Differences in Outcomes Between Patients Treated with Single- versus Dual-Chamber Implantable Cardioverter Defibrillators: A Substudy of the Multicenter Automatic Defibrillator Implantation Trial II

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Objectives: We sought to evaluate the influence of single- versus dual-chamber implantable cardioverter defibrillators (ICDs) on the occurrence of heart failure and mortality as well as appropriate and inappropriate ICD therapy in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II).

Background: In MADIT-II, ICD therapy in patients with a prior myocardial infarction and ejection fraction ≤ 0.30 was associated with a 31% reduction in risk of mortality when compared to conventionally treated patients. An unexpected finding was an increased occurrence of hospitalization for heart failure in the ICD group.

Methods: Data from 717 patients randomized to ICD therapy with single- or dual-chamber pacing devices in MADIT-II were retrospectively analyzed. Endpoints selected for analysis included death from any cause, new or worsening heart failure requiring hospitalization, death or heart failure, appropriate therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF), and inappropriate ICD therapy for atrial fibrillation or supraventricular tachycardia.

Results: A total of 404 single-chamber ICDs (S-ICDs) and 313 dual-chamber ICDs (D-ICDs) were implanted. Patients receiving D-ICDs were at a higher risk at baseline than those receiving S-ICDs, with older age, higher NYHA class, more frequent prior CABG, wider QRS complex, more LBBB, higher BUN level, a history of more atrial arrhythmias requiring treatment, and a longer time interval from their index myocardial infarction to enrollment. While there was a trend toward an increase in adverse outcomes in the D-ICD group, no statistically significant differences in heart failure or mortality were observed between S-ICD versus D-ICD groups.

Conclusions: Patients with D-ICDs had a nonsignificant trend toward higher mortality and heart failure rates than patients with S-ICDs.

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The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) investigated the prophylactic placement of an automatic implantable cardioverter defibrillator (ICD) compared to conventional medical therapy in patients with a previous myocardial infarction and ejection fraction

≤ 0.30 . This randomized, primary prevention trial demonstrated a 31% reduction in the risk of all-cause death in the defibrillator-treated group.¹ As the body of evidence supporting the use of ICDs for both primary and secondary prevention of sudden cardiac death (SCD) has grown, so has

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the technological sophistication of defibrillators. Each successive generation of devices has offered smaller size and enhanced features such as dual-chamber and rate-adaptive pacing capabilities, as well as advanced algorithms to identify and treat ventricular arrhythmias while avoiding inappropriate therapies for atrial tachyarrhythmias. Biventricular pacemaker/defibrillators provide the opportunity to treat both congestive heart failure (CHF) and ventricular tachyarrhythmias. Several landmark trials have confirmed the efficacy of ICDs for both primary and secondary prevention of SCD.¹⁻⁶ MADIT-II is the first of these trials to present data regarding a significant number of dual-chamber devices.

Lamas et al. demonstrated reductions in the incidence of atrial fibrillation, heart failure hospitalizations, and improvement in quality of life with dual-chamber pacing compared to ventricular pacing alone in patients with sinus node dysfunction.⁷ Dual-chamber permanent pacing with a short AV delay has been reported to benefit patients with severe heart failure⁸ as well as dilated and hypertrophic obstructive cardiomyopathies.⁹⁻¹¹ The generally agreed upon indications for concomitant dual-chamber pacing in patients requiring an ICD include sick sinus syndrome, medication-induced bradycardia, chronotropic incompetence, AV conduction abnormalities, and medically refractory hypertrophic cardiomyopathy.⁸⁻¹² Reported benefits of dual-chamber pacing in patients requiring defibrillators include prevention of atrial fibrillation¹³⁻¹⁵ and improved specificity for arrhythmia detection compared to single-chamber ICDs (S-ICDs).^{16,17}

