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# Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator

## An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial II

Ilan Goldenberg, MD; John Gillespie, MD; Arthur J. Moss, MD; W. Jackson Hall, PhD; Helmut Klein, MD; Scott McNitt, MS; Mary W. Brown, MA; Iwona Cygankiewicz, MD; Wojciech Zareba, MD, PhD; and the Executive Committee of the Multicenter Automatic Defibrillator Implantation Trial II

**Background**—The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) showed a significant 31% reduction in the risk of death with primary implantable cardioverter-defibrillator (ICD) therapy during a median follow-up of 1.5 years. However, currently there are no data on the long-term efficacy of primary defibrillator therapy.

**Methods and Results**—MADIT-II enrolled 1232 patients with ischemic left ventricular dysfunction who were randomized to ICD and non-ICD medical therapy and were followed up through November 2001. For the present long-term study, we acquired posttrial mortality data through March 2009 for all study participants (median follow-up, 7.6 years). Multivariate Cox proportional hazards regression modeling was performed to calculate the hazard ratio for ICD versus non-ICD therapy during long-term follow-up. At 8 years of follow-up, the cumulative probability of all-cause mortality was 49% among patients treated with an ICD compared with 62% among non-ICD patients ( $P<0.001$ ). Multivariate analysis demonstrated that ICD therapy was associated with a significant long-term survival benefit (hazard ratio for 0- through 8-year mortality=0.66 [95% confidence interval, 0.56 to 0.78];  $P<0.001$ ). Treatment with an ICD was shown to be associated with a significant reduction in the risk of death during the early phase of the extended follow-up period (0 through 4 years: hazard ratio=0.61 [95% confidence interval, 0.50 to 0.76];  $P<0.001$ ) and with continued life-saving benefit during the late phase of follow-up (5 through 8 years: hazard ratio=0.74 [95% confidence interval, 0.57 to 0.96];  $P=0.02$ ).

**Conclusions**—Our findings demonstrate a sustained 8-year survival benefit with primary ICD therapy in the MADIT-II population. (*Circulation*. 2010;122:1265-1271.)

**Key Words:** death, sudden ■ defibrillation ■ mortality

Current guidelines for device-based therapy of cardiac rhythm abnormalities provide a recommendation for primary implantable cardioverter-defibrillator (ICD) therapy in patients with an ejection fraction (EF) of  $\leq 35\%$ .<sup>1</sup> The class I recommendation is based on the results of major randomized clinical trials that have shown a significant reduction in the risk of mortality with an ICD in patients with left ventricular dysfunction.<sup>2-6</sup> These studies, however, assessed the benefit of the ICD during relatively short follow-up times. Thus, currently there are no long-term data on ICD efficacy over a time period that extends at least throughout the life span of the device, often 4 to 6 years.

### Clinical Perspective on p 1271

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) demonstrated a significant 31% reduction in the

risk of death with primary ICD therapy in patients with ischemic left ventricular dysfunction.<sup>4</sup> However, within the 3.5-year period of the study, ICD therapy was associated with an average survival gain of only 0.167 years (2 months) and a relatively high incremental cost-effectiveness ratio.<sup>7</sup> The present study was designed to evaluate the benefit of primary prevention with an ICD during an extended 8-year follow-up of the MADIT-II population.

### Methods

#### Study Sample

MADIT-II enrolled 1232 patients with a myocardial infarction  $\geq 1$  month before entry into the study and an EF  $\leq 30\%$ . Patients were randomly assigned in a 3:2 ratio to receive either an implanted defibrillator or non-ICD conventional medical therapy. Details of the design, methods, and results of the MADIT-II trial have been reported

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previously.<sup>4</sup> The protocol was approved by the institutional review board at each participating organization, and each patient provided written informed consent before enrollment.

### Data Acquisition and Follow-Up

The MADIT-II trial was performed from July 1997 through November 2001. For the present long-term outcome study, posttrial mortality data through March 2009 were obtained for all study participants. For patients enrolled in US centers (n=1123), information was obtained from the US National Death Registry; for study participants enrolled in non-US centers (n=109), information was obtained from the enrolling centers through hospital records and death registries.

The original MADIT-II publication was based primarily on the 0-through 4-year trial period, with a median follow-up of 1.5 years (interquartile range, 0.8 to 2.5 years) and a total follow-up of 2070 patient-years. The newly acquired long-term data comprise a median follow-up of 7.6 years (interquartile range, 3.5 to 9.0 years) and a total follow-up of 7815 patient-years during an 8-year period after enrollment. These incremental data provide 2116 additional patient-years of follow-up for the 0- through 4-year period and 3629 patient-years of follow-up for the 5- through 8-year period.

