MADIT-I and MADIT-II

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MADIT-I and MADIT-II. The MADIT-I study was a proof-of-principle study, and this randomized trial showed that the implantable cardioverter defibrillator (ICD) saves lives in high-risk patients with coronary heart disease. The MADIT-II study showed that prophylactic ICD therapy was associated with significantly improved survival in patients with ischemic cardiomyopathy, as defined by documented coronary heart disease and advanced left ventricular dysfunction, without requiring screening for ventricular arrhythmias or inducibility by electrophysiologic testing. Taken together, these two trials, as well as the results from several other randomized ICD trials, indicate that ICD therapy is indicated in coronary patients who meet MADIT-I or MADIT-II eligibility criteria and are not excluded by major noncardiac comorbidity. (J Cardiovasc Electrophysiol, Vol. 14, pp. S96-S98, September 2003, Suppl.)

implantable defibrillator, defibrillator, sudden cardiac death, ventricular arrhythmias

Introduction

Patients with coronary artery disease and a history of one or more myocardial infarctions are at risk for recurrent coronary events; the development of heart failure due to left ventricular dysfunction; electrical disorders of the heart, including ventricular arrhythmias and conduction disturbances; and cardiac death. Epidemiologic studies indicate that more than half of the mortality from cardiac disease is sudden.[1] The implantable defibrillator was introduced in 1980 to address the problem of sudden arrhythmic death,[2] and clinical experience with the life-saving potential of this implanted device during the 1980s was impressive. In 1991, publication of the Cardiac Arrhythmia Suppression Trial (CAST) highlighted the adverse mortality effects with traditional antiarrhythmic agents.[3] The net result of the landmark CAST study was to encourage more precise evaluation of the safety and efficacy of the implantable cardioverter defibrillator (ICD) in improving survival in high-risk patients with heart disease. It is this background that led to the initiation of two Multicenter Automatic Defibrillator Implantation Trial (MADIT) studies, the first in 1991 (MADIT-I) and the second in 1997 (MADIT-II).

MADIT-I

When MADIT-I was designed in 1991, the ICD required a thoracotomy for implantation. The MADIT Executive Committee recognized the need for a randomized clinical trial, but the need for thoracotomy in patients randomized to ICD therapy represented a real challenge for enrollment. Because of the potential risks associated with thoracotomy, eligibility criteria for MADIT-I were designed to be quite stringent and required that patients be at very high risk for sudden cardiac death. Studies prior to 1991 indicated that coronary patients with left ventricular dysfunction and nonsustained ventricular tachycardia would meet such a criterion.[4] Furthermore, coronary patients who had inducible ventricular tachyarrhythmias that were nonsuppressible with antiarrhythmic drugs at elec-

trophysiologic (EP) study were considered to be at particularly high risk for sudden death.

The MADIT-I study was designed as a proof-of-concept study to determine through a randomized trial if ICD therapy would result in improved survival in coronary patients at high risk for sudden death when compared to conventional medical therapy. Over the course of 4 years, 196 patients were enrolled in MADIT-I. During this period of time, implantation of the ICD progressed from a thoracotomy approach to a less invasive transvenous approach. In 1996, the Data Safety Monitoring Board recommended termination of the trial because of significantly improved survival with ICD therapy.[5] The major results from MADIT-I are shown in Figure 1. In brief, ICD therapy in these high-risk coronary patients was associated with a 54% reduction in the risk of death at any interval of time compared to patients who did not receive the ICD. This study was reviewed by the Food and Drug Administration (FDA) in 1996, and the ICD was quickly approved for a MADIT-I indication.

Because of the small sample size of the study and the limited number on mortality events, only a few secondary substudies were possible. One important secondary investigation evaluated ICD efficacy in various high-risk subsets, including those with ejection fraction (EF) <0.25, QRS duration >0.12 second, and those with congestive heart failure. The analyses revealed that the sicker patients achieved better benefit from the ICD.[6] These findings set the stage for the design and initiation of MADIT-II.