While these and other reports have suggested benefits to implanting dual-chamber ICDs (D-ICDs), clear benefits favoring the use of D-ICDs over S-ICDs in patients without a clear indication for concomitant pacing have not been definitively demonstrated. Saad and colleagues have reported that dual-chamber pacing ICDs may exacerbate CHF in patients without an indication for dual-chamber pacing, suggesting a deleterious effect of RV apical pacing in such patients.¹⁸ The DAVID trial demonstrated no advantage to dual-chamber (DDDR) pacing as compared to backup ventricular (VVI) pacing in patients requiring ICDs with left ventricular dysfunction and no indication for pacing.¹⁹ In fact, the combined endpoint of death and hospitalization for CHF was higher in the D-ICD group in that trial. Despite the lack of evidence

demonstrating proven benefit, and despite reports of possible deleterious effects of dual-chamber pacing ICDs, it has been estimated that dual-chamber devices accounted for 50% of defibrillators implanted in the United States in 1999,²⁰ and as many as two-thirds of the ICDs implanted between April 2000 and April 2001.²¹

An unexpected finding in the MADIT-II trial was a modestly increased frequency of hospitalization for new or worsening heart failure in the ICD group compared to the conventional therapy group.¹ In MADIT-II, the decision to implant a S-ICD or D-ICD was left to the discretion of the implanting physician. We sought to determine if there were differences with respect to death, heart failure, atrial arrhythmias, and device therapies between MADIT-II patients treated with single-chamber defibrillators compared to those with dual-chamber defibrillators.

METHODS

MADIT-II organization, recruitment, follow-up, randomization, and therapy have been presented previously.¹ For this study, we retrospectively obtained and analyzed the data from 717 patients in the defibrillator-treated group. (There were 742 patients randomized to the ICD arm in MADIT-II, but 22 never received an ICD and the type of ICD was not known in 3 patients.) These patients were further subdivided into S-ICD or D-ICD groups. Endpoints for our analysis included death from any cause, new or worsening heart failure requiring hospitalization, and death or heart failure as a compound endpoint as previously described.¹ In addition, appropriate therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF), and inappropriate ICD therapy for atrial fibrillation/flutter, supraventricular tachycardia, or sinus tachycardia were documented by device interrogation. Categorical variables were analyzed using the chi-square method, and continuous variables were analyzed using Student's *t*-test or the Wilcoxon rank-sum test as appropriate. All *P* values were 2-tailed. Multivariate analyses were performed using the Cox proportional hazards regression model.²² Survival curves were determined according to the method of Kaplan and Meier.²³

Device programming was at the discretion of the implanting physician. In general, single-chamber pacemakers were programmed to VVI mode at

40–50 bpm whereas dual-chamber units were programmed to DDD mode at 60–70 bpm with an AV interval averaging 190 ms.

RESULTS

MADIT-II enrollment began on July 11, 1997. The first Guidant D-ICD was market-released on July 1997 in the US, where most patients were enrolled. Initially more S-ICDs than D-ICDs were implanted but this evolved over time such that from 2000 to the end of the study in November 2001 the D-ICD implants exceeded S-ICD implants, as shown in Figure 1. S-ICDs had longer mean follow-up than D-ICDs, 24.3 months versus 16.4 months, respectively. Results were therefore analyzed by months of exposure.

The baseline clinical characteristics of 717 patients in the S-ICD and D-ICD groups are provided in Table 1. A total of 404 patients received S-ICDs, compared to 313 D-ICDs implanted. In general, the population receiving D-ICDs was older and had higher BUN and NYHA functional class. Compared

to the patients receiving S-ICDs, more patients in the D-ICD group had a history of atrial arrhythmias requiring therapy, use of amiodarone, and prior coronary bypass surgery. Similarly, there was a greater prevalence of bundle branch block, longer QRS duration, and a longer interval from previous myocardial infarction to enrollment in the D-ICD group.

The cumulative probabilities of a first CHF event or death over time by S-ICD or D-ICD are shown in Figure 2. Patients receiving a D-ICD had a higher risk of death, CHF, and death or CHF compared to S-ICDs, as noted in Table 2, but these hazard rates were not statistically significantly different from unity.

The cumulative probabilities for first appropriate ICD therapy for VT/VF and for inappropriate therapy for AF/SVT by S-ICD or D-ICD are shown in Figure 3. Since there were no evident differences in these therapies by ICD type, further analyses are not reported.

