Implantable Cardioverter Defibrillator Therapy in MADIT II Patients with Signs and Symptoms of Heart Failure

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Postinfarction patients with left ventricular dysfunction are at increased risk of mortality and sudden cardiac death. A decreased left ventricular ejection fraction (EF) remains the most effective predictor of mortality despite changing and improving clinical management of postinfarction patients. Over last two decades, numerous studies aiming to determine clinical usefulness of various pharmacologic and device strategies for preventing mortality in postinfarction patients used a decreased ejection fraction as the main criterion for patient enrollment. Multicenter Automatic Defibrillator Implantation Trial (MADIT), first primary prevention trial with implantable cardioverter defibrillator (ICD), used the combined risk stratification strategy (low EF, NSVT, and inducible arrhythmia) to identify high-risk patients (1). Similar strategy was utilized by subsequent Multicenter Unsustained Tachycardia Trial (MUSTT) (2) and both these studies demonstrated very substantial, over 50%, reduction of mortality with ICD therapy in the high-risk patients, who represented very narrow highly selected subset of postinfarction patients with low ejection fraction. These trials also brought the message that a decreased ejection fraction $\leq$30% alone identifies a very high risk of mortality (over 20% mortality at 2 years) that additional risk stratifiers like nonsustained ventricular tachycardia or inducible ventricular tachycardia might not be needed.

MADIT II was designed to evaluate the survival benefit of prophylactic ICD therapy in patients with a prior myocardial infarction and left ventricular ejection fraction $\leq$30%, without an eligibility requirement for arrhythmia induction using invasive electrophysiologic testing (3). Patients who were at least one month after myocardial infarction and who had an ejection fraction $\leq$0.30 were eligible for enrollment and randomly assigned to receive either an ICD or conventional medical therapy. Patients who were < 1 month after acute myocardial infarction or <3 months after coronary artery bypass grafting (CABG) surgery, and those with NYHA class IV were excluded. The primary end point was all-cause mortality. The MADIT II enrolled 1,232 patients of whom 490 were randomized to conventional therapy and 742 to ICD therapy. Fifty-four percent of patients were at age 65 years or older at enrollment. MADIT II patients had their last myocardial infarction 5 years before enrollment on average. Mean ejection fraction of studied patients was 23$\pm$5% with two-third of patients in NYHA class $\geq$II indicating that MADIT II population represented postinfarction patients with advanced left ventricular dysfunction and symptoms of heart failure in

most of them. Regarding therapy, the majority of patients underwent revascularization therapy in the past. Optimal pharmacological therapy was used in MADIT II patients with 70% of them receiving beta-blockers, and 70% receiving inhibitors of angiotensin convertase and statins.

During a mean 20-month follow-up there were 97 (19.8%) deaths in the conventional arm and 105 (14.2%) deaths in ICD arm. Figure 1 shows significantly improved survival in patients randomized to ICD therapy when compared to patients randomized to conventional therapy with a hazard ratio = 0.69 and respective adjusted p = 0.016. The ICD therapy resulted in a 31% reduction in the risk of all-cause mortality and 67% reduction in sudden cardiac death, achieved in addition to optimal ICD therapy.

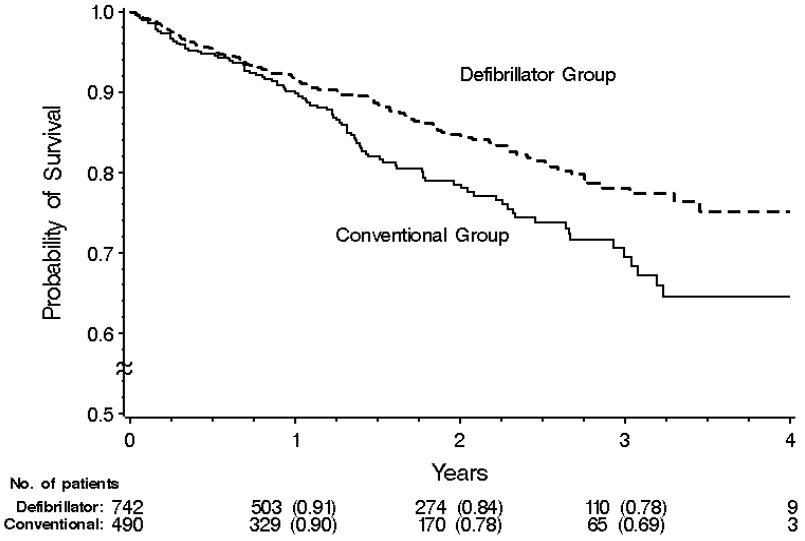

Figure 1. Cumulative probability of survival in MADIT II patients randomized to defibrillator or conventional therapy (from Moss et al. NEJM 2002; 346:877-83)

