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EDITORIAL

Primary Prevention of Sudden Cardiac Death: Implications of Recent Trials

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ABSTRACT

Based on the results of randomized multicenter studies, such as the MADIT I, MADIT II, DINAMIT, and SCD-HeFT and DEFINITE trials, patients can be identified who are at high risk for sudden cardiac death (SCD) who demonstrate a reduction in arrhythmic mortality and total mortality with the implantation of an implantable cardioverter defibrillator (ICD). These are patients with coronary artery disease, impaired left ventricular function, spontaneous nonsustained ventricular tachycardia and inducible ventricular tachycardia not suppressed by procainamide. Also patients with coronary artery disease and left ventricular ejection fraction <30% benefit from ICD placement. Based on the SCD-HeFT results, patients with ischemic or nonischemic cardiomyopathy and class II or III congestive heart failure also benefit from the ICD. At the same time, based on the results of the DINAMIT study, it has become apparent that the ICD does not play a role in patients within 45 days of myocardial infarction. The implications of these trials are further analyzed in this overview.

KEY WORDS: *sudden cardiac death; ventricular tachyarrhythmias; coronary artery disease; non-ischemic cardiomyopathy*

LIST OF ABBREVIATIONS:
ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-receptor blocker
CVD = cardiovascular disease
RAS = renin angiotensin system
SAGE = serial analysis of gene expression

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INTRODUCTION

Sudden cardiac death (SCD) remains the most common cause of death in every industrialized nation, with over 300,000 deaths each year in the United States alone. Prediction and prevention of SCD has been the objective of multiple trials evaluating techniques of risk stratification and antiarrhythmic agents. Epidemiological studies indicate that more than half of the mortality from cardiovascular disease is sudden. In 1991, publication of the Cardiac Arrhythmia Suppression Trial (CAST) highlighted the adverse mortality effects with traditional antiarrhythmic agents.[1] This landmark trial served as the impetus for the development of appropriately designed trials to assess the efficacy of the implantable cardioverter defibrillator (ICD) in improving survival in patients at high risk for SCD with ischemic heart disease. It is with this background that ICDs were evaluated in patients with coronary artery disease with a high risk of SCD in the MADIT I and MADIT II trials.[2-4] More recently, evaluation of the role of the ICD for prevention of SCD has been evaluated in the DINAMIT, SCD-HeFT and DEFINITE Trials.[5-7]

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RECENT TRIALS

The **MADIT I** study was designed as a proof of concept study to determine through a randomized trial if an ICD could result in improved survival in coronary artery disease patients at high risk for sudden death when compared to conventional medical therapy.[2] A total of 196 patients were enrolled in MADIT I during a four-year period selected based on a left ventricular ejection fraction (LVEF) ≤35%, spontaneous non-sustained ventricular tachycardia, and inducible ventricular tachycardia not suppressed by procainamide. The MADIT I trial showed a 54% reduction in the risk of sudden death compared to patients who did not receive the ICD and were treated with amiodarone. Based on this study the Food and Drug Administration approved the ICD in the United States for such patients with a MADIT I indication in 1996. Secondary investigations were performed to evaluate ICD efficacy in multiple high risk subsets, including those with an LVEF <25%, QRS duration >0.12 seconds, and those with congestive heart failure. These analyses revealed that the sicker patients achieved more benefit from the ICD.[4] It was based on these findings that the MADIT II trial was designed.[3]

The rationale for **MADIT II** trial was that by selecting patients with coronary artery disease and advanced left ventricular dysfunction (LVEF ≤30%), there would be sufficient myocardial scar to provide the substrate for malignant arrhythmias.[3,4] The MADIT II trial enrolled patients based selected solely on the presence of coronary artery disease and LVEF <30% with no arrhythmia qualifier. In this patient population, the mean LVEF was 23%. The ICD was associated with a 31% risk reduction for total mortality compared to patients not receiving the ICD. Importantly, approximately 70% of both treatment groups received optimal medical therapy with beta-blockers and angiotensin converting enzyme inhibitors. In long-term follow-up there is a 40% cumulative probability of appropriate ICD therapy for ventricular tachycardia or ventricular fibrillation during four years after ICD implant.