Kaplan–Meier curves reveal only the time to a first event; multiple events are not considered. The

Figure 1. Graph showing trends in the number of single and dual chamber defibrillator implantations in MADIT-II by year of trial.

Table 1. Baseline Clinical Characteristics of the 717 ICD Patients by Pacemaker Type

Characteristics	Single-Chamber Group (N = 404)	Dual-Chamber Group (N = 313)	P Value
Age (years)	63 ± 11	66 ± 10	<0.01
Male sex (%)	84	86	
NYHA class (%) ^a			
I	39	28	<0.01
II	35	37	
III or greater	26	35	
Treatment for hypertension (%)	55	51	
Diabetes (%)	34	34	
Current or former smoker (%)	80	79	
Coronary bypass surgery (%)	52	66	<0.01
Coronary angioplasty (%)	44	47	
Number of months between most recent myocardial infarction and enrollment	75 ± 75	98 ± 84	<0.01
History of ventricular arrhythmias requiring treatment (%)	10	10	
History of atrial arrhythmias requiring treatment (%)	22	35	<0.01
Cardiac findings at enrollment (%)			
Left ventricular ejection fraction	23 ± 5	23 ± 6	
Atrial fibrillation	10	6	
VVI pacemaker	0.6	3	
Left bundle branch block	15	25	<0.01
Right bundle branch block	7	11	
QRS interval (ms)	117 ± 31	135 ± 38	<0.01
Blood urea nitrogen (mg/dL)	22 ± 11	24 ± 12	0.01
Medications (%)			
Amiodarone	4	10	<0.01
Angiotensin converting enzyme inhibitors	79	76	
Beta-blockers	65	63	
Calcium channel blockers	13	11	
Digitalis	60	58	
Class I antiarrhythmic agents	2	3	
Diuretics	71	77	0.05
Lipid-lowering statin drugs	62	66	

^a“±” values are means ± SD.

^aValues reflect the highest New York Heart Association (NYHA) functional class recorded in the 3-month period before enrollment. Eligibility was limited to patients who were in NYHA class I, II, or III at the time of enrollment.

data on multiple events are reported in Table 3. Patients are grouped according to values of their event rates, i.e., by count of events per year of follow-up. The overall distributions of multiple events are quite similar by ICD type. Of note, approximately 75–90% of the patients experienced no ICD-related events in the S-ICD and D-ICD groups.

DISCUSSION

The MADIT-II trial demonstrated a mortality reduction for patients who received an ICD compared to those randomized to conventional medical therapy. However, patients with D-ICDs, as opposed to those with S-ICDs, had a nonsignificant trend toward higher mortality and heart failure rates. The

D-ICD group had a higher rate of atrial arrhythmias requiring treatment prior to enrollment. Nevertheless, no significant differences were observed in rates of inappropriate therapy in D-ICD versus S-ICD recipients. Appropriate therapy for VT/VF was virtually indistinguishable over the first 2 years, but diverged somewhat thereafter. However, average duration of follow-up was longer in the S-ICD group and there were a much larger number of patients available for analysis in the S-ICD group beyond 2 years.

We believe that the nonsignificant trend to increased rates of adverse events observed with D-ICDs (Table 2: all three hazard ratios > 1.0 but with confidence intervals overlapping 1.0) may be related to induction of ventricular dyssynchrony by

Figure 2. Kaplan-Meier curves illustrating: (A) Probability of first hospitalization for congestive heart failure; (B) probability for the composite endpoint of congestive heart failure or death; and (C) probability of death from any cause.

right ventricular pacing. Our findings are similar to those reported in the DAVID trial, with both studies suggesting higher rates of CHF in patients with D-ICDs compared to S-ICDs. Findings in a separate MADIT-II substudy analysis revealed that ICD patients with a high percentage of ventricular pacing had more CHF and greater mortality than those

Table 2. Proportional Hazards Regression Analyses of the Effect of ICD Type (Dual vs Single) on the Risk of Various Endpoint Events

Endpoint	D-ICD:S-ICD		
	Hazard Ratio	95% CI	P Value
IH-CHF	1.27	0.87, 1.86	0.21
Death	1.27	0.76, 2.12	0.36
IH-CHF or death	1.07	0.76, 1.50	0.71

IH-CHF = interim hospitalization for CHF.