Data on crossover between allocated treatment arms were recorded for all study participants during the study and after trial closure. Among the 742 patients randomized to ICD therapy, 22 patients did not receive an ICD after randomization, and 13 had the ICD extracted during the trial; among the 490 study participants who were allocated to non-ICD conventional medical therapy, 27 patients crossed over to the ICD arm during the trial, and 140 patients received an ICD within 4 months after trial closure. Available information indicates that there were relatively minor changes between treatment arms (<5%) during the subsequent posttrial follow-up period.

### Study Design and End Point

The primary end point of the present study was the occurrence of all-cause mortality during 8 years after enrollment. The original MADIT-II report assessed the end point according to the intention-to-treat principle and therefore did not consider changes between randomized treatment arms during the trial.<sup>4</sup> Because of the relatively large change in treatment allocation that occurred after the trial ended, the primary analysis in the present study was designed on an efficacy basis by including data on crossover between the treatment arms, and the consistency of the results was further validated in an intention-to-treat analysis.

### Device Pacing Types

Among the 720 patients who received an ICD during the study, information on device pacing type was available for 717 patients: 404 received a single-chamber ICD with the backup pacing rate programmed at VVI 40 to 50, and 313 received a dual-chamber ICD with the pacing programmed at DDD 60 to 70. The implanted devices included the VENTAK AV series, the VENTAK Mini series, and the VENTAK Prizm series (Guidant Corporation, St Paul, Minn). No investigational devices were utilized. Among the 140 patients who received an ICD after trial closure, 55 (39%) received a single-chamber device, and 85 (61%) received a dual-chamber device. Both device types that were implanted after trial closure were programmed to reduce right ventricular pacing by using lower rates of 40 to 50 bpm. Information on the cumulative rate of right ventricular pacing was available for 568 (79%) of ICD-treated patients in the study. These data demonstrated that 92% of patients receiving in-trial single-chamber devices received little or no pacing throughout the study, whereas among 66% of patients in whom a dual-chamber ICD was implanted during the study, the cumulative rate of right ventricular pacing exceeded 50% (primarily in the range of 90% to 100%). Because of significant differences in the programming of single- and dual-chamber ICDs, the long-term benefit of the ICD was also assessed by the device pacing type that was implanted during the study.

### Statistical Analysis

Characteristics of study patients at trial closure were compared with the use of the  $\chi^2$  test for categorical variables, the Kruskal-Wallis test for continuous variables among 3 subgroups (comprising patients with an ICD at trial closure, patients who remained without an ICD during the posttrial period, and patients who crossed over to the ICD arms after trial closure), and the Wilcoxon rank sum test for continuous variables between 2 subgroups (comprising patients who remained without an ICD during the posttrial period and those who crossed over to the ICD arm after trial closure). The probability of all-cause mortality by treatment group and by device pacing type, with follow-up censored for patients in the non-ICD arm on receiving an ICD and immediately after enrollment for patients in the ICD arm who never received an ICD, was displayed graphically according to the method of Kaplan and Meier, with comparison of cumulative events by the log-rank test. The life-years saved with an ICD during follow-up was calculated from the difference in the areas under the curves for the treatment groups, and the number of patients needed to treat with an ICD to save 1 life was calculated as the inverse of the survival difference between the 2 treatment arms at each time point. Cox proportional hazards regression modeling was used to evaluate the independent contribution of the ICD and each device pacing type to the occurrence of all-cause mortality during up to 8 years of follow-up. Hazard ratios (HRs) were computed in the multivariate models on the basis of the 8-year survival analysis conducted. Data on crossover between treatment arms (as defined above when describing censoring) were incorporated in the multivariate Cox models by assessing treatment group and device pacing type as time-dependent covariates in the models. To validate the consistency of the results that were obtained from the time-dependent models, we performed secondary analyses in which (1) follow-up time was censored on change in treatment arm and (2) outcomes were assessed on an intention-to-treat basis. Clinical and ECG factors previously shown to influence outcome in the MADIT-II population were prespecified as covariates in the multivariate models, including age (as a continuous variable), New York Heart Association (NYHA) functional class  $\geq$ II, QRS duration >120 ms, EF <25%, gender, and blood urea nitrogen levels >25 mg/dL. Because most randomized ICD trials (including MADIT-II) have provided follow-up data that are within 4 years, we further categorized the extended 8-year follow-up period into early (0 through 4 years) and late (5 through 8 years) phases. Accordingly, the benefits of the ICD and each device pacing type were assessed in the Cox proportional hazards multivariate models (1) during the overall 8-year follow-up period and (2) during the early and late phases of the extended follow-up period, by including a treatment-by-time period interaction term in the multivariate models that assessed 8-year follow-up. We also performed subgroup analyses by employing treatment-by-risk factor interaction term analysis, which evaluated (1) the benefit of the ICD during 8 years of follow-up in risk subsets that were categorized by clinical characteristics at enrollment (including age, NYHA class, QRS duration, EF, and gender) and (2) the benefit of the ICD during the posttrial period (ie, with follow-up time starting after trial closure) by heart failure status at trial closure (categorized as symptomatic among patients with NYHA class  $\geq$ II at trial closure and/or in-trial hospitalization for heart failure and categorized as asymptomatic among patients with NYHA class I at trial closure and no in-trial heart failure hospitalization).

