Cardiac Electrophysiology Review 2002;6:463–465

MADIT-II: Clinical Implications

Arthur J. Moss, James Daubert and Wojciech Zareba

Cardiology Unit, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Abstract. **The MADIT-II trial showed that in patients with a prior myocardial infarction and ejection fraction ≤0.30, prophylactic implantation of a defibrillator improves survival with a 31% reduction in mortality during an average follow-up of 20 months. Electrophysiologic inducibility was positive in 36% of patients at the time of ICD implantation. Inducibility was associated with increased ICD utilization for ventricular tachycardia during long-term follow-up, and decreased utilization for ventricular fibrillation. These preliminary findings raise questions about the clinical usefulness of electrophysiologic testing as a risk stratifier in patients with advanced left ventricular dysfunction.**

Key Words. **implantable defibrillator, coronary disease, heart failure**

Introduction

In 1980, Mirowski and associates reported the first three patients in whom the implanted defibrillator was used in the management of patients with recurrent ventricular tachyarrhythmias refractory to medical therapy [1]. During the 1980s the clinical experience with ICDs progressively increased, but mostly utilized in patients who had been resuscitated from out-of-hospital cardiac arrest or who had documented episodes of recurrent, life-threatening ventricular tachycardias. The 1990s ushered in a number of randomized primary and secondary ICD trials. In 1996, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) was published, and ICD therapy was associated with 54 percent reduction in all cause mortality when compared to conventional therapy in patients who had reduced ejection fraction (EF ≤0.35), non-sustained ventricular tachycardia, and inducible non-suppressible ventricular tachycardia or fibrillation at electrophysiologic study [2]. A study reported in 1999 by the Multicenter Unsustained Tachycardia Trial (MUSTT) confirmed the MADIT findings [3]. Both the MADIT and MUSTT trials were primary prevention studies. During the same period of time, several secondary prevention trials were reported including the Antiarrhythmics Versus Implantable Defibrillators (AVID) study [4], the Canadian Implantable Defibrillator Study (CIDS) [5], and the Cardiac Arrest Study Hamburg (CASH) [6]. In each of these studies, ICD therapy was associated with improved survival when compared to antiarrhythmic drug therapy.

The protocol used in most of the aforementioned studies included electrophysiologic testing (EPT) for inducibility. These published studies suggested that electrophysiologic testing should be used to screen and identify patients who would benefit from ICD therapy, but this approach has never been substantiated. In subset analyses from the original MADIT study, we showed that the survival benefit from the ICD was directly related to the severity of the cardiac dysfunction. More specifically, the combinations of the presence of one, two, or three non-invasive factors (EF <0.26, QRS duration on ECG ≥0.12 sec, history of heart failure requiring treatment) were associated with a progressively lower hazard ratio indicating better survival in higher risk patients with ICD therapy [7,8].

MADIT-II

When we designed the MADIT-II trial in 1997, we reasoned that in patients with a prior myocardial infarction and advanced left ventricular dysfunction, as manifest by an EF ≤0.30, the scarred myocardium would serve as a substrate for malignant ventricular arrhythmias and electrophysiologic testing would not be needed for risk stratification. The MADIT-II trial randomized 1,232 patients to ICD or conventional therapy. The eligibility and exclusion criteria are presented in Tables 1 and 2. The hazard ratio for the risk of death from any cause in the defibrillator group compared with the conventional-therapy group was 0.69 ($P = 0.016$), a finding indicating a 31 percent reduction in the risk of death at any interval with ICD therapy compared to conventional therapy (Figure 1) [9]. Both treatment groups received equivalent and appropriate beta-blocker, angiotensin converting enzyme (ACE) inhibitor, diuretic, digitalis, and aspirin therapy. In an editorial that accompanied the MADIT-II publication, Bigger suggested that improved risk stratification with identification

Address correspondence to: Arthur J. Moss, M.D., Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, NY 14642, USA. E-mail: heartajm@heart.rochester.edu

Table 1. *MADIT-II eligibility criteria*

1.	Chronic coronary artery disease with a documented prior myocardial infarction
2.	Ejection fraction ≤0.30
3.	No requirement for ventricular arrhythmias or electrophysiologic study
4.	Age ≥21 years with no upper age limitation

Table 2. *MADIT-II exclusion criteria*

1.	MADIT-I indication
2.	NYHA class IV at enrollment
3.	Myocardial infarction <1 month before enrollment
4.	Coronary revascularization <3 months before enrollment
5.	Advanced organ system disease

of higher risk subsets within the MADIT-II defined population might save almost as many lives as was observed in the overall MADIT-II population, and effective risk stratification might be more cost-effective [10].

