Impact of the Multicenter Automatic Defibrillator Implantation Trial on Clinical Practice

Ivan C.K. Ho, M.D., Jonathan J. Passeri, M.D., Mary L. Guy, R.N.,
Jeremy N. Ruskin, M.D., and Patrick T. Ellinor, M.D., Ph.D.

From the Department of Medicine and the Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, MA

Background: The first multicenter automatic defibrillator implantation trial (MADIT-I) was a landmark study that identified a significant reduction in mortality among high-risk patients with ischemic cardiomyopathy treated prophylactically with an implantable cardioverter defibrillator (ICD), yet the direct and indirect impact of this trial on clinical practice is unknown.

Methods: We performed a retrospective analysis of the 679 patients who underwent primary ICD implantation between 1994 and 2000 at a single academic center. The baseline characteristics of each patient were determined at the time of ICD implantation, and the vital status of all patients was determined as of January 1, 2004.

Results: The number of patients who received an ICD based on the MADIT-I criteria increased from 1.4% in 1994 to 6.1% in 2000. An additional 60 patients were identified that met many but not all of the trial criteria and consisted of patients with a history of a recent revascularization or myocardial infarction, syncope, or an ejection fraction $\geq 35\%$. The number of patients who received ICDs in this expanded MADIT-I subset also grew from 5.6% in 1994 to 14.6% in 2000. Mortality during a mean follow-up of 4.7 years was significantly higher in the MADIT-I group than in the expanded MADIT-I, or the remaining primary prevention and secondary prevention subsets.

Conclusion: The MADIT-I has not only led to an increase in the number of patients undergoing prophylactic ICD implantation, but in clinical practice it has also been extrapolated to a broader population that has a different degree of risk than originally studied.

A.N.E. 2006;11(1):20–27

Implantable cardioverter defibrillator; Multicenter Automatic Defibrillator Implantation Trial; ventricular arrhythmia; nonsustained ventricular tachycardia

Despite continued advances in medical therapy for cardiovascular disease, mortality in survivors of myocardial infarction with left ventricular dysfunction remains high. In this population, nonsustained ventricular tachycardia (NSVT) is a marker for poor prognosis with a 2-year mortality rate of nearly 30%.^{1–3} Implantable cardioverter defibrillators (ICDs) have been shown to be highly effective in treating malignant ventricular arrhythmias,^{4–8} especially in survivors of cardiac arrests.^{9–12} Further trials have found a mortality benefit in the prophylactic implantation of an ICD in a high-risk patient population with history of ischemic cardiomyopathy and asymptomatic NSVT.^{13–16} The multicenter automatic defibrillator implantation trial (MADIT-I) examined 196 high-risk patients with is-

chemic cardiomyopathy, NSVT, and inducible ventricular arrhythmias during electrophysiologic testing and showed that use of an ICD conferred a 54% reduction in all-cause mortality.¹³

To examine the impact of the MADIT-I on the clinical practice of prophylactic ICD placement, we performed a retrospective review of all patients who underwent ICD implantation at a single academic medical center over a 6-year period.

METHODS

All patients who underwent primary ICD implantation between 1994 and 2000 were identified through a centralized database maintained in the ICD clinic at Massachusetts General Hospital.

Address for reprints: Patrick T. Ellinor, M.D., Ph.D., Cardiac Arrhythmia Service, Massachusetts General Hospital, 55 Fruit Street, GRB 109, Boston, MA 02114. Fax: 617-726-2155; E-mail: pellinor@partners.org

This project is supported by an NIH award to Dr. Ellinor (HL71632).

©2006, Copyright the Authors
Journal compilation ©2006, Blackwell Publishing, Inc.

Patients who underwent an ICD pulse generator replacement, upgrade or revision of their defibrillators were excluded from this study. Patients enrolled in any ongoing ICD trials were also excluded from further analysis. The paper and electronic medical records of all study patients were reviewed and a detailed medical history, including presenting symptoms and arrhythmias, medications, and hospital course, was recorded. The results of electrocardiograms, echocardiogram, cardiac catheterization, electrophysiology studies, and details of defibrillator implantation were also obtained.

