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Microvolt T-Wave Alternans Identifies Patients With Ischemic Cardiomyopathy Who Benefit From Implantable Cardioverter-Defibrillator Therapy

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Objectives This study sought to assess whether implantable cardioverter-defibrillators (ICDs) have different mortality benefits among patients with ischemic cardiomyopathy who screen negative and non-negative (positive and indeterminate) for microvolt T-wave alternans (MTWA).

Background Microvolt T-wave alternans has been proposed as an effective tool for risk stratification. However, no studies have examined whether ICD benefits differ by MTWA group.

Methods We developed a prospective cohort of 768 patients with ischemic cardiomyopathy (left ventricular ejection fraction ≤35%) and no prior sustained ventricular arrhythmia, of which 392 (51%) received ICDs. The mean follow-up time was 27 ± 12 months. Propensity scores for ICD implantation based on the variables most likely to influence defibrillator implantation were developed for each MTWA cohort. Multivariable Cox analyses that controlled for propensity score, demographics, and clinical variables evaluated the degree to which ICDs decreased mortality risk for each MTWA group.

Results We identified 514 (67%) patients with a non-negative MTWA test result. After multivariable adjustment, ICDs were associated with lower all-cause mortality in MTWA-non-negative patients (hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.27 to 0.76, p = 0.003) but not in MTWA-negative patients (HR 0.85, 95% CI 0.33 to 2.20, p = 0.73) (for interaction, p = 0.04), with the mortality benefit in MTWA-non-negative patients largely mediated through arrhythmic mortality reduction (HR 0.30, 95% CI 0.13 to 0.68, p = 0.004). The number needed to treat with an ICD for 2 years to save 1 life was 9 among MTWA-non-negative patients and 76 among MTWA-negative patients.

Conclusions In patients with ischemic cardiomyopathy and no prior history of ventricular arrhythmia, mortality reduction with ICD implantation differs by MTWA status, with implications for risk stratification and health policy. (J Am Coll Cardiol 2007;49:50–8) © 2007 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) accounts for one-half of all deaths in patients with ischemic cardiomyopathy (1). Prophylactic placement of implantable cardioverter-defibrillators (ICDs) has been shown to lower mortality dramatically in this population (2,3). Recently, the Center for Medicare and Medicaid Services (CMS) approved reimbursement for ICD implantation for primary prevention (4,5). However, the use of left ventricular ejection fraction (LVEF) to identify patients at high and low risk for SCD is limited by its low specificity (6). As shown in the

See page 59

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study, 81% of patients with LVEF ≤35% derived no benefit from ICD therapy at 5 years (2). The need for more refined risk stratification strategies beyond simple LVEF cutoffs to identify further which patients are most and least likely to benefit from ICD therapy remains great (7).

Microvolt T-wave alternans (MTWA) has been shown to predict SCD and ventricular arrhythmic events in a number of high-risk populations (8). Prior studies of MTWA in patients

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with ischemic cardiomyopathy have been limited by small sample sizes, lack of adjustment for potential confounders, or nonmortality end points (9,10), thereby raising questions regarding its true prognostic utility (11). In a recent study, however, we showed that MTWA was indeed an independent predictor of all-cause mortality in patients with ischemic cardiomyopathy after multivariable adjustment for demographics, clinical comorbid conditions, medication treatment, QRS duration, and Holter testing (12). Moreover, we were able to show that this mortality reduction was mediated through reduction of arrhythmic deaths. Nevertheless, it has been argued that the true prognostic utility of MTWA will remain unknown unless it can be shown that ICD benefit differs by MTWA subgroup (11).

We therefore evaluated whether ICD benefit differed by MTWA status in ischemic cardiomyopathy patients. Specifically, because MTWA-negative patients have been shown to have lower rates of all-cause and arrhythmic mortality (12), we assessed whether ICD benefit occurred only in those higher risk patients who test MTWA-non-negative (positive and indeterminate).

Methods

Study population. The study design has been previously described (12). Briefly, a prospective cohort of patients with ischemic cardiomyopathy was developed from 7 outpatient cardiology clinics by the Ohio Heart and Vascular Center and the Lindner Clinical Trials Center. Consecutive patients who had ischemic heart disease (defined as cardiac catheterization with ≥70% stenosis in at least 1 coronary vessel, documented myocardial infarction, or a history of coronary revascularization) and LVEF ≤35% were enrolled between March 2001 and June 2004. In our prior study, patients were followed up through December 2004. For the present analysis, we include follow-up data collected through September 2005. Patients had to be 21 years of age or older, to have no history of a prior ventricular arrhythmic event, and to be in sinus rhythm at the time of MTWA testing. All patients gave informed consent to registry enrollment and follow-up, and the study was approved by the Institutional Review Board at The Christ Hospital (Cincinnati, Ohio).

