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Prospective Use of Microvolt T-Wave Alternans Testing to Guide Primary Prevention Implantable Cardioverter Defibrillator Therapy

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Background: We hypothesized that a negative microvolt T-wave alternans (MTWA) test would identify patients unlikely to benefit from primary prevention implantable cardioverter defibrillator (ICD) therapy in a prospective cohort.

Methods and Results: Data were pooled from 8 centers where MTWA testing was performed specifically for the purpose of guiding primary prevention ICD implantation. Cohorts were included if the ratio of ICDs implanted in patients who were MTWA "non-negative" to patients who were MTWA negative was >2:1, indicating that MTWA testing had a significant impact on the decision to implant an ICD. The pooled cohort included 651 patients: 371 MTWA non-negative and 280 MTWA negative. Among non-negative patients, 62% underwent ICD implantation whereas only 13% of MTWA-negative patients received an ICD (P<0.01). Despite a substantially lower prevalence of ICDs, long-term survival (6.9 years) was significantly better among MTWA-negative patients (68.2% non-negative vs. 87.1% negative, P=0.026).

Conclusions: MTWA-negative patients had significantly better survival than MTWA non-negative patients, the majority of whom had ICDs. Despite a very low prevalence of ICDs, long-term survival among patients with left ventricular ejection fraction ≤40% and a negative MTWA test was better than in the ICD arm of any study to date that has demonstrated a benefit of ICDs. This provides further evidence that MTWA-negative patients are unlikely to benefit from primary prevention ICD therapy. (*Circ J* 2015; **79:** 1912–1919)

Key Words: Implantable cardioverter defibrillator; Microvolt T wave alternans; Primary prevention; Risk stratification; Sudden cardiac death

Implantable cardioverter defibrillator (ICD) therapy reduces all-cause and arrhythmia-specific mortality in patients with left ventricular ejection fraction (LVEF) ≤35% but without a history of documented sustained ventricular tachyarrhythmia (primary prevention ICD therapy).[1,2] A number of studies, however, have found that only a small percentage of patients undergoing primary prevention ICD implantation actually receive appropriate device therapy during long-term follow-up.[3–6] Additionally, ICD implantation is itself associated with morbidity and mortality risk,[7] and thus should be avoided in patients unlikely to benefit from such therapy. Microvolt T-wave alternans (MTWA) testing using the spectral method

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Table 1. Baseline Characteristics vs. MTWA Status

	MTWA		P-value
	Non-negative (n=371)	Negative (n=280)	
Age (years)	63.1±11.4 (65, 28–81)	61.8±10.7 (63, 41–86)	0.05
Gender (male)	316 (85)	231 (83)	0.39
LVEF (%)	30.6±6.7 (30, 11–60)	33.2±5.8 (35, 18–60)	<0.01
Coronary artery disease	208 (56)	195 (70)	<0.01
ICD	231 (62)	37 (13)	<0.01
Medical therapy			
β-blockers	296 (80)	219 (78)	0.63
ACEI/ARB	310 (84)	228 (81)	0.53
Diuretics	286 (77)	163 (58)	<0.01
MTWA positive	257 (69)		
MTWA indeterminate	114 (31)		

Data given as mean±SD (median, range) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MTWA, microvolt T-wave alternans.

has emerged as an important predictor of ventricular tachyarrhythmic events (VTE) and sudden cardiac death (SCD) in at-risk populations. Numerous studies conducted in patients with both ischemic and non-ischemic cardiomyopathy have demonstrated that MTWA-negative patients have a very low risk of VTE/SCD during follow-up.[8–12] These data suggest that the risk of SCD among patients with negative MTWA tests may be so low that they are unlikely to benefit from an ICD. Furthermore, in a prospective study of patients with LVEF ≤35%, ICD therapy reduced annual mortality by approximately 50% among patients with a non-negative MTWA test and provided no benefit among those with a negative test.[9]

We sought to further assess the utility of MTWA testing in identifying patients at such low risk of death that they are unlikely to benefit from primary prevention ICDs. In order to achieve this objective, we analyzed data from a large, real-world cohort of patients pooled from centers where MTWA testing was performed specifically for guiding the decision about primary prevention ICD implantation.

