Incidence of Implantable Cardioverter Defibrillator Therapy and Mortality in Primary and Secondary Prevention of Sudden Cardiac Death

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ABSTRACT: **Background:** Implantable cardioverter defibrillators (ICDs) reduce mortality in patients implanted for primary and secondary prevention of sudden cardiac death. Data on the incidence of appropriate ICD therapies in primary vs. secondary prevention are limited.

Objectives: To compare ICD therapies and mortality in primary vs. secondary prevention of sudden cardiac death.

Methods: We conducted a retrospective analysis of 581 consecutive patients receiving an ICD for primary (66%) or secondary (34%) prevention indications.

Results: During long-term follow-up, 29% of patients implanted for secondary prevention received appropriate ICD therapy vs. 18% implanted for primary prevention. However, the overall 7 year mortality rate was not significantly different between the two groups (26.9%, $P = 0.292$). Multivariate analysis showed that patients implanted for primary prevention had a significantly lower risk of appropriate ICD therapy even after adjustment for age, left ventricular ejection fraction < 0.35 and chronic renal failure (HR 1.63, 95%CI 1.10–2.41, $P = 0.015$).

Conclusions: Patients implanted for secondary prevention were more likely to receive appropriate ICD therapy, with a significantly shorter time period from ICD implant to the first therapy. However, all-cause mortality was comparable between primary and secondary prevention groups.

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KEY WORDS: implantable cardioverter defibrillator (ICD), primary prevention, secondary prevention, sudden cardiac death

Implantable cardioverter defibrillators (ICDs) have been shown to reduce mortality in high risk cardiac patients without a history of sustained ventricular arrhythmia (primary prevention) [1,2] as well as in patients who survived a potentially fatal cardiac arrhythmia (secondary prevention) [3-5]. Data on the incidence of appropriate ICD therapies in the primary prevention versus secondary prevention population are limited. According to the Multicenter Automatic Defibrillator Implantation (MADIT) trial, the number needed to treat to save one life from arrhythmic death in the primary prevention population was 10 patients over 2.25 years follow-up [1]. However, among secondary prevention trials, this rate varied from 5 in the Cardiac Arrest Study Hamburg (CASH) to 27 in the Canadian Implantable Defibrillator Study (CIDS) over a 3 year follow-up [3,4]. Given the conflicting data, the aim of the current analysis was to compare ICD therapies and mortality in patients who received an ICD for primary vs. secondary prevention indication, and to assess the predictors of appropriate ICD therapies and mortality in these patients.

PATIENTS AND METHODS

The study enrolled 581 consecutive patients who underwent ICD implantation for primary or secondary prevention of sudden cardiac death in a tertiary care university medical center in Israel between the years 1996 and 2009. Patients were seen at the device clinic every 6 months during a median follow-up of 4.3 years (interquartile range 2.8–6.9 years). Patients who were not seen on a regular basis every 6 months were excluded from the current analysis. Devices were programmed according to physician discretion at the time of the implantation and reprogrammed as required during follow-up at the device clinic. By default, devices were programmed to three consecutive zones: (i) monitor zone without therapies, (ii) ventricular tachycardia (VT) zone with anti-tachycardia pacing (ATP), followed by shocks and (iii) ventricular fibrillation (VF) zone treated with shocks.

DEFINITIONS

Device interrogation was performed during each visit, and therapies were systematically analyzed and adjudicated by a cardiac electrophysiologist as appropriate (delivered because of ventricular tachycardia or fibrillation) or inappropriate (supraventricular arrhythmia, electrode dysfunction, T-wave over-sensing or electromagnetic interference). Patients were classified as having at least one appropriate shock or ATP, one inappropriate shock or ATP, both or none. Primary outcome was time to the first appropriate therapy. Secondary outcome was all-cause mortality.