MTWA testing protocol. All patients underwent baseline MTWA testing by treadmill exercise at study enrollment (Heartwave system, Cambridge Heart Inc., Bedford, Massachusetts) with elevation of the heart rate to a target level of 120 beats/min. Beta-blockers and non-dihydropyridine calcium channel blockers were withheld for >24 h before the test. All MTWA tests were interpreted according to standard criteria by an expert reader blinded to patient characteristics and clinical outcomes (13). A positive MTWA test result was defined as sustained alternans with an onset heart rate ≤110 beats/min. A negative MTWA test result was defined as the absence of criteria for a positive test with a maximum heart rate ≥105 beats/min. All other test results were classified as indeterminate. We classified both indeterminate and positive test results as "non-negative" for statistical analyses based on prior studies that have found similar prognostic utility for MTWA indeterminate and positive test results compared with negative test results (8,12).

Abbreviations and Acronyms

CI = confidence interval
CMS = Center for Medicare and Medicaid Services
EPS = electrophysiological study
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
MTWA = microvolt T-wave alternans
SCD = sudden cardiac death

Data collection. At study enrollment, patient data on demographic and clinical characteristics were collected and included age, gender, LVEF, QRS duration >120 ms, diabetes mellitus, hypertension, symptomatic heart failure, chronic obstructive pulmonary disease, chronic renal insufficiency, peripheral vascular disease, and history of myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, unexplained syncope, or revascularization therapy. In addition, data on baseline medication use of aspirin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, digoxin, diuretic, class I or III antiarrhythmic agent, statin, and spironolactone were obtained.

We also collected data on diagnostic testing with Holter monitoring and electrophysiological study (EPS) as well as ICD implantation in the cohort. We defined nonsustained ventricular tachycardia on Holter monitoring as >100 beats/min for ≥3 consecutive beats and <30 s. Testing with EPS in the cohort was based on clinical criteria, which included age, LVEF, comorbid conditions, and noninvasive studies. For those patients undergoing EPS, a positive study was defined as: 1) inducible sustained monomorphic ventricular tachycardia of cycle length ≥230 ms, or 2) inducible ventricular fibrillation, polymorphic ventricular tachycardia, or ventricular flutter (monomorphic ventricular tachycardia with a cycle length <230 ms) with ≤2 ventricular extrastimuli. Because not all patients underwent an EPS, 2 dummy variables were created to reflect 3 levels of EPS status in the cohort: no test, a positive test, and a negative test. Finally, ICD implantation in our cohort was primarily (93% of all ICDs implanted) based on a positive EPS, an abnormal Holter result, or a QRS >120 ms in the period the after the MADIT-II (Second Multicenter Automatic Defibrillator Implantation Trial-II) study (after mid 2002).

Primary end points and follow-up. The primary end point for the study was all-cause mortality. Secondary end points included cause-specific mortality and the delivery of appropriate ICD shocks for confirmed ventricular tachycardia or ventricular fibrillation in patients with ICDs. Cause-specific mortality was adjudicated by 2 study team members blinded to the decedent's clinical information (including MTWA and ICD status) and was classified as arrhythmic or nonar-

rhythmic in etiology using a modified Hinkle-Thaler system (14). Unwitnessed deaths (if stable when last observed before death and within 24 h), witnessed instantaneous deaths, and deaths as a sequelae of cardiac arrest were classified as arrhythmic deaths. In patients with ICDs, ICD shocks were reviewed by a physician similarly blinded to the patient's clinical information to determine their appropriateness. Clinical follow-up for mortality end points was achieved for all patients by quarterly office visits (97.5%), telephone contact with patient (99.4%), routine review of office charts, and an annual query of the National Death Index (100%) (15–17).

The index date for the non-ICD cohort was the date of initial cohort enrollment. To avoid survival bias against the non-ICD group (because all ICD patients had to survive until the time of ICD implantation), the index date for the ICD group was the date of ICD implantation, with the median time from cohort enrollment to ICD implantation being 58 days.

Data analysis. UNADJUSTED ANALYSES. The study cohort was first stratified by MTWA group (negative vs. non-negative). Baseline characteristics in ICD and non-ICD patients for each MTWA group were compared using Student *t* tests for continuous variables and chi-square tests for categorical variables. Survival curves between the ICD and non-ICD patients were constructed separately for each MTWA group using Kaplan-Meier estimates and assessed with univariate Cox proportional hazards analysis. Similar analyses were also performed for cause-specific mortality and for a composite end point of all-cause mortality or appropriate ICD shock therapy.

