD implantations.

**CONCLUSIONS**

Based on the ICD registry from 3 medical centers in Taiwan, ischemic cardiomyopathy was the most common primary cardiac diagnosis of ICD recipients. The
annual mortality rate was around 6.6% for all patients, which was higher in those with structural heart diseases. Furthermore, old age, low LVEF and the history of DM were significant predictors of mortality.

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DISCLOSURES

None.

REFERENCES