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Factors Influencing Appropriate Firing of the Implanted Defibrillator for Ventricular Tachycardia/Fibrillation

Findings From the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)

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OBJECTIVES The purpose of this study was to prospectively examine the role of clinical, laboratory, echocardiographic, and electrophysiological variables as predictors of appropriate initial implantable cardioverter-defibrillator (ICD) therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) or death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) population.

BACKGROUND There is limited information regarding the determinants of appropriate ICD therapy in patients with reduced ventricular function after a myocardial infarction.

METHODS We used secondary analysis in one arm of a multicenter randomized clinical trial in patients with a previous myocardial infarction and reduced left ventricular function.

RESULTS We analyzed baseline and follow-up data on 719 patients enrolled in the ICD arm of the MADIT-II study. Appropriate ICD therapy was observed in 169 subjects. Clinical, laboratory, echocardiographic, and electrophysiological variables, along with measures of clinical instability such as interim hospitalization for congestive heart failure (IH-CHF) and interim hospitalization for coronary events (IH-CE), were examined with proportional hazards models and Kaplan-Meier time-to-event curves before and after first interim hospitalization. Interim hospitalization-CHF, IH-CE, no beta-blockers, digitalis use, blood urea nitrogen (BUN) >25, body mass index (BMI) ≥30 kg/m^2, and New York Heart Association functional class >II were associated with increased risk for appropriate ICD therapy for VT, VF, or death. In a multivariate (stepwise selection) analysis, IH-CHF was associated with an increased risk for the end point of either VT or VF (hazard ratio [HR] 2.52, 95% confidence interval [CI] 1.69 to 3.74, $p < 0.001$) and for the combined end point of VT, VF, or death (HR 2.97, 95% CI 2.15 to 4.09, $p < 0.001$). Interim hospitalization-CE was associated with an increased risk for VT, VF, or death (HR 1.66, 95% CI 1.09 to 2.52, $p = 0.02$).

CONCLUSIONS These results provide important mechanistic information, suggesting that worsening clinical condition and cardiac instability, as reflected by an IH-CHF or IH-CE, are subsequently associated with a significant increase in the risk for appropriate ICD therapy (for VT/VF) and death. (J Am Coll Cardiol 2005;46:1712–20) © 2005 by the American College of Cardiology Foundation

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) has shown that patients with a previous myocardial infarction (MI) and advanced left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤30%) benefit from prophylactic implantation of a defibrillator (1). The results of this study have expanded the previously recommended use of implantable cardioverter-defibrillator (ICD) therapy, resulting in cost implications on the health care system. Calculations have suggested that this increase in the number of patients eligible for ICD implantation will result in many patients receiving ICDs that are never used (2). This, in turn, has caused much debate concerning the clinical acceptance of the MADIT-II results. Also, recently updated American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines have expressed the need for further risk stratification of the MADIT-II population to better identify patients likely to benefit from ICD therapy (3). The present study sought to determine the role of interim measures of clinical instability along with baseline clinical, laboratory, echocardiographic,

See page 1727

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Abbreviations and Acronyms

BMI	= body mass index
BUN	= blood urea nitrogen
CE	= coronary events
CHF	= congestive heart failure
CI	= confidence interval
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
IH	= interim hospitalization
LVEF	= left ventricular ejection fraction
MADIT-II	= Multicenter Automatic Defibrillator Implantation Trial II
MI	= myocardial infarction
NYHA	= New York Heart Association
VF	= ventricular fibrillation
VT	= ventricular tachycardia

and electrophysiological variables in predicting appropriate ICD therapy for ventricular tachyarrhythmias and death in the MADIT-II patient population. This might improve the post-ICD implantation care and also enable better risk stratification in this patient group.

METHODS

Study subjects. The MADIT-II was a prospective multicenter trial that enrolled subjects from 76 hospital centers. A description of the study design and protocol has been previously published (1,4). Patients >21 years of age and of either gender were eligible for the study if they had had an MI one month or more before entry, as documented by the finding of an abnormal Q-wave on electrocardiography, elevated cardiac enzymes during hospitalization for a suspected MI, a fixed defect on thallium scanning, or localized akinesis on ventriculography with evidence of obstructive coronary artery disease on angiography, and an ejection fraction of ≤0.30 within three months before entry as suggested by angiography, radionuclide scanning, or echocardiography (1,4).

Definitions of all clinical variables were outlined before the start of the MADIT-II. Subjects underwent a detailed clinical evaluation and a spectrum of invasive and non-invasive electrophysiological risk-stratification procedures. Baseline device settings were uniform among all subjects.