ADJUSTED ANALYSES. To examine whether ICD benefit differed by MTWA group, we first evaluated for a potential interaction (prespecified p value ≤ 0.10) between the MTWA and ICD variables. Multivariable Cox analyses using a propensity score for ICD receipt (see below) in the entire cohort found that an interaction existed ($p = 0.038$) between ICD status and MTWA test result for all-cause mortality, suggesting that ICD benefit differed by MTWA status.

Because cohort studies may have significant differences in baseline risk between the compared groups, and because multivariable analyses may not adequately adjust for such differences (i.e., the ICD and non-ICD patients in each MTWA group may not truly overlap in their mortality risk profiles), we used a propensity score analysis in our Cox proportional hazards models (18,19). A propensity score analysis is a statistical technique that examines factors that influence the likelihood of receiving a particular treatment (in this case, ICD implantation), thereby allowing for comparisons of patients with comparable risk. To generate the propensity score, multivariable logistic regression was used to model ICD placement (dependent variable) with the 3 independent variables (EPS testing, QRS duration >120 ms, and abnormal Holter monitoring) most likely to influence the clinical decision to implant ICDs in our cohort. The model provides the predicted probability (from 0 to 1) of receiving an ICD for each patient. A C-statistic, representing the area under the receiver-operating characteristic curve, indicates how well the propensity score model predicted ICD implantation.

For our study cohort, separate propensity scores were generated for the MTWA-negative and MTWA-non-negative groups. For each MTWA group, separate Cox models were performed using their MTWA group-specific propensity score. First, all study covariates except the ones used in developing the propensity score were examined for univariate associations with death ($p \leq 0.10$) through Cox proportional hazards analysis. Significant variables in univariate analyses were then systematically evaluated with Cox proportional hazards regression analyses to generate a multivariable model ($p \leq 0.05$) and reported as hazard ratio (HR) with 95% confidence interval (CI). Age, LVEF, ICD status, and propensity score were kept in the final model, regardless of level of significance.

The same Cox analyses were performed to evaluate ICD benefit for the secondary end points of arrhythmic and nonarrhythmic mortality. In addition, as a sensitivity test to further assess the potential mechanism of benefit with ICD therapy, we equated an appropriate defibrillator shock in ICD patients with death, and assessed whether ICD and non-ICD patients in each MTWA group were exposed to a similar baseline risk for mortality by comparing their risk for a composite outcome of all-cause mortality or ICD shock using similar Cox regression analyses as previously described.

Lastly, as a sensitivity analysis, we performed the above Cox regression analyses with a full, non-parsimonious propensity score using all study variables to model ICD placement in the cohort (Appendix). We also performed traditional multivariable Cox regression analyses without a propensity score to model mortality outcomes for comparative purposes. Results for all-cause and cause-specific mortality for each MTWA group did not change substantively in either case.

In all models, the assumption of proportionality for the Cox proportional hazards models was visually assessed with the (log-log [survival]) vs. log (survival time) to ensure parallelism. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics and summary of study end points. The study cohort was composed of 768 patients, of which 514 patients (67%) tested MTWA non-negative and 254 (33%) tested MTWA negative. In the MTWA-non-negative group, 317 (62%) had ICDs implanted, compared with 75 (30%) in the MTWA-negative group. The differential rate of ICD implantation between the MTWA subgroups was caused by higher rates of EPS inducibility

(37.7% vs. 15.0%, $p < 0.001$), abnormal Holter studies (16.1% vs. 6.7%, $p < 0.001$), and prolonged QRS duration (35.2% vs. 26.8%, $p = 0.02$) in the MTWA-non-negative cohort (Appendix).

A comparison of baseline characteristics between ICD and non-ICD patients for the MTWA-non-negative and MTWA-negative groups is given in Table 1 and Table 2. Among patients who tested MTWA non-negative, those with ICDs were younger; more likely to be male; more likely to have lower LVEF, EPS testing performed, EPS inducibility when studied, QRS >120 ms, and a history of myocardial infarction; and more likely to be on statin, beta-blocker, and digoxin therapy. Among patients who tested MTWA negative, those with ICDs had lower LVEF; were more likely to have EPS performed, EPS inducibility when studied, QRS >120 ms, abnormal Holter study, and symptomatic heart failure; and were more likely to be on spironolactone, digoxin, and diuretic therapy.