STATISTICAL ANALYSIS

Categorical data are expressed as absolute numbers and percentages; continuous parameters are presented as mean ± SD. Differences were assessed with the independent-sample *t*-test for continuous variables and chi-square test for categorical variables. Kaplan-Meier curves and log-rank test were used to compare the incidence of ICD therapy and/or mortality between patients who received an ICD for primary prevention vs. secondary prevention. Competing-risks analysis was used to compare time to the first appropriate ICD therapy, under the assumption of all-cause mortality as the competing-risk event. The association between baseline characteristics and outcome was assessed by Cox proportional hazards regression analysis and described as odds ratios (OR) and 95% confidence interval (CI). Statistical significance was calculated using the Gray and Fine method [6]. The following variables were introduced into the model: age, left ventricular ejection fraction (LVEF) < 0.35, history of chronic renal failure, implantation indication, ischemic heart disease and atrial fibrillation (AF). Additionally, we performed Cox proportional hazards regression analysis for the all-cause mortality outcome. Two-sided *P* values < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

BASELINE CHARACTERISTICS

Of the 581 patients assessed, 383 (66%) underwent ICD implantation for primary prevention and 198 (34%) for secondary prevention. Baseline characteristics of the study population are shown in Table 1. Approximately 80% of patients suffered from ischemic heart disease, and 25% had symptoms of heart failure in each group. There were no significant differences between the two groups with respect to age, gender, chronic renal failure or hypertension. However, the primary prevention population had a higher prevalence of diabetes (36% vs. 24%, $P = 0.006$) and LVEF < 0.35 (72% vs. 61%, $P = 0.013$). Cardiac resynchronization therapy (CRT) was significantly more common in the primary prevention group (31% vs. 15%, $P < 0.001$), whereas a single-chamber device was more prevalent in the secondary prevention group (43% vs. 27%, $P < 0.001$). This is most likely related to the significantly higher prevalence of LVEF < 0.35 among patients implanted for primary prevention since the major criterion for CRT implantation is severely reduced systolic LVEF in addition to clinical signs of heart failure and wide QRS, preferably with a left bundle branch block pattern.

APPROPRIATE ICD THERAPY

During 7 years of follow-up, 18% (Kaplan-Meier rate) of patients in the primary prevention group (annualized rate 2.8%) vs. 27% in the secondary prevention group (annualized rate 4.4%) received appropriate ICD therapy (shocks or ATP)

Table 1. Baseline characteristics of patients implanted for primary vs. secondary prevention

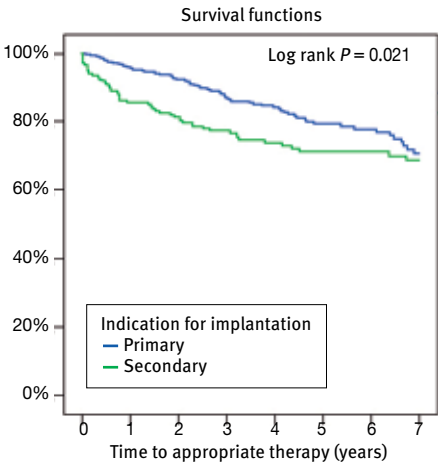
Variables		Primary prevention (N=383)	Secondary prevention (N=198)	*P* value
Age, years (mean ± SD)		65.0 ± 12.8	64.8 ± 13.5	0.857
Male gender		328 (86)	176 (89)	0.274
LVEF < 0.35		244 (72)	106 (63)	0.013
Ischemic heart disease		316 (83)	157 (79)	0.345
Congestive heart failure		96 (25)	51 (26)	0.856
Atrial fibrillation		80 (21)	50 (25)	0.231
Chronic renal failure		119 (31)	69 (35)	0.356
Diabetes mellitus		138 (36)	49 (25)	0.006
Essential hypertension		185 (48)	95 (48)	0.941
Pacing mode	Single chamber	104 (27)	85 (43)	< 0.001
	Dual chamber	194 (51)	117 (59)	0.053
	CRT	120 (31)	30 (15)	< 0.001

Data are presented as number of patients (%)

No. of patients = 581, no. of devices = 800. Notably, 219 patients had more than one device during the follow-up period

LVEF = left ventricular ejection fraction, CRT = cardiac resynchronization therapy

Figure 1. Kaplan-Meier curves of time period since ICD implantation to the first appropriate ICD therapy in primary vs. secondary prevention



($P = 0.021$) [Figure 1]. In univariate analysis only a secondary prevention indication was found to predict the first appropriate therapy [hazard ratio (HR) 1.54, 95%CI 1.07–2.22, $P = 0.021$], whereas age, LVEF < 35%, coronary artery disease, atrial fibrillation, diabetes and chronic renal failure were not found to predict the first appropriate ICD therapy.