The MADIT II results were confirmed by findings from two large studies: the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (4) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (5). COMPANION was primarily study focused on the effects of cardiac resynchronization therapy in patients with advanced heart failure and QRS≥120 ms, but one of the arms of the trial received device combining ICD with cardiac resynchronization pacemaker therapy. The ICD-resynchronization therapy in ischemic patients (55% of study population) was associated with 27% reduction in mortality (p=0.082), which was secondary endpoint of the study (Figure 2).

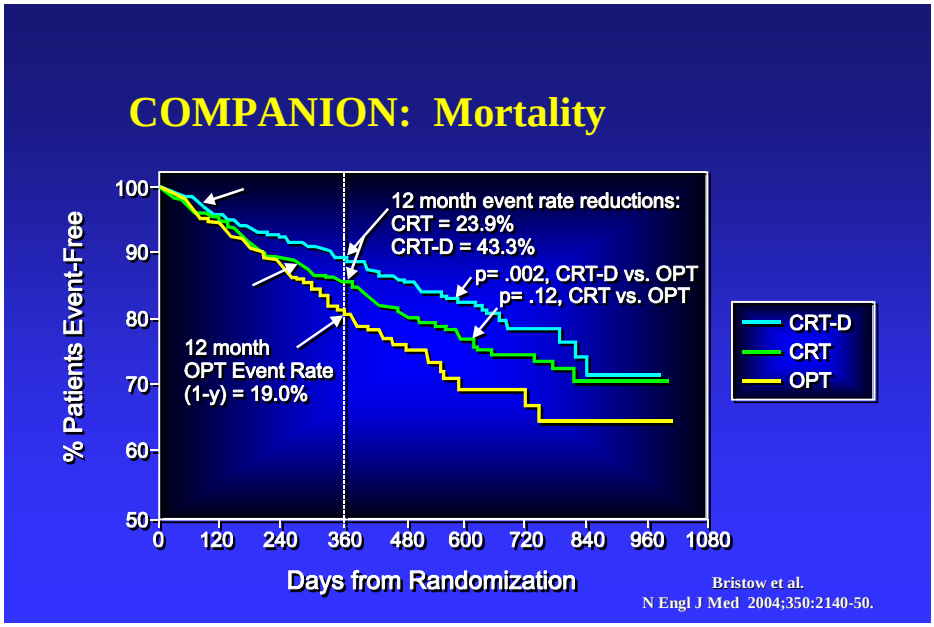

Figure 2. Cumulative probability of survival in COMPANION patients randomized to CRT vs CRT-D, vs. conventional therapy (from Bristow et al. NEJM 2004;350:2140-50)

The SCD-HeFT was a primary prevention trial randomizing 2,521 patients with EF≤35% and ischemic or nonischemic cardiomyopathy NYHA class II or III to amiodarone, ICD, or placebo therapy (5). The mortality rate in placebo arm of the study was 7.2% annually, with 5-year mortality 36%, further proving that such patients are at very high risk (Figure 3). There was no benefit from amiodarone therapy, whereas ICD therapy contributed to a significant 23% reduction in mortality when compared to placebo (HR=0.77; p=0.007). Subset analysis showed that there was a 21% reduction in mortality in ischemic patients. The main benefit was observed in patients with EF≤30%.

