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ORIGINAL ARTICLE

Long-term clinical outcomes in implantable cardioverter defibrillator recipients on the island of Crete

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KEYWORDS
Implantable cardioverter defibrillator;
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Complications

Abstract *Purpose:* The aim of the current study is to disseminate long-term "real-world" data on mortality and device therapies in primary and secondary prevention implantable cardioverter defibrillator (ICD) recipients on the island of Crete.
Methods: We analyzed data for all consecutive patients who received an ICD in our tertiary university hospital from 1993 until December 2013. Follow-up visits were performed every 6 months or more frequently when indicated. Survival status was recorded, and all stored episodes during interrogation were registered and classified as appropriate or inappropriate.
Results: In total, 854 patients received an ICD; 623 (73%) for primary and 231 (27%) for secondary prevention. Most of these patients (490) suffered from ischemic cardiomyopathy. During the mean follow-up of 12.4 ± 7.8 years, 218 (25.5%) patients died; 19.7% in the primary prevention group ($p=0.008$) and 41.1% in the secondary prevention group. Overall, 248 patients (29%) received appropriate therapy; however, the percentage was significantly higher in the secondary prevention group (44.2%) than in primary prevention group (23.4%). The cumulative incidence of inappropriate therapies during the mean follow-up period was 11.6%. Lead-related complications were noted in 49 patients (5.7%), while only 13 patients (1.5%) suffered device-related infections.

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Conclusions: The long-term data related to clinical outcomes in ICD recipients in our center are in accordance with those of other international centers and confirm the high efficacy and safety of these devices in preventing sudden cardiac death.

1. Introduction

Thirty-five years after its first implantation in humans, the implantable cardioverter defibrillator (ICD) remains the cornerstone therapy for the prevention of sudden cardiac death (SCD).[1] This therapy's clinical superiority over optimum pharmacological therapy has been validated in a number of well-designed prospective randomized trials.[2–4]

These clinical trials were performed in well-selected and protected patient populations, and the implications for routine clinical practice have always been an attractive challenge.

The benefits of ICDs in reducing all-cause mortality have been proven in both patients surviving a life-threatening event (secondary prevention),[2,3,5] and those at high risk, but without such an event (primary prevention).[4,6–8]

Beyond the borders of randomized clinical trials, a relative scarcity of data exists on the long-term follow-up outcomes of such patients in the context of tertiary hospital-ICD implantation centers.

Therefore, the aim of the current study is to disseminate long-term "real-world" data on mortality and device therapies in primary and secondary prevention in ICD recipients on the island of Crete.

2. Methods

2.1. Patient population

From 1993, when the first ICD was implanted in a patient on the island of Crete, until today, the Electrophysiology Lab (EP) of the Cardiology Department at Heraklion University Hospital remains the only implantation center on the island. Therefore, all patients on our island, who were subjected to ICD implantation from 1993 to December 31, 2013, were included.

Device implantations were based on international guidelines, and all implantations were performed after approval by the Central Board of Health (KESY), as required by law.

The study population was grouped according to prevention type: primary or secondary for SCD, and the implanted device type: single-chamber ICD, dual-chamber ICD, or Cardiac Resynchronization Therapy - Defibrillator (CRT-D).

All patients were followed from the time of their initial ICD implantation until their death from any cause or until the end of the study period.

All-cause mortality and appropriate defibrillator therapies (ATP and shocks) were considered the primary endpoints of the study, while device replacements, device-related complications and inappropriate shocks were considered as secondary endpoints.

The study was conducted in accordance with the Declaration of Helsinki (1989),World Medical Association (WMA), as revised in Edinburgh (2000). No ethical approval is required for retrospective registry-based studies in Greece.

2.2. Devices

Implanted systems, devices and electrodes, were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, MA, USA, formerly CPI, Guidant (St. Paul, MN, USA)), ELA Medical Inc. (Sorin Group), Medtronic (Minneapolis, MN, USA) and St. Jude Medical (St. Paul, MN, USA).

2.3. Follow-up and device interrogation

Baseline clinical characteristics for all patients were collected preoperatively and were recorded by the implanters, including demographics, medical history, and underlying cardiac disease. After the implantation procedure, all of the possible perioperative complications and initial ICD programming characteristics were recorded. Periodical follow-up visits were performed every 6 months or more frequently when indicated. At each visit, device interrogation was performed by electrophysiologists. During interrogation, all stored episodes were registered and classified as appropriate or inappropriate. All other device-related complications and clinical observations were also recorded. Survival status was retrieved by the patient's relatives (after communication, in case of loss of a date), and in most cases was confirmed after contact with their physicians.