Substudy analyses of the MADIT II patients were performed and the patients were stratified into four groups based on their baseline ECG.[4] These included (1) pacemaker related wide QRS complex; (2) intrinsic QRS ≤0.12 seconds; (3) intrinsic QRS 0.12 seconds to 0.15 seconds, (4) intrinsic QRS ≤0.15 seconds. The hazard ratio in patients with a pacemaker was 0.99 indicating no benefit from ICD therapy. The ICD was associated with progressively lower hazard ratio (greater ICD efficacy) with greater increased intrinsic QRS duration, although the beneficial trend was not significantly different within the three QRS groups.

An important issue related to these findings relates to the value of electrophysiology testing in patients with randomized ICD therapy.[4] Electrophysiology testing was performed in 593 patients randomized to the ICD, and 36% of the patients were found to have inducible ventricular tachycardia or ventricular fibrillation using standard induction protocol and traditional criteria for inducibility.[4] In this group of patients, the clinical significance of inducibility and non-inducibility before or at ICD implantation was evaluated in terms of appropriate use of ICD. Patients who had inducible ventricular tachycardia at electrophysiology testing had significantly increased utilization of ICD therapy for documented ventricular tachyarrhythmias than those who had no inducible arrhythmias. However, the latter patients had significantly increased utilization of ICD therapy with documented ventricular fibrillation than those who had inducible ventricular tachycardia. The noninducible patients were significantly sicker than the inducible patients in terms of more advanced New York Heart Association (NYHA) class, higher blood urea nitrogen values, and lower use of beta-blockers. Among 29 patients who had documented episodes of ventricular fibrillation recorded by the ICD, 83% of the recorded ventricular fibrillation events were in the noninducible group.[4]

More recently in the **DINAMIT** study, patients with a recent myocardial infarction (MI) were studied relative to benefit of the ICD. DINAMIT was designed to test single chamber ICD therapy in patients who had an MI within the previous 6 to 45 days, LVEF ≤35%, and low heart rate variability.[5] Researchers enrolled 674 patients at 73 centers in 10 countries and randomized them in an open label fashion to ICD therapy or control. All patients received best medical therapy with 80% receiving beta blockers, 90% receiving angiotensin converting enzyme (ACE) inhibitors, 75% receiving lipid lowering drugs, and 90% receiving antiplatelet therapy.

The mean age of the patients was 61 years. Overall, 39% received thrombolytic therapy and the mean LVEF was 28%. The mean time since the MI was 18 days. About one third of the patients had a MI prior to the index event and a small number had a prior angioplasty. The patients were followed for 2.5 years to assess mortality rates. It was determined that an overall mortality of 17.8% in 30 months, or about 7% per year, was present with no difference between the two treatment groups. However, when arrhythmic and nonarrhythmic deaths were analyzed separately, researchers noted a significant increase in nonarrhythmic deaths in the ICD group (hazard ratio-HR 1.75; 95% confidence intervals-CI 1.11-2.76) as well as a significant decrease in the arrhythmic deaths (HR 0.42; 95% CI 0.22-0.83). Further subanalysis divided these patients into three groups, those who were randomized with no ICD, those who received an ICD but had no shocks, and those who got an ICD with appropriate shocks. It was determined that among the ICD patients, those receiving appropriate shocks (55 patients) had a 15.4% annual risk of nonarrhythmic death, compared to 3.9% mortality risk in ICD patients who did not receive appropriate shocks (257 patients).