Follow-up. All data of baseline characteristics, including the results of the invasive and non-invasive cardiac evaluation, were prospectively collected in the MADIT-II study population. Patients were followed up in each center, and data concerning all ICD therapy were obtained at the time of device interrogation and retrieval of stored electrograms. The end point review committee received detailed reports of the events, reports from the emergency room, hospital records, and outpatient visits. Careful records were obtained of the time to death after symptom onset, site of death, and ischemic symptoms. Records of interim hospitalization for heart failure (IH-CHF) or interim hospitalization for coronary events (IH-CE) were kept by the caring physicians and used as post-implantation surrogates of clinical instability.

Statistical analysis. Baseline clinical characteristics were compared between two groups with and without ICD therapy or those with and without experience of interim hospitalizations by the chi-square test. Multivariate Cox proportional hazards regression analysis was used to identify and evaluate risk factors associated with first occurrence of appropriate ICD therapy. These risk factors comprised measured baseline characteristics of patients and time-dependent factors during follow-up, such as "time of first" IH-CHF or IH-CE (angina or MI). Two combined end points were used, namely, the first appropriate therapy for ventricular tachycardia (VT) or for ventricular fibrillation (VF), hereafter VT/VF, and VT/VF/death; the former is of primary interest, but results of the analyses are somewhat biased by the necessity of censoring patients at death, whereas the latter provides a fully valid comparison analysis. The final regression analysis was built in three steps: 1) stepwise selection from all available variables of interest, but omitting drug usage at baseline, for each end point separately (with $p < 0.1$ for retention); 2) addition to the model of each category of drugs used at baseline, one at a time, and retained if providing a significant effect; and 3) re-fitting each end point model with risk factors retained in at least one of the two end point models. Upon finding interim hospitalization variables as significant risk factors, we re-fitted the models, allowing for different effects of these hospitalizations in patients initially in New York Heart Association (NYHA) functional classes I to II and classes III to IV and tested for significant interaction. Freedom from arrhythmia (ICD therapy) was evaluated by the Kaplan-Meier method. Before and after interim hospitalization of the follow-up period shows the probability of an end-point event. For these, the follow-up of a patient is moved from before to after, and initialized to zero, upon occurrence of the hospitalization. No formal statistical testing comparing before and after curves is feasible, owing to overlapping groups of patients. The p values are two-sided and considered statistically significant when <0.05.

RESULTS

Baseline characteristics. We analyzed baseline and follow-up data on 719 of 742 patients in the ICD arm of the MADIT-II study, having excluded 22 patients who did not receive an ICD and one patient who dropped out shortly after the implantation. Patient characteristics for the two groups (i.e., with and without ICD therapy) are listed in Table 1. The subjects receiving ICD therapy had a higher body mass index (BMI) and worse functional NYHA functional class at baseline and a lower ejection fraction. These patients were more likely to have had an IH-CHF or IH-CE. There were no significant differences in age, gender distribution, blood pressure, or other cardiac risk factors. There were no differences between the two groups with

Table 1. Clinical Characteristics of ICD Patients With and Without ICD Therapy

Variables	No ICD Therapy (n = 550)*	Appropriate ICD Therapy (n = 169)*	p Value
Clinical examination			
Female	16.5	12.4	0.197
Age ≥65 yrs	52.7	55.0	0.600
Heart rate ≥80 (beats/min)	29.5	30.5	0.797
BMI ≥30 kg/m^2	28.0	37.3	0.022
Diastolic BP ≥80 mm Hg	26.7	30.2	0.380
Systolic BP >130 mm Hg	34.5	37.9	0.429
Clinical history			
Hypertension (on Rx)	53.7	52.7	0.805
Diabetes	34.2	32.5	0.694
CHF (NYHA functional class >II)	28.3	36.9	0.034
IH-CHF	18.9	37.9	<0.001
IH-CE	12.0	18.9	0.022
S/P CABG	58.7	46.8	0.658
Medications			
Beta-blockers	65.6	59.2	0.125
ACE inhibitor	77.6	77.5	0.974
Diuretic	72.0	78.1	0.116
Digitalis	58.2	65.1	0.109
Statin	65.5	59.2	0.137
Laboratory tests			
BUN >25 mg/dl	27.2	33.5	0.113
Creatinine ≥1.4 mg/dl	26.4	23.1	0.385
ECG			
QRS >0.12	38.0	42.0	0.348
Left bundle branch block	18.5	20.9	0.506
Right bundle branch block	8.9	9.5	0.808
Atrial fibrillation	8.4	9.5	0.674
Echocardiography			
LVEF <25%	45.6	53.8	0.062
Electrophysiological study			
Inducible	34.3	39.7	0.240

*All values expressed as percentages with the indicated variable.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CE = coronary events (angina or myocardial infarction); CHF = congestive heart failure; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; IH = interim hospitalization; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; S/P CABG = status post coronary artery bypass graft surgery.

respect to electrocardiographic, invasive and non-invasive electrophysiological tests, or ejection fraction. Of note, beta-blocker and angiotensin-converting enzyme (ACE) inhibitor use was similar in both groups. Electrocardiographic findings of a wide QRS duration, left bundle branch block or right bundle branch block, and atrial fibrillation were not associated with increased ICD therapy. There was a higher incidence of sudden (7.1% vs. 2.4%) and non-sudden cardiac (10.1% vs. 4.8%) death in the patient population receiving appropriate ICD therapy (for VT/VF) versus those free of ICD intervention.