Methods

Patient-level data were gathered from 10 European and Japanese centers where MTWA testing was performed specifically for the purpose of making decisions regarding primary prevention ICD implantation. Eligible patients included those with LVEF ≤40% and no documented history of ventricular arrhythmias. Centers were included in the pooled analysis if the ratio of ICDs implanted in patients who were MTWA non-negative (ie, positive or indeterminate) to patients who were MTWA negative was >2:1, suggesting that MTWA testing had a significant impact on the decision to implant an ICD. Although MTWA testing was performed at each of these centers for the purpose of making decisions regarding primary prevention ICD implantation, the ultimate decision to implant or not implant an ICD in any given patient was left to the discretion of the treating physician.

From the original 10 cohorts, 2 cohorts consisting of a total of 167 patients were excluded because the ratio of ICDs implanted in MTWA-non-negative to -negative patients was not >2:1 at those centers. Patients from the remaining 8 cohorts were pooled to form the final study cohort for this analysis.

This study complied with the Declaration of Helsinki. Of the original 10 participating centers, 4 centers collected data as part of a study protocol with informed patient consent approved by the Institutional Review Board (IRB) at the authors' institution. At the remaining 6 centers, data were collected as part of usual clinical care. Patients included in this analysis were recruited beginning on 4 May 2001, and follow-up finished on 28 December 2012.

MTWA Testing

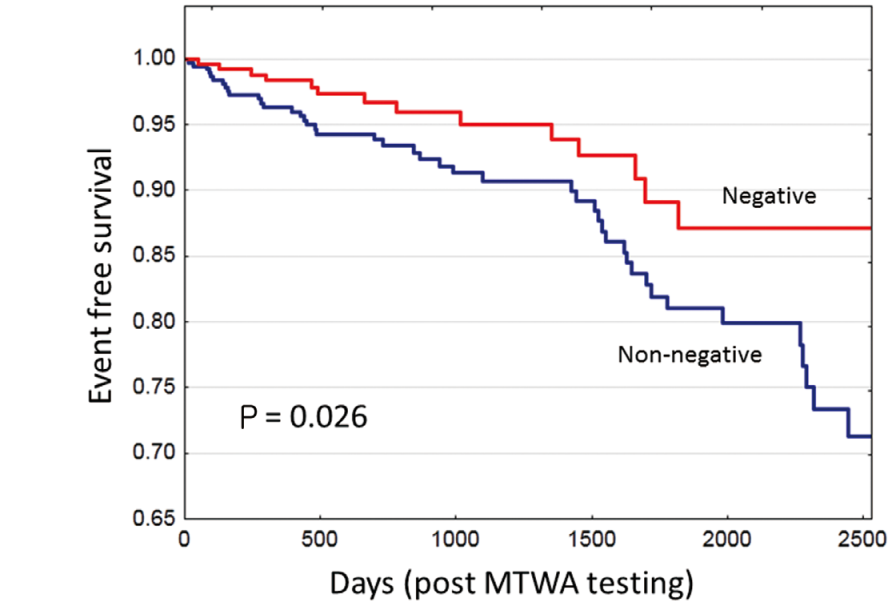
All centers utilized MTWA testing with the spectral method[13] (Cambridge Heart, Bedford, MA, USA) and the results of each MTWA test (positive, negative or indeterminate) were classified by the investigators at each center based on established criteria.[14] In brief, MTWA test was classified as positive for sustained alternans >1.9 μV for at least 1 min with alternans ratio (k score) >3.0 with onset heart rate (HR) <110 beats/min. The test was classified as negative if criteria for positive were not met in an artifact-free period of data collection with HR ≥105 beats/min for at least 1 min. All remaining tests not meeting criteria for either positive or negative were classified as indeterminate. The investigators all had the results of the Cambridge Heart automated MTWA test classifier available to them.

