

# Implantable Cardioverter Defibrillator Therapy: A Single Center Experience in Saudi Arabia

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**Abstract:** *Introduction:* Internal Cardioverter Defibrillators (ICD) has been shown to decrease mortality in patients such as those with structural heart disease or at high risk of sudden cardiac death. To date there is no data regarding the clinical features, and outcomes of ICD patients in Saudi Arabia. Accordingly, we explored the clinical features and outcomes of ICD therapy among Saudis.

*Methods:* Patients who had ICD implantation in King Khalid University Hospital from November 2007 until January 2010 were enrolled.

*Results:* One hundred and eight ICD were implanted between November 2007 and February 2010. The mean age was  $58.6 \pm 13.2$  years. The majority were male 94 (87%), the rate of Diabetes Mellitus (DM) was 58.3%, Hypertension (HTN) was 61.1%, and 63% were smokers. The mean ejection fraction (EF) was 24.5%. Of the 108 patient 90(83.3%) had ICD insertion for primary prevention and 18(16.7%) for secondary prevention. Of the 90 patients who ICD for primary prevention 62 (57.4%) had ischemic cardiomyopathy, 39(36.1%) had dilated cardiomyopathy and 7 (6.5%) had channelopathy. Over a mean follow-up of 18 months 4 (3.7%) died

*Conclusions:* Our study describes for the first time patients characteristic and outcomes for ICD therapy in Saudi Arabia. Our patients are younger and have higher prevalence of risk factors that those in Western countries.

**Keywords:** Implantable Cardioverter-Defibrillator, Saudi Arabia.

## INTRODUCTION

The implantable cardioverter defibrillator (ICD) provides a remarkably effective therapy for ventricular tachycardia (VT) and ventricular fibrillation (VF). Several large, multi-center, randomized clinical trials showed that an ICD is superior to antiarrhythmic drugs in the secondary prevention of sudden cardiac death (SCD) [1-4]. Furthermore, ICD therapy is well-established for primary prevention of SCD, and improves survival in patients with structural heart disease [1, 3-6]. To date, no data are available on characteristics and outcomes of recipients receiving ICD therapy in Saudi Arabia. In the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, areas in need of further research included identifying and describing "long-term outcomes and risk factors for patients receiving ICDs in general practice compared with trial populations and at academic centers [1]. Accordingly, our objective was to explore clinical features and outcomes of ICD therapy recipients during a 2-year interval in a single academic center in Saudi Arabia.

## METHODS

Patients who had ICD implantation at King Khalid University Hospital in Riyadh, Saudi Arabia, from December

2007 through January 2010 were included in this analysis. Data on patient demographics, clinical history and indication for implantation of the ICD, device type, incidence of shocks, antiarrhythmic medication use, and total mortality were collected. Left ventricular ejection fraction (LVEF) was determined using the Simpson method or by ventriculography during cardiac catheterization. All patients had transvenous ICD insertion *via* the left axillary vein. None (the electrophysiological study is not anymore a pre-request to ICD insertion as per the guidelines) had an electrophysiological study (EPS) prior to ICD implantation. Patients were required to have Class I indication for ICD therapy as per AHA/ACC/ESC guidelines [1]. In brief, patients qualified for ICD therapy who had: 1) ischemic cardiomyopathy (IC),  $\geq 40$  days post myocardial infarction (MI), NYHA functional Class I, and LVEF  $\leq 30\%$ ; 2) IC,  $\geq 40$  days post MI, NYHA Class II or III, and LVEF  $\leq 35\%$ ; 3) dilated cardiomyopathy (DCM) with LVEF  $\leq 35\%$  and NYHA Class II or III; 4)  $\geq 40$  days post-MI, LVEF  $\leq 40\%$ , and with nonsustained VT and VF or VT inducible at EPS; or 5) cardiac arrest without identifiable reversible cause. After implantation, patients were followed-up regularly in our device clinic. Shocks were documented by device interrogation and confirmed by an electrophysiologist.

