Implantable Cardioverter-Defibrillators for Primary Prevention of Sudden Cardiac Death in Patients with Left Ventricular Systolic Dysfunction: 14 Years after MADIT

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Sudden cardiac death (SCD) is the most common cause of death among patients with heart failure and left ventricular systolic dysfunction. Implantable cardioverter-defibrillators (ICDs) have been shown to be the single most effective therapy for primary prevention of SCD in patients with heart failure. The superiority of this therapy was clearly established for patients with ischemic cardiomyopathy by large clinical trials, such as the Multicenter Automatic Defibrillator Implantation Trial (MADIT), Multicenter Unsustained Tachycardia Trial (MUSTT), and MADIT-II studies. On the other hand, there was much debate on whether these results could be extrapolated for patients with non-ischemic cardiomyopathy until the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated a significant benefit of this therapy. Given the high costs of this therapy and the limited resources allocated to health care multiple studies have attempted to identify patients at higher risk of suffering SCD, who in theory will benefit the most out of this therapy. However, these studies have not established a reliable way to predict which patients will receive a direct survival benefit from ICD therapy. Until we are capable of further defining which patients will derive the absolute highest benefit from an ICD, we must rely on the information available from published trials and adhere to current clinical practice guidelines regarding this pressing issue. [*P R Health Sci J 2011;30:78-83*]

Key words: Implantable cardioverter-defibrillator, Primary prevention, Sudden cardiac death, Heart failure, Left ventricular systolic dysfunction

Heart disease is responsible for 1 of every 2.9 deaths in the United States each year, making it the leading cause of death among Americans (1). Sudden cardiac death (SCD), defined as sudden loss of cardiac function usually due to ventricular arrhythmia, is responsible for nearly half of these deaths and is estimated to claim over 400,000 lives in the United States each year (2). Ventricular arrhythmias are the most common cause of death in patients with heart failure (3). The severity of left ventricular systolic dysfunction is known to correlate strongly to the risk of SCD, left ventricular ejection fraction (LVEF) being the most consistent and powerful predictor of all-cause mortality in these patients (4). Multiple studies have confirmed the efficacy of implantable cardioverter-defibrillators (ICDs) in primary prevention of SCD in heart failure patients. However, forty years after the first successful ICD implantation in a human by Dr. Michael Mirowsky, controversies remain regarding the appropriate use for these devices.

ICD in Ischemic Cardiomyopathy

ICDs were introduced into clinical practice in 1980 for secondary prevention of SCD in survivors of SCD. The first randomized clinical trial to demonstrate the benefit of ICD implantation as primary prevention of SCD was the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (5) in 1996. This trial enrolled 196 patients in New York Heart Association (NYHA) functional Class I, II, or III with a prior myocardial infarction, documented non-sustained ventricular tachycardia (NSVT), LVEF less than 35%, and inducible sustained monomorphic ventricular tachycardia (VT) during invasive electrophysiologic testing. Subjects were randomly assigned to treatment with either amiodarone or placement of an ICD. After more than two years of follow up, there were significant reductions in the incidence of overall mortality, cardiac mortality, and arrhythmic deaths in patients in the ICD arm, with a hazard ratio of 0.46 in these patients.

Following this, the Multicenter Unsustained Tachycardia Trial (MUSTT) (6), a multicenter, randomized clinical trial published in 1999, showed similar results. A total of 2202

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patients with established coronary artery atherosclerotic disease, LVEF of 40% or less, and asymptomatic NSVT, were assigned to either no therapy or electrophysiologic study (EPS)-guided antiarrhythmic therapy with drugs and/or ICD. The overall mortality rates at five years were 24% among patients who received an ICD and 55% among those who did not. The increase in survival benefit associated with EPS-guided therapy was due solely to the use of ICDs.

These two studies had established the superiority of ICD over antiarrhythmic therapy as primary prevention of SCD in patients with LV systolic dysfunction due to ischemic cardiomyopathy but required electrophysiologic testing. In order to solve this controversy, the MADIT-II (7) trial, published in 2002, expanded the study population to include patients with a myocardial infarction more than 30 days prior to enrollment and a LVEF of 30% or less, with or without evidence of presence of NSVT. Patients were randomly assigned to receive an ICD versus conventional medical therapy. Invasive electrophysiologic testing for risk stratification was not required as part of the protocol. During a follow-up of nearly two years, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the ICD group, for a significant risk reduction and a hazard ratio of 0.69 in favor of the ICD group.