MADIT-II

The primary and secondary findings from MADIT-I were helpful in the design of MADIT-II. The rationale for MADIT-II was that by selecting patients with coronary disease and advanced left ventricular dysfunction (EF ≤0.30), the myocardium would be sufficiently scarred that it would provide the substrate for malignant ventricular arrhythmias. Furthermore, pilot data showed that coronary patients with this degree of impairment of left ventricular function had a high frequency of ventricular ectopy; thus, it was reasoned that detection of ventricular ectopy should not be required for eligibility. The MADIT-II Executive Committee wrestled with the question of whether to require EP inducibility for entry. An abstract by Sweeney et al.[7] in February 1997

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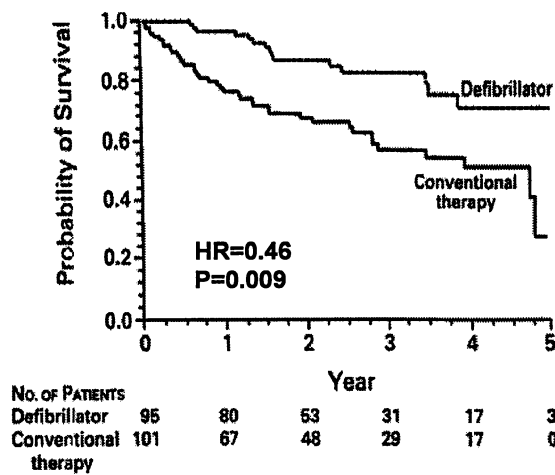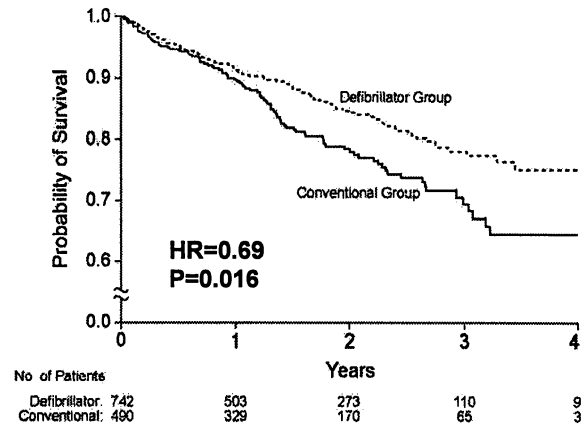
MADIT-I (1996)   MADIT-II (2002)

Figure 1. *Kaplan-Meier graphs of the probability of survival in the group assigned to the implantable cardioverter defibrillator (ICD) and the group assigned to conventional medical therapy in the MADIT-I (left) and MADIT-II (right) trials. The hazard ratios (HR) and P values were derived from the sequential design with use of the Cox proportional hazards regression model, which took into account the sequential stopping rule.*

provided preliminary data indicating only 38% repeat inducibility of EP testing when the test was repeated on 2 consecutive days. Several members of the Executive Committee noted similar experiences in their own practice, and the Executive Committee decided to test a new paradigm, that is, to not require EP inducibility of ventricular arrhythmias for eligibility into MADIT-II. However, EP testing was strongly recommended at the time of ICD implant in those randomized to device therapy. It was this reasoning that led to the design of a 3 : 2 ICD–to–non-ICD randomization so that a high-level secondary hypothesis relating to inducibility and appropriate ICD utilization could be tested.

MADIT-II was initiated in July 1997, and the trial was stopped by the Data Safety Monitoring Board in November 2001 after 1,232 patients had been enrolled. The primary results have been reported,[8] and the primary findings are summarized in Figure 1. Mean EF was 0.23, and ICD therapy was associated with a 31% reduction in the risk of mortality at any interval of time compared to patients not receiving an ICD. It should be noted that approximately 70% of both treatment groups was receiving optimal medical therapy with beta-blockers and angiotensin-converting enzyme inhibitors.