2.4. Statistical analysis

Summary descriptive statistics are presented as frequency (%), or mean $+/-$ standard deviation, as appropriate. Comparisons between primary and secondary prevention groups were performed using independent samples t-test and chi-square test for continuous and categorical variables, respectively. Kaplan-Meier product-limit estimate survival curves were constructed and compared via the log-rank test. All statistical tests were two-sided with a 5% level of significance using the IBM-SPSS software package.

3. Results

3.1. Demographics

During the period 1993-2013, a total of 854 patients were subjected to initial ICD implantation. The annual

implantation rate is shown in Fig. 1. Male patients were more prevalent, 757 (88.6%) versus 97 (11.4%) females. The mean age of patients was 62.9 ± 11.6 years old (range 18–88).

From the total 854 patients, 623 (73%) were subjected to ICD implantation for primary and 231 (27%) for secondary prevention.

Out of the same total, the majority of these patients 490 (57.4%) suffered from ischemic cardiomyopathy, 265 patients (31%) from non-ischemic dilated cardiomyopathy (DCM), 41 (4.8%) from hypertrophic cardiomyopathy (HCM) and 58 (6.8%) patients had a primary electrical disorder (channelopathy). The baseline clinical characteristics of our patients are illustrated in Table 1.

The distribution of ICDs was as follows: 69.6% of our patients received a dual-chamber ICD, 20.5% received a single-chamber ICD, and in 9.9% a CRT-D device was implanted.

3.2. Mortality

During a mean follow-up of 11.2 ± 7.8 years, 218 (25.5%) patients died. Compared with the primary prevention group, the incidence of all-cause mortality was significantly higher in the secondary prevention patient group. In particular, the cumulative incidence of mortality during follow-up was 41.1% for secondary prevention patients and 19.7% for primary prevention patients, (log rank = 7.117 p = 0.008), (Fig. 2).

The deaths occurred mainly due to cardiovascular causes (54.1%), followed by malignancies (25.7%) and other non-cardiovascular causes (20.2%).

3.3. Defibrillator therapies

A total of 1,453 appropriate ICD interventions (ATP or shock) were received by 248 patients (29%). The cumulative incidence of appropriate therapy during follow-up was 23.4% in primary prevention patients, compared to 44.2% in secondary prevention patients (log rank 8.362 p<0.004), (Fig. 3).

From the 146 primary prevention patients who received an appropriate therapy, the cumulative incidence of first appropriate ICD therapy was 23.9% in the first year post-implantation, which increased to 44.4% in the second year, and in the fifth year reached 85.6%.

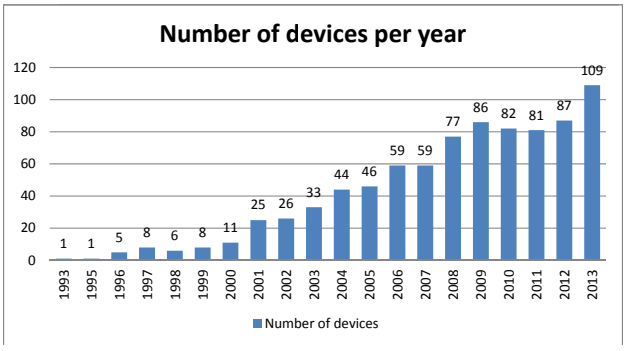

Figure 1 Number of implantation devices per year 1993–2013.

Table 1 Patient baseline clinical characteristics.

	Primary prevention n = 623	Secondary prevention n = 231	p
Age (years)	62.5±11.3	63.9±12.6	0.129
Sex			0.021
Male	562 (90.21%)	195 (84.42%)	
Female	61 (9.79%)	36 (15.58%)	
Ejection Fraction (%)	28±13	39±9	0.01
Underlying heart disease			<0.001
ICM	358 (57.46%)	132 (57.14%)	
DCM	199 (31.94%)	66 (28.57%)	
HCM	35 (5.62%)	6 (2.60%)	
Channelopathy	31 (4.98%)	27 (11.69%)	
History			0.03
MI	307 (49.28%)	118 (51.08%)	
GABG	184 (29.53%)	39 (16.88%)	
PCI	169 (27.13%)	75 (32.47%)	
Co-morbidities			0.51
Hypertension	162 (26.00%)	49 (21.21%)	
Diabetes mellitus	124 (19.90%)	46 (19.91%)	
Atrial fibrillation	78 (12.52%)	21 (9.09%)	
Type of device			0.266
DR	426 (68.38%)	168 (72.73%)	
VR	129 (20.71%)	46 (19.91%)	
CRT-D	68 (10.91%)	17 (7.36)	

From the 102 secondary prevention patients who received an appropriate therapy, the cumulative incidence of first appropriate ICD therapy was 21.6% in the first year post-implantation, which increased to 34.3% in the second year, and in the fifth year was 62.7%.