Determinants of ICD therapy and death. During the 17.2-month average follow-up, appropriate ICD therapy was observed in 169 (24%) of 719 subjects. The index arrhythmia was VF in 30 patients (18%) and VT in 139 patients (82%). Of the patients with ICD therapy for VT/VF, 37% were in NYHA functional class >II. The mean duration of the VT or VF episodes triggering device therapy from the onset until termination of the arrhythmia was 20.1 and 27.3 s for VT and VF, respectively. Interim hospitalization-CHF, IH-CE, no beta-blockers, digitalis use, male gender, blood urea nitrogen (BUN) >25 mg/dl, BMI ≥30 kg/m^2, and NYHA functional class >II were associated with increased risk for appropriate ICD therapy for VT or VF and death. Multivariate stepwise regression analysis with the Cox proportional hazards model identified the time-dependent risk factor IH-CHF as associated with a two- to three-fold increased risk for ICD therapy for VT or VF, with a hazard ratio (HR) of 2.52 (95% confidence interval [CI] 1.69 to 3.74, $p < 0.001$) and for a combined end point of VT, VF, and death, HR 2.97 (95% CI 2.15 to 4.09, $p < 0.001$). An IH-CE was associated with an increased risk for VT, VF, and death, HR 1.66 (95% CI 1.09 to 2.52, $p = 0.02$). When stratified by NYHA functional class, the risk associated with IH-CHF and IH-CE for VT/VF and death was higher in patients with NYHA class ≤2, compared with those with a higher NYHA class (Table 2). An IH-CE did not significantly increase the risk for VT/VF alone and was not associated with risk for VT/VF and death in the sicker patients with NYHA functional class III and IV function.

The clinical profile of patients with IH-CHF was markedly different from those without IH-CHF (Table 3). Subjects with IH-CHF were more likely to be women, diabetics, have an elevated BUN and creatinine, NHYA functional class >2, have atrial fibrillation, lower ejection fractions, lower use of beta blockers and higher use of digitalis, heart rate >80 beats/min, and QRS duration of >120 ms (Table 3). From these clinical characteristics, only a worse functional class (NYHA >II), no beta-blockers, digitalis use, BUN >25 mg/dl, and BMI >30 kg/m^2 were associated with ICD therapy in the multivariate model (Table 2). Patients with IH-CE were noted to be hypertensive and to have an elevated serum BUN and creatinine, as compared with those without IH-CE.

Kaplan-Meier curves show an increased probability for appropriate ICD therapy after (post-CHF) compared with before (pre-CHF) hospitalization for CHF. The pre-CHF curve refers to follow-up time of patients before IH-CHF, and post-CHF refers to follow-up time after hospitalization for CHF. These results were consistent for combined end points: VT and VF, as well as a combined end point of VT, VF, and death (Figs. 1A and 1B). Similar trends were observed among patients with IH-CE for the combined end point of VT/VF and death but not for VT/VF alone (Figs. 2A and 2B).

Separate Kaplan-Meier graphs were constructed for IH-CHF, sub-stratified by NYHA functional class. In the lower NYHA classes (I and II), there was a significantly higher probability of ICD therapy for VT/VF for those who had IH-CHF (Fig. 3A); however, hospitalization for CHF had little impact on the probability of appropriate ICD

Table 2. Multivariate Proportional-Hazards Model for Time to ICD Therapy, Including Interim Cardiac-Related Hospitalizations as Risk Factors

Risk Factor	VT/VF End Point		VT/VF/Death End Point	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
IH-CHF*	2.52 (1.69–3.74)	<0.001	2.97 (2.15–4.09)	<0.001
IH-CHF in NYHA functional class I–II	3.20 (1.97–5.19)	<0.001	3.93 (2.65–5.83)	<0.001
IH-CHF in NYHA functional class III–IV	1.90 (1.02–3.55)	0.04	2.22 (1.37–3.62)	0.001
IH-CE*	1.43 (0.84–2.42)	0.19	1.66 (1.09–2.52)	0.02
IH-CE in NYHA functional class I–II	1.76 (0.96–3.22)	0.07	2.36 (1.48–3.77)	<0.001
IH-CE in NYHA functional class III–IV	1.02 (0.38–2.75)	0.97	0.87 (0.38–1.99)	0.74
NYHA functional class >II	1.32 (0.95–1.83)	0.10	1.41 (1.06–1.86)	0.02
BUN >25 mg/dl	1.29 (0.93–1.79)	0.13	1.56 (1.18–2.05)	0.002
Male	1.71 (1.07–2.75)	0.03	1.54 (1.04–2.28)	0.03
BMI ≥30 kg/m^2	1.45 (1.05–2.00)	0.02	1.21 (0.90–1.61)	0.20
Digitalis at baseline	1.14 (0.83–1.58)	0.42	1.35 (1.01–1.80)	0.04
No beta-blockers at baseline	1.18 (0.86–1.62)	0.31	1.33 (1.01–1.75)	0.04