ICD in Non-Ischemic Cardiomyopathy

Even though two previous small trials had failed to demonstrate survival benefit from prophylactic ICD implantation in patients with nonischemic dilated cardiomyopathy (8-9), in 2004 the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) (10) trial started to change this view. In this study, 458 patients with nonischemic dilated cardiomyopathy, LVEF less than 36%, and premature ventricular complexes or NSVT were randomly assigned to receive standard medical therapy only versus standard therapy plus ICD. The incidence of SCD was significantly lower in the ICD group with a hazard ratio of 0.20 compared to the standard therapy group.

In 2005, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (11) validated these findings. A total of 2521 patients with LVEF of 35% or less due to either ischemic or nonischemic cardiomyopathy and NYHA functional class II or III were randomized to conventional therapy plus placebo, amiodarone, or ICD. Patients treated with conventional therapy plus placebo or amiodarone experienced similar risks of death, demonstrating no benefit of amiodarone therapy. On the other hand, those who received an ICD had a decreased risk of death of 23% after five years, compared to these two groups. These results were similar for patients with ischemic and nonischemic cardiomyopathy.

ACC/AHA/HRS Recommendations

Based on the patient-specific inclusion criteria of these studies, the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (12) developed by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Rhythm Society (HRS), recommend ICD implantation for primary prevention of SCD in the following patients: 1) those with LVEF less than or equal to 35% due to prior myocardial infarction who are at least 40 days post-myocardial infarction and are in NYHA functional Class II or III (Class I indication); 2) those with LV dysfunction due to prior myocardial infarction who are at least 40 days post-myocardial infarction, have an LVEF less than or equal to 30%, and are in NYHA functional Class I (Class I indication); 3) patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III (Class I indication); and 4) patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I (Class IIb indication). As stated by the writing committee, these recommendations are intended for patients who are receiving optimal medical therapy and have a reasonable expectation of survival with good functional status for more than one year.

Predicting Who Will Get an ICD Shock

The number of patients that receive an ICD has grown significantly over the last 14 years, particularly after the publication of MADIT-II and SCD-HeFT studies. However, studies have demonstrated that out of all patients who receive an ICD, only 20 to 25% of them will receive an appropriate shock within five years after implantation (11,13). In MADIT, nearly 60% of patients received an ICD shock within two years of ICD implantation but the appropriateness of these shocks could not be assessed due to limitations in electrogram storing capabilities in this generation of devices. On the other hand, 31% of patients from SCD-HeFT were known to receive ICD shocks with 68% of these (21% of ICD patients) receiving appropriate shock for VT or ventricular fibrillation (VF). These numbers represent twice the reported mortality of patients in control groups that did not receive an ICD and roughly translates in half of appropriate shocks (about 10% of patients with an ICD) considered as life-saving therapy. Similarly, the Acute Decompensated Heart Failure National Registry Longitudinal Module (ADHERE LM) (14) registry, demonstrated that only 17% of deaths were caused by ventricular arrhythmias in patient with advanced heart failure and high mortality risk.

Given the high costs of this therapy and the limited resources allocated to health care multiple studies have attempted to identify patients at higher risk of suffering VT/VF, who in theory will benefit the most out of this therapy. In a small clinical trial involving 70 patients with idiopathic dilated cardiomyopathy who received an ICD for primary prevention of sudden cardiac death on the basis of either asymptomatic

nonsustained VT on ambulatory electrocardiographic (Holter) monitoring and a LVEF of 30% or less despite optimal medical therapy or unexplained syncope, multiple baseline clinical characteristic were evaluated as potential predictors for development of VT/VF in these patients. The characteristics under study included: age, gender, LVEF, NYHA functional class, nonsustained VT on Holter, history of syncope, left bundle branch block, baseline medications, and heart rate variability on Holter. Out of these variables, only LVEF was found to correlate with development of ventricular arrhythmias (15). Even though LVEF is still considered the strongest predictor for SCD, patients with decreased LV systolic function are clinically heterogenous in terms of prognosis for overall mortality and SCD (16).