In this study, subjects described as MADIT-I patients were required to meet all of the inclusion criteria of the trial including a history of coronary disease with a Q wave myocardial infarction in the past, left ventricular systolic dysfunction with ejection fraction (EF) $\leq 35\%$, a documented episode of asymptomatic NSVT, and electrophysiologic study with inducible ventricular tachyarrhythmias. The requirement of inducible sustained ventricular tachyarrhythmias on electrophysiologic study not suppressible by procainamide was not included in this initial group definition. The presence of any of the following fulfilled one of the exclusion criteria for the MADIT-I: recent syncope from ventricular arrhythmia not associated with acute myocardial infarction, myocardial infarction within the past 3 weeks, coronary artery bypass grafting in the last 2 months, or coronary angioplasty in the last 3 months.

All other subjects not meeting criteria for the MADIT-I were further divided into non-MADIT-I primary prevention and secondary prevention groups, based on whether these patients received the ICD prophylactically (primary prevention) or after a cardiac arrest or resuscitation from ventricular arrhythmias (secondary prevention). Within the non-MADIT-I primary prevention category, we identified an additional subset of patients who fulfilled many but not all of the MADIT-I inclusion criteria (defined as the "expanded MADIT-I group"). This subset included patients with one or more of the following: (1) recent myocardial infarction; (2) recent revascularization (percutaneous or surgical); (3) presyncope or syncope as the presenting symptom; (4) EF between 36% and 50%; (5) others, including patients with normal EF ($\geq 50\%$ by echocardiography), negative, or no electrophysiology study.

The vital status of all patients as of January 1, 2004, was assessed through hospital records and the Social Security Death Index database.

For statistical analysis, continuous variables are presented as the mean value $\pm$ SD. Continuous variables were tested for normality of distribution and two-sided *t*-tests were used for comparisons of means. The chi-square test was used for the comparison of categorical variables between two groups. *P* values of <0.05 were considered to be significant. The Kaplan-Meier survival method was used to estimate the cumulative probability of survival after ICD implantation. Software packages used for data compilation and analysis included MS Access 2000 and MS Excel 2000 (Microsoft Office 2000, Redmond, WA, USA), and Intercooled Stata 8.0 (Stata Corp, College Station, TX, USA).

RESULTS

A total of 679 patients underwent primary implantation of an ICD at Massachusetts General Hospital from 1994 to 2000. The baseline characteristics of these patients are illustrated in Table 1. During the study period, 27 subjects (4%) met the strict inclusion and exclusion criteria for the MADIT-I. There was no significant difference in the age or sex of the patients between the MADIT-I group and the non-MADIT-I primary prevention group. By definition, patients who met the criteria for the MADIT-I had a lower mean left ventricular EF, lower rate of recent revascularization, and higher incidence of coronary artery disease and electrophysiology testing than the remaining patients. The MADIT-I patients also had an increased prevalence of hypertension, hypercholesterolemia, prior surgical or percutaneous revascularization, and use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, digoxin, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor (statin) or nitrate therapy. Additionally, significantly more of these patients received a dual-chamber device compared to the non-MADIT-I primary prevention patients (Table 1).

The non-MADIT-I group consisted of 242 patients (36%) who received an ICD for other primary prevention indications and 410 patients (60%) who received an ICD for secondary prevention. The most common presenting cardiac disorder at ICD implantation in both the primary prevention and the secondary prevention groups was ischemic