Endpoints

The primary endpoint for this study was all-cause mortality and the secondary endpoint was cardiac death. In order to assess long-term survival, the duration of follow-up for the primary and secondary endpoints was extended until the last time point at which there were at least 10 patients surviving in each arm who were free from the endpoint and still being followed. All events after that time point were censored. All endpoints were adjudicated by the investigators at each center.

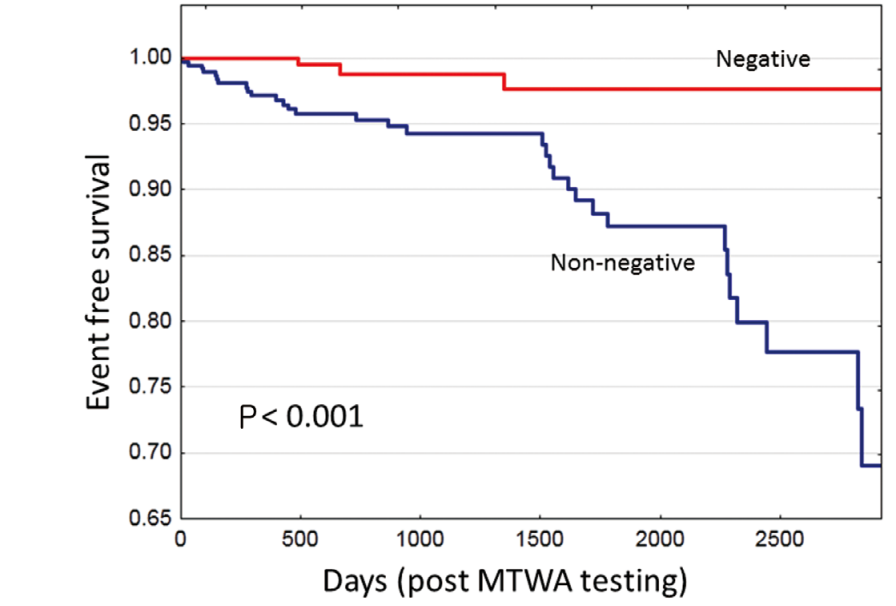
Statistical Analysis

The time course of the primary and secondary endpoints, stratified by MTWA result and ICD status, was estimated using Kaplan-Meier time-to-first-event curves. The association between MTWA test result, ICD status and the primary and secondary endpoints was assessed using Kaplan-Meier product-limit estimates and tested with the log-rank test. Cox proportional hazards models were used to identify correlates of all-cause mortality and cardiac death and to correct for pos-



Days	0	1260	2520
Non-negative	371	149	18
Negative	280	100	10

Figure 1. All-cause mortality-free survival. Despite a significantly lower percentage of implantable cardioverter defibrillators, survival was significantly better in the microvolt T-wave alternans (MTWA)-negative cohort compared with the MTWA-non-negative group.



Days	0	1460	2920
Non-negative	371	132	15
Negative	280	84	10

Figure 2. Cardiac death-free survival. Despite a significantly lower percentage of implantable cardioverter defibrillators, cardiac death-free survival was significantly better in the microvolt T-wave alternans (MTWA)-negative cohort than in the MTWA-non-negative group.

