Are the MADIT II Criteria for ICD Implantation Appropriate for Japanese Patients?

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Background The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II investigators concluded that prophylactic use of an implantable cardioverter defibrillator (ICD) improved survival in patients with prior myocardial infarction (MI) and reduced the left ventricular ejection fraction (LVEF). However, it is unclear whether MADIT II criteria for ICD implantation are appropriate for Japanese patients.

Methods and Results During the period 1997 to 2001 90 (M/F: 75/15; mean age: 65 ± 9 years) of the 3,258 patients who underwent elective cardiac catheterization met MADIT II criteria (Q-wave MI more than 4 weeks prior; LVEF ≤ 0.30 ; >21 years of age; electrophysiologic testing not required) and were selected in this retrospective study of patient prognosis after catheterization. During the 37 ± 12 -month follow-up period, 15 patients died of congestive heart failure ($n=9$), sudden cardiac death ($n=2$), acute MI ($n=1$), or noncardiac causes ($n=3$). The survival rate in the present series was comparable with that in the MADIT II defibrillator group, but higher than that in the MADIT II conventional therapy group. A significantly greater percentage of the present patients were found to be in New York Heart Association class I and have undergone percutaneous coronary intervention than in MADIT II.

Conclusion These results suggest that it may be inappropriate to apply MADIT II criteria to Japanese patients. (Circ J 2005; 69: 19–22)

Key Words: Implantable cardioverter defibrillator; Left ventricular dysfunction; Myocardial infarction; Sudden cardiac death

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II revealed that prophylactic use of an implantable cardioverter defibrillator (ICD) improved the prognosis of patients with left ventricular (LV) dysfunction and no history of ventricular tachyarrhythmia after myocardial infarction (MI).¹ The prognosis of patients with LV dysfunction after MI is poor even in Japan;^{2,3} although treatment strategies have greatly reduced the number of post-MI cardiac events in recent years. However, because it is not clear whether prophylactic ICD use would improve the prognosis of Japanese patients with LV dysfunction, we conducted a retrospective study to clarify the prognosis of MADIT II-like Japanese patients who did not undergo ICD implantation.

Methods

The MADIT II criteria for ICD implantation are as follows: Q-wave MI >4 weeks prior, LV ejection fraction (LVEF) $<30\%$ and age >21 years. Nonsustained ventricular tachycardia and electrophysiologic testing are not part of the eligibility criteria. Among 3,258 patients who underwent cardiac catheterization at Showa University Hospital during the period 1997 to 2001, 90 met the MADIT II criteria

and were included in this study. There were 75 men and 15 women, with an average age of 65 ± 9 years. The date of cardiac catheterization was regarded as day 1 of the study. The follow-up period lasted until either patient death or March 2003. The survival rate, cause of death, and clinical characteristics of these patients were examined and compared with those of the MADIT II patients.

All data measured are shown as average $\pm$ standard deviation. ANOVA or χ^2 test was used to analyze differences when there were more than 2 groups; unpaired t-test or χ^2 test was used for comparison between nonsurvivors and survivors. $P < 0.05$ was considered to be statistically significant.

Results

Outcome

During the follow-up period of 37 ± 12 months, 15 (16.7%) of the 90 patients died of congestive heart failure ($n=9$), sudden cardiac death ($n=2$), acute MI ($n=1$), or noncardiac causes ($n=3$). Four patients had sustained ventricular tachycardia (VT) during the follow-up period. None of them had a history of cardiopulmonary arrest and 3 underwent ICD implantation after documentation of sustained VT. They were the only patients who underwent ICD implantation in this group of 90 patients. The fourth patient died of noncardiac disease before ICD implantation.

Comparison With MADIT II

Analysis of the Kaplan-Meier curves plotted with data from our study and from MADIT II (Fig 1) indicated a

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Fig 1. Probability of survival. Event-free survival, depicted by Kaplan-Meier curves, of patients in our series (solid line) and patients in the MADIT II study who underwent conventional therapy (dotted line) and defibrillator implantation (dashed line).

Table 1 Patient Characteristics

	MADIT II		
	Present series (n=90)	Defibrillator (n=742)	Conventional therapy (n=490)
Age (years)	64±10	64±10	65±10
Male sex (%)	80	84	85
NYHA functional class			
I	79*	35	39
II	18	35	34
III	3	25	23
IV		5	4
Hypertension (%)	73	53	53
Diabetes (%)	37	33	38
Coronary bypass surgery (%)	10*	58	56
Percutaneous coronary intervention (%)	77*	45	42
Acute myocardial infarction > 6 months (%)	78	88	87

NYHA, New York Heart Association. * $p < 0.05$ derived from χ^2 test.

Table 2 Electrocardiographic Findings

	MADIT II		
	Present series	Defibrillator	Conventional therapy
Atrial fibrillation (%)	5	9	8
QRS > 0.12 (%)	21*	50	51
Nonspecific conduction defect	9	22	26
Right bundle branch block	9	9	7
Left bundle branch block	3	19	18
LVEF (%)	24±4	23±5	23±6

LVEF, left ventricular ejection fraction. * $p < 0.05$ derived from χ^2 test.

higher event-free survival rate in our patients than in MADIT II patients at 3 years after enrollment. The survival rate in our series was comparable with that in the defibrillator group of the MADIT II study, but higher than that in the conventional therapy group of the MADIT II study. Therefore, we compared the characteristics of our patients with those of these 2 MADIT II groups (Table 1). Compared with MADIT II, a significantly greater percentage of the present patients were found to be in New York Heart Association (NYHA) functional class I and to have undergone percutaneous coronary intervention (PCI) and a significantly lower percentage had undergone coronary artery bypass grafting. In addition, a significantly higher prevalence of a QRS width of more than 0.12 s was observed in the MADIT II patients (Table 2). There was a significantly greater percentage of patients taking a β -blocker, digitalis, or lipid-

lowering statin drug in the MADIT II study than in our series, but there was a significantly greater percentage of patients taking a Ca-antagonist in our series (Fig 2).