Statistical analysis: Continuous variables were summarized as mean  $\pm$  standard deviation or median and interquartile range (IQR), as appropriate and categorical variables was summarized as percentages. Group differences between

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categorical variables were analyzed with chi square or Fisher exact test, and between normally distributed continuous variables using Student's t test. For all analyses,  $p < 0.05$  was considered significant. Analysis was performed using SPSS version 17.

## RESULTS

From December 2007 through January 2010, 108 ICD implantations were performed. The majority of patients ( $n = 94$ ; 87%) were male, and there was a high prevalence of diabetes mellitus (DM:  $n = 63$ ; 58.3%), hypertension (HTN:  $n = 66$ ; 61.1%), dyslipidemia ( $n = 51$ ; 47.2%), smoking ( $n = 68$ ; 63%), and history of previous MI ( $n = 57$ ; 52.8%) (Table 1). The mean LVEF was  $24.6 \pm 9.43$ . The majority were in sinus rhythm ( $n = 86$ ; 79.6%), and 22 (20.4%) were in atrial fibrillation (AF). Sixteen (14.8%) were NYHA Class I, 64 (59.3%) were Class II, and 28 (25.9%) were Class III. Of the 108 implantations, 90 (83.3%) were for primary prevention, and 18 (16.7%) were for secondary prevention. The patients who had ICD therapy for primary prevention were more likely to have ischemic cardiomyopathy ( $n = 53$ ; 58.9%) than DCM ( $n = 35$ ; 38.9%;  $p = 0.003$ ) Table 2. Of the patients who had ICD for secondary prevention, 7 (38.9%) had VT with syncope, 8 (44.4%) had cardiac arrest, 2 (11.1%) had long QT syndrome, and 1 (5.5%) had Brugada syndrome. Ninety-two (85.2%) patients had single chamber and 16 (14.8%) had dual chamber ICDs implanted. Over a mean follow-up of  $13.4 \pm 9.5$  months, 12 patients (11.1%) had ICD shocks, 8 (66.7% of shocks; 7.4% of patients) of which were classified as appropriate and 4 (33.3% of shocks, 3.7% of patients) as inappropriate. Seven of the appropriate shocks were in patients with VVI-ICD (7.6% of VVI patients) and one in a patient with DDD-ICD (6.3% of DDD patients). Appropriate shocks occurred in 5 patients with IC and 3 with DCM. The 4 inappropriate shocks were in patients with VVI-ICD (4.3% of VVI patients), 2 of whom had IC and 2 DCM.

All-cause mortality was 3.7% ( $n=4$ ); all patients who died had IC, and the indication for implantation was primary prevention, resulting in a 4.4% mortality rate in that group. The 4 deaths were male, with single chamber ICD, one was in NYHA Class II and 3 were NYHA Class III, 1 was in AF and 3 were in sinus rhythm. None of the deaths occurred in patients experiencing shocks.

## DISCUSSION

Data from multiple clinical trials support the use of ICDs for both primary and secondary prevention of SCD. Several risk factors were used to identify purported high-risk populations to include in those studies [7]. Three large, early RCTs investigating secondary prevention (AVID, CASH, CIDS) enrolled patients who had at least survived VT/VF/cardiac arrest. Although the ICD groups in each study had reduced total mortality, the difference was significant only in the AVID study. The appropriateness of the study risk factors used for eligibility was questioned, however, when a registry of patients not meeting AVID eligibility criteria had worse survival than AVID ICD patients [8] Primary prevention trials had more variable inclusion criteria, and, despite differences in design among the trials, 7 of 9 major trials demonstrated the benefits of ICD therapy [7] The current guidelines on the use of ICDs are based on a writing committee

consensus that ICD patients should have clinical profiles closely aligned with those of patients included in those clinical trials; [1] while the controversy over ideal patient characteristics remains, with others reporting that the benefit of ICDs also includes populations not represented in the trials [4].