Table 1 Baseline Comparisons of ICD and Non-ICD Patients for the Cohort Testing MTWA Non-Negative

Covariates	ICD (n = 317)	Non-ICD (n = 197)	p Value
Age, yrs	67.4 ± 9.8	69.6 ± 9.8	0.02
Gender, % male	87.1	76.7	0.004
LVEF, %	26.1 ± 6.0	27.3 ± 6.7	0.04
EP study performed, % (n)	74.1 (235)	40.6 (80)	<0.0001
EP inducibility, % (n)	57.7 (183)	5.6 (11)	<0.0001
QRS >120 ms, %	39.1	28.9	0.02
Abnormal Holter, %	17.0	14.7	0.49
CABG, %	57.4	54.8	0.57
PTCA, %	52.1	46.7	0.24
Myocardial infarction, %	88.3	78.7	0.005
Symptomatic CHF, %	75.4	70.1	0.18
History of atrial fibrillation, %	14.2	16.8	0.43
Diabetes mellitus, %	39.1	42.1	0.50
Hypertension, %	36.0	35.5	0.92
COPD, %	8.5	8.1	0.88
PVD, %	5.7	3.1	0.14
Stroke/TIA, %	16.4	18.3	0.59
Renal failure, %	2.5	3.1	0.72
Syncope, %	14.8	16.8	0.56
Medications, %			
Aspirin	75.4	76.7	0.75
ACE-I or ARB	84.5	82.2	0.49
Beta-blocker	84.9	76.1	0.02
Spironolactone	17.4	15.2	0.53
Statin	64.7	53.8	0.01
Digoxin	44.2	33.0	0.01
Diuretic	65.9	65.0	0.82
Class I AA	0.3	1.0	0.37
Class III AA	8.8	9.1	0.91

AA = antiarrhythmic agent; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; EP = electrophysiological; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MTWA = microvolt T-wave alternans; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; TIA = transient ischemic attack.

Table 2 Baseline Comparisons of ICD and Non-ICD Patients for the Cohort Testing MTWA Negative

Covariates	ICD (n = 75)	Non-ICD (n = 179)	p Value
Age, yrs	64.7 ± 9.3	65.2 ± 9.9	0.75
Gender, % male	81.3	81.0	0.95
LVEF, %	26.9 ± 5.1	29.3 ± 5.0	0.001
EP study performed, % (n)	54.7 (41)	11.2 (20)	<0.0001
EP inducibility, % (n)	44.0 (33)	2.8 (5)	<0.0001
QRS >120 ms, %	36.0	22.9	0.03
Abnormal Holter, %	17.3	2.2	0.001
CABG, %	54.7	55.9	0.86
PTCA, %	54.7	53.1	0.82
Myocardial infarction, %	88.0	86.0	0.68
Symptomatic CHF, %	80.0	63.7	0.01
History of atrial fibrillation, %	18.7	12.9	0.23
Diabetes mellitus, %	26.7	34.6	0.22
Hypertension, %	37.3	34.6	0.68
COPD, %	6.7	3.9	0.35
PVD, %	2.7	6.7	0.13
Stroke/TIA, %	8.0	12.3	0.32
Renal failure, %	1.3	3.4	0.29
Syncope, %	16.0	16.2	0.97
Medications, %			
Aspirin	81.3	76.0	0.35
ACE-I or ARB	90.7	84.4	0.15
Beta-blocker	84.0	83.2	0.88
Spironolactone	26.7	12.3	0.01
Statin	69.3	64.8	0.49
Digoxin	32.0	20.7	0.05
Diuretic	72.0	60.3	0.07
Class I AA	2.7	0.0	0.16
Class III AA	6.7	7.8	0.75

Abbreviations as in Table 1.

The mean follow-up time was 27 ± 12 months for the entire cohort (847 ± 393 days for the non-ICD cohort; 787 ± 350 days for the ICD cohort indexed from implant date). There were a total of 129 deaths (99 in the MTWA-non-negative group and 30 in the MTWA-negative group), of which 56 were arrhythmic (44 in the MTWA-non-negative group and 12 in the MTWA-negative group) (Table 3). In addition, there were 35 appropriate ICD shocks in patients who did not die in the ICD group.

Unadjusted analyses. Kaplan-Meier curves comparing overall survival between ICD and non-ICD patients for each MTWA group are shown in Figure 1. Univariate Cox models found that ICD therapy was associated with lower all-cause mortality in the MTWA-non-negative group (HR 0.52, 95% CI 0.35 to 0.78) but not in the MTWA-negative group (HR 1.36, 95% CI 0.62 to 3.00) (Table 4). For cause-specific mortality, ICD therapy in the MTWA-non-negative group was associated with lower unadjusted arrhythmic mortality (HR 0.32, 95% CI 0.17 to 0.60), but had no impact on unadjusted nonarrhythmic mortality (HR 0.77, 95% CI 0.45 to 1.31). In patients testing MTWA negative, no significant differences were seen for unadjusted arrhythmic or nonarrhythmic mortality between patients

