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Applicability of a Risk Score for Prediction of the Long-Term (8-Year) Benefit of the Implantable Cardioverter-Defibrillator

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Objectives The present study was designed to explore the 8-year survival benefit of a nonresynchronization implantable cardioverter-defibrillator (ICD) according to a simple risk stratification score.

Background There is limited information regarding factors that predict the benefit of primary prevention with an ICD during long-term follow-up.

Methods This study used a previously developed risk score including 5 clinical factors (New York Heart Association functional class >II, age >70 years, blood urea nitrogen >26 mg/dl, QRS duration >0.12 s, and atrial fibrillation) to evaluate 8-year ICD survival benefit within risk score categories among 1,191 MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) patients.

Results Patients with low (0 risk factors, n = 345) and intermediate risk (1 to 2 risk factors, n = 646) demonstrated a significantly higher probability of survival at 8-year follow-up when treated by ICD as compared with non-ICD therapy (75% vs. 58%, p = 0.004; and 47% vs. 31%, p < 0.001, respectively). By contrast, among high-risk patients (3 or more risk factors, n = 200), there was no significant difference in 8-year survival between the ICD and non-ICD subgroups (19% vs. 17%, p = 0.50). Consistently, multivariate analysis showed that ICD therapy was associated with a significant long-term survival benefit among low- and intermediate-risk patients (hazard ratio [HR]: 0.52, p < 0.001, and HR: 0.66, p < 0.001, respectively), whereas treatment with an ICD was not associated with a significant benefit among high-risk patients (HR: 0.84, p = 0.25).

Conclusions These findings suggest that a simple risk score can identify patients who derive significant long-term benefit from primary ICD therapy. High-risk patients with multiple comorbidities composed 17% of the MADIT-II population and did not derive long-term benefit from nonresynchronization device therapy. (J Am Coll Cardiol 2012; 59:2075–9) © 2012 by the American College of Cardiology Foundation

Multiple randomized clinical trials have demonstrated a significant reduction in the risk of death with an implantable cardioverter-defibrillator (ICD) among patients with a left ventricular ejection fraction (LVEF) ≤35% (1–3). However, the benefit of the ICD within the low-LVEF population may not be uniform because this group of patients is a heterogeneous group comprising symptomatic and asymptomatic HF patients who may also have different comorbidities and different prognoses. We have recently developed a risk score for the assessment of ICD efficacy in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) population (4). The study showed that 5 simple clinical parameters (comprising age, heart failure functional class, blood urea nitrogen [BUN], QRS duration, and atrial fibrillation) can be used to stratify patients into a low-risk group (with none of the 5 clinical risk factors) who did not derive a significant survival benefit from the ICD in MADIT-II; an intermediate high-risk group (1 to 2 risk factors) who derived a pronounced benefit from primary ICD implantation; and a very high-risk group (with advanced comorbidities), in whom the benefit of the ICD was attenuated. This study, however, was based on

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Abbreviations and Acronyms

BUN = blood urea nitrogen
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

the in-trial phase of MADIT-II, comprising a median follow-up of only 1.5 years.

We have recently shown that the beneficial effects of the ICD were sustained during an 8-year follow-up of the MADIT-II population, thus extending the evidence for ICD efficacy at least throughout the life span of the implanted device (5). The present study was designed to evaluate the yield of the previously identified risk score for the assessment of the long-term survival benefit of primary ICD therapy.

Methods

Study population and MADIT-II extended 8-year follow-up. MADIT-II enrolled 1,232 patients with a myocardial infarction 1 month or more before entry into the study and an LVEF ≤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 previously reported (1). 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). The newly acquired long-term data comprise a median follow-up of 7.6 years (interquartile range 3.5 to 9.0 years) (5). Data regarding crossover between allocated treatment arms were recorded for all study participants during the study and following trial closure and is provided in the Online Appendix. Of the 1,232 study participants, 41 were excluded due to missing data on 1 of the 5 clinical risk factors; thus, the current study includes 1,191 (97%) patients who were enrolled in MADIT-II.