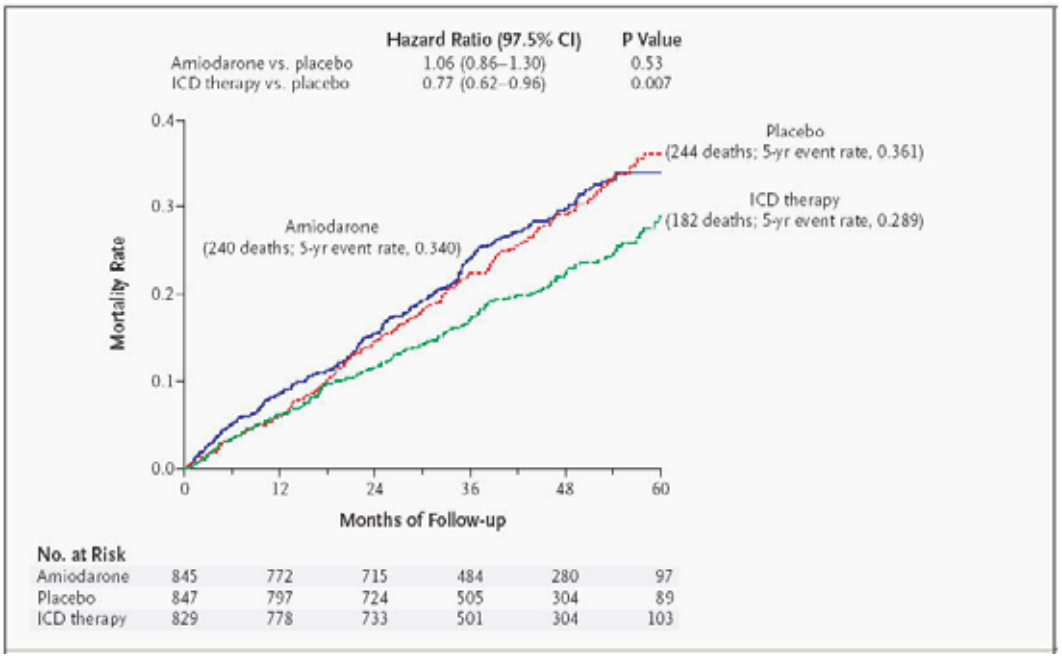

Figure 3. Cumulative probability of mortality in SCD-HeFT patients randomized to defibrillator, amiodarone, or conventional therapy (from Bardy et al. NEJM 2005; 352:225-237)

The MADIT II, created a paradigm for primary prevention of mortality in postinfarction patients confirming that low ejection fraction (≤30%) is a sufficient marker of high (22% at 2 years) mortality without need for additional risk stratifiers and that ICD therapy reduces this high mortality by 31%. Nevertheless, there are numerous questions regarding whether various subsets of MADIT II patients could benefit more or less from ICD therapy. Results from the Sudden Death in Heart Failure Trial (SCD-HeFT) indicated that subgroup of patients with NYHA class III show less benefit from an ICD than patients with less advanced heart failure (Figure 4).

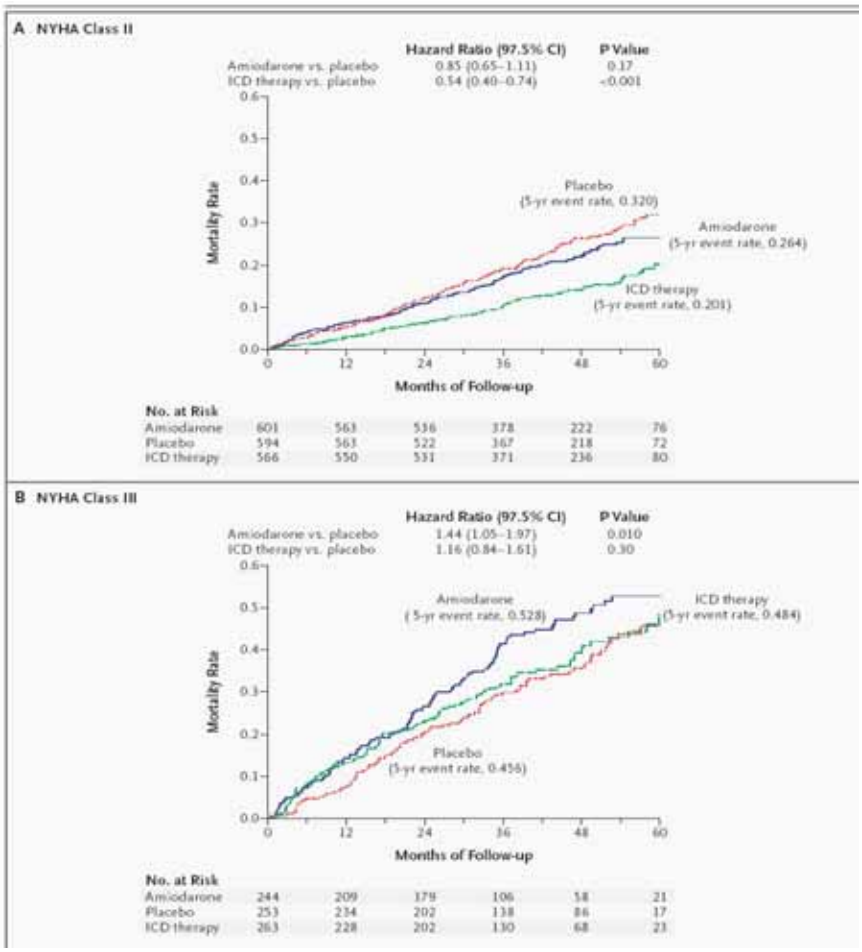

Figure 4. Cumulative probability of mortality in SCD-HeFT patients randomized to defibrillator or conventional therapy according to NYHA class (from Bardy et al. NEJM 2005; 352:225-237)