**Table 1. Patient Characteristics and Therapy**

Variable	n (%)
Age, mean years $\pm$ SD	58.6 $\pm$ 13.2
Gender (Male)	94 (87.0)
DM	63 (58.3)
HTN	66 (61.1)
Dyslipidemia	51 (47.2)
Stroke	3 (2.8)
Smoker	68 (63.0)
MI	57 (52.8)
EF (mean $\pm$ SD)	24.6 $\pm$ 9.43
<b>Cardiomyopathy:</b>	
Ischemic	62 (57.4)
DCM	39 (36.1)
Other	7 (6.5)
<b>ICD Indication:</b>	
Primary	90 (83.3)
Secondary	18 (16.7)
<b>Secondary Prevention:</b>	
VT with syncope	7 (38.9)
Post cardiac arrest	8 (44.4)
Long QT	2 (11.1)
Burgada	1 (5.6)
<b>Device Type:</b>	
VVI - ICD	92 (85.2)
DDD - ICD	16 (14.8)
Shocks	12(11.1)
Appropriateness	8 (66.6)
<b>NYHA:</b>	
Class I	16 (14.8)
Class II	64 (59.3)
Class III	28 (25.9)
Class IV	0
<b>Rhythm:</b>	
SR	86 (79.6)
AF	22 (20.4)
Death	4 (3.7)

Table 1. contd....

Variable	n (%)
<b>Medications:</b>	
Beta-Blocker	80 (74.1)
Digoxin	45 (41.7)
ACE-I	95 (87.9)
ARB	14 (13.0)
Statin	98 (90.7)
Diuretics	92 (85.2)
Aspirin	92 (85.2)
Plavix	60 (55.5)
Warfarin	10 (9.3)
Nitrate	23 (21.3)
Spirolactone	39 (36.1)
Amiodarone	12 (11.1)

KEY: AF – atrial fibrillation; EF – ejection fraction; ICD - ; SR – sinus rhythm;

LVEF values in the major trials were summarized in a recent systematic review that included 12 efficacy RCTs [4]. Patient LVEF ranged from 21% to 28% in primary prevention studies, and 32% to 46% in secondary prevention trials. In addition, results from 53 observational effectiveness studies were reviewed, which included patients with mean LVEF ranging from 19% to 46%. The mean LVEF of 25% for our patients was within the ranges of the primary prevention RCTs and the observational studies. However, recent studies and commentaries emphasize the importance of identifying risk stratification tools in addition to EF that can be used in the selection of patients suitable for ICD implantation, and remind that not all patients whose EF is  $\leq 30\%$  are proper candidates for ICDs [9] In addition, when data from the MUSTT trial were analyzed for the relationship of EF and inducible ventricular tachyarrhythmias with the mode of death, results suggested that ICDs may reduce mortality in patients whose EF is  $\geq 30\%$  as well as in those with lower EF [10].

Several reports investigated outcomes in patients who met the inclusion criteria of the major studies. For example, a Japanese study retrospectively evaluated data from 90 patients who did not have ICD implantation, but who had the

Table 2. Patients Stratified Based on the Underlying Heart Disease

Variable	Ischemic Cardiomyopathy 62(57.4)	DCM 39(36.1)	P-value
Age	60.8 $\pm$ 11.3	57.2 $\pm$ 14.0	0.15
Gender(male)	59(95.2)	32(82.1)	0.037
DM	52(57.8)	11(61.1)	0.50
HTN	41(66.1)	20(51.3)	0.10
Dyslipidemia	34(54.8)	16(41.0)	0.12
Stroke	1(1.6)	2(5.1)	0.37
Smoker	45(72.6)	22(56.4)	0.07
MI	55(88.7)	2(5.1)	<0.0001
NYHA Class			0.32
I	6(9.7)	4(10.3)	
II	42(67.7)	21(53.8)	
III	13(20.9)	14(35.9)	
EF	23.8 $\pm$ 7.5	22.1 $\pm$ 5.3	0.29
ICD indication			
Primary	53(85.5)	35(89.7)	0.38
Secondary	9(14.5)	4(10.3)	0.38
Shocks	7(11.3)	5(12.8)	0.08
Appropriate shocks	5(8)	3(7.7)	0.3
Death	4(6.5)	0(0)	0.12