Notably 42 patients (4.9%) received their first appropriate therapy after device replacement.

The total number of appropriate defibrillator shocks was 1,108. One or more appropriate shocks were received by 184 patients; 131 in the primary prevention group and 53 in the secondary prevention group.

In total, 331 inappropriate therapies occurred in 99 patients. The cumulative incidence of inappropriate therapies during the mean follow-up period of 11.2 ± 7.8 years was 11.6%. The majority (81.5%) were due to supraventricular tachycardias, mainly atrial fibrillation.

3.4. Device replacements

During follow-up, 187 devices (21.9%) were replaced. ICD recipients required their first device replacement after a mean follow-up of 5.8±1.6 years; whereas, in CRT-D recipients device replacement was required after a mean follow-up of 4.5±1 years.

3.5. Device-related complications

There were 13 patients (1.5%) who suffered from a device-related infection requiring device extraction or revision. Lead-related complications were noted in 49 patients

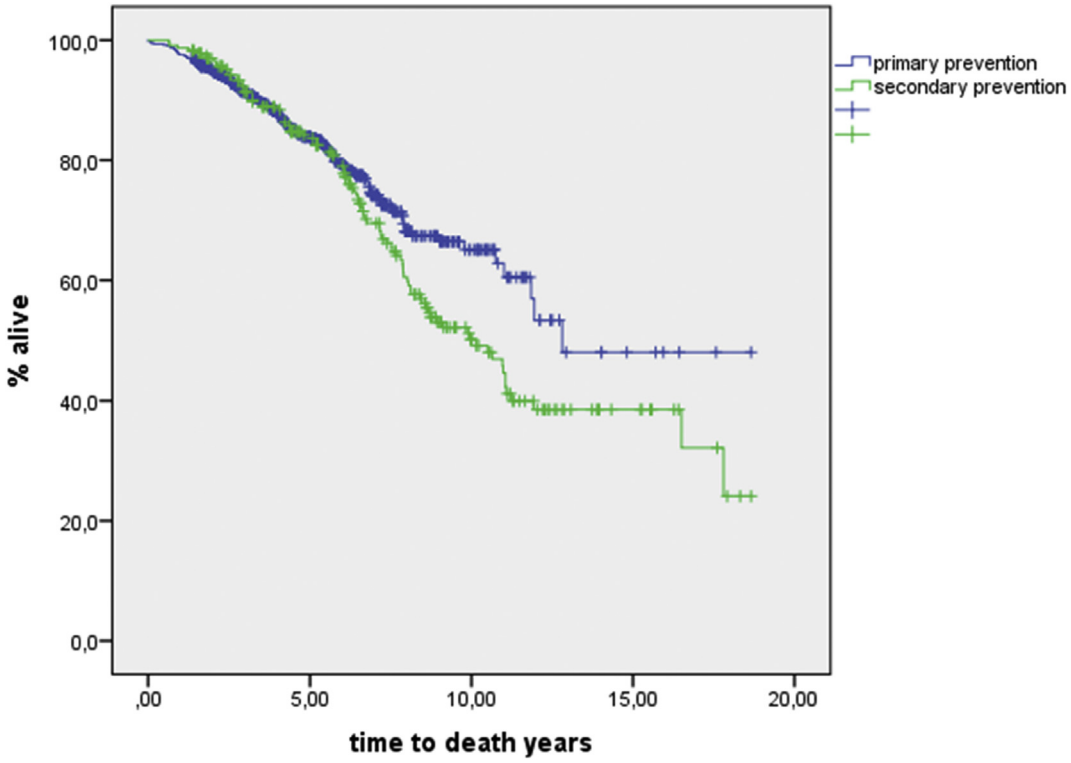

Figure 2 All-cause mortality. Kaplan Meier curves of all-cause mortality for primary and secondary prevention ICD recipients.