*Time-dependent risk factors: IH-CHF; IH-CE. The analysis was repeated, allowing different IH effects in NYHA functional classes I to II and classes III to IV, with results shown in the indented rows. Tests for differences between the class-specific hazard ratios had p values of 0.19 and 0.07 for the respective end points for IH-CHF and 0.35 and 0.04 correspondingly for IH-CE.

CI = confidence interval; VF = ICD therapy for ventricular fibrillation; VT = ICD therapy for ventricular tachycardia; other abbreviations as in Table 1.

therapy in the sicker heart failure patients (NYHA functional classes III and IV; Fig. 3B).

DISCUSSION

This study addresses the frequently asked question of whether there are any clinical determinants of ICD therapy and death within the population of patients with previous MIs and advanced left ventricular dysfunction. Our results show that 1) among a comprehensive list of baseline clinical, echocardiographic, and electrophysiological variables (used within this study), more symptomatic patients (NYHA functional class >II) with BUN >25 mg/dl, higher BMI, and less beta-blocker use and increased digitalis use at baseline are at a greater risk for a first time appropriate ICD therapy for VT/VF and/or death; 2) IH-CHF exacerbation and IH-CE are strongly associated with an increased risk for ICD therapy and death; and 3) increased ICD therapy was observed in less sick patients (NYHA functional classes I and II) who had worsening of their clinical status. To our knowledge, this is the first study to highlight the importance of interim measures of clinical instability and their power to identify a subgroup (within this already high-risk population) at greater risk for ICD therapy and death.

Determinants of ICD therapy and death. Among the several clinical variables assessed for their role as predictors of ICD therapy or death in the MADIT-II patient population, interim measures of hospitalization stood out as significant determinants of appropriate ICD therapy. Previous reports have indicated that QRS duration is associated with overall cardiac mortality (5,6) and sudden death (7). In our study, there was no association of ICD therapy with QRS width, when the latter was examined as either a continuous or dichotomized (>120 ms) variable.

Previous reports have shown that an elevated heart rate at baseline is associated with future occurrences of ventricular tachyarrhythmias (8) and that beta-blocker therapy is associated with a reduced recurrence of VT/VF and ICD shocks (9,10). In the current analysis, an inverse association between beta-blocker use and ICD therapy was observed, whereas an elevated heart rate was not predictive of ICD therapy and/or death. The absence of this association between heart rate and ICD therapy could be explained by the high use of beta-blockade in our study and slight differences in the mean heart rate between the two groups.

Severity of left ventricular dysfunction has been consistently shown to be a predictor of overall mortality and sudden death (11–13). In this study, it was observed that further sub-stratification of LVEF in this pre-selected high-risk group (LVEF <30% and coronary artery disease) was not associated with an increased risk for VT, VF, or death. Our findings are dissimilar to the results of other studies, such as Levine et al. (14), who found that an ejection fraction <25% was predictive of cardiac events. This difference is most likely a consequence of the underlying differences in the patient population and comparative groups being evaluated as well as treatment strategies available at that time. A recent retrospective analysis of the Canadian Implantable Defibrillator Study (15) showed that patients with LVEF ≤35% and aged >70 years were more likely to benefit from an ICD. Our results found no association with age and further sub-stratification of the LVEF <25%. The presence of an association between

JACC Vol. 46, No. 9, 2005
November 1, 2005:1712–20

Table 3. Comparison of Clinical Characteristics of Patients With and Without Interim Hospitalization for Heart Failure (IH-CHF) or Coronary Events (IH-CE)