Figure 2 depicts the cumulative incidence of the first appropriate therapy with comparison between primary and secondary prevention adjusted for the competing risk of all-cause mortality. The competing-risks Cox regression model demonstrated that patients in the primary prevention group had a significantly

Figure 2. Cumulative incidence of appropriate therapy in primary prevention vs. secondary prevention with all-cause mortality as competing-risks event (dashed lines correspond to 95% confidence interval)

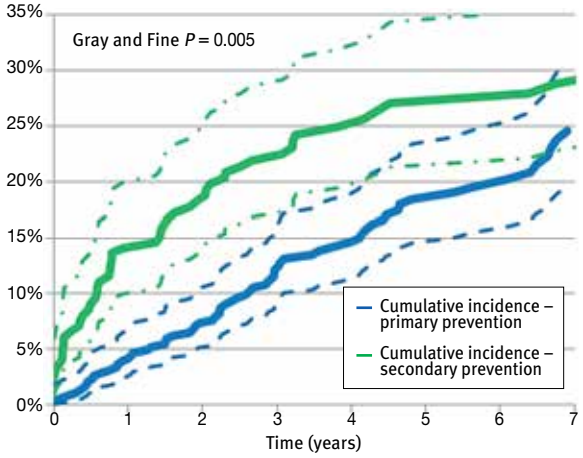
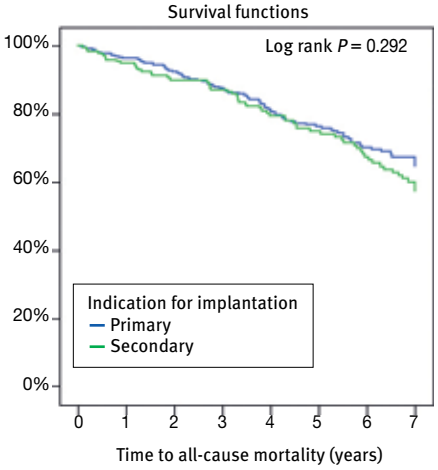


Figure 3. Kaplan-Meier curves of all-cause mortality in primary vs. secondary prevention



lower risk of appropriate ICD therapy, after adjustment for age, LVEF < 0.35 and chronic renal failure (HR 1.63, 95%CI 1.10–2.41, $P = 0.015$).

The first appropriate ICD therapy was administered for VT in approximately 90% of patients, whereas only 10% of the first appropriate therapy was administered for VF. Notably, a substantial number of patients received an anti-arrhythmic medication at the time of the first appropriate ICD therapy (47% of subjects with a history of AF vs. 25% without).

INAPPROPRIATE ICD SHOCKS

The rate of inappropriate shocks was relatively low, with no significant difference between primary or secondary prevention groups (3.6% vs. 5.7% appropriately). Importantly and in accordance with the literature, a history of atrial fibrillation was found to predict inappropriate ICD shocks delivery (OR 2.3, 95%CI 1.04–5.31, $P = 0.04$), whereas gender, LVEF, coronary artery disease, chronic renal failure, diabetes, hypertension and implantation indication (primary vs. secondary prevention) were not found to predict the risk of inappropriate ICD shocks.

MORTALITY

During the study period, 23% of patients in the primary prevention group (annualized rate 3.7%) and 30% of patients in the secondary prevention group died (annualized rate 5.0%, $P = 0.292$) [Figure 3]. Overall mortality was 26.9% (annualized rate 4.2%). Median follow-up time for the primary and secondary prevention groups was 4.3 years (IQR 2.8–6.5) and 4.6 years (IQR 3.2–8.2) respectively ($P = 0.044$). In multivariate Cox proportional regression analysis, age (HR 1.04, 95%CI 1.02–1.06), LVEF < 0.35 (HR 2.60, 95%CI 1.60–4.20) and chronic renal failure (HR 1.57, 95%CI 1.09–2.26) were found to be independent predictors of all-cause mortality, whereas the indication for ICD (primary vs. secondary) was not found to predict all-cause mortality (HR 1.11, 95%CI 0.78–1.57).