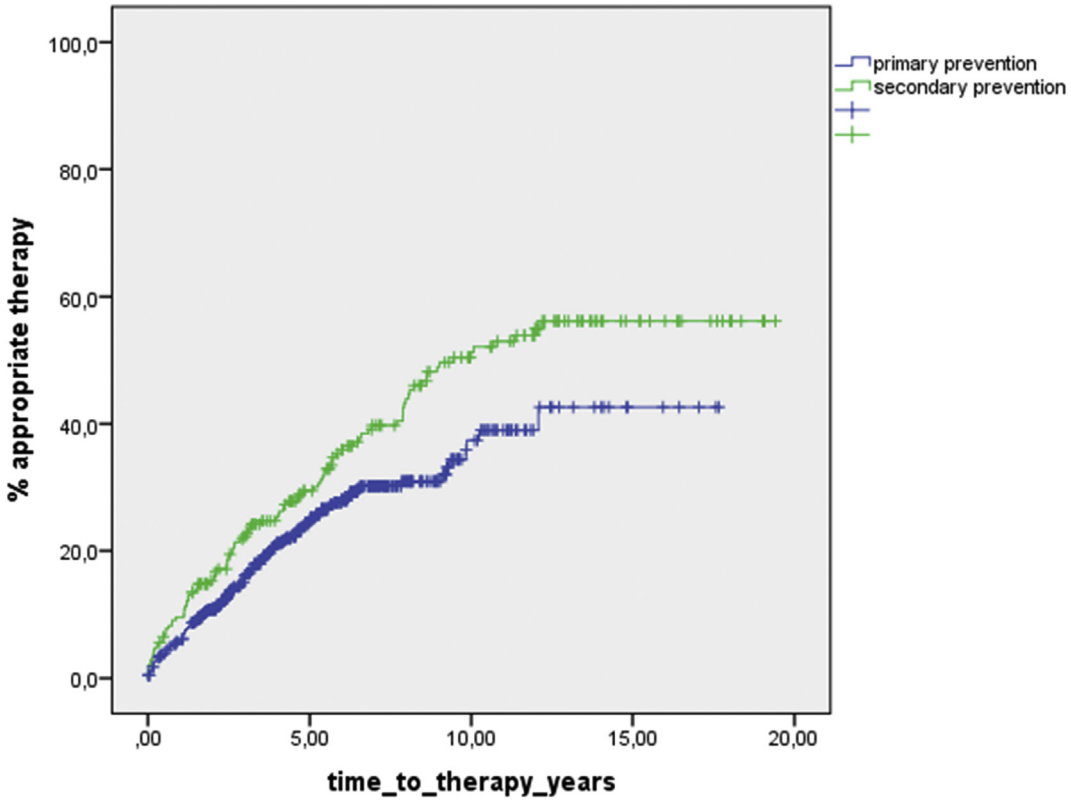

Figure 3 Appropriate therapy. Kaplan-Meier curves of appropriate therapy for primary and secondary prevention ICD recipients.

(5.7%); 32 patients were subjected to replacement or repositioning, and in 17 patients the lead was inactivated. In 22 (2.6%) of these cases, failure was attributed to leads with known lead failure (Sprint Fidelis or Riata leads).

3.6. Other analyses

We also performed multivariate Cox regression analysis on the risk of mortality or appropriate therapies with the underlying heart disease type and co-morbidities (hypertension, diabetes, atrial fibrillation). No association between change in risk and any of the covariates was identified.

4. Discussion

The main findings of the current registry from the only ICD implantation center on Crete, the University Hospital of Heraklion, are summarized as follows: during a long period of 21 years, 854 ICDs were implanted; 25.5% of ICD recipients died and 29% received an appropriate therapy by their device. Most patients received an ICD for primary prevention of SCD, and the majority suffered from ischemic cardiomyopathy. Inappropriate shocks occurred in 11.6%, device-related infection was noted in 1.5% and lead failure in 2.6% of our patients. During the study period, 21.9% of the patients had their device replaced, and it is noteworthy that 4.9% of these received their first appropriate therapy after device replacement.

To the best of our knowledge, this report describes the largest ICD registry from Greece to be published to date. Heraklion's implantation center is one of 24 implantation centers in Greece, and it is worth highlighting that such registries are extremely useful, as they provide all physicians, research scientists, healthcare providers, healthcare economists and politicians the opportunity to evaluate a wide range of data and to extract valuable information from the elaborated findings, as they provide real-world data, which may be used to improve Greek health, and moreover, the Greek healthcare system.

