# Long-Term Survival With Implantable Cardioverter-Defibrillator in Different Symptomatic Functional Classes of Heart Failure

Yitschak Biton, MD[a,b,1,*], Spencer Rosero, MD[a,1], Arthur Moss, MD[a], Wojciech Zareba, MD, PhD[a], Valentina Kutyifa, MD, PhD[a], Jayson Baman, MD[a,c], Alon Barsheshet, MD[b], Scott McNitt, MS[a], Bronislava Polonsky, MS[a], and Ilan Goldenberg, MD[a,b]

**The ACC/AHA/HRS (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society) guidelines recommend implantable cardioverter-defibrillator (ICD) therapy primary prevention in all patients with severely reduced left ventricular ejection fraction (≤30%) regardless of New York Heart Association (NYHA) functional class, whereas recent European guidelines limit the indication to those with symptomatic heart failure (NYHA ≥ II). We therefore aimed to evaluate the long-term survival benefit of primary ICD therapy among postmyocardial infarction patients with and without heart failure (HF) symptoms who were enrolled in MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II). We classified 1,164 MADIT-II patient groups according to the baseline NYHA class (NYHA I [n = 442], NYHA II [n = 425], and NYHA III [n = 297]); patients with NYHA IV were excluded. Multivariate Cox proportional hazards regression modeling was performed to compare the mortality reduction with ICD versus non-ICD therapy during 8 years of follow-up between the 3 NYHA groups. The median (interquartile range) follow-up time was 7.6 (3.5 to 9) years. At 8 years of follow-up, the cumulative probability of mortality in the non-ICD treatment arm was 57% for NYHA I, 57% for NYHA II, and 76% for NYHA III (p <0.001). Multivariate models demonstrated similar long-term mortality risk reduction with ICD compared with the non-ICD treatment arm regardless of HF symptoms: NYHA I (HR = 0.63, 0.46 to 0.85, p = 0.003), NYHA II (HR = 0.68, 0.50 to 0.93, p = 0.017), and NYHA III (HR = 0.68, 0.50 to 0.94, p = 0.018); p for NYHA class by treatment arm interaction >0.10. In conclusion, primary ICD therapy provides consistent long-term survival benefit among patients with previous myocardial infarction and severe left ventricular dysfunction, regardless of HF symptoms.**  **(Am J Cardiol 2017;■■:■■–■■)**

Current clinical guidelines provide class IA recommendation for implantable cardioverter-defibrillator (ICD) utilization in patients with symptomatic heart failure (HF) (New York Heart Association [NYHA] class II-III) and reduced left ventricular ejection fraction (LVEF) ≤ 35% for the primary prevention of sudden cardiac death (SCD).[1,2] There is a disagreement regarding the role of ICD in patients with asymptomatic HF (NYHA class I) and reduced LVEF, despite some data to suggest that the rate of SCD may not be negligible in this group. The ACC/AHA/HRS (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society guidelines for device therapy[2] recommend implantation of an ICD in those with NYHA I and LVEF ≤ 30% (class I indication), whereas the European guidelines, until recently,[1,3] do not support the utilization of an ICD in asymptomatic patients regardless of LVEF due to limited evidence for efficacy in this population. In the present study, we aimed to evaluate (1) the long-term survival benefit of primary ICD therapy by NYHA class in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)[4] population, and (2) whether asymptomatic patients (i.e. NYHA I) who were enrolled in the trial derived a similar long-term survival benefit from primary device implantation.

## Methods

The design and results of the MADIT II and the long-term follow-up have been previously described.[4,5] Briefly, the study comprised 1,232 patients who were enrolled if they had a myocardial infarction (MI) within 1 month and LVEF ≤ 30%. Patients who had undergone recent revascularization procedures and patients with major co-morbidities were excluded. Patients were randomized to ICD or non-ICD therapy (3:2

[a]Division of Cardiology, Heart Research Follow-Up Program, Department of Medicine, University of Rochester Medical Center, Rochester, New York; [b]Heart Institute, Sheba Medical Center, Ramat Gan, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; and [c]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois. Manuscript received September 8, 2017; revised manuscript received and accepted November 20, 2017.

[1]These authors contributed equally to this work.

See page •• for disclosure information.

*Corresponding author: Tel: +1 585 276 5228; fax: +1 585 273 5283.

*E-mail addresses:* yitschak.biton@heart.rochester.edu, yitscb@gmail.com (Y. Biton).

0002-9149/
https://doi.org/10.1016/j.amjcard.2017.11.032

ratio), with high utilization of β blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins in both groups. The NYHA functional class was determined by trained study nurses and was validated by the enrolling physicians in each center. In the present analysis, we excluded 68 MADIT-II patients who had NYHA class IV at enrollment. Thus, the final study population comprised 1,164 MADIT-II patients with NYHA class I-III at enrollment.

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

Data on crossover between allocated treatment arms were recorded for all study patients during the study and after trial closure. Among the 742 patients randomized to ICD treatment arm, 22 patients did not receive an ICD after randomization and 13 had the ICD extracted during the trial; among the 490 study participants 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 post-trial follow-up period.