Table 1. Clinical Characteristics of MADIT-I and Other ICD Patients

	All Patients	MADIT-I Primary Prevention	Other Primary Prevention	Secondary Prevention	P*
Total	679	27 (4)	242 (36)	410 (60)	
Age in years	63	64	59	66	
Male	549 (81)	22 (81)	198 (82)	329 (80)	
Female	130 (19)	5 (19)	44 (18)	81 (20)	
Mean ejection fraction (%)	35	23	36	36	<0.001
Presenting arrhythmia					
Syncope or presyncope	208 (31)	0 (0)	160 (66)	48 (12)	<0.001
VFA	194 (29)	0 (0)	0 (0)	183 (45)	<0.001
VT	223 (33)	0 (0)	0 (0)	223 (55)	0.001
NSVT	163 (24)	27 (100)	134 (55)	0 (0)	<0.01
Medications					
Aspirin	398 (59)	14 (54)	114 (47)	270 (66)	
β -blocker	418 (62)	18 (69)	141 (58)	259 (63)	
ACEI or ARB	400 (59)	22 (85)	137 (56)	241 (59)	0.01
Diuretic	334 (49)	16 (62)	126 (52)	192 (47)	
Digoxin	279 (41)	16 (62)	98 (41)	165 (40)	0.02
Amiodarone	78 (12)	4 (15)	20 (8)	54 (13)	
Sotalol	75 (11)	2 (8)	24 (10)	49 (12)	
Other antiarrhythmics	40 (6)	0 (0)	16 (7)	24 (6)	
Calcium-channel-blocker	76 (11)	2 (8)	30 (12)	44 (11)	
Statin	244 (36)	15 (58)	79 (33)	150 (37)	0.005
Nitrates	145 (21)	11 (42)	42 (17)	92 (23)	0.001
Medical history					
Hypertension	245 (36)	14 (52)	75 (31)	156 (38)	0.02
Coronary artery disease	484 (72)	27 (100)	136 (57)	327 (80)	<0.001
Diabetes mellitus	136 (20)	4 (15)	39 (16)	93 (23)	
Hypercholesterolemia	251 (37)	16 (59)	78 (32)	157 (38)	0.003
CABG—more than 30 days prior to ICD	175 (26)	10 (37)	51 (21)	114 (28)	0.03
PCI—more than 30 days prior to ICD	50 (7)	6 (22)	17 (7)	27 (7)	0.004
Any old revascularization	212 (31)	14 (52)	64 (26)	134 (33)	0.003
CABG—within 30 days of ICD	83 (12)	0 (0)	21 (9)	62 (15)	
PCI—within 30 days of ICD	56 (8)	0 (0)	12 (5)	44 (10)	
Revascularization within 30 days of ICD	138 (20)	0 (0)	33 (14)	105 (26)	0.02
EPS and devices					
Single chamber	505 (74)	12 (44)	170 (70)	87 (21)	0.003
Dual chamber	174 (26)	15 (56)	72 (30)	323 (79)	0.003
EPS done	484 (71)	27 (100)	196 (81)	260 (63)	0.006
Positive EPS	382 (56)	27 (100)	153 (63)	202 (49)	<0.001
SMVT	241 (35)	22 (81)	82 (54)	137 (68)	
PMVT	31 (5)	1 (4)	18 (12)	12 (6)	
VF	97 (14)	4 (15)	26 (17)	30 (15)	
Negative EPS	102 (15)	0 (0)	43 (18)	58 (14)	<0.001

Values presented as n (percentage) unless otherwise indicated. *P values are based on comparisons between the MADIT-I and the non-MADIT-I primary prevention groups.

Statin = 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; EPS = electrophysiologic study; NSVT = nonsustained ventricular tachycardia; PCI = percutaneous coronary intervention; PMVT=polymorphic ventricular tachycardia; SMVT = sustained monomorphic ventricular tachycardia; VFA = ventricular fibrillation arrest; VT = ventricular tachycardia.

cardiomyopathy, accounting for 64% and 80% of the group's patients, respectively (Fig. 1) Other cardiac disorders resulted in ICD implantation included idiopathic dilated cardiomyopathy (28% vs

10%), hypertrophic cardiomyopathy (5% vs 1%) and congenital heart disease (1% in both primary and secondary prevention groups). Congenital long QT syndrome, arrhythmogenic right ventricular

Figure 1. Clinical history of patients who underwent ICD implantation from 1994 to 2000 for primary and secondary prevention. CM = cardiomyopathy; LQTS = long QT syndrome; ARVD = arrhythmogenic right ventricular dysplasia; MADIT-I = first multicenter automatic defibrillator implantation trial; Brugada = Brugada syndrome; congenital = congenital heart disease.

dysplasia, Brugada's syndrome, and other clinical presentations such as valvular heart disease and coronary vasospasm accounted for the remaining 16% of the ICD patients in the primary prevention group and 7% in the secondary prevention group.