Variables	No IH-CHF (n = 550)*	IH-CHF (n = 168)*	p Value	No IH-CE (n = 621)*	IH-CE (n = 98)*	p Value
Clinical examination						
Female	13.8	21.4	0.02	15.6	15.3	0.937
Age ≥65 yrs	51.3	60.1	0.04	53.6	51.0	0.631
Heart rate ≥80 beats/min	26.5	40.4	0.001	29.7	29.9	0.972
BMI ≥30 kg/m^2	30.2	29.8	0.917	29.1	36.7	0.128
Diastolic BP ≥80 mm Hg	29.5	21.4	0.04	27.5	27.6	0.998
Systolic BP >130 mm Hg	36.7	31.0	0.171	35.1	36.7	0.754
Clinical history						
Hypertension (on Rx)	52.5	57.2	0.280	51.9	63.3	0.037
Diabetes	30.2	45.8	<0.001	33.5	35.7	0.666
CHF (NYHA functional class >II)	26.7	41.7	<0.001	29.6	34.7	0.312
IH-CE	9.8	26.2	<0.001	0	100	
IH-CHF	0	100		20.0	44.9	<0.001
S/P CABG	58.4	57.7	0.886	58.1	59.2	0.844
Medications						
Beta-blockers	67.3	53.6	0.001	64.4	62.2	0.678
ACE inhibitor	78.2	75.6	0.482	77.5	78.6	0.806
Diuretic	68.5	89.3	<0.001	72.5	79.6	0.138
Digitalis	56.9	69.0	0.005	58.8	66.3	0.157
Statins	67.1	53.6	0.001	64.4	61.2	0.541
Laboratory tests						
BUN >25 mg/dl	24.4	42.9	<0.001	27.1	38.8	0.017
Creatinine ≥1.4 mg/dl	22.2	36.5	<0.001	23.9	36.7	0.007
ECG						
QRS >0.12	36.3	47.0	0.013	39.3	36.7	0.631
Left bundle branch block	17.4	24.2	0.06	19.6	15.7	0.389
Right bundle branch block	8.8	9.8	0.701	9.5	5.6	0.230
Atrial fibrillation	6.8	14.9	0.001	8.3	11.2	0.334
Echocardiography						
LVEF <25%	44.0	58.9	0.001	46.4	55.1	0.1208
Electrophysiologic study						
Inducible	36.2	33.8	0.600	35.5	35.9	0.950

*All values expressed as percentages with the indicated variable.
Abbreviations as in Table 1.

NYHA (functional class >II) and ICD therapy in the multivariate model was similar to a recent report from Whang et al. (16); however, the present study provides more than a single baseline gauge of CHF severity (i.e., NYHA functional class) and incorporates a measure of change in clinical state through IH-CHF or angina, unlike the previous report (16). Of note, other electrophysiological measures (invasive and non-invasive) were not noted to be determinants of ICD therapy in the MADIT-II population (17,18).

CHF, CE, and ICD therapy. Congestive heart failure secondary to coronary artery disease is associated with a higher mortality and sudden cardiac death rate when compared with other etiologies (1,19–21). Whereas the clinical outcome of patients with coronary artery disease and left ventricular dysfunction has improved with the use of beta-blockers and ACE inhibitors, sudden cardiac death continues to take its toll and remains a significant problem in this population. Although functional class correlates poorly with LVEF (12,22), both LVEF and cardiac functional status have been shown to be independent risk factors for arrhythmic death and device discharges (13,16). In our study, the results of the multivariate Cox regression analysis of baseline clinical variables suggests that in a pre-selected high-risk population with LVEF <30%, further sub-stratifying the population by ejection fraction (<25% vs. 25% to 30%) did not add to the predictive value for ICD therapy. Although in the MADIT-II population, a significant association was noted between NYHA functional class >II and ICD therapy, there is relatively reduced ICD therapy after IH-CHF in this group of patients. This suggests that this subset of patients is already so sick that other variables (i.e., worsening of clinical status) do not have additional predictive value as a determinant of ICD therapy. This also supports the evidence that in sicker heart failure subjects, the cause of death is more likely owing to pump failure, sudden bradyarrhythmias, or electromechanical dissociation (12). Our results highlight the increased incidence of ICD therapy in less sick patients (NYHA functional class ≤II). This is supported by recent data from the Sudden Cardiac Death in Heart Failure Trial, where patients with NYHA functional class II (as opposed to NYHA functional class III) seemed to benefit more from ICDs (23). New data from the MADIT-II study have also shown that patients receiving ICD therapy are at higher risk for developing heart

