MADIT-II and its implications

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The major risks associated with coronary disease are angina, acute myocardial infarction, reduced cardiac function as manifest by depressed left ventricular ejection fraction and congestive heart failure, and sudden arrhythmogenic cardiac death. During the past three decades, considerable advances have been made in the management of patients with coronary heart disease with beta-blockers, calcium-channel blockers, angiotensin converting-enzyme (ACE) inhibitors, angiotensin receptor blockers, thrombolytics, balloon-stent angioplasty, and coronary artery bypass graft surgery. The clinical course of patients with coronary disease has been meaningfully improved by these therapies, but sudden cardiac death remains a major problem and has not been impacted by these therapeutic interventions. Recently, the Center for Disease Control reported that more than 460 000 sudden cardiac deaths occur annually in the U.S., with sudden cardiac death accounting for 63% of all cardiac mortality events.1

Following the introduction of the implanted defibrillator in 1980, the defibrillator was initially utilized as secondary prevention for patients with aborted cardiac arrest or documented life-threatening ventricular tachycardia. In 1991, the Cardiac Arrhythmia Suppression Trial (CAST) investigators reported the ineffectiveness and actual harm associated with several promising antiarrhythmic drugs that were being used to improve survival in cardiac patients with manifest ventricular arrhythmias.2 That same year, our Multicenter Automatic Defibrillator Implantation Trial (MADIT) research group initiated the first randomized trial to determine if an implanted cardioverter defibrillator (ICD) would save lives in coronary patients with prior myocardial infarction, reduced ejection fraction, non-sustained ventricular tachycardia, and inducible non-suppressible ventricular tachycardia at electrophysiologic testing. MADIT showed that the ICD saved lives when compared to patients managed with conventional, non-ICD therapy (ICD:non-ICD hazard ratio 0.46, \( P = 0.001 \)).3 Secondary analyses of the MADIT database revealed that patients with more advanced electrical and mechanical cardiac dysfunction received greater life-saving benefit than those with less severe cardiac disease.4

Prior to the start-up of MADIT-II, three randomized, placebo-controlled, clinical trials showed that amiodarone was not effective in reducing all-cause mortality in patients with coronary disease and varying degrees of left ventricular dysfunction.5–7 MADIT-II was initiated in July 1997 to determine if the ICD would save lives in coronary patients with a prior myocardial infarction and advanced left ventricular dysfunction (ejection fraction \( <0.30 \)), but without requiring manifest or inducible ventricular tachycardia for eligibility. In view of the known ineffectiveness of antiarrhythmic medications, including amiodarone, in reducing all-cause mortality in patients with coronary heart disease and the high frequency of adverse side effects associated with the long-term administration of antiarrhythmic medications, the MADIT-II protocol included the following statement: ‘Every effort will be made to minimize the use of conventional antiarrhythmic medications and to optimize the use of standard therapy, including beta-blocking drugs and angiotensin-converting enzyme inhibitors, when indicated, in both treatment groups.’8 MADIT-II enrolled 1232 high-risk coronary patients, with participants randomized in a 3:2 ratio to ICD:non-ICD therapy. The ICD was associated with improved survival (ICD:non-ICD hazard ratio 0.69, \( P = 0.016 \)).9 In MADIT-II, over 70% of patients in both treatment arms were receiving beta-blockers and ACE inhibitors. ICD efficacy was similar in various age, sex, ejection fraction, New York Heart Association, and QRS duration subsets.
Prophylactic ICD therapy improves survival in patients with coronary heart disease and moderate to severe left ventricular dysfunction. How does ICD therapy compare with other drug and surgical therapies widely used in the treatment of patients with coronary artery disease? The accompanying figure (Fig. 1) provides a comparison of the mortality reduction from ICD therapy in MADIT-II with findings from three classic articles involving therapies that have had a positive influence on the management of patients with coronary heart disease. The reduction in all-cause mortality was larger with ICD therapy than with beta-blockers, coronary bypass graft surgery, or ACE inhibitors. It should be noted that ICD effectiveness in MADIT-II was on top of high utilization of beta-blockers and ACE inhibitors in the MADIT-II study population.

ICD therapy increases the survival probability in patients with coronary disease and advanced left ventricular dysfunction. The technique of implanting a transvenous ICD is similar to that involved in implanting a pacemaker, and the implantation procedure is performed during a same-day hospitalization or an overnight hospital stay. What about the cost of ICD therapy? Presently, the up-front cost is in the range of $20 000 for the device, with the total professional and hospital costs similar to the costs associated with coronary artery bypass graft surgery. In the earlier MADIT study, the cost effectiveness of ICD therapy was in the range of $25 000 per life-year saved. It is likely that the ICD cost effectiveness ratio will be larger in MADIT-II than in the first MADIT study. An evaluation of the cost effectiveness of treatment with an ICD in MADIT-II is under way. Current analyses indicate that 11 high-risk coronary patients need to be treated over a 3-year period to save one life.

MADIT-II has implications for patients, physicians, and society. For cardiac patients with a prior myocardial infarction and left ventricular dysfunction, prophylactic implantation of an ICD is associated with a significantly improved survival. Physicians are now in a position to identify patients who will benefit from ICD therapy. With further improvement in risk stratification, higher-risk subsets of coronary patients will be identified, and more focused ICD therapy will be carried out.

The widespread use of ICD therapy in high-risk coronary patients has cost implications for society that impact on the finances of the health care system. What can society afford, and how should society prioritize its financial expenditure in the delivery of health care? What financial expenditure is appropriate to improve survival among functioning individuals with cardiac disease? These are challenging questions that require thoughtful solutions. As a physician, I believe that society has an obligation and a responsibility to provide to its citizens life-saving therapy that has been shown to be scientifically efficacious. When viewed in this light, I am convinced that solutions to the cost implications associated with prophylactic ICD therapy will be worked out.

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**References**