Risk score and outcome measures. The present study employs a previously developed risk score (4) for the endpoint of all-cause mortality that was developed based on follow-up data from the in-trial phase of MADIT-II. A simple risk score was constructed as a count of risk factors identified in each patient, among the selected following 5 risk factors: New York Heart Association (NYHA) functional class >II; age >70 years; BUN >26 mg/dl; QRS duration >0.12 s; and atrial fibrillation. For the present study, patients were categorized into 3 subgroups: 1) low-risk subgroup (n = 345), including patients with no risk factors; 2) intermediate-risk subgroup (n = 646), including patients with 1 or 2 risk factors; and 3) high-risk subgroup (n = 200), including patients with 3 or more risk factors. Risk score counts were truncated at ≥3 because of small numbers of patients with counts of 4 or 5 risk factors. The primary endpoint was time to all-cause mortality during the 8-year extended follow-up.

Table 1 Patient Characteristics by Risk Score Category

	Low Risk (No Risk Factors)	Intermediate Risk (1–2 Risk Factors)	High Risk (≥3 Risk Factors)	p Value
Patients, n	345	646	200	
ICD	57	63	59	0.118
Age, yrs	59 (52–64)	66 (59–72)	74 (71–78)	NA*
Age >70 yrs	0	35	76	NA*
Female	14	17	14	0.469
Diabetes	28	38	40	0.003
Hypertension	48	55	58	0.043
Smoking	85	80	74	0.005
NYHA functional class >II	0	34	66	NA*
Atrial fibrillation	0	8	28	NA*
Systolic blood pressure, mm Hg	120 (110–132)	120 (110–134)	118 (104.5–130)	0.039
QRS duration, s	0.10 (0.09–0.11)	0.12 (0.10–0.15)	0.15 (0.13–0.16)	NA*
QRS duration >0.12 s	0	43	80	NA*
LBBB	2	21	42	<0.001
LVEF, %	25 (20–29)	24 (20–27)	20 (16.5–25)	<0.001
BUN, mg/dl	16 (13–20)	21 (16–28)	35 (27–44)	NA*
BUN >26 mg/dl	0	28	79	NA*
Creatinine, mg/dl	1 (0.9–1.2)	1.2 (1.0–1.4)	1.5 (1.3–1.8)	<0.001
Medications at enrollment				
ACEI/ARB	90	89	85	0.253
Beta-blockers	69	63	49	<0.001
Diuretics	58	78	92	<0.001
Digitalis	48	63	66	<0.001
Antiarrhythmic	2	3	3	0.607

Values are % or median (interquartile range). *A statistical comparison was not made because the risk score was based on these factors.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BUN= blood urea nitrogen; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NA = not available; NYHA = New York Heart Association.

We also evaluated the proportion of patients from each risk group who changed category during the MADIT-II in-trial period for 4 of the 5 pre-specified risk factors with available follow-up data (NYHA functional class, age, BUN, atrial fibrillation). The last ascertainment of risk score was obtained at the end of the MADIT-II trial.

Statistical analysis. Characteristics of study patients were compared using the Wilcoxon rank sum, chi-square, or Fisher exact tests, as appropriate. The probability of all-cause mortality by treatment group for each risk group, with follow-up censored by change in treatment arm was graphically displayed according to the Kaplan-Meier method, with comparison of cumulative events by the log-rank test. The number of patients that needed to have been treated with an ICD to save 1 life in each risk subgroup was calculated as the inverse of the survival difference between the 2 treatment arms using the Kaplan-Meier estimates at 8 years. Cox proportional hazards regression modeling was used to evaluate the independent contribution of each of the pre-specified covariates to the occurrence of all-cause mortality during 8 years of follow-up, with follow-up censored by change in treatment arm. Pre-specified covariates in the multivariate models included treatment (ICD vs. non-ICD), and the high risk score covariates: age >70 years; NYHA functional class >II; QRS duration >0.12s; BUN levels >26 mg/dl; and atrial fibrillation. In addition, Cox proportional hazards regression modeling was used to evaluate the independent contribution of the ICD treatment within each risk group category (low, intermediate, and high) to predict the risk of all-cause mortality during 8 years of follow-up. An ICD treatment–by–risk group interaction term was used to both estimate the ICD to conventional treatment hazard ratio for each risk group as well as test for an overall interaction between risk group and ICD treatment. This 1 degree-of-freedom interaction term used risk group as a 3-level ordinal variable. A Bonferroni correction was used when examining the statistical significance of ICD treatment within each risk group, which resulted in a corrected significance level of 0.050/3 = 0.017. A 2-sided p value <0.05 was used for declaring statistical significance for all other analyses. The statistical software used for the analyses was SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Patient characteristics. The baseline characteristics of study patients by risk score category are shown in Table 1. As expected, patients in the high-risk subgroup were sicker and had higher prevalence of the 5 pre-specified risk factors as compared with the lower-risk subgroups. In addition, patients in the high-risk subgroup as compared with the low-risk subgroups exhibited a higher prevalence of diabetes mellitus, hypertension, and left bunch branch block; they had lower LVEF and were treated more frequently with diuretics and digitalis and less frequently with beta-blockers.