NYHA Class and ICD Effectiveness in MADIT II

In MADIT II population, ejection fraction and other signs and symptoms of heart failure were tested regarding their differential risk on mortality and different ICD effectiveness (6). NYHA class is a popular although imprecise and subjective measure of the advancement of heart failure. MADIT II population consisted of 36% patients in NYHA class I, 35% in class II and 29% in class III. As shown in Figure 5, mortality was significantly ($p<0.05$) higher in patients with NYHA class III than in patients with NYHA class I and II. Proportion of sudden death was not different among patients with different NYHA class: 56% in class I, 61% in class II, and 59% in class III.

Consistently with total mortality, appropriate ICD therapy defined as antitachycardia pacing or ICD shocks for VT or VF was more frequently observed in patients with more advanced disease (Figure 5). As shown in Table 1, ICD was similarly effective regardless of NYHA class indicating that NYHA class III patients benefit from ICD therapy.

Similar results were observed when evaluating blood urea nitrogen levels (BUN) dichotomized ≤25 mg/dl and >25 mg/dl, probably more objective measure of the advancement of heart failure. Hazard ratios for ICD effectiveness for patients with BUN ≤25mg/dl and >25 mg/dl were 0.65 (p=0.031) and 0.71 (p= 0.091) respectively.

Table 1. Cox Proportional Hazard Ratios for the Implantable Cardioverter Defibrillator Effectiveness (Implantable Cardioverter Defibrillator versus Conventional Therapy) in MADIT II Patients by NYHA Class (from Zareba et al. Am J Cardiol 2005;95:1487-91).

		Mortality			
Subgroups	N	ICD vs. Conventional Therapy			P Value for Interaction
		HR	95% CI	p value	
NYHA Class					
I	442	0.72	0.43-1.21	0.216	
II	425	0.65	0.38-1.10	0.109	0.95
III	350	0.65	0.43-0.99	0.044	