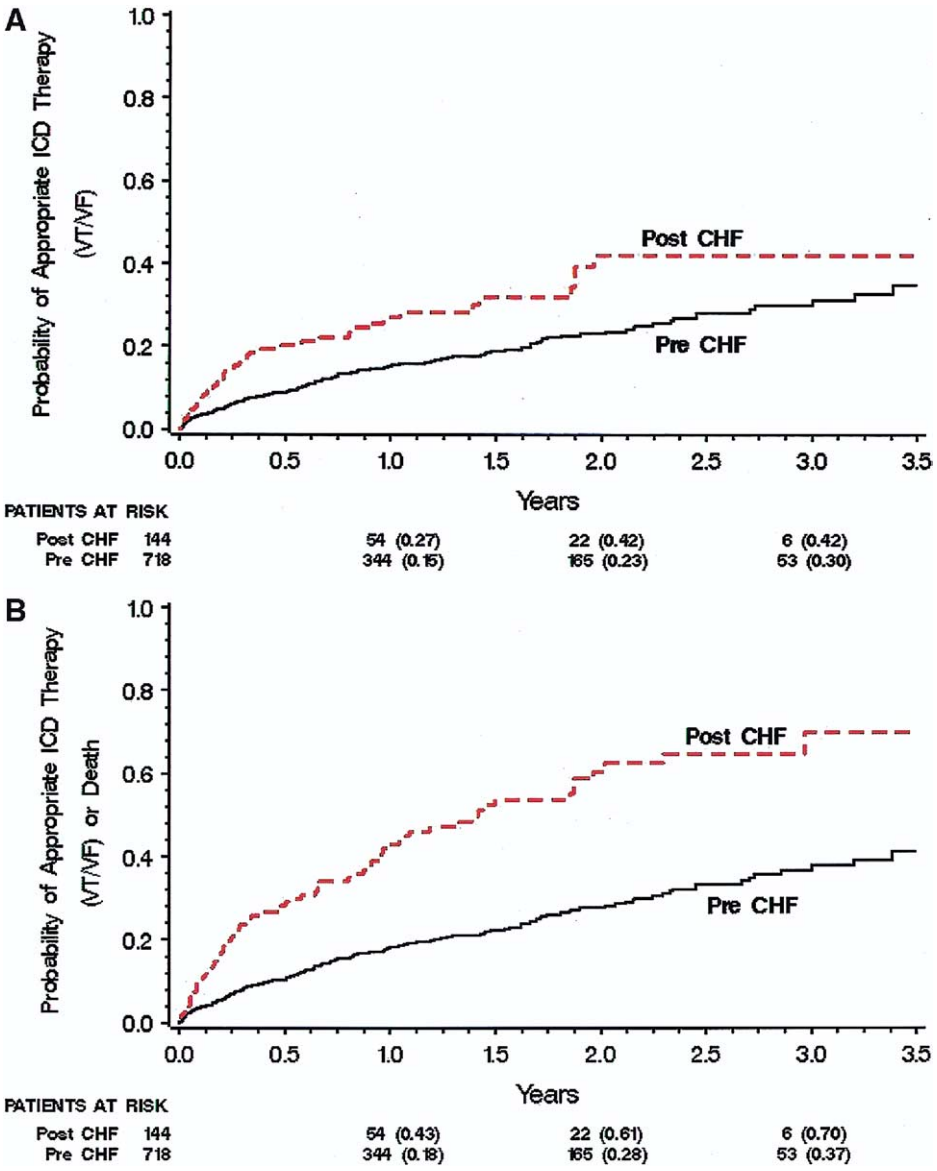

Figure 1. Kaplan-Meier curves for the probability of receiving appropriate implantable cardioverter-defibrillator (ICD) therapy in patients after interim hospitalization for congestive heart failure (CHF) (Post CHF) compared with a period before any such hospitalization (Pre CHF). **Panels A and B** show the curves for combined ventricular tachycardia (VT) and ventricular fibrillation (VF) (with censoring at death), and for combined VT, VF, and death, respectively.

failure and late non-sudden cardiac death, emphasizing the need for increased clinical vigilance and continued medical care after ICD therapy (24).

Myocardial ischemia and its association with ventricular arrhythmias are well described. Recent data have shown angina to be a predictor of new malignant arrhythmias in patients with coronary artery disease (25). There are, however, scant prospective data showing this mechanistic relationship between angina and ICD therapy in patients with coronary artery disease. Our data demonstrate that angina and coronary events requiring hospitalization are predictive of ICD therapy and death in this group of patients. By logical extension, IH-CHF and IH-CE are also likely to be predictive of subsequent sudden cardiac death in patients who meet MADIT-II criteria, but do not have defibrillators.

Clinical implications. The ICD has become the therapy of first choice to prevent sudden cardiac death in high-risk patients. Our study also supports the well-understood clinical notion that continued clinical vigilance toward preventing heart failure exacerbations and coronary events might decrease the risk of sudden cardiac death and ICD therapy in this high-risk population. Interestingly, the increase in ICD therapy and death was seen primarily during follow-up after an interim hospitalization, suggesting that this is a vulnerable period with regard to ventricular arrhythmias in patients with ischemic cardiomyopathy. This could be reflective of a change in clinical status, cardiac function, and