The statistical software used for the analyses was SAS version 9.2. A 2-sided value of  $P < 0.05$  was used for declaring statistical significance.

### Results

Baseline and follow-up clinical characteristics of the 1020 study patients who survived to trial closure are shown in Table 1. Patients with an ICD at study end (n=630) displayed clinical characteristics similar to those of non-ICD patients (n=390), with the exception of a somewhat older age and a higher digitalis use among ICD-treated patients at trial closure. Similarly, within the non-ICD group at trial closure, patients who crossed over to ICD therapy after trial closure (n=140) were nonsignificantly younger but otherwise had characteristics similar to those who remained without an ICD during the posttrial period (n=250 [Table 1]).

**Table 1. Baseline and Follow-Up Characteristics of MADIT-II Patients who Survived to Trial Closure by ICD Treatment Status at Trial Closure**

|  | ICD Group<br>(n=630) | Non-ICD Group                |                                       | P        |                          |
|--|----------------------|------------------------------|---------------------------------------|----------|--------------------------|
|  |                      | Posttrial Non-ICD<br>(n=250) | Posttrial Crossover<br>to ICD (n=140) | Overall* | Within Non-ICD<br>Group† |
| <b>Characteristics at enrollment</b>     |                      |                              |                                       |          |                          |
| Age, mean±SD, y                          | 63.6±10.6            | 64.0±10.6                    | 63.2±8.9                              | 0.12     | 0.06                     |
| Age ≥65 y, %                             | 51                   | 52†                          | 43†                                   | 0.07     | 0.05                     |
| Female gender, %                         | 15                   | 17                           | 14                                    | 0.68     | 0.40                     |
| NYHA class ≥II, %‡                       | 63                   | 60                           | 61                                    | 0.54     | 0.77                     |
| EF <0.25, %                              | 45                   | 47                           | 42                                    | 0.67     | 0.38                     |
| Hypertension, %                          | 53                   | 49                           | 57                                    | 0.32     | 0.15                     |
| Diabetes mellitus, %                     | 33                   | 35                           | 35                                    | 0.68     | 0.99                     |
| Atrial fibrillation, %                   | 8                    | 8                            | 4                                     | 0.51     | 0.16                     |
| CABG, %                                  | 59                   | 55                           | 55                                    | 0.50     | 0.97                     |
| PCI, %                                   | 47                   | 45                           | 43                                    | 0.76     | 0.66                     |
| BUN >9 mmol/L (25 mg/dL), %              | 25                   | 29                           | 28                                    | 0.36     | 0.71                     |
| Left bundle-branch block, %              | 17                   | 17                           | 14                                    | 0.71     | 0.55                     |
| QRS duration >0.12 s, %                  | 37                   | 33                           | 29                                    | 0.12     | 0.37                     |
| Blood pressure, mm Hg                    |                      |                              |                                       |          |                          |
| Systolic ≥130, %                         | 37                   | 34                           | 33                                    | 0.58     | 0.80                     |
| Diastolic ≥80, %                         | 29                   | 26                           | 27                                    | 0.53     | 0.76                     |
| Dual-chamber ICD, %                      | 45                   | NA                           | 61¶                                   | <0.001   | NA                       |
| Smoking at any time, %                   | 79                   | 81                           | 84                                    | 0.51     | 0.49                     |
| <b>Characteristics at trial closure§</b> |                      |                              |                                       |          |                          |
| Age, mean±SD, y                          | 65.5±10.5            | 65.8±10.4                    | 64.9±9.0                              | 0.07     | 0.06                     |
| Age ≥65 y, %                             | 55                   | 57                           | 48                                    | 0.20     | 0.09                     |
| NYHA class ≥II, %                        | 55                   | 54                           | 61                                    | 0.43     | 0.21                     |
| Blood pressure, mm Hg                    |                      |                              |                                       |          |                          |
| Systolic ≥130, %                         | 26                   | 29                           | 33                                    | 0.28     | 0.42                     |
| Diastolic ≥80, %                         | 21                   | 21                           | 22                                    | 0.97     | 0.83                     |
| Symptomatic HF, %                        | 62                   | 60                           | 58                                    | 0.32     | 0.13                     |
| NYHA class ≥II, %                        | 55                   | 54                           | 61                                    | 0.43     | 0.21                     |
| In-trial HF hospitalization, %           | 18                   | 18                           | 14                                    | 0.10     | 0.07                     |
| In-trial ReMI/angina hospitalization, %  | 12                   | 15                           | 11                                    | 0.73     | 0.47                     |
| In-trial appropriate ICD shock, %        | 23                   | NA                           | NA                                    |          |                          |
| ACE inhibitors, %                        | 74                   | 69                           | 79                                    |          |                          |
| Digitalis, %                             | 58                   | 54                           | 48                                    | 0.03     | 0.08                     |
| β-blockers, %                            | 79                   | 75                           | 81                                    | 0.22     | 0.17                     |
| Amiodarone, %                            | 13                   | 9                            | 11                                    | 0.18     | 0.54                     |
| Diuretics, %                             | 76                   | 78                           | 79                                    | 0.61     | 0.77                     |