Table 2. All-Cause Mortality and Cardiac Death Event Rates vs. MTWA and ICD Status

	MTWA non-negative (n=371)			MTWA negative (n=280)				
	ICD (n=231)	No ICD (n=140)	P-value	ICD (n=37)	No ICD (n=243)	P-value	P-value†	P-value‡
24 months								
All-cause mortality	5.2	7.9	0.34	5.7	3.1	0.29	0.20	0.03
Cardiac death	4.2	4.0	0.94	0	1.5	0.49	0.05	0.06
60 months								
All-cause mortality	18.8	19.7	0.73	12.7	13.1	0.82	0.14	0.08
Cardiac death	13.4	10.7	0.70	0	3.0	0.34	0.01	0.03
Long-term follow-up								
All-cause mortality (83.0 months)	33.2	24.1	0.91	13.0	13.4	0.82	0.06	0.05
Cardiac death (96.8 months)	41.4	11.3	0.26	0	2.9	0.34	<0.01	0.03

†Non-negative with ICDs vs. negative without ICDs; ‡non-negative without ICDs vs. negative without ICDs. Abbreviations as in Table 1.

sible confounders. Variables of interest included in the model were age, gender, LVEF, New York Heart Association (NYHA) class, presence of coronary artery disease (CAD), use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and diuretics, MTWA status and presence of an ICD. Age, LVEF and NYHA class were modeled as continuous variables. Variables with P≤0.1 on univariate analysis were included in the multivariate models.

Continuous variables are presented as mean±SD and categorical data as frequencies and percentages. Comparisons across groups were performed using the chi-squared test of independence or T-test, as appropriate. For all comparisons, P<0.05 was considered to be statistically significant. Analysis was performed using STATISTICA (Statsoft, Tulsa, OK, USA).

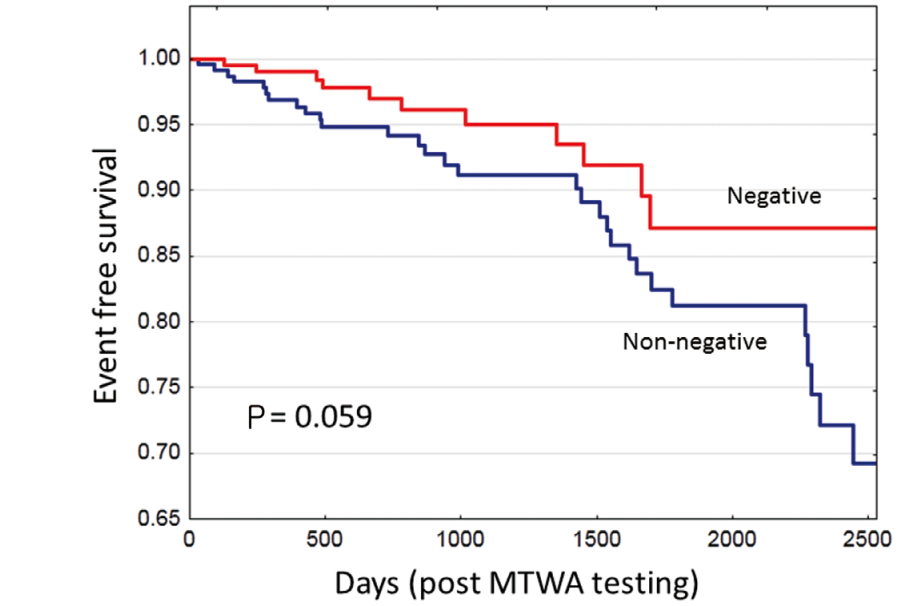
Results

The final study cohort included 651 patients pooled from 8 centers. MTWA testing was positive in 257 patients, indeterminate in 114 and negative in 280. The baseline characteristics of the final pooled cohort, stratified by MTWA test result, are presented in Table 1. At baseline, non-negative patients were slightly older (63.1±11.4 vs. 61.8±10.7 years, P=0.05), had a lower LVEF (30.6±6.7 vs. 33.2±5.8%, P<0.01) and were less likely to have an ischemic substrate (56 vs. 70%, P<0.01). Among non-negative patients, 62% underwent ICD implantation, whereas only 13% of MTWA-negative patients were implanted with an ICD (P<0.01). For patients who underwent ICD implantation, the mean time between MTWA testing and implantation was 2.7±1.5 months.