DISCUSSION

The present study enrolled 581 consecutive patients who underwent ICD implantation for primary or secondary prevention between the years 1996 and 2009. A retrospective analysis of ICD therapies and mortality was performed, revealing several important findings. First, patients implanted for secondary prevention were more likely to receive an appropriate ICD therapy, with a significantly shorter time period from ICD implant to the first therapy, even after adjustment for competing risk of all-cause mortality [Figure 2]. Although the rates of ICD therapy tend to overestimate arrhythmic death risk, we have no reason to assume differences between the primary and secondary groups. Thus, the higher event rate in the secondary prevention group points to a higher risk of recurrent arrhythmia and death. This finding is further emphasized by the fact that the currently known major risk factor for arrhythmic death, reduced LVEF, was more prevalent in the primary prevention group. Our findings are further supported by data reported by van Welsenes et al. [7], who assessed the differences in mortality and ICD therapy in 2134 primary and secondary ICD recipients and found that primary prevention patients exhibit a lower risk of appropriate therapy but comparable mortality rates. Both groups showed similar occurrence of inappropriate shocks [7]. Likewise, Dichtl et al. [8] who analyzed ICD therapy and mortality in 1117 patients implanted for primary or secondary prevention of sudden cardiac death concluded that patients implanted for secondary prevention were more likely to receive appropriate therapy, while mortality was not different between the two groups [8]. Thus,

our data, along with those of others [7,8], suggest that additional treatment may be required to prevent future ICD therapies in patients implanted for secondary prevention indication. The SMASH-VT trial (Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia) [9] demonstrated a significant 73% reduction in future ICD shocks with radiofrequency catheter ablation in post-myocardial infarction patients implanted with an ICD for secondary prevention.

Another important finding is the constant cumulative incidence of the first appropriate ICD therapy in the primary prevention population that reaches 20% at 6 years post-implantation, implying that patients implanted for primary prevention remain at risk for a potentially lethal arrhythmia over the years. It demonstrates the long-term benefit of an ICD in patients implanted for a primary prevention indication, even among those who did not experience ventricular arrhythmia over the first few years following device implantation. This is supported by the extended follow-up of the MADIT II trial, which demonstrated that treatment with an ICD for primary prevention was associated with a significant reduction in the risk of death throughout a long-term period including the late phase of follow-up between the 5th and 8th years [10].

The current analysis, which also assessed mortality differences between primary and secondary prevention patients, revealed an interesting finding. Despite the higher incidence of appropriate ICD therapies in the secondary prevention group, overall mortality was similar between the two groups. This may be explained by the higher incidence of non-arrhythmic death in the primary prevention group, related to more comorbidities such as diabetes and low ejection fraction in the latter. Following the recently published MADIT-RIT [11], more liberal programming of ICDs might reduce the rate of therapies in the primary prevention population.

Ultimately, in Cox regression analysis, age, LVEF < 0.35, chronic renal failure and secondary prevention were all found to predict the composite endpoint of the first appropriate ICD therapy or death. Reduced ejection fraction is currently the major criterion for ICD implantation in the primary prevention population, but it also has an important predictive role in patients implanted for a secondary prevention indication. In a meta-analysis of the secondary prevention trials (AVID, CIDS, CASH), patients with LVEF ≤ 35% derived the most benefit from ICD therapy as compared to amiodarone therapy [12]. Optimization of medical therapy for heart failure, and the use of cardiac resynchronization therapy in appropriately selected patients, might improve outcome in both primary and secondary prevention patients with a significant LV dysfunction.

LIMITATIONS

This was a retrospective analysis performed in a single medical center. In addition, since data regarding the cause of death are missing, we cannot draw firm conclusions regarding the differences in mortality between patients implanted for primary vs. secondary prevention of sudden cardiac death. ICD programming was left to physician discretion, which might have influenced the rate of therapies. Finally, we did not analyze separately ATP and ICD shocks among patients implanted for primary prevention vs. secondary prevention.

CONCLUSIONS

Patients implanted with an ICD for a secondary prevention indication were more likely to receive appropriate ICD therapy, with a significantly shorter time period from ICD implant to the first appropriate therapy. However, a considerable cumulative incidence of a first appropriate ICD therapy was also demonstrated in the primary prevention group (20% at 6 years post-implantation). Overall mortality was not significantly different between primary and secondary prevention patients.

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