Table 3 Summary of Study End Points for ICD and Non-ICD Patients Stratified by MTWA Test Status

Outcomes	MTWA Non-Negative		MTWA Negative	
	+ICD (n = 317)	−ICD (n = 197)	+ICD (n = 75)	−ICD (n = 179)
Mean follow-up, days ± SD	790 ± 348	796 ± 402	772 ± 355	903 ± 376
Total deaths (%)	46 (14.5%)	53 (26.9%)	9 (12.0%)	21 (11.7%)
Arrhythmic deaths (%)	15 (4.7%)	29 (14.7%)	3 (4.0%)	9 (5.0%)
Nonarrhythmic deaths (%)	31 (9.8%)	24 (12.2%)	6 (8.0%)	12 (6.7%)
Total deaths + shocks (%)	77 (24.3%)	53 (26.9%)	13 (17.3%)	21 (11.7%)

Abbreviations as in Table 1.

with and without ICDs. When the combined end point of all-cause mortality and appropriate ICD shock was examined, neither MTWA group showed significant unadjusted event-free survival differences between the ICD groups (Table 4).

ADJUSTED ANALYSES. The propensity score derived from the 3 variables (EPS testing, QRS duration, and Holter monitoring) most likely to predict ICD placement in our cohort showed good discrimination, with a C-statistic of 0.807 in the MTWA-non-negative group and 0.778 in the MTWA-negative group. Among MTWA-non-negative patients, the variable most strongly associated with ICD placement was a positive EPS (Wald chi-square = 88.6, odds ratio 27.0, 95% CI 13.5 to 52.6), although a QRS >120 ms was also a strong predictor (Table 5). In the MTWA-negative group, a positive EPS remained the variable most likely to predict ICD placement (Wald chi-square = 39.5, odds ratio 27.8, 95% CI 9.8 to 76.9).

Multivariable Cox proportional hazards analyses adjusted for the propensity score and all other study covariates showed that ICDs were associated with significantly reduced all-cause mortality in MTWA-non-negative patients (HR 0.45, 95% CI 0.27 to 0.76, p = 0.003) but not in MTWA-negative patients (HR 0.85, 95% CI 0.33 to 2.20, p = 0.73) (Table 4). Multivariable Cox analyses for the entire cohort found a statistically significant difference in mortality reduction benefit with ICD therapy when comparing those testing MTWA non-negative with those testing MTWA negative (p value for interaction term evaluating ICD mortality benefit by MTWA group = 0.038). When confining the outcome to arrhythmic deaths, ICDs were associated with dramatic reductions in arrhythmic mortality in the MTWA-non-negative group only (HR 0.30, 95% CI 0.13 to 0.68, p = 0.004). No significant differences in nonarrhythmic mortality were found between the ICD groups in either the MTWA-non-negative or -negative cohorts. Finally, when a composite outcome of all-cause mortality or appropriate ICD shocks was examined, ICD and non-ICD patients had similar event-free survival rates in the MTWA-non-negative (HR 0.79, 95% CI 0.50 to 1.26, p = 0.33) and MTWA-negative (HR 1.15, 95% CI 0.48 to 2.77, p = 0.76) cohorts, suggesting that ICD and non-ICD patients were exposed to similar baseline combined rates of mortality and arrhythmic events.

Discussion

This study found that the mortality reduction seen with ICD therapy may not be consistent across MTWA subgroups, with patients testing MTWA non-negative receiv-

Table 4 Summary of Unadjusted and Adjusted Cox Proportional Hazards Models

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	p Value
TWA non-negative			
All-cause	0.52 (0.35–0.78)	0.45 (0.27–0.76)	0.003
Arrhythmic	0.32 (0.17–0.60)	0.31 (0.14–0.71)	0.005
Nonarrhythmic	0.77 (0.45–1.31)	0.60 (0.30–1.22)	0.16
All-cause + shocks	0.95 (0.67–1.35)	0.79 (0.50–1.26)	0.33
TWA negative			
All-cause	1.36 (0.62–3.00)	0.85 (0.33–2.20)	0.73
Arrhythmic	1.06 (0.28–3.98)	0.94 (0.21–4.24)	0.93
Nonarrhythmic	1.56 (0.58–4.28)	1.32 (0.41–4.29)	0.64
All-cause + shocks	1.89 (0.92–3.88)	1.15 (0.48–2.77)	0.76

Univariate (unadjusted) and multivariable Cox proportional hazards models adjusted for propensity score and patient covariates for all-cause and cause-specific mortality are depicted. The ICD therapy reduced all-cause mortality through prevention of arrhythmic deaths in the MTWA-non-negative patient group, but showed no benefit in the MTWA-negative group. When a combined end point of all-cause mortality or appropriate ICD shocks was used, there were no differences in baseline exposure risk between the ICD and non-ICD groups for either MTWA group.

