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Letter to the Editor

Clinical use of microvolt T-wave alternans in patients with depressed left ventricular function eligible for ICD implantation: mortality outcomes after long term follow-up ☆

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Letter to the editor

Implantable cardioverter-defibrillators (ICDs) reduce mortality in patients with left ventricular dysfunction. However, left ventricular dysfunction alone has significant limitations as a risk stratifier for guiding ICD therapy [1,2]. In the SCD-HeFT trial [3], the ICD-mediated reduction in absolute mortality was 1.4% per year (7.2% over 5 years) indicating that only a very small fraction of patients with ICDs actually receive life saving therapy from the devices. Moreover, ICD implantation [4] is associated with a high rate of subsequent complications such as infections, inappropriate shocks, lead and generator failures and recalls. Consequently there is a need to more accurately identify those individuals who will benefit from ICD implantation.

Microvolt T-wave alternans (MTWA) has been linked mechanistically to the development of ventricular tachyarrhythmias [5] and is a clinical marker of increased risk of sudden cardiac death (SCD) [6–8]. Conversely, patients with a negative MTWA test have a very low risk of SCD [8].

In our department we routinely measure MTWA in patients without a history of cardiac arrest being considered for prophylactic ICD implantation [9] and the result is a major determinant of the decision of whether or not to implant an ICD. From 2001 to March 2011 MTWA tests were performed on 178 consecutive patients with ischemic and non-ischemic cardiomyopathy who were eligible for ICD implantation according to clinical guidelines in place at the time of evaluation. Patients with a normal test were offered the option to not receive an ICD. We conducted long-term follow-up of these patients. The primary endpoint was defined as all-cause mortality and the secondary endpoint was defined as cardiac mortality.

Table 1
Baseline characteristics according to MTWA testing.

	Overall population (n = 178)	Abnormal MTWA (n = 129)	Normal MTWA (n = 49)	p-value
Gender (male)	145 (81%)	104 (81%)	41 (84%)	0.829*
Age (yrs)	69(10)	70 (10)	68 (10)	0.127°
BMI(kg/m^2)	26 (06)	26 (6)	27 (4)	0.557°
NYHA functional class				0.007*
II	122 (69%)	81 (63%)	41 (84%)	
III	56 (31%)	48 (37%)	8 (16%)	
Ischemic cardiomyopathy	63 (35%)	40 (31%)	23 (47%)	0.065^
Myocardial infarction	45 (25%)	28 (22%)	17 (35%)	0.075^
Cardiovascular intervention				
PTCA	33 (19%)	22 (17%)	11 (22%)	0.408^
Stent	20 (11%)	12 (9%)	8 (16%)	0.185^
Bypass	8 (4%)	5 (4%)	3 (6%)	0.686*
Valvular surgery	3 (2%)	3 (2%)	0 (0%)	1.000*
QRS (ms)	139 (33)	142 (34)	129 (29)	0.029°
LVEF (%)	30 (6)	30 (7)	32 (6)	0.044°
LVEDD (mm)	70 (14)	69 (7)	70 (24)	0.057°
LVESD (mm)	53 (12)	54 (9)	51 (19)	0.010°
LVEDV (ml)	190 (60)	199 (62)	160 (40)	0.005°
LVESV (ml)	134 (47)	141 (49)	112 (32)	0.006°
Treatment				
ACE inhibitors	159 (89%)	123 (95%)	36 (73%)	0.0001*
Beta-blockers	125 (70%)	93 (72%)	32 (65%)	0.4631*
Digitalis	39 (22%)	35 (27%)	4 (8%)	0.0075*
Diuretics	123 (69%)	100 (78%)	23 (47%)	0.0020*
Aldosterone antagonists	87 (49%)	71 (55%)	16 (33%)	0.0140*
MTWA results				
Negative	49 (28%)	–	49 (100%)	–
Positive	107 (60%)	107 (83%)	–	–
Indeterminate	22 (12%)	22 (17%)	–	–
Implanted ICD	118 (66%)	103 (80%)	15 (31%)	<0.001^

Values in parentheses represent standard deviations for continuous variables or percentages for discrete variables. ACE = angiotensin-converting enzyme; BMI = body mass index; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; MTWA = T-wave alternans; * Fisher's Exact test; ^ Chi-square test; ° Wilcoxon non-parametric test.

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Table 2
Multivariate Cox regression.