Regression analyses are adjusted for elevated BUN, left bundle branch block, age ≥ 65 years, and NYHA class $>I$, the only factors identified in Table 1 that affected one or more of the endpoint events.

with a low percentage of ventricular pacing.²⁴ Patients with a high percentage of pacing were predominately those with dual-chamber devices.

When MADIT-II patients were being enrolled in the trial, it was thought that maintenance of a

Figure 3. Kaplan-Meier curves illustrating: (A) Probability of inappropriate therapy for atrial fibrillation or supraventricular tachycardia and (B) probability of first appropriate therapy for ventricular tachycardia or ventricular fibrillation.

Table 3. Percentage Distributions of Patient-Specific Event Rates for Several Types of Events, by ICD Type

Number of Events per Year	Percentage Distributions by Type of Event					
	Hospitalization for CHF		Appropriate ICD Rx for VT/VF		Inappropriate ICD Rx for AF/SVT	
	S-ICD	D-ICD	S-ICD	D-ICD	S-ICD	D-ICD
No events	77.4	75.1	73.4	80.2	86.8	90.1
0 < rate ≤ 1	13.2	10.5	13.9	7.0	6.0	2.9
1 < rate ≤ 6	8.7	13.7	9.4	9.9	6.7	5.1
Rate > 6	0.7	0.6	3.2 ^a	2.9 ^a	0.5 ^b	1.9
Total	100%	100%	100%	100%	100%	100%

When comparing percentages of the 404 S-ICD and 313 D-ICD patients having no events, it needs to be recognized that S-ICD patients with no events were observed for an average of 23 months whereas D-ICD patients with no events were observed for an average of 15–16 months. Thus, the D-ICD patients had less time to experience an event. For patients with events, observation time is reflected in the rates.

^aIncludes four outlier rates (>24/year) of 53 events in 668 days, 52 events in 494 days, 28 events in 212 days, and 24 events in 14 days, with 1 in the S-ICD and 3 in the D-ICD; ^bIncludes one outlier rate (>24/year) of 37 events in 97 days in the S-ICD.

higher minimum heart rate and a physiologic AV interval would improve hemodynamics. There was little concern about avoiding ventricular dyssynchrony related to pacing from the right ventricular apex. Technical device limitations often made it difficult, if not impossible, to extend the AV interval and allow intrinsic AV conduction with a dual-chamber device in DDD mode.

Nielsen et al. examined AAIR versus DDDR pacing in patients with sick sinus syndrome and a normal left ventricular ejection fraction (mean 0.60).²⁵ Three groups of patients were randomized: (1) DDDR pacing and a fixed 300 ms AV delay (DDDR-l: 17% ventricular pacing), (2) DDDR pacing and an AV delay ≤150 ms (DDDR-s: 90% ventricular pacing), and (3) AAIR pacing. In both DDDR groups, the left atrial diameter increased significantly. In the DDDR-s group, left ventricular fractional shortening decreased significantly. Atrial fibrillation was least common in the AAIR group. The incidence of atrial fibrillation was intermediate in the DDDR-l group and highest in the DDDR-s group. In MADIT-II we also saw an increased occurrence of atrial fibrillation in the D-ICD group.

The MADIT-II database did not contain information on programming of algorithms designed to enhance specificity for detecting VT versus supraventricular tachyarrhythmias. Since the goal of ICD therapy is to prevent SCD, many physicians initially program ICDs for maximum sensitivity and utilized atrial tachyarrhythmia detection enhancement algorithms only as needed if problems with inappropriate shocks occurred.