Since the publication of the primary results in March 2002, numerous secondary analyses have been performed using the MADIT-II database. Cox proportional regression analyses have been carried out in all conceivable subgroups. The hazard ratios within all subgroups were <1.0, and there were no significant differences in the hazard ratios within any subgroup. In other words, a subset of patients could not be identified who obtained a significantly better or a significantly worse result from ICD therapy compared to conventional therapy. Although some trends in ICD efficacy were observed, the overall conclusion is that ICD therapy was similar across the various subsets.

In view of the benefit of cardiac resynchronization therapy in heart failure patients with wide QRS complexes, the

efficacy of ICD therapy in patients with varying degrees of QRS width was investigated. MADIT-II patients were divided into four groups based on their baseline ECG: (1) pacemaker-related wide QRS complex; (2) intrinsic QRS <0.12 second; (3) intrinsic QRS 0.12–0.15 second; and (4) intrinsic QRS >0.15 second. The hazard ratio in patients with a pacemaker was 0.99, indicating no benefit from ICD therapy. The ICD was associated with a progressively lower hazard ratio, that is, greater ICD efficacy, with greater intrinsic QRS durations, although the beneficial trend was not significantly different within the three QRS-duration groups.

Overall, there was a 40% cumulative probability of appropriate ICD therapy (antitachycardia pacing or shock) for ventricular tachycardia or ventricular fibrillation during 4-year follow-up after ICD implantation. An important question relates to the value of EP testing in the patients randomized to ICD therapy. EP 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. In this group of patients, the clinical significance of inducibility and noninducibility before or at ICD implantation was evaluated in terms of the appropriate use of ICD therapy for ventricular tachycardia or ventricular fibrillation as determined by device interrogation during clinical follow-up that averaged 20 months per patient. Patients who had inducible ventricular tachycardia at EP testing had significantly increased utilization of ICD therapy for documented ventricular tachycardia than those who had no inducible ventricular arrhythmias. However, the latter patients had significantly increased utilization of ICD therapy for 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 a documented episode of ventricular fibrillation aborted by the ICD, 83% of the aborted fibrillation events were in the noninducible group.

The DAVID study was published in December 2002, and this randomized trial evaluated the efficacy of dual-chamber pacing at 70 beats/min versus single-chamber backup ventricular pacing at 40 beats/min in patients with standard indications for ICD therapy.[9] Dual-chamber pacing offered no clinical advantage over single-chamber ventricular backup pacing, and the detailed findings indicated that dual-chamber pacing might be somewhat detrimental. In MADIT-II, 44% of the patients randomized to the ICD received dual-chamber pacing units. Preliminary findings from MADIT-II are in excellent agreement with the DAVID findings. Most patients with dual-chamber pacing were programmed to a DDD setting in the 70 beats/min range. High utilization of right ventricular pacing was associated with an increased risk for congestive heart failure.

The MADIT-II study was reviewed by the FDA, which approved ICD therapy for the MADIT-II indication in 2002. In the same year, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines,[10] as well as a similar task force on sudden cardiac death of the European Society of Cardiology,[11] rendered a high-level IIA recommendation for prophylactic implantation of ICD in MADIT-II type patients.

Conclusion

The MADIT-I study was a proof-of-principle study, and this randomized trial showed that the ICD saves lives in high-risk patients with coronary heart disease. The MADIT-II study showed that prophylactic ICD therapy was associated with significantly improved survival in patients with ischemic cardiomyopathy, as defined by documented coronary heart disease and advanced left ventricular dysfunction, without requiring screening for ventricular arrhythmias or inducibility by EP testing. Taken together, these two trials, as well as the results from several other randomized ICD trials, indicate that ICD therapy is indicated in coronary patients who meet MADIT-I or MADIT-II eligibility criteria and are not excluded by major noncardiac comorbidity.

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