Covariate	HR	95% CI	p-value
MTWA	3.65	1.08–12.30	0.037
LVEF	1.00	0.95–1.05	0.913
NYHA	1.14	0.50–2.58	0.759
QRS	1.00	0.99–1.02	0.581

HR = hazard ratio; CI = confidence interval

Patients underwent an MTWA exercise bicycle testing that was interpreted both automatically within the HearTwave system and by two expert readers. Because patients with positive and indeterminate MTWA tests results display elevated event rates [8], all comparisons in this analysis were made between patients with normal (negative) and abnormal (positive or indeterminate) MTWA tests.

The baseline characteristics of the 178 patients are listed in Table 1. All participants were in New York Heart Association functional class II or III and had left ventricular ejection fraction ≤ 40% (mean 30 ± 6). The MTWA abnormal patients compared to the MTWA normal patients, on a statistically univariate basis, had higher NYHA class, wider QRS, and lower LVEF. MTWA was abnormal in 129 (72%) and normal in 49 patients (28%). Substantially fewer patients (15/49, 31%) in the MTWA normal group received an ICD than did patients in the MTWA abnormal group (103/129, 80%), $p = 0.0001$.

During the follow-up (median 64 months) a total of 35 deaths occurred. In the MTWA normal group 4 patients died – all of non-cardiac cause; in the MTWA abnormal group 31 deaths occurred and were classified as follows: 20 cardiac deaths, 7 non-cardiac and 4 unknown.

With respect to the primary end-point (all-cause mortality), the MTWA normal group had an annual event rate of 0.015 per year of follow-up versus a rate of 0.049 for the MTWA abnormal group ($p = 0.018$). With respect to the secondary end-point (cardiac death), the MTWA normal group had an annual event rate of 0.000 per year of follow-up versus a rate of 0.031 for the MTWA abnormal group ($p = 0.001$). A multivariate Cox regression analysis of these parameters (Table 2) found that MTWA was the only parameter predictive of the primary endpoint ($p = 0.037$).

Fig. 1 shows Kaplan–Meier plots illustrating the accrual of all-cause mortality events. Event-free survival for the MTWA normal group was significantly higher than for the MTWA abnormal group (log-rank test: $p = 0.020$). Fig. 2 shows Kaplan–Meier plots illustrating the accrual of cardiac mortality events. Event-free survival for the MTWA normal group was significantly higher than for the MTWA abnormal group (log-rank test: $p = 0.004$).

To specifically examine the impact of not implanting ICDs in MTWA normal patients versus implanting ICDs in MTWA abnormal patients, we performed a subgroup analysis comparing MTWA normal patients who did not have ICDs implanted (34 patients) versus MTWA abnormal patients who did receive implants (103 patients). With respect to the primary end-point (all-cause mortality), the MTWA-normal no-ICD group had an annual event rate of 0.013 per year of follow-up versus a rate of 0.048 for the MTWA-abnormal ICD group ($p = 0.020$). With respect to the secondary end-point (cardiac death), the MTWA-normal no-ICD group had an annual event rate of 0.000 per year of follow-up versus a rate of 0.034 for the MTWA-abnormal ICD group ($p = 0.004$).

We believe that this paper provides strong data on long-term mortality outcomes in patients, eligible for prophylactic ICD implantation, for whom MTWA testing was used prospectively in making the decision of whether or not to implant an ICD. Despite the fact that the ICD implantation rate was 2.6 times lower in the MTWA normal group compared to the MTWA abnormal group, both all-cause mortality and cardiac mortality rates were substantially lower in the MTWA normal group than in the MTWA abnormal group. Multivariate analysis revealed that the difference in all-cause mortality rates was associated only with the difference in MTWA test results and not with differences in other baseline clinical variables. Furthermore, subgroup analysis revealed that both all-cause mortality and cardiac mortality rates were also substantially lower among MTWA normal patients who did not receive an ICD versus MTWA abnormal patients who did receive an ICD. Our data shows that an inexpensive non-invasive MTWA test can