CI = confidence interval; other abbreviations as in Table 1.

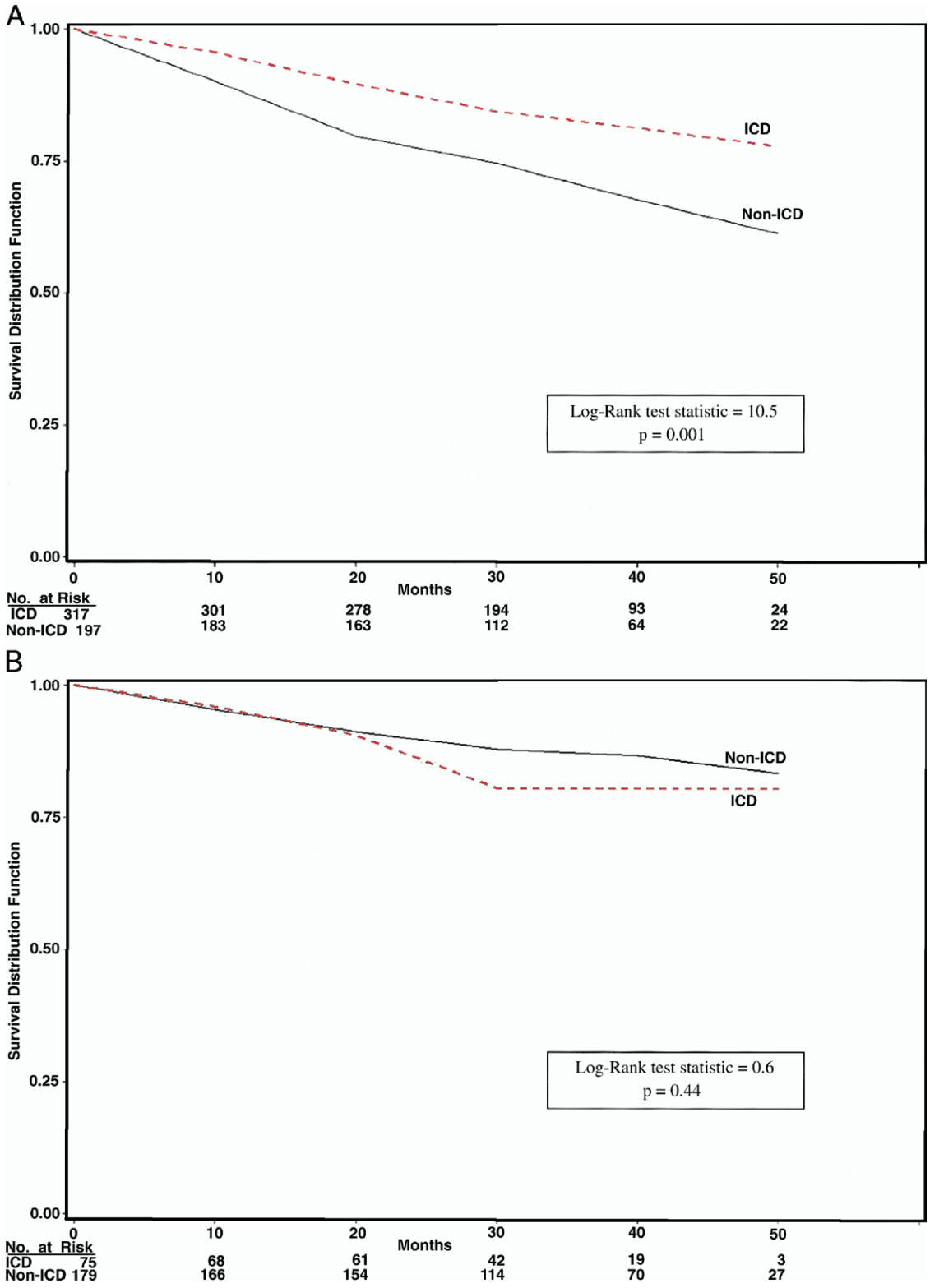

Figure 1 **Kaplan-Meier Curves Comparing Overall Survival Between Patients With and Without ICDs**

Survival curves for all-cause mortality are separately depicted for the microvolt T-wave alternans (MTWA)-non-negative **(A)** and MTWA-negative **(B)** cohorts. Unadjusted results suggest a benefit with implantable cardioverter-defibrillator (ICD) therapy in the MTWA-non-negative cohort only.