DM (diabetes mellitus); HTN (hypertension); MI(myocardial infarction); EF(ejection fraction).

primary prevention RCT MADIT II criteria that included Q-wave MI >4 weeks prior, LVEF <30%, and age >21 years [11]. Survival rates were similar to the ICD group in MADIT II, and greater than the conventional therapy group. However, most patients (79%) were in NYHA functional Class I, compared with 35% and 39% of MADIT-II ICD and conventional therapy patients, respectively [12]. The authors concluded that MADIT-II criteria may be inappropriate for Japanese patients; however, the efficacy of ICDs in Class I patients is not known [1]. In another study, in fact, subgroup analysis of data from 459 patients randomly assigned to standard therapy or standard therapy plus an ICD revealed that LVEF  $\geq$ 20%, male gender, and NYHA Class III but not Class I or II, were significantly associated with improved survival [13]. A Brazilian study compared 102 patients who did not receive an ICD to patients in the placebo arm of another major primary prevention study, SCD-HeFT, and found that the mortality rates were similar between the 2 groups, causing them to conclude that their patients were similar, and may benefit from ICD therapy if economic constraints could be removed [14]. Likewise, our patients shared several similarities with the RCT patients; for example age, gender, proportion of patients with ischemic cardiomyopathy, and distribution among NYHA functional classes was similar to those in the 12 RCTs included in the systematic review by Ezekowitz *et al.* [4].

The 3.7% mortality in our entire cohort during a mean follow-up of 13 months is less than that reported in the 11 controlled observational studies included in the systematic review of Ezekowitz *et al.*, where 19 to 1442 patients in each study received an ICD [4]. In follow-up intervals of 12 to 132 months in those studies, all-cause mortality ranged from 6.8% to 36.8%, with a pooled reduction in all-cause mortality in ICD patients of 46%, which was greater than the 20% reduction in 9 pooled RCTs [4]. All deaths in our study were in patients treated for primary prevention, and the resulting 4.4% all cause mortality in these patients is less than the 12.3% to 26.0% in the 9 primary prevention RCTs in the review. Reduced mortality in ICD patients in observational studies compared with RCTs was suggested by Ezekowitz *et al.* to indicate that practicing clinicians select healthier patients for ICD insertion [4].

Although ICD effectiveness depends on the device being able to deliver appropriate shock therapy, both therapeutic and inappropriate shocks in patients with ICDs have been shown in several studies to seriously impact quality of life, resulting in decreased physical functioning and mental well-being, and increased anxiety that may reach the point of panic disorder or agoraphobia [15]. In fact, in a recent report from China, 1 of 7 deaths following ICD implantation was a suicide response to emotional stress after multiple shocks were received during an electrical storm [16]. Appropriate shocks can be caused by ventricular fibrillation, monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and Torsades de pointes [15]. From 5% to 12% of trial participants received an appropriate shock per year, with reports that it can increase to 30% of patients by 3 years [4, 17, 18]. In our study, 7.4% of patients received an appropriate shock, which is much less than the 25% to 33% reported in several other observational studies [4]. Brignole [19]

emphasizes that “appropriate” and “necessary” shocks are not synonymous, and notes that the low number of patients receiving appropriate shocks was twice the mortality rate in control groups in 2 reports [20].