The percentage of patients who met the criteria for the MADIT-I increased steadily every year from 1.4% of total implants in 1994 to 6.1% in 2000 (Fig. 2). In addition to the limited number of patients who met the strict MADIT-I criteria, we

identified an additional 60 patients within the primary ICD implant population who met many but not all of the original trial criteria. As with the MADIT-I group, there was also a steady increase in the number of patients in this expanded MADIT-I group increasing from 5.6% in 1994 to 14.7% in 2000. These patients were further categorized into three subgroups: 13 patients with a recent myocardial infarction, 24 patients with a recent percutaneous or surgical revascularization procedure, and

Figure 2. ICD implantations of the MADIT-I, expanded MADIT-I, and other primary and secondary prevention groups by year. Numbers adjacent to each bar indicate the total number of patients in each group.

32 patients with one or more of other trial exclusion criteria (such as an EF over 35%, negative or no electrophysiology study, presentation with syncope) (Fig. 3). Of note, 26 of the 60 patients (43%) belonged to more than one of these subgroups. For example, a number of these patients who had recent myocardial infarction also underwent surgical revascularization prior to their prophylactic ICD implantation.

During an average follow-up of 4.7 years, there were 15 deaths in the MADIT-I group (55%), 20 deaths in the expanded MADIT-I group (33%), 39 deaths in the remaining primary prevention group (21%), and 141 deaths in the secondary prevention group (34%) (Fig. 4). The mortality rate was significantly higher in the MADIT-I compared to the expanded MADIT-I ($P = 0.03$) and the remaining primary prevention ($P < 0.001$) or the secondary prevention ($P = 0.01$) population.

DISCUSSION

Over the last 15 years, the number of ICDs implanted worldwide continues to increase and currently exceeds 100,000 devices per annum.¹⁵ The expanded use of these devices is due to the combination of increasing familiarity with the technology

and the evolving indications for defibrillator implantation.^{16,17} The MADIT-I was the first of these large-scale studies to demonstrate the effectiveness of ICD therapy in a high-risk subset of patients. While the indications for the MADIT-I study are widely known, the impact of this study on clinical practice has not been assessed. In the current study, we sought to explore the role of the MADIT-I on ICD implantations at a single academic medical center by determining the practice patterns before and after the publication of this study.

From 1996 through 2000, we observed an increase in the number of patients who received an ICD based on the criteria used in the MADIT-I. While this increase was expected, it was surprising to find that MADIT-I patients constituted such a small minority of total ICD implantations. Presumably the small number of MADIT-I patients observed was due to the stringent inclusion criteria of the trial. From 1997 to 2000, the total number of ICD implantations increased by 191%, and although the number of MADIT-I patients increased by 900%, the percentage of MADIT-I patients remained small, increasing from 1.8% in 1997 to 6.1% in 2000.

We found that the greatest impact of the MADIT-I appeared to have been in a broader clinical

Figure 3. Extrapolation of the MADIT-I. Subjects who met some but not all of the MADIT-I criteria are indicated by year. The solid bar indicates the group of patients that met all of the MADIT-I criteria.

population than originally studied. There were a larger number of patients receiving ICDs in the expanded MADIT-I group compared to the MADIT-I group in every year studied. This broader group consisted largely of patients with a recent myocardial infarction, revascularization, or EF over 35%. These patients reflect a commonly encountered clinical scenario in which hospitalized patients with

reduced left ventricular function are noted to have NSVT and are referred for electrophysiologic testing.

Although this expanded MADIT-I population was noted to have a lower mortality in long-term follow-up than the MADIT-I patients due to their more favorable baseline risk profile, the mortality in this population is still in excess of 30% at 5 years. The findings in this expanded MADIT-I population are consistent with a recent meta-analysis of ICD trials in which the impact of ICD therapy on overall mortality was found to be dependent on underlying patient characteristics even within the already established high-risk group.¹⁸

We observed a higher 2-year mortality rate in the MADIT-I group ($n = 27$) of 24% compared to 13% 2-year mortality rate observed in the defibrillator arm of the original MADIT-I despite a similar age and mean EF. The difference in mortality rate in the two studies may be explained by the higher degree of comorbidities in our patients compared to those enrolled in the trial. This observation may also reflect the relatively conservative practice of ICD implantation at our center as highlighted by the results of a recent international survey in which MADIT-I indications accounted for 18% of all new implants in 1999 versus 4% at our center.²⁴

Figure 4. Kaplan-Meier survival curves of the MADIT-I, expanded MADIT-I, other primary prevention, and secondary prevention groups over the follow-up period from January 1, 1994 to January 1, 2004.