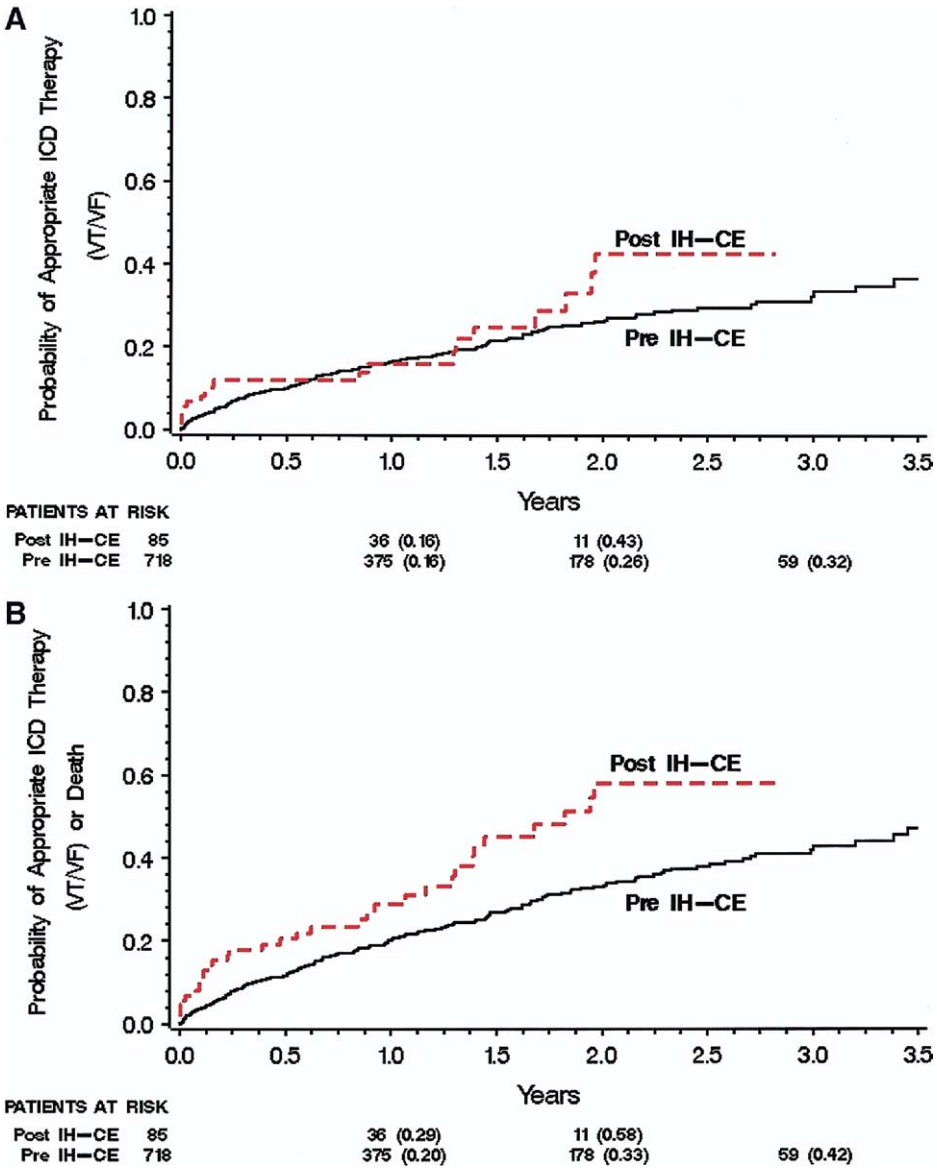

Figure 2. Kaplan-Meier curves for the probability of receiving appropriate implantable cardioverter-defibrillator (ICD) therapy in patients after interim hospitalization for coronary events (Post IH-CE) compared with the period before any such hospitalization (Pre IH-CE). **Panels A and B** show the curves for combined ventricular tachycardia (VT) and ventricular fibrillation (VF) (with censoring at death), and for combined VT, VF, and death, respectively.

substrate as well as change in medical regimen or milieu (e.g., electrolyte balance).

These findings are pertinent to the entire MADIT-II population, independent of NYHA functional class. These results are corroborated by recent studies that show that preventing progression of heart failure with cardiac resynchronization therapy reduces the incidence of arrhythmic events (26,27). In interpreting these results, it must be recognized that not all arrhythmias triggering appropriate ICD shocks for VT/VF would have resulted in sudden cardiac death and also that not all sudden cardiac deaths are a consequence of ventricular tachyarrhythmias. Because the true arrhythmogenic contribution of clinical characteristics can be better assessed by appropriate ICD use (rather than overall survival), the current study restricted its primary evaluation to appropriate ICD therapy and not mortality (although the latter was also evaluated). Our results also point to the overall increase in mortality in patients once they have been hospitalized for heart failure or coronary events. It is also important to emphasize that the most important predictor of ICD therapy (IH-CHF) became apparent only after the implant, during the follow-up period.