Rates of inappropriate discharges were reported at 19.1 per 100 patient years in 2 RCTs, and 4.9 per 100 patient-years in 27 observational studies [4]. In fact, inappropriate shocks are the most common complication associated with ICD therapy [21]. In one study of 778 patients receiving ICDs, 13% received an inappropriate shock in follow-up averaging 4 months [22]. These shocks are most commonly due to misdiagnosis of atrial fibrillation or other supraventricular tachycardias, and can also result from double counting, atrial flutter, multiple premature ventricular contractions, oversensing of T waves or diaphragmatic myopotentials, oversensing due to lead failure or insulation break, electromagnetic interference, and ectopy [23]. Mortality is 2- to 5-fold increased in patients who have ICD shocks [17, 19]. This exemplifies the “conversion hypothesis;” that is, patients who are saved from sudden cardiac death by successful shocks may be at high risk of death from other cardiovascular-related causes [24]. Mishkin *et al.* report that the time from the first ICD shock to death is related to the appropriateness of ICD therapy as well as heart failure etiology, and occurs after a median interval ranging from 168 to 294 days [17].

Our 2-year data revealed that single-chamber devices are primarily used (85.2% of patients) in our institution. Proclemer *et al.* evaluated data in the Italian Pacemaker Registry and found dual chamber devices in higher use than single chamber devices, with increasing trends toward use of dual chamber devices, similar to trends reported in the world survey [25]. They noted that this was despite a meta-analysis that failed to show a heart failure or overall mortality benefit between the 2 types [26]. In fact, of the 9 RCTs reviewed by Ezekowitz, only 2 (MADIT-II and COMPANION) evaluated dual chamber devices [4]. Of 20 observational studies of effectiveness that reported the type of device used, 18 included both single- and dual-chamber devices, and one each included only single or dual. Ezekowitz highlighted the paucity of data on dual chamber devices, remarking that, in addition to 3 observational studies and 1 RCT that failed to show benefit, an RCT suggested that the device can exacerbate heart failure in patients implanted with the dual chamber device without an indication, such as such as chronotropic incompetence, sick sinus syndrome, or atrioventricular conduction abnormalities [27]. There is some evidence to suggest, however, that dual chamber ICDs may be associated with fewer inappropriate shocks [28, 29]. In a recent RCT in which 85% of patients had indications for secondary prevention, 3% and 12% of patients with dual and single-chamber ICDs, respectively, experienced inappropriate shocks in a mean follow-up of 16 months [27]. In our small sample, 4.3% of patients with single-chamber ICDs had inappropriate shocks. While none of the 16 patients with dual-chamber ICDs had inappropriate shocks, the numbers are too small to allow a valid comparison, which should become possible with the acquisition of additional data on these and other patients.

This study has several limitations and benefits. In addition to limitations inherent in observational studies, the small numbers reflect that we are just beginning to collect data from a single center. Also, we do not have control group comparisons at this time. However, we are continuing to collect data, and intend to expand participation to include other centers in Saudi Arabia, to acquire data from unimplanted patients for comparison, and to continue follow-up on the patients included in the present report. Our database will be expanded with additional salient variables that will allow more detailed comparisons with data from outside Saudi Arabia, especially those that may be shown to be related to risk factors that could have an impact on patient management and outcome. This report provides the first data from Saudi Arabia on patients implanted with an ICD, establishes a baseline for future comparisons, and launches exploration of the similarities and differences between our patients and those in other populations.

In summary, in our sample of Saudi Arabian patients selected for ICD insertion following practice guidelines, mortality was less than that reported for many RCTs and observational studies [4] suggesting a benefit from ICD insertion in these patients. The importance of acquiring additional data on ICD patients is exemplified by the number of reports questioning patient selection and outcome. For example, in a recent editorial Brignole summarizes ICD efficacy evidence and then questions whether complications may have been underestimated and benefits overestimated [21]. He emphasizes the need to develop reliable tools to identify patients who should receive ICD therapy. Real world data such as ours provide additional information outside of clinical trials, and ongoing surveillance and evaluation of outcomes and relevance of prediction models can help guide management of these patients. Our work is in line with the conclusion of the Guideline Committee that an area in need of further research is determining long-term outcomes and risk factors for patients receiving ICDs in general practice, and comparing them with trial populations and at academic centers. The acquisition of additional data will allow more meaningful comparisons between our data and that obtained in RCTs and observational studies in other populations.

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