Table 5 Logistic Regression Model for Propensity Score Based on Likely Variables Predicting ICD Placement

Variable	Coefficient	Wald Chi-Square	OR (95% CI)	p Value
MTWA non-negative				
Intercept	0.86	10.6	—	0.001
EPS+	1.65	88.6	27.0 (13.5–52.6)	<0.0001
EPS−	0.11	0.8	1.24 (0.77–1.99)	0.38
Holter+	0.05	0.1	1.10 (0.60–1.99)	0.77
QRS >120 ms	1.10	13.2	3.01 (1.66–5.46)	0.0003
MTWA negative				
Intercept	0.99	4.5	—	0.001
EPS+	1.66	39.5	27.8 (9.8–76.9)	<0.0001
EPS−	0.28	1.1	1.75 (0.62–4.95)	0.29
Holter+	0.89	6.9	5.95 (1.57–22.73)	0.009
QRS >120 ms	0.64	0.2	1.89 (0.75–4.79)	0.18

A propensity score was derived using the variables most likely to predict ICD receipt in the cohort: electrophysiologic study (EPS), abnormal Holter result, and QRS duration >120 ms on electrocardiogram. Because not every patient underwent an EPS in the cohort, 2 dummy variables were created to reflect 3 levels of testing: no test (reference), a positive test, and a negative test. The final propensity score model for the MTWA non-negative and negative cohorts had C-statistics of 0.808 and 0.783, respectively, suggesting very good discrimination.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

ing a 55% all-cause mortality risk reduction mediated largely through prevention of arrhythmic deaths. In contrast, patients who tested MTWA negative received no substantial mortality benefit. Although prior studies have shown that patients with ischemic cardiomyopathy testing MTWA non-negative have higher mortality risks (9,10,12), no studies to date have shown that actual ICD benefit differs by MTWA subgroup in either this or other high-risk populations. It has been suggested that the true prognostic utility of MTWA will remain unclear until ICD benefit is evaluated by MTWA status (11). We found that MTWA may effectively risk stratify patients with ischemic cardiomyopathy by identifying test subgroups receiving substantial and minimal benefit with ICD therapy.

A particular strength of our study was our ability to show that the mortality reduction seen with ICD therapy in patients testing MTWA non-negative was mediated through prevention of arrhythmic deaths. The 70% arrhythmic mortality reduction attributed to ICD therapy in our study is similar to the 62% rate found from post hoc analyses of the MADIT-II study (1). Adding further validity to our findings, we were able to show in our sensitivity analysis that ICD and non-ICD patients in each MTWA group were exposed to similar combined mortality and SCD rates, suggesting that our propensity score analyses successfully matched patients with similar baseline risk for sudden cardiac death in each MTWA group.

Adequate control of potential confounders is critical in cohort studies, especially when differences in patient disease severity exist. In this study, patients with ICDs in both MTWA groups were found to have lower LVEF and higher frequencies of EPS testing and EPS inducibility, which have been shown to be prognostic indicators of higher risk for SCD. Although ICD patients in the MTWA-non-negative group also had higher utilization rates for beta-blockers, statins, and digoxin, none of these medications significantly predicted all-cause mortality in the final Cox model (not shown). The good discrimination found with our propensity score models for both MTWA groups (C-statistic of 0.81 and 0.78 for MTWA-non-negative and -negative patients, respectively) suggests that we successfully modeled a patient's likelihood to receive an ICD and were therefore able to adequately compare ICD and non-ICD patients with similar propensities in our study cohort. Our ability to show that ICD and non-ICD patients in each MTWA group were exposed to similar baseline combined mortality and sudden cardiac death event rates also strongly supports this finding.

Although no significant differences were seen with ICD therapy in the MTWA-negative group, our study may not have been adequately powered to detect a statistically significant difference in this cohort. Prior studies have repeatedly shown that patients who test MTWA negative have much lower arrhythmic event rates (9,10,12), and a larger study may have found a significant although less robust benefit with ICD therapy in the MTWA-negative group. For instance, to have 80% power to detect an absolute annual mortality risk reduction of 1.5% (<50% that seen in the MADIT-II study) at a 2-sided significance level of 0.05, a sample size of 278 MTWA-negative patients with the same accrual and follow-up periods would have been needed. However, such a larger study of MTWA-negative patients is unlikely to yield an absolute risk reduction that will ultimately prove cost effective, given that these patients have dramatically lower baseline all-cause and arrhythmic mortality risks than MTWA-non-negative patients. Indeed, based on Kaplan-Meier survival estimates for all-cause mortality in the non-ICD cohort (annualized rate of 8%), a 33% MTWA-negative screen rate, an adjusted hazard ratio of 2.24 for mortality comparing those testing MTWA non-negative versus negative (12), and the current hazard ratios of 0.45 (MTWA-non-negative patients) and

0.85 (MTWA-negative patients), the number needed to treat for 2 years with an ICD to save 1 life would be 9 among MTWA-non-negative patients and 76 among MTWA-negative patients (Appendix).