Moreover, NYHA functional class is not linearly related to the prevalence of SCD, as patients with NYHA class II and III symptoms are more likely to die of VT/VF than patients with class IV symptoms (17). In MADIT II, the survival benefit was entirely due to a reduction in SCD and it was similar in subgroup analyses stratified by age, sex, LVEF, NYHA functional class, and QRS width. On the other hand, patients from the DEFINITE trial who had NYHA class III symptoms experienced a 63% reduction in relative risk of death following ICD implantation. Similarly, a study involving 502 heart failure patients, Whang et al (18) suggested that baseline NYHA functional class III at the time of implantation and LVEF of 20% or less have a multiplicative effect as a predictor of appropriate ICD discharges for VT/VF with a 3.6-fold 1-year risk for appropriate shock compared to patients with LVEF above 20% and NYHA Class I or II. This appears to be somewhat contradictory to initial results from SCD-HeFT, in which a 46% relative reduction in the risk of death in patients with NYHA class II symptoms but no apparent reduction in the risk of death with ICD therapy in patients with NYHA class III symptoms.

Other possible predictors of VT/VF, including signal-averaged electrocardiogram, baroreflex sensitivity, QTc dispersion, and T-wave alternans have not consistently been proven useful for arrhythmias risk stratification in this study (4,19-24). Electrophysiologic testing may have limited utility because of a relatively high number of false-negative results, non-inducibility of VT during EPS may not imply a lack of risk for SCD (8).

A common denominator in the studies we have already discussed is that ICD therapy invariably decreases the incidence of SCD in the heart failure population, but it does not necessarily decreases all-cause mortality (8,25-26). Patients who have suffered a recent myocardial infarction, such as those studied in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) seem to experience a counterbalancing increase in nonarrhythmic death that appears to offset the benefit of ICD therapy early during course of infarction (26). Similarly, increasing number of comorbidities is associated with increased mortality along with decreased ICD benefit (28-32). The reason for this is thought to be that some comorbidities may increase the risk of all-cause mortality without a corresponding increase in risk of preventable SCD.

The Prospective Analysis of Risk Factors for appropriate ICD Therapy (PROFIT) (33) study, which included 250 ICD patients -92.4% of which had received this therapy as secondary prevention following successful resuscitation after VT/VF- demonstrated a 100% 2-year risk for occurrence of VT/VF in patients that had a least two of the following risk factors: LVEF below 40%, permanent atrial fibrillation, and/or QRS width of at least 150 milliseconds. Each of these factors were found to be independent predictors for development of VT/VF. However, due to the limited number of patients who received an ICD for primary prevention in this study, whether this risk score applied to them or not was unclear. More recently, a study following 245 patients with ischemic dilated cardimopathy established LVEF of 35% or less, advanced age, and renal impairment as long-term predictors of appropriate ICD therapy in these patients (34).

Similarly, a study provided insight into long-term follow-up of patients from the MADIT-II (35). They found that over a period of nine years, patient from this study had a median survival of eight years. Age 65 years or older, NYHA functional class III or IV, diabetes mellitus, non-sinus rhythm, and increased serum blood urea nitrogen (BUN) levels were independent risk predictors of mortality. Patients with three or more of these risk factors had a 6-year mortality of 68% whereas those with one or two risk factors had a 43% mortality rate, and 19% in those with no risk factors.

The Seattle Heart Failure Model (SHFM) has been validated by large clinical trials as a multivariate risk model that predicts all-cause and cause-specific mortality in heart failure patients (36-37). Recently, Levy and colleagues (38) applied a modified version of the SHFM to patients from the SCD-HeFT in order to examine the relationship between baseline predicted mortality risk and the relative and absolute survival. They found that ICD treatment decreased risk of SCD by 88% in the lowest-risk group versus 24% in the highest-risk group. All-cause mortality was decreased by 54% in patients from lowest-risk group whereas no clinical benefit was observed in highest-risk group. Overall, ICD treatment added 6.3 additional years of life to patients from lower-risk group versus 0.2 year to those in highest-risk group. These results support the idea that patients multiple comorbidities are unlikely to derive benefit from this therapy despite the decrease in SCD incidence.

Patients within the lower-risk subgroup had a similar ratio of SCD to pump failure death at two years, regardless of NYHA functional class, including NYHA class IV patients. However, this study could not establish whether or not patients with

severe symptoms but at lower risk would benefit from an ICD. A regression analysis on patients from the MADIT II (13) demonstrated a U-shaped curve for efficacy of ICD in primary prevention of SCD. Patients with the lowest and highest risk scores had little benefit from this therapy. Contrary to these results, no subgroup of patients from the SCD-HeFT data analysis by Levy and colleagues (38) was found to be at such low risk of SCD as to make ICD implantation a frivolous intervention.