Risk score and long-term outcome. At 8 years of follow-up, the cumulative probability of mortality among all study patients was 54%, with patients treated with ICD having a significantly lower cumulative probability of mortality as compared with non-ICD patients (50% and 64%, respectively, p < 0.001). When survival was assessed by the risk score (Fig. 1), there was a direct relationship between risk categories and long-term mortality rates.

Multivariate analysis showed that each of the 5 pre-specified risk factors included in the risk score was a significant independent predictor of all-cause mortality in the MADIT-II population during 8 years of follow-up (Table 2). Furthermore, when outcome was assessed by the risk score, the intermediate- and high-risk subgroups were shown to have respective 2.4-fold (p < 0.001) and 5-fold (p < 0.001) increases in the risk of long-term mortality as compared with the low-risk subgroup.

ICD benefit by risk score categories. Kaplan-Meier survival analyses demonstrated that ICD was associated with a significant survival benefit in the low-risk subgroup (Fig. 2). Thus, at 8 years, the cumulative survival rate was 75% for patients treated with ICD as compared with 58% among non-ICD patients (p = 0.004). Among intermediate-risk patients, ICD therapy was also associated with a significant survival benefit (Fig. 3). Thus, in this subgroup, the 8-year cumulative survival rate was 47% for patients treated with ICD and 31% among non-ICD patients (p < 0.001). The survival difference corresponded to ICD being associated with 6 patients that needed to have been treated to save 1 life within 8 years in both the low- and the intermediate-risk subgroups. By contrast, among high-risk patients (Fig. 4), there was no significant difference in 8-year survival between ICD and non-ICD subgroups (19% vs. 17%, p = 0.50).

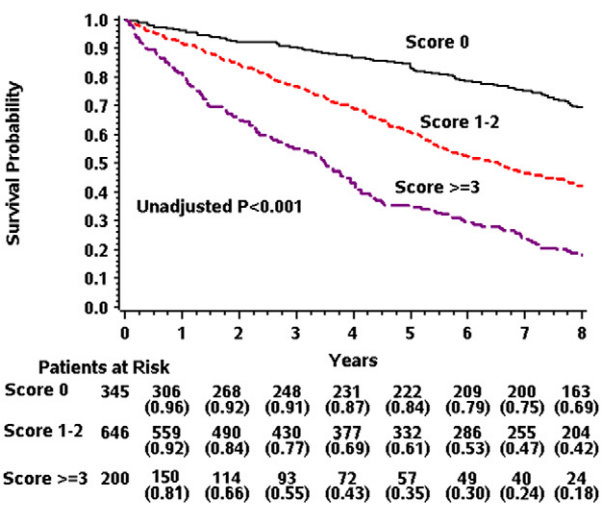

Figure 1 Probability of Survival by Risk Score Category

The risk score was constructed as a count of risk factors identified in each patient, among the selected following 5 risk factors: New York Heart Association functional class >II; age >70 years; BUN >26 mg/dl; QRS duration >0.12 s; and atrial fibrillation. BUN = blood urea nitrogen.

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Table 2 Multivariate Analysis: Risk of Long-Term (8-Year) Mortality in the MADIT-II Population by the Type and Number of Risk Factors

	Hazard Ratio	95% CI	p Value
Risk factor			
BUN >26 mg/dl	1.90	1.59–2.27	<0.001
NYHA >II	1.79	1.50–2.13	<0.001
AFIB	1.45	1.12–1.86	0.004
Age >70 yrs	1.38	1.16–1.65	<0.001
QRS >120 ms	1.33	1.12–1.58	0.001
Risk score*			
Low risk (risk score 0)		Reference	
Intermediate risk (scores 1–2)	2.44	1.92–3.10	<0.001
1	2.10	1.61–2.74	<0.001
2	2.86	2.21–3.72	<0.001
High risk (risk score ≥3)	4.97	3.80–6.51	<0.001

Adjusted also for ICD versus non-ICD treatment (HR: 0.68, 95% CI: 0.57 to 0.81, p<0.001); 41 patients were excluded due to missing data. *Analysis was carried out in a separate model adjusting for ICD treatment and risk score groups.