Data are given as percentage or mean±SD. CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; BUN, blood urea nitrogen; HF, heart failure; ReMI, repeat myocardial infarction; and ACE, angiotensin-converting enzyme.

\*Denotes the P value for the overall difference among the 3 subgroups (comprising ICD patients, posttrial non-ICD, and posttrial crossover to ICD).

†Denotes the P value for the difference within the non-ICD group at closure (between those who remained without an ICD during the posttrial period and those who crossed over to the ICD arm after trial closure).

‡NYHA functional class represents the highest class during the 3 months before enrollment.

§Data acquired at closeout visit.

||Heart failure status at trial closure was defined as symptomatic among patients with NYHA class ≥II at trial closure and/or in-trial hospitalization for heart failure and as asymptomatic among patients with NYHA class I at trial closure and no in-trial heart failure hospitalization.

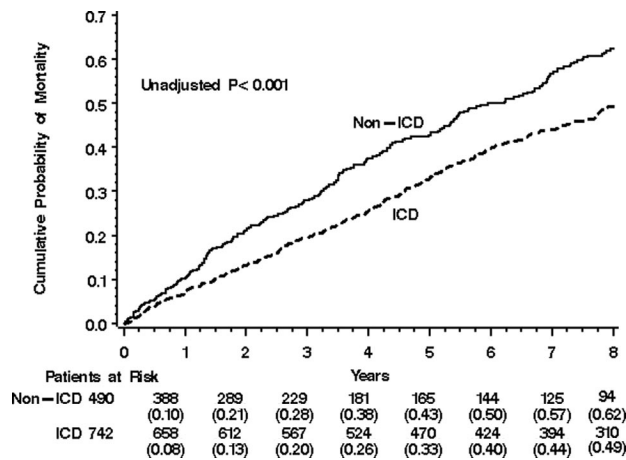
¶Denotes percentage of dual-chamber devices that were implanted after trial closure.

**ICD Benefit During Long-Term Follow-Up**

Unadjusted Kaplan-Meier survival analysis, with follow-up censored on change in treatment arm (Figure 1), demonstrated a significantly lower cumulative probability of all-cause mortality at 8 years of follow-up among patients who were treated with an ICD (49%) compared with non-ICD patients (62%; both log-

rank P value for the mortality difference during follow-up and P value for the mortality difference at 8 years <0.001). The survival difference corresponded to ICD being associated with 0.52 life-year saved and 8 patients needed to treat to save 1 life within 8 years. Notably, the long-term benefit of the ICD was also evident in an intention-to-treat survival analysis that evalu-





**Figure 1.** Kaplan-Meier estimates of the cumulative probability of all-cause mortality in ICD and non-ICD patients. All enrolled patients are included at time 0 by treatment allocation, and follow-up is censored on change in treatment arm after enrollment.

ated the long-term outcome of study patients by the original randomization group (log-rank  $P$  value for the difference during 8 years of follow-up in an intention-to treat analysis=0.017).