Electrophysiologic Testing

In MADIT-II, EPT was not an eligibility criterion. However, in patients randomized to ICD therapy, investigators were encouraged to carry out EPT at the time of ICD implantation. It was hypothesized that inducibility would be associated with a greater utilization of ICD therapy for ventricular tachycardia and ventricular fibrillation than would non-inducibility. This electrophysiologic question is currently under investigation as a high-priority substudy, and some preliminary findings have been reported at the Cardiostim meeting in Nice, France in June 2002.

Table 3. *Cox proportional hazard ratios for ICD utilization for ventricular tachyarrhythmias during follow-up by electrophysiologic inducibility at ICD implant*

	Hazard ratio for ICD utilization (EP+:EP−)[a]		
	VT	VF	VT/VF
	1.57	0.46	1.28
P-value	0.07	0.08	0.26

EP+: inducible at electrophysiologic testing; EP−: not inducible at electrophysiologic study; VT: ventricular tachycardia; VF: ventricular fibrillation.

[a]Hazard ratio (EP+:EP−): risk of utilizing ICD therapy for VT, VF, and VT/VF per unit time in those who were electrophysiologically inducible as compared with that among patients who were not inducible. Hazard ratio >1.0 indicates increased ICD utilization for the specified arrhythmia, and hazard ratio <1.0 indicates decreased ICD utilization.

Of the 742 patients randomized to ICD therapy, EPT was carried out in 583 ICD-treated patients. Electrophysiologic inducibility (sustained monomorphic or polymorphic ventricular tachycardia with ≤3 extrastimuli or ventricular fibrillation with ≤2 extrastimuli), was found in 210 of the 583 tested patients (36%); 373 were non-inducible (64%). Using the findings from routine ICD interrogation during follow-up, the frequency of use of appropriate ICD therapy for ventricular tachycardia (antitachycardia pacing or shock) and ventricular fibrillation

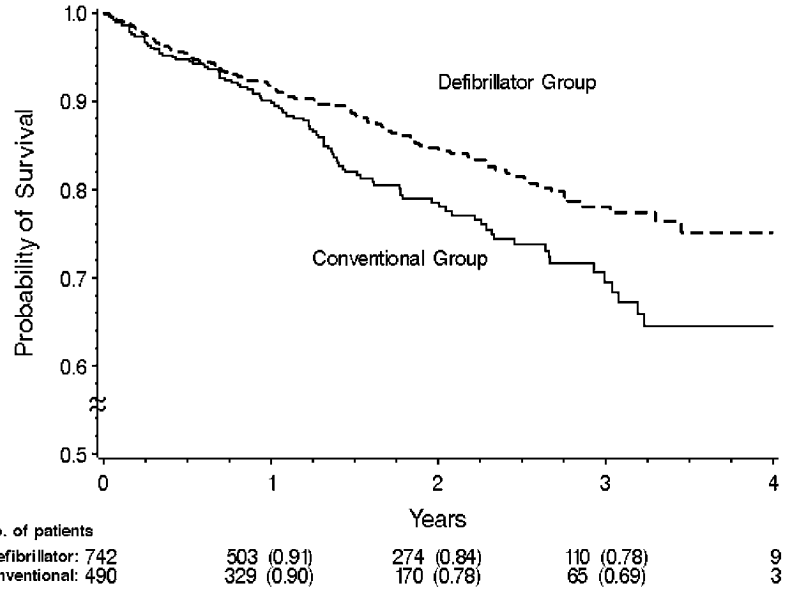

Fig. 1. *Kaplan-Meier estimates of the probability of survival in the defibrillator and conventional-therapy groups over time. The difference in survival between the two groups was significant (nominal P = 0.007, by log-rank test). Reprinted from Ref. [9] with permission.*