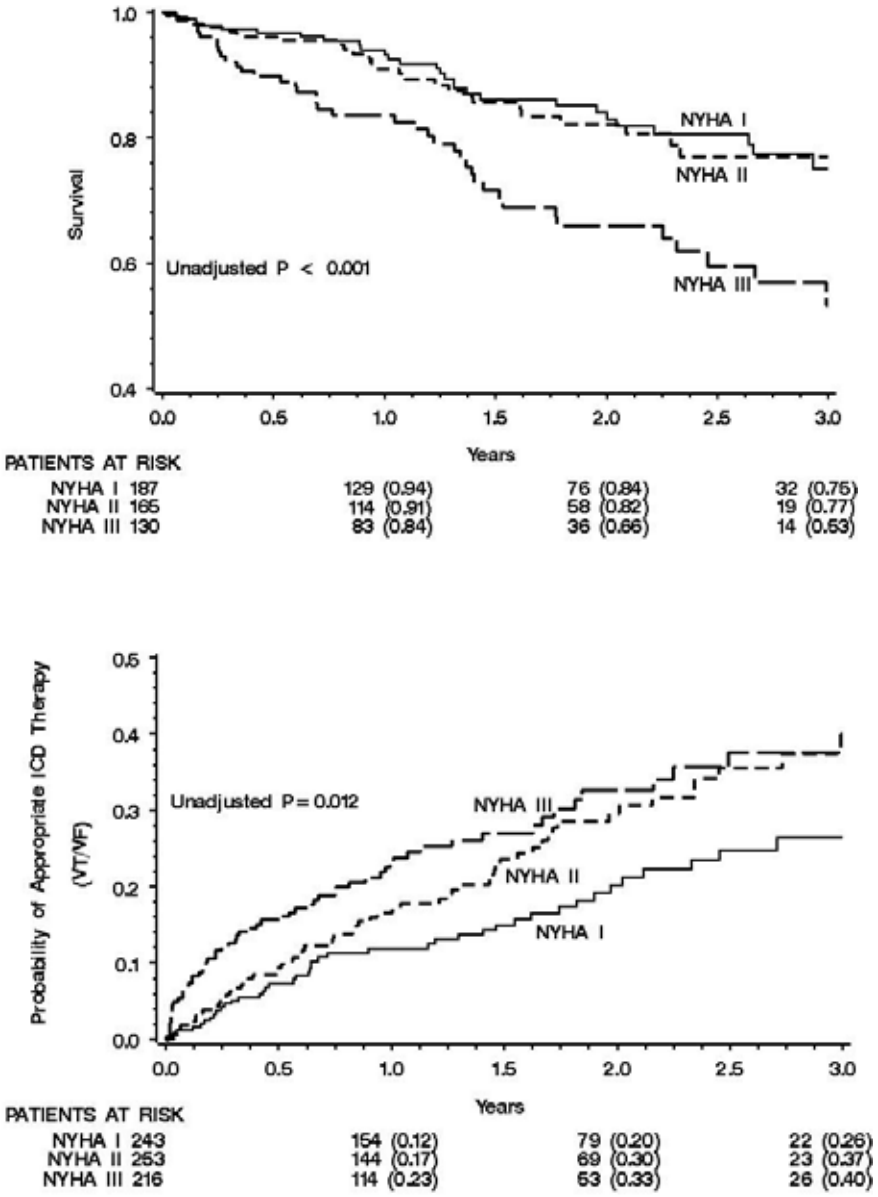

Figure 5. Cumulative probability of survival (top) and ventricular arrhythmias requiring appropriate ICD therapy (bottom) in MADIT II patients randomized to defibrillator or conventional therapy according to NYHA class (from Zareba et al. Am J Cardio 2005; 95:1487-91)

Ejection Fraction and ICD Effectiveness in MADIT II

In MADIT II, there were 472 (38%) patients with EF ≤20%, 359 (29%) patients with EF = 21-25%, and 401 (33%) with EF = 26-30%. Patients with EF 21-25% and ≤20% had nonsignificantly different survival in comparison to patients with EF>25% (Figure 6).

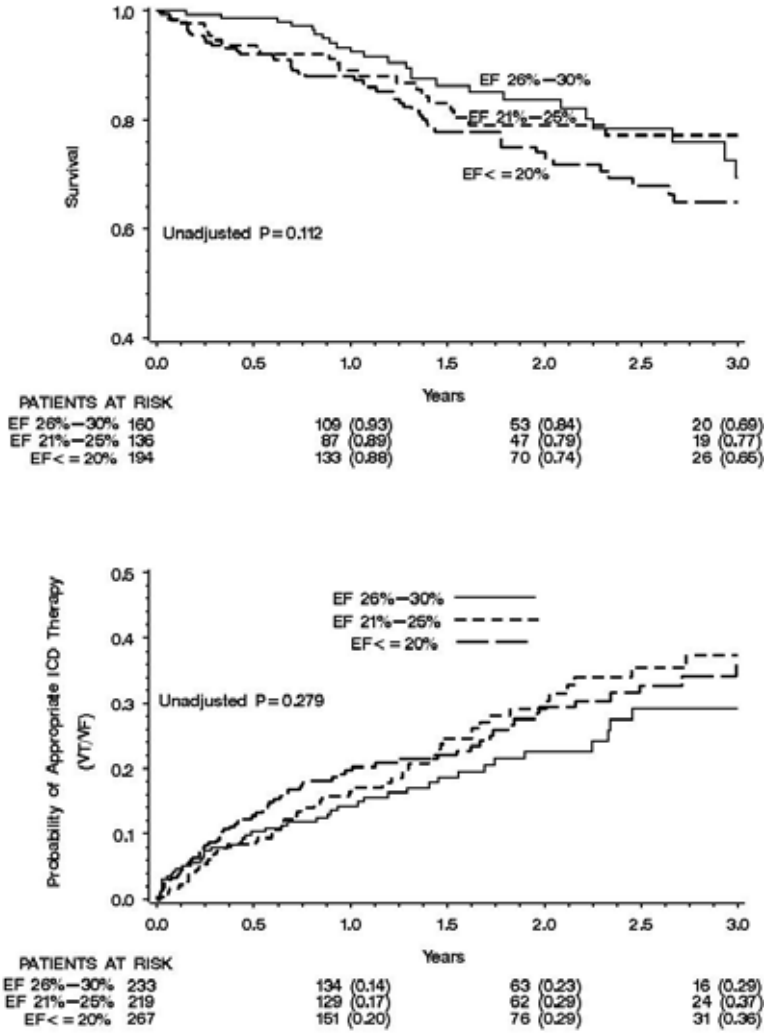

Figure 6. Cumulative probability of survival (top) and ventricular arrhythmias requiring appropriate ICD therapy (bottom) in MADIT II patients randomized to defibrillator or conventional therapy according to EF (from Zareba et al. Am J Cardiol 2005; 95:1487-91)