Multivariate analysis, employing treatment arm as a time-dependent covariate (Table 2), demonstrated a significant 34% reduction in the risk (hazard rate) of death with ICD therapy during 8 years of follow-up (95% confidence interval [CI], 44% to 22% risk reduction;  $P < 0.001$ ). The benefit of the ICD was evident during the early phase of the extended follow-up period (0 through 4 years: HR=0.61 [95% CI, 0.50 to 0.76];  $P < 0.001$ ) and continued during the late phase (5 through 8 years: HR=0.74 [95% CI, 0.57 to 0.96];  $P = 0.02$ ). Interaction-term analysis did not identify a statistically significant difference between the benefit of the ICD during the early and late phases of the extended follow-up period (treatment-by-time interaction=0.32). Consistent results, demonstrating sustained long-term ICD efficacy, were shown in the multivariate models in which follow-up time was censored on change in treatment arm (HR=0.67 [95% CI, 0.56 to 0.80];  $P < 0.001$ ) and in an intention-to-treat analysis (HR=0.77 [95% CI, 0.65 to 0.91];  $P = 0.005$ ).

### ICD Benefit by Device Pacing Type

Unadjusted Kaplan-Meier survival analysis (Figure 2) demonstrated that patients who received a single-chamber ICD at enrollment (programmed to minimal pacing) experienced a pronounced and sustained reduction in 8-year mortality rates with an ICD, which corresponded to defibrillator therapy being associated with 0.7 life-year saved and number of patients needed to treat of 6 within 8 years of follow-up. In contrast, patients who received a dual-chamber device at enrollment (predominantly programmed to include right ventricular pacing) experienced a late increase in mortality rates (Figure 2), which was evident in patients who had either stable (NYHA class I) or more advanced (NYHA class  $\geq$ II) heart failure functional class at enrollment (not shown). Consistent with these findings, multivariate analysis (Table 2) showed that patients with single-chamber ICDs experienced similar and significant reductions in mortality risk during both the early and late phases of the

**Table 2. ICD vs Non-ICD Risk for 0- to 8-Year Mortality\***

|                                       | Patients (Events)† | Adjusted Risk |           |        |
|---------------------------------------|--------------------|---------------|-----------|--------|
|                                       |                    | HR            | 95% CI    | $P$    |
| Total ICD population‡                 |                    |               |           |        |
| 0–8 y: ICD vs non-ICD                 | 1232 (647)         | 0.66          | 0.56–0.78 | <0.001 |
| 0–4 y: ICD vs non-ICD§                | 1232 (364)         | 0.61          | 0.50–0.76 | <0.001 |
| 5–8 y: ICD vs non-ICD§                | 786 (283)          | 0.74          | 0.57–0.96 | 0.02   |
| By device pacing type                 |                    |               |           |        |
| 0–8 y: Single-chamber ICD vs non-ICD  | 815 (434)          | 0.64          | 0.53–0.78 | <0.001 |
| 0–4 y: Single-chamber ICD vs non-ICD¶ | 815 (259)          | 0.64          | 0.50–0.82 | <0.001 |
| 5–8 y: Single-chamber ICD vs non-ICD¶ | 556 (175)          | 0.67          | 0.49–0.90 | 0.008  |
| 0–8 y: Dual-chamber ICD vs non-ICD    | 773 (450)          | 0.68          | 0.57–0.83 | <0.001 |
| 0–4 y: Dual-chamber ICD vs non-ICD#   | 773 (261)          | 0.59          | 0.46–0.76 | <0.001 |
| 5–8 y: Dual-chamber ICD vs non-ICD#   | 512 (189)          | 0.82          | 0.61–1.09 | 0.16   |

\*Treatment efficacy was assessed as a time-dependent covariate in the models; findings are adjusted for age as a continuous variable, blood urea nitrogen  $> 25$  mg/dL, NYHA functional class  $\geq 2$ , gender, EF  $< 25\%$ , and QRS  $> 120$  ms; the benefit of the ICD in each time period was assessed by adding an ICD-by-time interaction term to the multivariate models.

†The number of patients in each time period represents those who were alive at the beginning of the follow-up period (resulting in an identical number of patients in the 0- to 8-year and 0- to 4-year time periods); in the analysis of outcomes by device pacing type, the non-ICD group is included as the reference group to both single- and dual-chamber devices (resulting in a total number of patients in the analyses of the 2 devices that is greater than the total study population).

‡Similar results were obtained in the multivariate models that censored follow-up time on change in treatment (ICD vs non-ICD adjusted HR=0.67 [95% CI, 0.56 to 0.80];  $P < 0.001$ ). An intention-to-treat multivariate analysis also demonstrated a statistically significant 0- to 8-year risk reduction with an ICD (ICD vs non-ICD adjusted HR=0.77 [95% CI, 0.65 to 0.91];  $P = 0.005$ ).

§ $P$  value for 0- to 4-year vs 5- to 8-year difference in HRs=0.32.

¶Similar results were obtained in multivariate models that censored follow-up on change in treatment (single-chamber ICD vs non-ICD: HR=0.63 [95% CI, 0.51–0.78],  $P < 0.001$ ; dual-chamber ICD vs non-ICD: HR=0.68 [95% CI, 0.56–0.85];  $P < 0.001$ ).