AFIB = atrial fibrillation; CI = confidence interval; HR = hazard ratio; MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II; other abbreviations as in Table 1.

Multivariate analysis (Table 3) showed that ICD therapy was associated with a significant long-term survival benefit among low- and intermediate-risk patients (hazard ratio [HR]: 0.52, $p < 0.001$, and HR: 0.66, $p < 0.001$, respectively), whereas treatment with an ICD was not associated with a significant benefit among high-risk patients (HR: 0.84, $p = 0.25$). This analysis shows a p value for the overall ICD-by–risk group interaction = 0.075.

To further evaluate a possible bias that might have contributed to the lack of a significant long-term ICD effect in high-risk patients, we carried out sensitivity analyses and found consistent results with the primary analysis (Online Appendix).

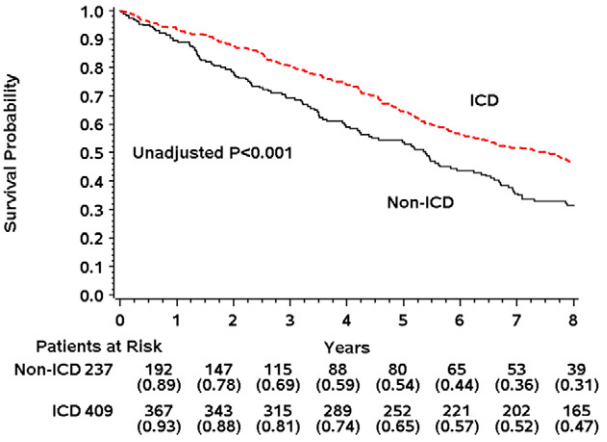

Figure 3 Probability of Survival Among Intermediate-Risk Patients

Kaplan-Meier estimates of the probability of survival in patients with risk scores 1 to 2 by treatment group. ICD = implantable cardioverter-defibrillator.

Discussion

We used a previously developed risk score among MADIT-II patients to explore ICD efficacy in reducing all-cause mortality during 8 years of follow-up among patients who had low-, intermediate-, and high-risk clinical characteristics at enrollment in the trial. Our findings suggest that: 1) important time-dependent changes in the clinical characteristics of study patients occurred during the trial, resulting in corresponding changes in risk categories during follow-up; 2) ICD therapy conferred a long-term survival benefit in patients who had low-risk characteristics at enrollment, in whom the benefit of the ICD was not apparent during the early phase of follow-up; 3) the early benefit of ICD therapy among intermediate-risk

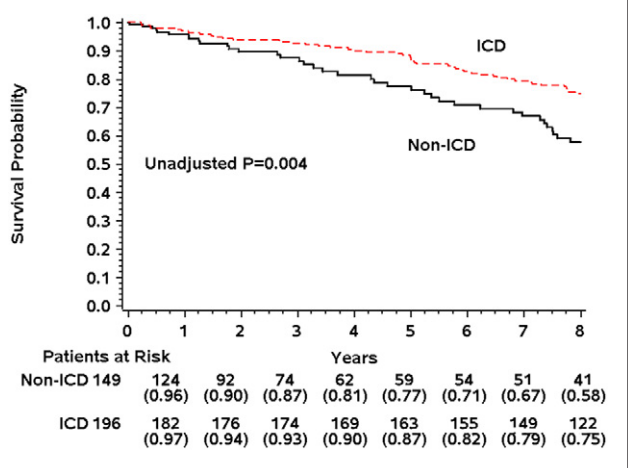

Figure 2 Probability of Survival Among Low-Risk Patients

Kaplan-Meier estimates of the probability of survival in patients with risk score = 0 by treatment group. ICD = implantable cardioverter-defibrillator.

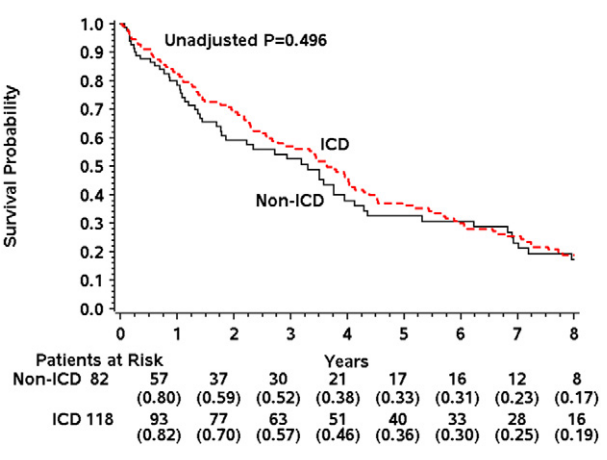

Figure 4 Probability of Survival Among High-Risk Patients

Kaplan-Meier estimates of the probability of survival in patients with risk score ≥3 by treatment group. ICD = implantable cardioverter-defibrillator.