Despite a substantially higher percentage of ICDs among non-negative patients, the primary endpoint of survival free of all-cause mortality during long-term follow-up (6.9 years) was significantly better among MTWA-negative patients (68.2% in non-negative vs. 87.1% in negative patients, P=0.026; Figure 1). Survival free of all-cause mortality was also numerically better among patients with negative MTWA tests at 24 months (93.9% in MTWA non-negative vs. 96.6% in MTWA negative, P=0.108) and 60 months (80.9% in MTWA non-negative vs. 87.1% in MTWA negative, P=0.070), although the results did not reach statistical significance at these earlier time points. The secondary endpoint of cardiac death-free survival during long-term follow-up (8.0 years) was also significantly better among MTWA-negative patients (69.0% in MTWA non-negative vs. 97.3% in MTWA negative, P<0.001), despite the significantly lower percentage of ICDs (Figure 2). Survival free of cardiac death was also significantly better among MTWA-negative patients at 24 months (95.8% in MTWA non-negative vs. 98.7% in MTWA negative, P=0.020) and 60 months (87.4% in MTWA non-negative vs. 97.6% in MTWA negative, P=0.002).

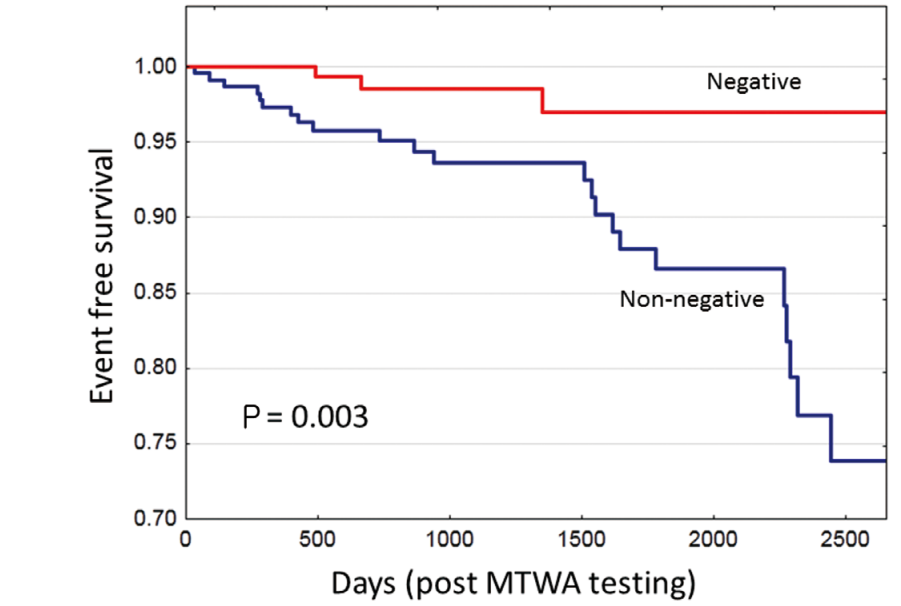
The event rates for the primary and secondary endpoints, stratified by MTWA and ICD status, are presented in Table 2. During long-term follow-up (6.9 years), there was a trend toward better survival free of all-cause mortality among patients with a negative MTWA test without ICDs (86.6%) compared with patients with a non-negative MTWA test with ICDs (68.8%, P=0.059; Figure 3). Cardiac death-free survival during long-term follow-up (8.0 years) was significantly better among patients with negative MTWA tests without ICDs (97.1%) compared with patients with non-negative MTWA tests with ICDs (58.6%, P=0.003; Figure 4). Cardiac death-free survival in negative MTWA patients without ICDs was also significantly better than in non-negative MTWA patients with ICDs at both 24 and 60 months (Table 2). Likely due to limited statistical power in sub-groups, there was no significant difference in all-cause or cardiac death-free survival at any of the time points tested in either the MTWA-non-negative or -negative groups when stratified by ICD status (Table 2). Among patients without ICDs, survival free of cardiac death was significantly better in the MTWA-negative cohort than the non-negative cohort at both 60 months and 8 years (Table 2). Overall survival among MTWA-negative patients without ICDs was also significantly better than for non-negative patients without ICDs at both 24 months and 6.9 years, with a strong trend toward better survival at the 60-month time point.