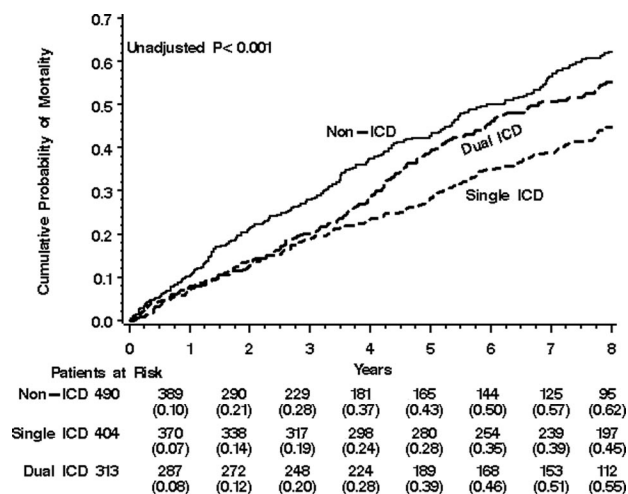
# $P$  value for 0- to 4-year vs 5- to 8-year difference in HRs=0.81.

# $P$  value for 0- to 4-year vs 5- to 8-year difference in HRs=0.10.

extended follow-up period, whereas the survival benefit associated with dual-chamber ICDs was not statistically significant during the late phase of follow-up.

### Subgroup Analyses

Multivariate analysis showed that the long-term benefit of primary ICD therapy in MADIT-II was consistent in each baseline risk subset analyzed (Table 3), including younger and older patients; male and female patients; patients with stable or advanced baseline heart failure class; and those with baseline normal or prolonged QRS duration. However, the benefit of the ICD during the posttrial period appeared to be influenced by heart failure status at trial closure (Table 3). Thus, patients who did not develop symptomatic heart failure during the trial derived a pronounced reduction in the risk of mortality with ICD therapy during the posttrial period, whereas the benefit of the



**Figure 2.** Kaplan-Meier estimates of the cumulative probability of all-cause mortality by in-trial device pacing type and in non-ICD patients. Follow-up is censored on change in treatment arm.

ICD after study end was attenuated among patients who developed symptomatic heart failure during the trial (*P* value for heart failure-by-treatment interaction=0.05 [Table 3]). Notably, the benefit of the ICD during the posttrial period after the development of symptomatic heart failure was attenuated among patients whether they received single- or dual-chamber pacing devices (single-chamber ICD versus non-ICD therapy: HR=0.87 [95% CI, 0.61 to 1.25]; dual-chamber ICD versus non-ICD therapy: HR=1.03 [95% CI, 0.72 to 1.48]).

### Discussion

Our study is the first to assess the long-term benefit of primary ICD therapy in the low-EF population. We have shown that the life-saving benefit of the ICD was sustained at 8 years of follow-up, providing a significant 34% reduction in the risk of death during this time period. Furthermore, our findings suggest enhanced long-term survival benefit from primary defibrillator therapy among patients who receive backup pacing devices and among those who do not develop symptomatic heart failure after ICD implantation.

Implantation of a defibrillator differs from administration of a drug in that the therapeutic benefit may continue to evolve long after the administration. Therefore, meaningful clinical implications of primary ICD therapy should derive from long-term follow-up data that extend at least throughout the life span of the device. This information, however, is currently not available from defibrillator trials that are designed to avoid long-term clinical testing and are therefore terminated when statistical cutoffs are reached at a predetermined trial stopping point. In MADIT-II, only approximately one third of ICD-treated patients received appropriate device therapy during the in-trial phase,<sup>8</sup> suggesting that a substantial proportion of study patients did not derive benefit from device implantation during the trial. The possible different outcomes after short-term clinical trials have led investigators to assess the potential long-term benefit of the ICD by employing posttrial projections and hypothetical modeling.<sup>7,9,10</sup> Our study provides evidence for continued ICD