SCD-HeFT was a trial comparing three separate arms with placebo and optimal medical therapy, amiodarone and optimal medical therapy, and ICD to optimal medical therapy in patients with ischemic and nonischemic cardiomyopathy.[6]

A total of 2521 patients with ischemic cardiomyopathy (51%) or nonischemic dilated cardiomyopathy (49%) were enrolled. The inclusion criteria included symptomatic heart failure, NYHA class II or III for at least three months in the presence of a LVEF ≤35% despite optimal medical therapy including ACE inhibitors and beta blockers. SCD-HeFT had a 90% probability of detecting a 25% mortality reduction by ICD therapy. This was based on the assumption of a total mortality of 25% in the placebo arm in 2.5 years with 50% of deaths being due to arrhythmias. The major finding of SCD-HeFT was significant reduction in the total mortality in the ICD group, whereas amiodarone did not improve survival. A subgroup analysis revealed a similar survival benefit in the ICD group of patients with ischemic cardiomyopathy compared to patients with nonischemic cardiomyopathy. Due to these results and due to high power SCD-HeFT as a randomized control trial, currently available guidelines for prophylactic ICD therapy are being reevaluated in the United States.

An important **sub-study of the SCD-HeFT trial** demonstrated that electrocardiogram measurements can not be used to predict who will benefit from an ICD therapy.[7] This analysis of the SCD-HeFT patients was performed based on the width of QRS interval. The secondary analysis of the electrocardiographic data demonstrated that patients who have a QRS duration of at least 0.12 seconds and receive an ICD had a 33% reduction of relative risk of all cause mortality in five years, compared with similar patients on medical therapy. However, the 59% of SCD-HeFT patients with a QRS <0.12 seconds, also had clinically and statistically significant 16% reduction mortality with the ICD. Redefining a narrow QRS as 0.12 seconds or less, the population that benefits more from ICD therapy becomes SCD-HeFT group with a narrow QRS not a wide one. The patients with QRS of 0.12 seconds or less showed a 26% reduction in all cause mortality compared with the 20% relative reduction in patients who have a QRS >0.12 seconds. Accordingly, no particular QRS duration provides sufficient specific risk categorization to select or exclude patients for ICD therapy. Clinical trials investigators have taken issue which what they view as a post hoc data analysis on a part of officials in the United States in approving reimbursement for ICDs in patients with QRS width >0.12 seconds.

The **DEFINITE** trial focused on a patient population with nonischemic dilated cardiomyopathy and LVEF of ≤30% and premature ventricular complexes or nonsustained ventricular tachycardia.[8] A total of 229 patients were randomly assigned to receive standard medical therapy, and 229 to receive the medical therapy plus single chamber ICD. The patients were followed for a mean of 29.0±14.4 months. The mean LVEF was 21%. A vast majority of patients were treated with ACE inhibitors (86%) and beta blockers (85%). There were 68 deaths: including 28 in the ICD group, as compared to 40 in the standard therapy group. The mortality rate at two years was 14.1% in the standard therapy group and 7.9% in the ICD group (P=0.06). There were 17 sudden deaths from arrhythmia including three in the ICD group, and 14 in the standard group. It was concluded based on the DEFINITE Trial in patients with severe, nonischemic dilated cardiomyopathy, who were treated with ACE inhibitors and beta blockers, the implantation of an ICD significantly reduced the risk of sudden death from arrhythmia. The ICD also was associated with a nonsignificant risk reduction for all cause mortality.

CONCLUSION

Based on the results of the MADIT I, MADIT II, DINAMIT, and SCD-HeFT and DEFINITE trials, patients can be identified who are at high risk for sudden cardiac death who demonstrate a reduction in arrhythmic mortality and total mortality with the implantation of an ICD. This includes patients with coronary artery disease, impaired left ventricular function, spontaneous nonsustained ventricular tachycardia and inducible ventricular tachycardia not suppressed by procainamide. Also patients with coronary artery disease and LVEF <30% benefit from ICD placement. Based on the SCD-HeFT results, patients with ischemic or nonischemic cardiomyopathy and class II or III congestive heart failure also benefit from the ICD. At the same time, based in DINAMIT, it has become apparent that the ICD does not play a role in patients within 45 days of myocardial infarction.

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