Physicians' Attitudes Towards ICD Therapy

Despite ICD therapy being associated with a significant decrease in SCD in patients with heart failure and having demonstrated cost-effectiveness (39-40), not all patients who would benefit from device-based therapy are referred for ICD implantation (41-42). Surveys among physicians suggest that despite most physicians being aware of the current guidelines for ICD implantation in heart failure patients, only about two-thirds of them refer their patients to cardiac rhythm specialists in order to consider ICD therapy (42-44).

Table 1. Landmark Clinical Trials on ICD Therapy for Primary Prevention of SCD

Year	Study	Patient Characteristics	Results
1996	MADIT	Ischemic cardiomyopathy, LVEF <35%, NYHA class I, II, or III, documented NSVT or inducible VT on invasive testing	Mortality decreased from 39% in non-ICD group to 16% in ICD group
1999	MUSTT	Ischemic cardiomyopathy, LVEF < 40%, asymptomatic NSVT	Mortality decreased from 55% in non-ICD group to 24% in ICD group
2002	MADIT-II	Ischemic cardiomyopathy, LVEF < 30%, myocardial infarction more than 30 days prior to enrollment	Mortality decreased from 19.8% in non-ICD group to 14.2% in ICD group
2004	DEFINITE	Non-ischemic cardiomyopathy, LVEF < 36%, NSVT or premature ventricular complexes	Mortality decreased from 6.1% in non-ICD group to 1.3% in ICD group
2005	SCD-HeFT	Ischemic and non-ischemic cardiomyopathy, LVEF < 35%, NYHA II or III	Mortality decreased from 29% in placebo group and 28% in amiodarone group to 22% in ICD group

Table 2. ACC/AHA/HRS Recommendations on ICD for Primary Prevention of SCD

Class	Recommendation
I	Patients with LVEF less than or equal to 35% due to prior myocardial infarction who are at least 40 days post-myocardial infarction and are in NYHA functional Class II or III
	Patients with LV dysfunction due to prior myocardial infarction who are at least 40 days post-myocardial infarction, have an LVEF less than or equal to 30%, and are in NYHA functional Class I
	Patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III
IIb	Patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I

Conclusion

ICDs have clearly been established as the single most effective therapy in primary prevention of SCD in patients with LV systolic dysfunction, either due to ischemic or nonischemic cardiomyopathy. Until we are capable of further defining which patients will derive the absolute highest benefit from an ICD, we must rely on the information available from published trials. Patients with a LVEF 40% or less, and particularly those with a clear-cut indication for device-based therapy, should be referred to a cardiac rhythm specialist in order to determine if they are eligible to ICD therapy. We must also adhere and disseminate current clinical practice guidelines regarding this pressing issue.

Resumen

Muerte súbita cardíaca es la causa más común de muerte en pacientes de fallo cardiaco y disfunción sistólica del ventrículo izquierdo. Los defibriladores implantables (ICD, por sus siglas en inglés) han demostrado ser el método de prevención primaria de muerte súbita cardíaca más efectivo. La superioridad de esta terapia ha sido claramente demostrada en pacientes de cardiomiopatía isquémica en estudios clínicos, tales como el Estudio Multicéntrico de Implante de Desfibrilador (MADIT, por sus siglas en inglés), Estudio Multicéntrico Sobre Taquicardia No Sostenida (MUSTT, por sus siglas en inglés) y MADIT II. Por otro lado, por mucho tiempo hubo debate con respecto si estos resultados podían ser extrapolados a pacientes de cardiomiopatía no isquémica hasta que el Estudio Sobre Muerte Súbita en Fallo Cardíaco (SCD-HeFT, por sus siglas en inglés) demostró la efectividad de la misma en esta población. Debido al alto costo de esta terapia y a los recursos limitados del sistema de salud, múltiples estudios han intentado identificar aquellos pacientes a mayor riesgo de sufrir muerte súbita, quienes en teoría se beneficiarían más de esta terapia. Sin embargo, hasta el momento no se ha establecido una manera confiable de predecir qué pacientes recibirán

un beneficio directo del ICD. Hasta que podamos definir qué pacientes se benefician más del implante de ICD, debemos basar nuestras decisiones en la información disponible derivada de estudios clínicos y adherirnos a las guías establecidas.

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