

Editorial

Clinical Implications of the MADIT-II Trial

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Patients with coronary heart disease die either from progressive heart failure or from a cardiac arrhythmia, mostly ventricular fibrillation. The available data suggest that sudden arrhythmic death accounts for 50% or more of all deaths due to coronary heart disease. In the early 1990s, the Cardiac Arrhythmia Suppression Trial (CAST) reported that several antiarrhythmic drugs were ineffective in improving survival in cardiac patients at high risk for malignant ventricular arrhythmias; rather, these antiarrhythmic agents contributed to an increased mortality-(1). The implanted cardioverter defibrillator (ICD) had been available since 1980, but by the early 1990s, insertion of an ICD still required a surgical thoracotomy. At that time, ICD therapy was utilized mostly in patients who had been resuscitated from a cardiac arrest. Following the report of the CAST trial, a Multicenter Automatic Defibrillator Implantation Trial (MADIT) Executive Committee was formed to determine if an ICD trial was clinically feasible. A MADIT-I trial was designed as a proof of concept study to evaluate the safety and efficacy of ICD therapy in a high-risk group of patients with a prior myocardial infarction, non-sustained ventricular arrhythmias, and inducible-nonsuppressible ventricular tachycardia or ventricular fibrillation at electrophysiologic study. MADIT-I was concluded in 1996, and the study demonstrated a 54% reduction in all-cause mortality in patients randomized to the ICD compared with those receiving conventional therapy (2). Secondary analyses of the MADIT-I database revealed that patients with more severe coronary heart disease, as manifest by lower ejection fraction, more congestive heart failure, or wider QRS complexes, received greater benefit from the ICD than did

those with less severe heart disease and more compensated heart function (3).

MADIT-II, initiated shortly after the completion of MADIT-I, was designed to evaluate the prophylactic use of ICD therapy in a large, more representative population of patients with coronary heart disease. By the mid-1990s, the transvenous approach was available for ICD insertion. The MADIT-II study population involved patients with an enzyme-confirmed prior myocardial infarction and advanced left ventricular dysfunction (ejection fraction <0.30), without a requirement for overt manifestations of cardiac arrhythmias or electrophysiologic testing for arrhythmic risk stratification. The MADIT-II study enrolled 1,232 patients and was stopped by the Data Safety Monitoring Committee when patients randomized to ICD therapy were found to have a 31% reduction in all-cause mortality compared to patients receiving conventional therapy. This marked improvement in survival with ICD therapy was superimposed on optimal therapy with beta-blockers, angiotensin converting enzyme inhibitors, and diuretics -- drug therapy that was received by approximately 70% of the patients in both arms of the trial (4).

Since publication of the MADIT-II trial in 2002, the MADIT-II investigative group has carried out a number of secondary analyses involving the MADIT-II database. The life-saving benefit achieved by ICD therapy in the MADIT-II study population is consistent across all subgroups. The efficacy of ICD therapy is similar in: 1) those <65 years of age and >65 years; 2) in males and females; 3) those with ejection fractions above and below 0.25; and 4) in those with and without atrial fibrillation, history of hypertension, diabetes,

left bundle branch block, and prior coronary bypass surgery. In fact, we could not identify any subgroup that behaved differently from the benefit achieved with the ICD in the entire study population. Detailed analyses of all the mortality events revealed that the reduction in 20-month mortality from 19.8% in the conventional therapy group to 14.2% in the ICD group was due almost exclusively to a specific reduction in sudden arrhythmic cardiac death. Thus, the ICD accomplishes what it is designed to do -- terminate life-threatening ventricular fibrillation.

The clinical implications of the MADIT-II trial are quite profound. We now have clinical trial proof that ICD therapy significantly improves survival in patients with coronary heart disease and ventricular dysfunction. This population makes up a meaningful percentage of patients with coronary disease. This favorable outcome with ICD therapy is on top of standard pharmacologic therapy that is prescribed for these patients. The ICD is now indicated as first-line prophylactic therapy to improve survival in patients with coronary heart disease and reduced ejection fraction (5). Presently, the cost of an ICD device is expensive, about equivalent to the cost of coronary bypass surgery. It is anticipated that as more ICD devices are used clinically, market forces will reduce the cost of the ICD and permit an unrestricted use of this life-saving device for all those in need.

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