Table 3 Hazard Ratios of ICD Versus Conventional Medical Treatment by Risk Score Subgroups During 8-Year Follow-Up

	Hazard Ratio	95% CI	p Value
All patients	0.69	0.58–0.82	<0.001
By risk score*			
Low risk (risk score 0)	0.52	0.38–0.73	<0.001
Intermediate risk (risk scores 1–2)	0.66	0.56–0.79	<0.001
High risk (risk score ≥3)	0.84	0.63–1.13	0.247

*p value for the overall ICD-by–risk group interaction = 0.075.
Abbreviation as in Table 2.

patients, shown in the earlier report (4) was maintained during 8 years of follow-up; and 4) we observed no significant long-term ICD benefit among the high-risk subgroup comprising 17% of study patients, who experienced very high mortality rates during long-term follow-up, regardless of treatment group.

ICDs are costly technologies, with implantation costs of more than $25,000 per patient (6); thus, although ICD implantation can reduce the risk of sudden cardiac death, it may do so at a relatively high cost. Improved cost-effectiveness estimates for primary ICD implantation can be obtained if appropriate risk subgroups are identified. Accordingly, we have previously identified 5 high-risk clinical factors—NYHA functional class >II, age > 70 years, BUN >26 mg/dl, QRS duration >0.12 s, and atrial fibrillation—that were independently associated with increased mortality in the non-ICD arm of MADIT-II, and we developed a simple risk score as a count of risk factors identified in each patient (4). In that study, we observed a U-shaped pattern for ICD efficacy, in which ICD therapy was shown to be associated with a significant reduction in the risk of death only among patients with 1 or 2 risk factors.

In the present study, follow-up of the MADIT-II population was extended to 8 years. Similar to the earlier report, we have also shown a significant survival benefit with an ICD among intermediate-risk patients (1 to 2 risk factors) with 34% mortality risk reduction ($p < 0.001$) and no significant ICD benefit among high-risk patients (3 or more risk factors; HR: 0.84, $p = 0.25$). By contrast, among low-risk patients (no risk factors), primary ICD was associated with a pronounced 48% reduction in 8-year mortality ($p < 0.001$), possibly due to the development of higher-risk clinical characteristics in this subgroup during long-term follow-up (Online Appendix). Thus, ICD was most effective in the low-risk group, was associated with moderate benefit in the intermediate-risk group, and not associated with any benefit in the high-risk group (p for ICD-by–risk group interaction = 0.075).

Study limitations. Our analysis did not incorporate data on the mode of death following trial closure, which could have facilitated further clarification of the relationship between ICD efficacy and risk score categories. We had no data on risk factors following trial closure, thus we were limited in our ability to calculate the percentage of patients who moved to other risk categories during the post-trial period. It should also be noted that, similar to the original MADIT-II risk score (4), the current study population was not sufficiently powered to show significant ICD treatment–by–risk subgroup interactions. However, we did identify a trend across risk groups providing, for the first time, data regarding the relative effectiveness of the ICD across risk groups during long-term follow-up.

Conclusions

Risk stratification among the low-LVEF population has important clinical implications for predicting outcome, selection of treatment, and reduction in the costs of treatment. In the present study, we have shown that employing a simple risk score for the assessment of ICD efficacy results in the identification of low- and intermediate-risk patients with ischemic cardiomyopathy, who derive a pronounced long-term survival from the device, with a number-needed-to-treat of 6 to save 1 life during 8 years of follow-up. By contrast, patients with high-risk clinical characteristics prior to ICD implantation do not appear to derive a significant survival benefit from the nonresynchronization device during long-term follow-up, possibly due to the competing risks of heart failure death and additional causes of noncardiac mortality that are more prevalent in this population. In this patient subset, additional therapeutic interventions, including combined cardiac resynchronization–defibrillator therapy, may be necessary to provide improved long-term survival.

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Key Words: implantable cardioverter-defibrillator ■ mortality ■ risk stratification.

APPENDIX

For data regarding crossover between the allocated treatment arms of MADIT-II and additional secondary analyses, please see the online version of this article.