Survivors vs Nonsurvivors

We noted 2 significant differences between survivors and nonsurvivors in our series (Table 3): the nonsurvivors were older and had a higher NYHA functional status. None of the other factors, including the electrocardiographic findings (Table 3), differed significantly between survivors and nonsurvivors.

Sudden Death

Two patients died suddenly during the follow-up period. One died during the night and could not be revived by the ambulance officers when they were called in the morning;

Fig 2. Medical treatments. There was a significantly greater percentage of patients taking a β -blocker, digitalis, or lipid-lowering statin drug in the MADIT II study than in our series, but there was a significantly greater percentage of patients taking a Ca-antagonist in our series than in the MADIT II study. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 3 Characteristics of Nonsurvivors and Survivors in the Present Series

	Nonsurvivors (n=15)	Survivors (n=75)	p value
Age (years)	69±8.1	63±10	<0.05
M/F	12/3	60/15	NS
NYHA functional class			
I	5	65	<0.05
II	7	10	
III	3	0	
Hypertension	9	56	NS
Diabetes	7	26	NS
Coronary bypass surgery	3	6	NS
Percutaneous coronary intervention	9	59	NS
Acute myocardial infarction > 6 months	10	61	NS
ECG findings*			
RR	0.781±0.102	0.819±0.147	
PR	0.175±0.026	0.170±0.042	
QRS	0.122±0.038	0.110±0.024	
QT	0.390±0.048	0.386±0.041	
QTc	0.442±0.045	0.429±0.032	
QTd	94±24	85±28	
QTcd	103±26	95±32	

NYHA, New York Heart Association. p values derived from unpaired t-test or χ^2 test.

*Differences were not statistically significant.

the other patient felt chest discomfort during a daytime meeting and then lost consciousness. His colleagues started cardiopulmonary resuscitation and upon arrival at the emergency room, the first electrocardiogram showed sinus rhythm and pulseless electrical activity. However, despite emergency PCI and cardiopulmonary support by intra-aortic balloon pumping and mechanical ventilation, he died several hours later.

Discussion

The survival rate of the present patients who met the MADIT II criteria was comparable or superior to that of the MADIT II patients. Heart failure was the most frequent cause of death. The prognosis of patients with MI is improving with the increasing use of aggressive coronary revascularization and administration of angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor

blocker (ARB), or β -blocker.^{2,4-6} Although the medical therapy of the present patients was comparable or inferior to that in MADIT II, a significantly greater percentage of them underwent PCI than in MADIT II. Furthermore, 60% of the patients underwent primary PCI at the onset of AMI, which may account for the improved survival rate of our patients.⁷⁻⁹ Primarily, event rates of AMI and coronary death are very low in Japan¹⁰ compared with other industrialized nations reported in the WHO-MONICA project.¹¹ Aggressive therapy that includes primary PCI, ACEI, ARB or β -blocker can prevent LV remodeling, preserve LV function and keep the QRS width short^{2,4,6,9} and these factors may be associated with a greater percentage of patients in NYHA class I, which may be related to the improved outcomes in this series.

There was a significantly fewer percentage of patients with a wide QRS compared with MADIT II, which may be related to the better outcomes of the present patients. How-

ever, there was no significant difference in the QRS width between survivors and nonsurvivors, probably because of the small number of patients with a wide QRS: 5 of 19 patients with a wide QRS died compared with 10 of 71 patients with a narrow QRS who died. The total mortality of patients with a wide QRS was higher than that of patients with a narrow QRS, but was not statistically significant ($p=0.178$).

Two patients died suddenly during the follow-up period. Could an ICD have saved their lives? One patient showed sinus rhythm and electromechanical dissociation after cardiac arrest, which cannot be reversed with an ICD. Although we agree that the ICD is currently the most effective and reliable method of preventing sudden cardiac death, it is not effective in all cases.¹² Studies of automated external defibrillators revealed that ventricular fibrillation occurred in 44–71% of patients who suffered cardiac arrest.^{13,14} The incidence of sudden cardiac death by any cause other than ventricular fibrillation increases in patients with low cardiac function.^{15,16} An ICD is effective for terminating ventricular tachyarrhythmias and restore sinus rhythm, but it is not useful for pulseless electrical activity.¹² Therefore, we should not place too much confidence in the ICD.

Ventricular tachycardia occurred in 4 patients, 3 of whom subsequently underwent ICD implantation. Twenty-two patients in the conventional therapy group in the MADIT II study underwent ICD implantation during the trial, 21 for documented or suspected malignant ventricular arrhythmias and 1 at the physician's discretion. Ventricular tachyarrhythmias do not always lead to sudden cardiac death and the types of patients likely to benefit most from ICD implantation needs to be clarified.^{17,18}

Conclusion

There were more positive outcomes in the MADIT II-like patients in our series than in the MADIT II patients. Only 2 of 90 MADIT II-like patients died suddenly, 1 of whom might have been saved by an ICD. Thus, it may be inappropriate to apply MADIT II criteria for ICD implantation to Japanese patients.

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