Our findings of a lower risk in the expanded MADIT-I group are in keeping with the results of the more recent The Coronary Artery Bypass Graft (CABG) Patch Trial¹⁹ and The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) trials²⁰ in which ICD therapy was not effective for primary prevention of sudden cardiac death in patients with recent revascularization or myocardial infarction.

Since our population is limited by referral patterns at an academic medical center, it may not be typical of all clinical populations. The small number and clinical heterogeneity of the subjects in the expanded MADIT-I cohort also limits accurate assessment of the long-term outcome of this group of patients. Additionally, it is difficult in this study to assess the impact of other trials on clinical practice during the study period. In particular, the 1998 American College of Cardiology/American Heart Association guidelines for implantation of ICDs did not specifically exclude patients who had recent revascularization or myocardial infarction but otherwise fulfilled the MADIT-I criteria for ICD therapy.²¹ These guidelines may partially explain the increase observed in the expanded MADIT-I group during the study period. These limitations highlight the need for continued risk stratification of patients by prospective, multicenter clinical trials.²²⁻²⁴

The MADIT-I has led to the expanded use of a prophylactic defibrillators not only in a strictly defined subset of high-risk patients with ischemic cardiomyopathy but also in a broader cohort that has a different degree of risk than that observed in the original study.

Acknowledgment: We are grateful to Dr. Moussa Mansour for his thoughtful comments on this manuscript.

REFERENCES

1. Anderson KP, DeCamilla J, Moss AJ. Clinical significance of ventricular tachycardia (3 beats or longer) detected during ambulatory monitoring after myocardial infarction. *Circulation* 1978;57:890-897.
2. Bigger JT Jr, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250-258.
3. Buxton AE, Marchlinski FE, Waxman HL, et al. Prognostic factors in nonsustained ventricular tachycardia. *Am J Cardiol* 1984;53:1275-1279.
4. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322-324.
5. Echt DS, Armstrong K, Schmidt P, et al. Clinical experience, complications, and survival in 70 patients with the automatic implantable cardioverter/defibrillator. *Circulation* 1985;71:289-296.
6. Kelly PA, Cannom DS, Garan H, et al. The automatic implantable cardioverter-defibrillator: Efficacy, complications and survival in patients with malignant ventricular arrhythmias. *J Am Coll Cardiol* 1988;11:1278-1286.
7. Lehmann MH, Steinman RT, Schuger CD, et al. The automatic implantable cardioverter defibrillator as antiarrhythmic treatment modality of choice for survivors of cardiac arrest unrelated to acute myocardial infarction. *Am J Cardiol* 1988;62:803-805.
8. Winkle RA, Mead RH, Ruder MA, et al. Long-term outcome with the automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989;13:1353-1361.
9. Kuck KH, Cappato R, Siebels J, et al. 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.
10. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs implantable defibrillator study. *Cardiac Arrest Study Hamburg. Canadian implantable defibrillator study. Eur Heart J* 2000;21:2071-2078.
11. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297-1302.
12. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;337:1576-1583.
13. Moss AJ, Hall WJ, Cannom DS, et al. 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.
14. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The cardiomyopathy trial (CAT). *Circulation* 2002;105:1453-1458.
15. Berstein A, Parsonnet V. Survey of cardiac pacing and implanted defibrillator practice patterns in the United States in 1997. *Pacing Clin Electrophysiol* 2001;24:842-855.
16. Buxton AE, Lee KL, Fisher JD, et al. 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.
17. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.
18. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: A systematic review of randomized, controlled trials. *Ann Intern Med* 2003;138:445-452.
19. Bigger JT for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *New Engl J Med* 1998;337:1569-1575.
20. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of implantable cardioverter-defibrillator after acute myocardial infarction. *New Engl J Med* 2004;351:2481-2488.

21. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on pacemaker implantation). *Circulation* 1998;97(13):1325-1335.
22. Kadish A. Primary prevention of sudden death using ICD therapy: Incremental steps. *J Am Coll Cardiol* 2002;39:788-789.
23. Nisam S, Farre J. Is prophylaxis the best use of the ICD? *Eur Heart J* 2002;23:700-705.
24. Bigger JT. Expanding indications for implantable cardiac defibrillators. *N Engl J Med* 2002;346:931-933.