The limitations of our study include the lack of randomization to S-ICDs or D-ICDs, as the original trial was not designed to investigate this question. The two ICD groups are not entirely comparable; patients receiving D-ICDs were a somewhat higher risk group as indicated by differences in age, NYHA functional class, history of prior CABG, QRS duration, and BUN level. However, after adjusting for these variables, the D-ICD:S-ICD hazard ratios for death, CHF requiring hospitalization, and death or CHF requiring hospitalization were consistently >1 indicating a trend toward greater risk for such events in D-ICD patients.

Device programming was left entirely to the discretion of the individual investigator and was not randomized or controlled in any way in this study. This includes brady and tachy parameters as well as detection enhancement algorithms. Specific data regarding these parameters are not part of the MADIT-II database.

Dual-chamber devices that allow for very long AV intervals, allowing atrial pacing and intrinsic AV conduction, may be beneficial. The role of biventricular pacing in the subset of patients with sinus node dysfunction in whom RV pacing cannot be avoided, many of whom do not have significant native intraventricular conduction delays, remains to be explored.

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REFERENCES

1. 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.
2. 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.
3. Connolly SJ, Gent M, Roberts R, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297-1302.
4. Kuck K-H, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable cardioverter defibrillators in patients resuscitated from cardiac arrest: The cardiac arrest study Hamburg (CASH). *Circulation* 2000;102:748-754.
5. 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. *N Engl J Med* 1996;335:1933-1940.
6. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-1890.
7. Lamas GA, Lee KL, Sweeney MO, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;346:1854-1862.
8. Auricchio A, Sommariva L, Salo RW, et al. Improvement in cardiac function in patients with severe congestive heart failure and coronary artery disease by dual chamber pacing with shortened AV delay. *Pacing Clin Electrophysiol* 1993;16:2034-2043.
9. Trappe H-J, Ahtelik M, Pfitzner P, et al. Single-chamber versus dual-chamber implantable cardioverter defibrillators: Indications and clinical results. *Am J Cardiol* 1999;83:8D-16D.
10. Hochleitner M, Hörtnagl H, Fridrich L, et al. Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992;70:1320-1325.
11. Kappenberger L, Linde C, Daubert C, et al. Pacing in hypertrophic obstructive cardiomyopathy. *Eur Heart J* 1997;18:1249-1256.
12. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. *Circulation* 2002;106:2145-2161.
13. Santini M, Ansalone G, Auriti A, et al. Indications for dual-chamber (DDD) pacing in implantable cardioverter-defibrillator patients. *Am J Cardiol* 1996;78(Suppl. 5A):116-118.
14. Raatikainen MJP, Huikuri HV. Management of atrial fibrillation in patients with implantable cardioverter defibrillator. Do all need a dual chamber device? *Eur Heart J* 2002;23:1412-1414.
15. Friedman PA, Dijkman B, Warman EN, et al. Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. *Circulation* 2001;104:1023-1028.
16. Wilkoff BL, Kühlkamp V, Volosin K, et al. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection: Results and technical considerations. *Circulation* 2001;103:381-386.
17. Dijkman B, Wellens HJJ. Importance of the atrial channel for ventricular arrhythmia therapy in the dual chamber implantable cardioverter defibrillator. *J Cardiovasc Electrophysiol* 2000;11:1309-1319.
18. Saad EB, Marrouche NF, Martin DO, et al. Frequency and associations of symptomatic deterioration after dual-chamber defibrillator implantation in patients with ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2002;90:79-82.
19. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The dual chamber and VVI implantable defibrillator (DAVID) trial. *J Am Med Assoc* 2002;288:3115-3123.
20. Swygman C, Wang PJ, Link MS, et al. Advances in implantable cardioverter defibrillators. *Curr Opin Cardiol* 2002;17:24-28.
21. Wilkoff BL. Should all patients receive dual chamber pacing ICDs? The rationale for the DAVID trial. *Curr Control Trials Cardiovasc Med* 2001;2:215-217.
22. Cox DR. Regression models and life-table. *J R Stat Soc [B]* 1972;34:187-220.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
24. Steinberg JS, Fischer A, Wang P, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol* 2005;16:359-365.
25. Nielsen JC, Kristensen L, Andersen HR, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome. *J Am Coll Cardiol* 2003;42:614-623.