The ICDs have been shown to be modestly cost effective at approximately $57,000 per quality-adjusted life-year in patients with ischemic heart disease and left ventricular dysfunction (20). It has been estimated that 32,000 patients are newly eligible by the MADIT-II study criteria annually (20). This recent cost-effectiveness study showed that ICD therapy (compared with medical therapy) is associated with an incremental lifetime cost of approximately $90,000 for each patient. Thus, full implementation of the recent CMS decision to expand indications for ICD coverage would translate into an incremental annual cost of $2.9 billion (beyond best medical therapy) just to cover all the MADIT-II eligible patients for life—a cost likely to be prohibitive for an increasingly resource-strained U.S. health care system. Indeed, a recent cost-effectiveness analysis for ICD placement in the MADIT-II study population found the current CMS strategy of making ICDs available to all eligible patients was not cost effective compared with a strategy of implanting ICDs only among those testing MTWA non-negative (21). In that study, ICDs were modeled to reduce arrhythmic mortality by 62%, regardless of MTWA status. If the rates of ICD efficacy from this study had been modeled instead, the current CMS strategy would have been even less cost effective relative to a more discriminate strategy of only implanting ICDs in the higher-risk MTWA-non-negative group (Chan et al., personal communication, February 2006).

Clearly, cost-effective therapies may remain cost-unaffordable to society if the cost of the intervention is high and the disease burden is great. As such, the benefits of ICD therapy need to be weighed against the potential for adverse events (22), and recent recalls of defective ICDs are a reminder that the diffusion of efficacious therapies outside of clinical trial settings are not without obstacles. Moreover, some studies have suggested that ICD therapy may even decrease quality of life (23,24). Therefore, the challenge for policymakers and clinicians alike is to find effective risk stratification strategies that further define which patients are most and least likely to benefit from ICD therapy. Ideally, such a strategy would identify patients who receive little to no benefit, thereby making the intervention more cost effective when implemented and allowing society to lower costs without sacrificing life. Our findings suggest that MTWA indeed may identify such a low-risk subgroup, with as many as one-third of patients deriving minimal benefit from prophylactic ICD implantation. Given this, 1 potential option for patients screening MTWA negative is to rescreen annually, although data on the conversion rate from MTWA-negative to MTWA-non-negative status, as well as the prognostic utility for such conversion, is lacking.

Our study had several limitations. As in all cohort studies, there exists the potential for residual confounding despite our efforts to adjust for differences between the ICD and non-ICD groups. We did not have information on certain covariates (such as laboratory values) that could have affected our findings. However, the use of propensity scores with good model discrimination is a particular strength of our study. Our cohort was composed of outpatients from 1 region of the country. As such, our findings would not apply to patients with acutely decompensated heart failure, and differences in practice patterns or patient risk geographically may limit the generalizability of our results. Our study cohort included only patients with ischemic heart disease, and therefore does not apply to patients with nonischemic cardiomyopathy, who are also eligible for prophylactic ICD implantation. Although we equated appropriate ICD shocks with mortality as part of our sensitivity analysis, we caution that these are not equivalent end points. Therefore, our analyses with this combined end point should be interpreted as a sensitivity analysis only. Microvolt T-wave alternans can be performed only in patients in sinus rhythm, so our findings cannot be extrapolated to the 8% to 15% of trial patients with ischemic cardiomyopathy in atrial fibrillation or flutter (2,3). Finally, our examination of whether ICD benefit differs by MTWA group was justified by a test for interaction that was significant with a prespecified p value of 0.10. However, we caution that our findings should not be overinterpreted as justification for using MTWA screening for ICD placement without subsequent validation in larger cohort studies or future randomized clinical trials, in which ICD benefit can conclusively be shown to differ by MTWA status and potential residual confounding can be minimized.

Conclusions. In patients with ischemic cardiomyopathy, ICDs were associated with lower all-cause and arrhythmic rates of mortality in patients testing MTWA non-negative but not in patients testing MTWA negative. Our findings suggest that MTWA may be an effective risk stratification tool in identifying patients most and least likely to benefit from ICD therapy, with potential policy implications for ICD coverage.

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APPENDIX

For the alternative multivariable Cox regression analyses, rates for ICD implantation in the MTWA groups, and the number needed to treat to save 1 life, please see the online version of this article.

Microvolt T-Wave Alternans Identifies Patients With Ischemic Cardiomyopathy Who Benefit From Implantable Cardioverter-Defibrillator Therapy

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