**Table 3. Subgroup Analyses for 0- to 8-Year Mortality\***

| Risk Subsets   | Patients (Events) | HR   | 95% CI    | <i>P</i> for Interaction |
|--|-------------------|------|-----------|--------------------------|
| <b>ICD benefit from enrollment by baseline clinical characteristics</b>                  |                   |      |           |                          |
| <b>Age</b>   |                   |      |           |                          |
| <65 y: ICD vs non-ICD  | 573 (225)         | 0.57 | 0.44–0.75 | 0.29                     |
| ≥65 y: ICD vs non-ICD  | 659 (422)         | 0.69 | 0.56–0.84 |                          |
| <b>NYHA class</b>  |                   |      |           |                          |
| NYHA=I: ICD vs non-ICD   | 442 (198)         | 0.59 | 0.44–0.78 | 0.68                     |
| NYHA=II: ICD vs non-ICD  | 425 (203)         | 0.68 | 0.51–0.92 |                          |
| NYHA ≥III: ICD vs non-ICD  | 350 (241)         | 0.68 | 0.53–0.89 |                          |
| <b>QRS duration</b>  |                   |      |           |                          |
| >120 ms: ICD vs non-ICD  | 445 (279)         | 0.60 | 0.47–0.77 | 0.48                     |
| ≤120 ms: ICD vs non-ICD  | 775 (366)         | 0.68 | 0.55–0.84 |                          |
| <b>EF</b>  |                   |      |           |                          |
| <25%: ICD vs non-ICD   | 583 (343)         | 0.61 | 0.49–0.76 | 0.45                     |
| ≥25%: ICD vs non-ICD   | 649 (304)         | 0.69 | 0.54–0.88 |                          |
| <b>Gender</b>  |                   |      |           |                          |
| Male: ICD vs non-ICD   | 1040 (546)        | 0.62 | 0.52–0.74 | 0.26                     |
| Female: ICD vs non-ICD   | 192 (101)         | 0.80 | 0.53–1.21 |                          |
| <b>ICD benefit during the posttrial period by heart failure status at trial closure†</b> |                   |      |           |                          |
| No symptomatic heart failure at trial closure: ICD vs non-ICD                            | 393 (102)         | 0.55 | 0.35–0.86 | 0.05                     |
| Symptomatic heart failure at trial closure: ICD vs non-ICD                               | 613 (260)         | 0.95 | 0.69–1.30 |                          |

\*The benefit of the ICD in each risk subset was assessed by adding an ICD-by-risk factor interaction term to the multivariate models described in the footnote of Table 2.

†In the models that assessed the benefit of the ICD during the posttrial period, further adjustment was made for age and heart failure status at trial closure (defined in Table 1).

benefit during up to 8 years of follow-up. Furthermore, we have also shown that the long-term benefit of the ICD was consistent among subsets of patients who exhibited either lower or higher clinical risk characteristics at enrollment. These findings suggest that even the relatively large subset of lower-risk patients in MADIT-II, in whom the benefit of the ICD appeared to be more limited during the in-trial phase,<sup>11</sup> derived incremental life-saving benefit from the device with increasing follow-up time, possibly because of a time-dependent change in clinical risk in the low-EF population. These long-term clinical implications should be considered

during risk assessment among candidates for primary ICD implantation.

Our findings also have important health-economic implications. For device interventions, in which the incremental costs are largely the result of the initial intervention, the in-trial incremental cost-effectiveness ratio is a poor estimate of the lifetime value. Accordingly, during a 3.5-year follow-up of the MADIT-II trial, ICD therapy was associated with only 0.167 life-year saved and an incremental cost-effectiveness ratio of \$235 000 per discounted life-year saved.<sup>7</sup> The continued life-saving benefit of the ICD at 8 years of follow-up in the present study, with a HR of 0.66, is similar to the more favorable MADIT-II posttrial projection that we reported recently, which predicted a HR of 0.68 for ICD versus non-ICD therapy and an estimated incremental cost-effectiveness ratio of \$60 000 to \$80 000 per discounted life-year saved with 8 years of follow-up.<sup>7</sup>

Our findings demonstrate an association between device pacing type and long-term mortality in the MADIT-II population. Patients who received backup pacing devices derived a pronounced survival benefit from the ICD during long-term follow-up (including similar early and late reductions in the risk of long-term mortality, number of patients needed to treat of 6, and 0.7 life-year saved within 8 years), whereas patients who received dual-chamber devices, which were predominantly programmed to deliver right ventricular pacing, experienced a late increase in mortality. The different outcomes associated with the 2 device pacing types suggest that the combined overall benefit of the ICD during the extended follow-up period of MADIT-II may underestimate the potential long-term survival benefit of contemporary ICDs, which are currently programmed to avoid right ventricular pacing.

Dual-chamber ICDs were programmed to active DDD pacing in MADIT-II regardless of conduction abnormalities because at the time of the study it was hypothesized that atrioventricular sequential pacing improves heart failure symptoms and outcomes in patients with left ventricular dysfunction. After trial closure, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial<sup>12</sup> provided evidence that a high frequency of right ventricular pacing with dual-chamber defibrillator units was a contributing factor to increased heart failure events and mortality. Accordingly, dual-chamber ICDs that were implanted during the posttrial period were set to provide primarily backup pacing. The present study extends the findings of the DAVID trial and demonstrates increased mortality risk during long-term follow-up among MADIT-II patients who were treated with dual-chamber devices. These findings suggest that among patients with left ventricular dysfunction who receive primary ICD therapy, device pacing type should be recommended according to current guidelines,<sup>1</sup> with implantation of dual-chamber ICDs reserved for those who have a pacing indication.