Proportion of sudden deaths in patients with EF = 26-30% was 58%, in patients with EF = 21-25% was 48%, and in those with EF≤20% was 62%. There was no significant difference in the risk of ventricular arrhythmias requiring appropriate ICD therapy among three groups. Table 2 also shows similar ICD effectiveness regardless of ejection fraction in MADIT II patients.

Table 2. Cox Proportional Hazard Ratios for the Implantable Cardioverter Defibrillator Effectiveness (Implantable Cardioverter Defibrillator versus Conventional Therapy) in MADIT II Patients by Ejection Fraction. (from Zareba et al. Am J Cardiol 2005; 95:1487-91)

		Mortality			
Subgroups	N	ICD vs. Conventional Therapy			P Value for
		HR	95% CI	p value	Interaction
Ejection Fraction					
26-30%	401	0.65	0.37-1.15	0.136	
21-25%	359	0.65	0.38-1.13	0.127	0.91
≤20%	472	0.74	0.50-1.08	0.120	

NYHA, EF, BUN combined and ICD Effectiveness

When analyzing ICD effectiveness according to combined presence of the above signs and symptoms of heart failure: NYHA>II, EF≤25%, and BUN>25 mg/dl, there were 382 patients with none of these factors, 452 patients with 1 factor, 274 patients with 2 factors, and 95 patients with all three factors present. As shown in Figure X, there were no significant differences in ICD effectiveness among patients with different number of these heart failure risk factors. .

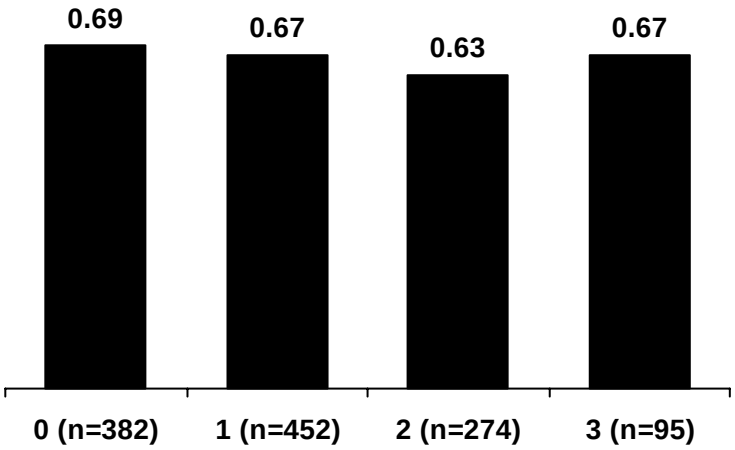

Figure 7. Hazard ratios for the ICD effectiveness in MADIT II patients stratified based on number of heart failure related risk factors: NYHA>II, EF≤25%, and BUN>25 mg/dl.

Conclusive Remarks

The MADIT II data indicate that postinfarction patients with EF≤30% who present with signs and symptoms of advanced heart failure measured by the NYHA class (and BUN level) have significantly increased mortality. They also have increased risk of arrhythmic events as determined by ICD interrogation in ICD arm of the study. Ejection fraction does not differentiate risk of mortality and arrhythmic events within MADIT II patients with already substantially compromised left ventricular function. Ejection fraction is a very gross and imprecise measure of left ventricular function and most likely some other echocardiographic measures of wall motion abnormalities might identify high-risk subset.

Importantly, MADIT analyses indicate that ICD is equally effective in patients with signs and symptoms of less and more advanced heart failure or left ventricular dysfunction. If anything, advanced CHF patients (NYHA class III, and BUN>25 mg/dl) benefit more than patients with less

advanced disease. All presented above groups showed benefit from ICD with about 28%-35% reduction in mortality indicating that ICDs are justified in all considered subset of MADIT II type patients.

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