The majority of ICD implantations (73%) at our center were for primary prevention of SCD. This finding is in contrast to previously published registry data from North Greece, where the majority of patients received an ICD for secondary prevention (72%). This difference can be explained from the registration time period. The North Greece center recorded ICD implantations from 2002—2007, before the publication of large randomized clinical trials that influenced international guidelines and clinical practice on the primary prevention of SCD.[9]

A typical example of this shift in trend was demonstrated by the Italian registry, where it was reported that in 2005, 44.2% of the ICD procedures were for primary prevention and 55.8% for secondary prevention; but in 2007, 55.7% of such implantations were for primary prevention and 44.3% for secondary prevention.[10]

Our percentages are similar to other European registries, demonstrating that current international guidelines have been adopted by Greek cardiologists.[11,12]

Undoubtedly, ICDs improve survival in patients at high risk of SCD. This benefit is confirmed after a relatively short period of follow-up time. In MADIT-II and SCD-HeFT survival was 19.5 and 46.1 months, respectively.[4,7] Data on the long-term efficacy of defibrillator therapies are rare. In a primary prevention population, an extended 8-year follow-up of MADIT-II demonstrated a sustained survival benefit.[13] In secondary prevention patients, the benefit of ICD over amiodarone was confirmed after an extended follow-up of 11 years, in a subset of CIDs.[14]

Whether these benefits differ from those of trial-eligible patients receiving an ICD in routine clinical practice remains a challenging question.

Comparing mortality during long-term follow-up in randomized clinical trials and other registries with similar follow-up, the mortality of primary prevention patients in our registry was very low (25.5%). In MADIT-II, 44% of the ICD recipients died after 8 years. A very recently published registry from Leiden University showed a high rate of mortality (42%) in the same population during a 12-year follow-up.[15]

This difference could be attributed to the fact that our patients seem to have a lower rate of co-morbidities, such as diabetes, hypertension or atrial fibrillation, clinical risk factors that are associated with worse prognosis in ICD recipients.[16]

Appropriate therapies were delivered in both primary and secondary prevention patients, but as expected, the prevalence of these therapies was higher in patients who already have survived an episode of malignant arrhythmias. The cumulative incidence of appropriate therapies in the current registry is lower than that observed in the Dutch registry,[11,15] but is higher than in Danish patients.[12]

It is notable that the first appropriate therapy took longer to occur in primary prevention patients than in secondary prevention patients. In some cases, the first appropriate therapy occurred when the life duration of the first device had expired, and thus, why replacement of ICDs appears to be indicated for all patients.

It is noteworthy that the percentage of women in our registry is very low, but in almost all registries, the percentage of men approaches 80%.[11—13]

Finally, no fatal complications were recorded during implantation. The percentage of infections was expected, in accordance with the international bibliography, while the lead problems were already known.

The results from our study are very encouraging, especially regarding infections, which are the most important complication and nightmare for clinicians and patients alike. These low rates were achieved mainly due to the high level of experience of the medical team and operating room staff, coupled with adherence to current periprocedural recommendations.[17]

This is a single-center ICD registry in an isolated prefecture of South Greece, which corresponds to 1/20 of the total population of the country, which could be a limitation, but conversely, it is a fact that studies in isolated areas, such as the island of Crete, have the advantage of a well-controlled population without missing data. Moreover, the implanters were the same doctors responsible for the follow-up and programming of the devices. Data were collected prospectively and accurately, in order to record the long-term clinical outcomes of consecutive patients who were subjected to ICD implantation. However, the prolonged period of the study has several limitations. For

example, the population is less homogeneous because the guidelines for ICD recipients have evolved and therapeutic interventions are differentiated, due to device-technology progress. The annual implantation rate illustrates the incremental number of patients, considering that the indications for ICDs have broadened, due to publication of large randomized, primary prevention trials.

5. Conclusions

This single-center registry includes all ICD recipients on the island of Crete and demonstrates the long-term efficacy of these devices in preventing SCD and total mortality. However, the substantial proportion of patients without any therapy remains high. Additional and joint efforts are required to improve the predictive value of risk stratification techniques.

Moreover, the low rate of complications confirms the safety of this type of therapy. However, additional collaboration between physicians and medical device makers is needed, in order to address the weak links of inappropriate shocks and lead failures.

Currently, in the era of economic recession, concerns about the economics of health arise from all stakeholders. Therefore, medical and economic reasons logically call for a nationwide Greek registry that will evaluate all of the factors that influence the implantation of these life-saving devices in the battle against sudden cardiac death.

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