Conclusions. The present study shows that among a comprehensive list of baseline clinical, echocardiographic, and electrophysiological variables (used in the MADIT-II study), more symptomatic patients (NYHA functional class >II) with BUN >25 mg/dl, BMI ≥30 kg/m^2, increased digitalis use at baseline, and no beta-blocker use are at a higher risk for first appropriate ICD therapy and death.

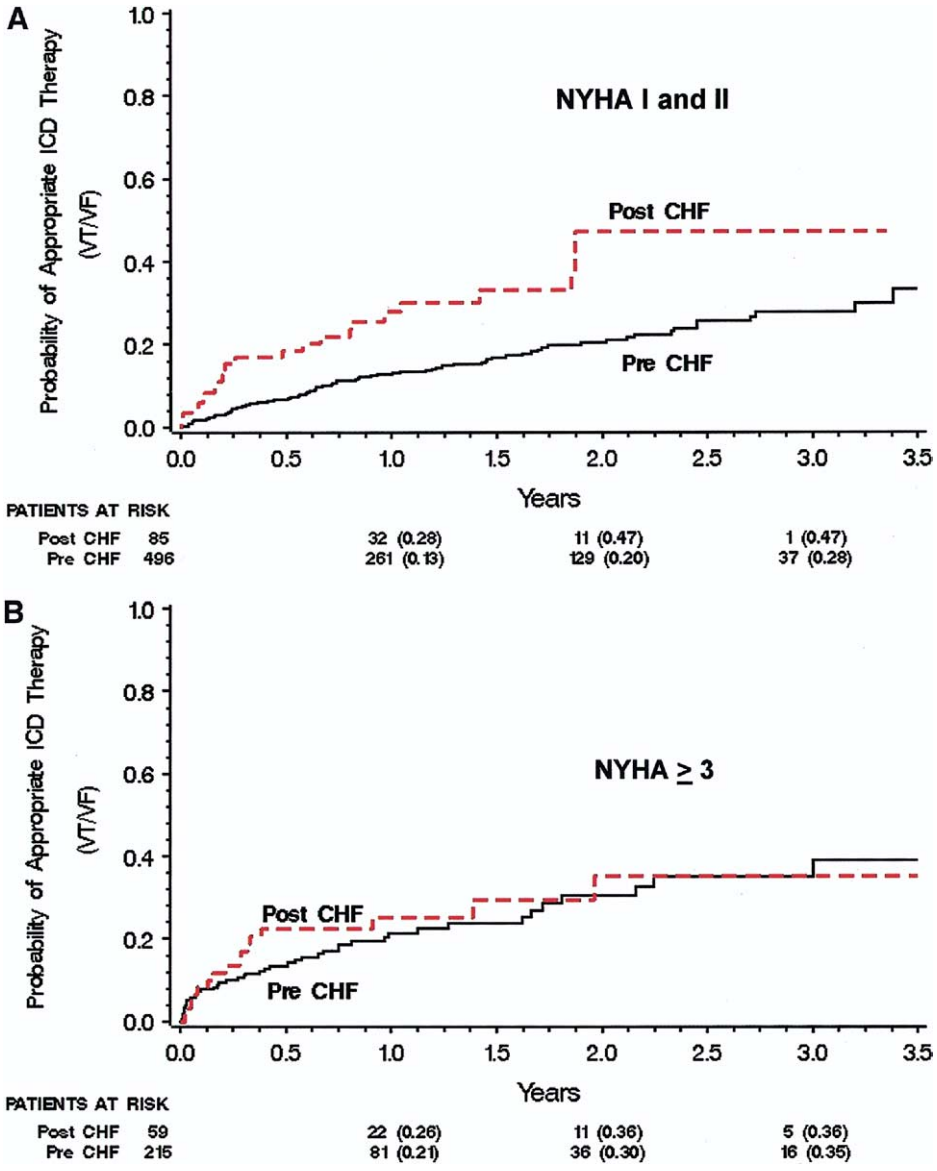

Figure 3. Kaplan-Meier curves for receiving implantable cardioverter-defibrillator (ICD) therapy in patients after interim hospitalization for heart failure (Post CHF) in patients sub-stratified by New York Heart Association (NYHA) functional class. **Panel A** shows that patients with NYHA class ≤II have a higher propensity to receive ICD therapy after hospitalization, as opposed to an absence of this effect in patients with NYHA class III or IV function **(B)**. Other abbreviations as in Figures 1 and 2.

This analysis also provides important mechanistic information, suggesting that worsening clinical condition, as reflected by an IH-CHF or IH-CE, is associated with a significant increase in the risk for appropriate ICD therapy and death. This emphasizes the need for continued clinical vigilance during the follow-up period after ICD implantation to prevent heart failure exacerbations and coronary events, which, in turn, might decrease the risk of sudden cardiac death and ICD therapy in this high-risk population.

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