In the current study, patients were categorized into 3 subgroups according to the NYHA functional class (I, II, and III) for the primary analysis. For the secondary analysis, we classified the patients into 2 subgroups based on HF symptoms, either asymptomatic (NYHA I) or symptomatic (NYHA II-III). We then compared the outcomes between the ICD treatment arm and the non-ICD treatment arm. The analyses in the present study were designed on an efficacy basis by including data on crossover between the treatment arms (patients were censored at the time of crossover). The outcome of the study was all-cause mortality.

Categorical data are presented as frequencies and percentages, and continuous variables are presented as mean ± SD. Baseline clinical characteristics were compared between NYHA subgroups using the chi-square test or Fisher's exact test for dichotomous variables and Wilcoxon signed-rank test for continuous variables.

Multivariable Cox proportional hazards regression analysis was used to assess the long-term all-cause mortality risk reduction with ICD compared with non-ICD according to the NYHA class in the primary analysis and HF symptoms in the secondary analysis. The model was adjusted for high-risk clinical variables that were previously shown to predict mortality (age > 70 years, QRS duration > 120 milliseconds, blood urea nitrogen [BUN] > 26 mg/dl, and atrial fibrillation).[6] To examine the consistency of our results, we performed subanalyses using 6 prespecified variables including 4 high-risk variables (Age [categorized at 70], QRS [categorized at 120], BUN [categorized at 26%], atrial fibrillation [yes or no]) and 2 more variables of interest (LVEF [categorized at 25%] and gender [male or female]). All statistical tests were two-sided, a p value <0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4, SAS Institute, Cary, North Carolina).

## Results

The study population comprised 442 patients with NYHA class I, 425 patients with NYHA class II, and 297 patients with NYHA class III. The clinical characteristics are presented in Table 1. Age, gender, ejection fraction (EF), diabetes, atrial fibrillation, and ACE inhibitors and β-blocker treatment were equally distributed between the groups. Patients with NYHA class III had slightly lower systolic blood pressure and higher baseline creatinine and BUN. They were more likely to receive diuretics and less likely to be on aspirin regimen. During the trial period (short-term), patients with NYHA class III were more likely to have HF hospitalizations, and patients with NYHA class I had lower frequency of appropriate ICD shocks.

The median ± interquartile range follow-up time was 7.6 (3.5 to 9) years. At 8 years of follow-up, the cumulative probability of death in the non-ICD treatment arm (Figure 1), as determined by the Kaplan-Meier estimates, was similar between patients with either NYHA I or II and significantly higher in the NYHA class III group (57%, 57%, and 76% respectively, log-rank p value <0.001). Accordingly, in a multivariate Cox analysis (Table 2), the risk of mortality among

Table 1
Clinical characteristics of study patients at baseline and at closure of the initial follow-up

| Clinical Characteristics | New York Heart Association Class | | |
|---|---|---|---|
| | I (n = 442) | II (n = 425) | III (n = 297) |
| Age (years) | 64.0 ± 10.6 | 64.8 ± 9.8 | 64.7 ± 10.7 |
| Women | 13% | 15% | 18% |
| Ejection fraction < 25% | 42% | 42% | 61% |
| Hypertension requiring treatment | 47%*† | 57% | 58% |
| Diabetes mellitus | 30%*† | 38% | 37% |
| Atrial Fibrillation | 7% | 10% | 9% |
| Cigarette smoker | 80% | 82% | 78% |
| Coronary artery bypass graft | 57% | 58% | 58% |
| Non-CABG Revascularization | 46% | 45% | 42% |
| Systolic blood pressure (mmHg) | 123 ± 18† | 123 ± 18‡ | 119 ± 19 |
| Creatinine (mg/dl) | 1.2 ± 0.5† | 1.2 ± 0.4‡ | 1.3 ± 0.5 |
| Blood urea nitrogen (mg/dl) | 21 ± 11*† | 23 ± 11‡ | 27 ± 14 |
| Left bundle branch block | 14%*† | 20% | 21% |
| QRS duration > 120 msec | 32%† | 37% | 42% |
| Aspirin use | 71%† | 73%‡ | 63% |
| ACE Inhibitor use | 78% | 77% | 78% |
| Angiotensin receptor blocker use | 8%*† | 16% | 15% |
| β-blocker use | 63% | 65% | 60% |
| Diuretic use | 61%*† | 77%‡ | 88% |
| Statin | 67% | 62% | 61% |
| NYHA class ≥2 | 38%*† | 88% | 92% |
| In-trial heart failure hospitalization | 15%† | 19%‡ | 31% |
| In-trial appropriate ICD Shock | 21%† | 28% | 30% |
| ACE Inhibitor | 75%† | 71% | 66% |
| β-blocker | 75%† | 73%‡ | 65% |
| Diuretic | 65%*† | 82%‡ | 88% |

* Denotes p value <0.05 for the comparison between NYHA I and NYHA II.

† Denotes p value <0.05 for the comparison between NYHA I and NYHA III.

‡ Denotes p value <0.05 for the comparison between NYHA II and NYHA III.