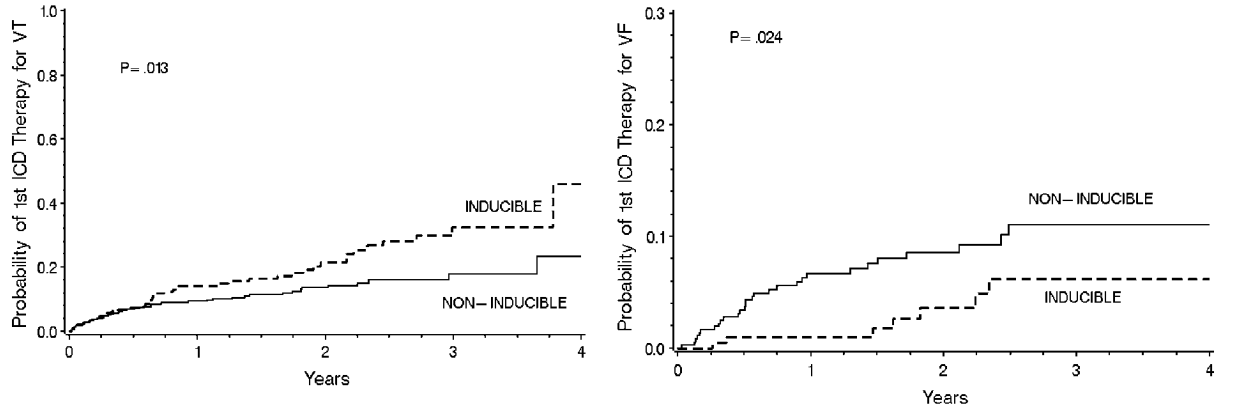

Fig. 2. *Cumulative probability of first ICD therapy for ventricular tachycardia (left panel) and for ventricular fibrillation (right panel) during follow-up in patients who were inducible and non-inducible with electrophysiologic testing at the time of ICD implant.*

(shock) was determined. The preliminary findings are presented in Figure 2 and Table 3. In brief, we found an intriguing paradox: inducibility was associated with increased ICD therapy for ventricular tachycardia, and non-inducibility was associated with increased ICD therapy for ventricular fibrillation. When ventricular tachycardia or ventricular fibrillation, which ever occurred first, was used as a combined end point, inducibility was not useful in identifying which patients would use appropriate ICD therapy for malignant ventricular arrhythmias. Overall, electrophysiologic testing was not an effective stratifier for high-risk arrhythmias in the MADIT-II study population with EF $\leq$0.30.

Conclusion

In patients with a prior myocardial infarction and ejection fraction $\leq$0.30, prophylactic implantation of a defibrillator improves survival. Electrophysiologic inducibility at the time of ICD implantation is associated with increased ICD utilization for ventricular tachycardia during long-term follow-up and decreased utilization for ventricular fibrillation. These preliminary findings raise questions about the clinical usefulness of EPT as a risk stratifier in patients with advanced left ventricular dysfunction.

References

1. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322–324.
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter automatic defibrillator implantation trial investigators. *N Engl J Med* 1996;335:1933–1940.
3. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter unsustained tachycardia trial investigators. *N Engl J Med* 1999;341:1882–1890.
4. The antiarrhythmics versus implantable defibrillators (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–1583.
5. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297–1302.
6. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The cardiac arrest study hamburg (CASH). *Circulation* 2000;102:748–754.
7. Moss AJ. Implantable cardioverter defibrillator therapy: The sickest patients benefit the most. *Circulation* 2000;101:1638–1640.
8. Moss AJ, Fadl Y, Zareba W, Cannom DS, Hall WJ. Survival benefit with an implanted defibrillator in relation to mortality risk in chronic coronary heart disease. *Am J Cardiol* 2001;88:516–520.
9. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–883.
10. Bigger JT. Expanding indications for implantable cardiac defibrillators. *N Engl J Med* 2002;346:931–933.