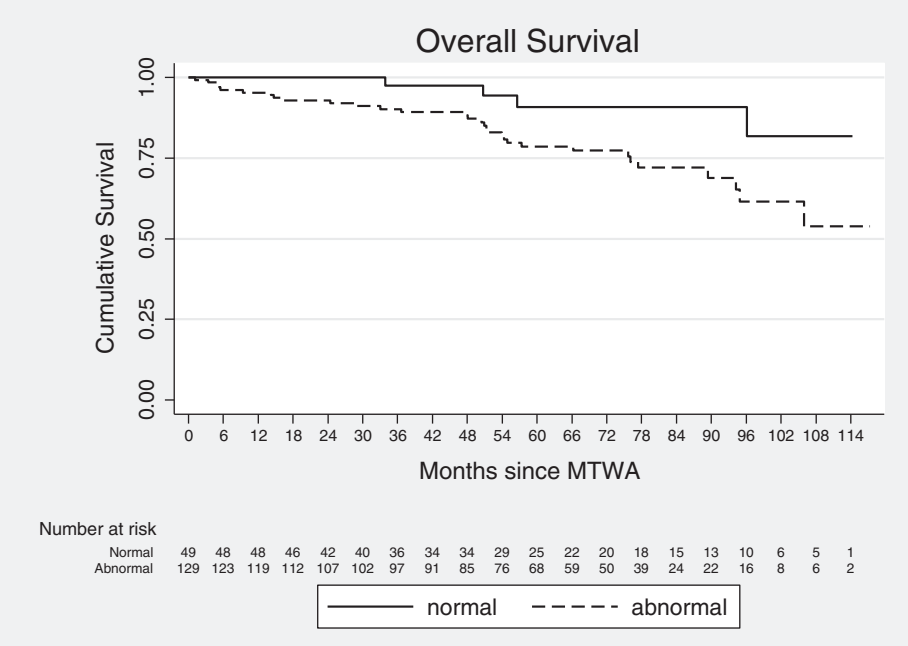

Fig. 1. Event-Free Survival - All Cause Mortality. Kaplan–Meier plots illustrating the accrual of all-cause mortality (primary end-point) events. Event-free survival for the MTWA normal group was significantly higher than for the MTWA abnormal group (log-rank test: $p = 0.020$).

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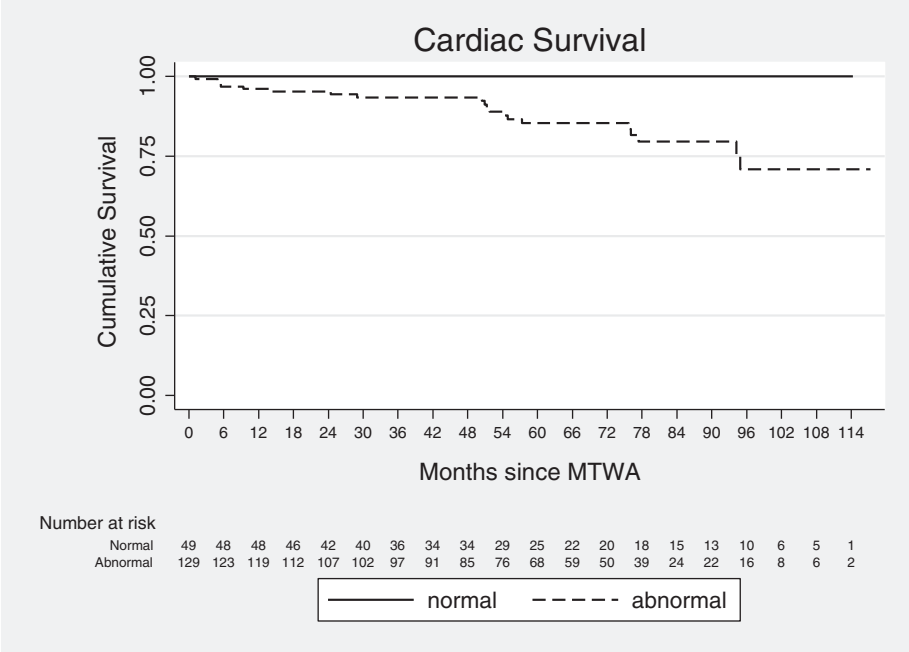

Fig. 2. Event-Free Survival – Cardiac Mortality. Kaplan–Meier plots illustrating the accrual of cardiac mortality (secondary end-point) events. Event-free survival for the MTWA normal group was significantly higher than for the MTWA abnormal group (log-rank test: $p = 0.004$).

be used to identify low-risk patients who are unlikely to benefit from ICD therapy and can avoid being exposed to the risks of this treatment. Our study indicates that use of MTWA testing in guiding ICD decision-making is both safe and effective.

Not implanting an ICD in an MTWA normal patient could reduce cost to the health care system, eliminate the morbidity and mortality associated with ICD implantation and is associated with substantially lower all-cause and cardiac mortality rates than those observed in patients with an abnormal MTWA test result who do receive an ICD.

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