We have shown recently that the development of heart failure is a powerful predictor of mortality in ICD-treated patients.<sup>13</sup> Our long-term data are consistent with this observation and suggest that the benefit of the ICD is attenuated among patients who develop symptomatic heart failure after device implantation. By contrast, the long-term benefit of the ICD was pronounced (45% reduction in the risk of posttrial mortality) among patients who did not develop symptomatic heart failure during

the study. These findings demonstrate the potential long-term benefit of the ICD, even among asymptomatic patients with left ventricular dysfunction, and stress the importance of providing measures for the prevention of heart failure progression after device implantation.

### Limitations

The present study was designed primarily as an efficacy analysis that incorporated data on crossover between the 2 treatment arms. Furthermore, patients who were randomized to non-ICD therapy at enrollment and crossed over to the ICD group after trial closure were nonsignificantly younger than those who were not treated with an ICD throughout follow-up. We therefore employed 3 different statistical approaches to validate our findings in the multivariate models, including a time-dependent assessment of treatment arms, censoring of follow-up time on change in treatment arm, and intention-to-treat analysis that compared the outcome in the original randomized groups. These 3 confirmatory methods provide support for the consistency of our results on the long-term survival benefit associated with primary ICD therapy in MADIT-II.

Because of incomplete collection of crossover data during the late phase of the extended follow-up period, we did not incorporate in the analyses information related to changes in treatment arms after the early posttrial period. Available data indicate that during this late time period, there were relatively minor changes in treatment allocation. A sensitivity analysis that was performed by incorporating full posttrial available crossover information showed a somewhat more enhanced benefit of the ICD (HR, 0.64;  $P < 0.001$ ), suggesting that our present findings may represent a more conservative estimate of the long-term benefit of the ICD.

Complete follow-up interrogation data during the posttrial period were available only for study patients who were enrolled in non-US centers. Analysis of interrogation information in this patient subset showed that the cumulative probability of a first appropriate ICD therapy for ventricular tachycardia or fibrillation during 8 years of follow-up was 68%.

### Conclusions and Clinical Implications

The application of implantable device therapy has increased markedly in the past 2 decades from secondary prevention with an ICD in survivors of a cardiac arrest to primary prevention of sudden cardiac death in asymptomatic patients with ischemic and nonischemic left ventricular dysfunction. However, the ICD still remains underutilized in a substantial proportion of patients who meet the guidelines for primary prevention, possibly because of the invasive nature of the procedure in a population of patients who have not yet experienced prior life-threatening arrhythmias and additional cost considerations. Our data on the continued life-prolonging benefit of the ICD during long-term follow-up provide support for a more widespread use of the ICD in a primary prevention setting. However, our findings also suggest that more measures should be taken to improve long-term device efficacy in the low-EF population. These may include improved device programming, designed to limit the amount of right ventricular pacing, and measures for prevention of heart failure progression after ICD implantation, possibly through optimization of adjunctive medical therapy or the



combined use of cardiac resynchronization therapy in appropriately selected patients.

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**CLINICAL PERSPECTIVE**

Current guidelines for device-based therapy provide a recommendation for primary prevention with implantable cardioverter-defibrillator (ICD) therapy in patients with an ejection fraction of  $\leq 35\%$ . Presently, however, there are no data from clinical trials on the long-term benefit of ICD therapy. The present study is the first to assess the long-term survival benefit associated with primary prevention with an ICD in the low–ejection fraction population. We provide 8-year follow-up data for all participants in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). The study shows that the life-saving benefit of the ICD was sustained during the extended follow-up period, providing a significant 34% reduction in the risk of death during 8 years of follow-up. The survival benefit of the ICD was evident during both the early (0 to 4 years) and late (5 to 8 years) phases of the extended follow-up period. Furthermore, we show enhanced long-term survival benefit from primary ICD therapy among patients who received backup pacing devices and among those who did not develop symptomatic heart failure after ICD implantation. Our findings on the continued life-prolonging benefit of the ICD during long-term follow-up provide support for a more widespread use of the ICD in a primary prevention setting. However, our data also suggest that more measures should be taken to improve long-term device efficacy in the low–ejection fraction population, including appropriate device programming as well as measures for prevention of heart failure progression after ICD implantation.