Subgroup analysis was done by stratifying the cohort on the basis of LVEF into 2 groups: LVEF ≤35% (n=481) and 36–40% (n=170). Among those with LVEF ≤35%, there was a trend toward better survival among those who were MTWA negative at both 24 months (MTWA non-negative 94.2% vs. MTWA negative 97.7%, P=0.08) and during long-term follow-up at 6.9 years (71.4% vs. 88.4%, P=0.06). Survival free of cardiac death in the LVEF ≤35% subgroup was significantly better among MTWA-negative patients at all time points assessed, despite the lower percentage of ICDs: 24 months, 95.7% vs. 98.9% (P=0.05); 60 months, 90.1% vs. 98.9% (P=0.01); and 8.0 years, 67.4% vs. 98.8% (P<0.01). In the LVEF 36–40% subgroup, there was a trend toward better survival among those patients who were MTWA negative at 24 months (90.0% vs. 97.6%, P=0.09), which became significant at 60 months (70.3% vs. 91.1%, P=0.02) and at 6.9 years (63.6% vs. 90.8%, P=0.01).



Days	0	1260	2520
Non-negative	231	104	18
Negative	243	79	10

Figure 3. All-cause mortality-free survival in the microvolt T-wave alternans (MTWA)-non-negative cohort with implantable cardioverter defibrillators (ICD) compared with the MTWA-negative cohort without ICDs. There is a trend toward better survival among MTWA-negative patients without ICDs compared with the MTWA-non-negative patients with ICDs.



Days	0	1460	2920
Non-negative	231	84	15
Negative	243	55	10

Figure 4. Cardiac death-free survival in the microvolt T-wave alternans (MTWA)-non-negative cohort with implantable cardioverter defibrillators (ICD) compared with the MTWA-negative cohort without ICDs. Cardiac death-free survival is significantly better in MTWA-negative patients without ICDs compared with MTWA-non-negative patients with ICDs.

Table 3. Predictors of 24-Month Mortality and Cardiac Death

	Univariate		Multivariate	
	HR	P-value	HR	P-value
Predictors of 24-month mortality				
Age	1.04 (1.00–1.07)	0.02	1.03 (0.99–1.07)	0.08
Male	5.11 (0.69–37.72)	0.11		
LVEF	0.95 (0.89–1.00)	0.07	0.95 (0.89–1.01)	0.09
NYHA class	1.14 (0.65–2.01)	0.65		
Coronary artery disease	2.14 (0.86–5.33)	0.10	2.13 (0.85–5.36)	0.11
β-blockers	0.36 (0.17–0.79)	0.01	0.41 (0.19–0.90)	0.03
ACEI/ARB	1.51 (0.45–5.02)	0.50		
Diuretics	1.84 (0.69–4.88)	0.22		
MTWA non-negative	2.95 (1.11–7.82)	0.03	2.71 (1.00–7.33)	0.05
Presence of an ICD	1.44 (0.67–3.13)	0.35		
Predictors of 24-month cardiac death				
Age	1.04 (1.00–1.08)	0.05	1.04 (1.00–1.09)	0.03
Male	3.12 (0.74–11.16)	0.99		
LVEF	0.89 (0.83–0.96)	<0.01	0.90 (0.84–0.97)	<0.01
NYHA class	1.35 (0.67–2.74)	0.41		
Coronary artery disease	2.79 (0.79–9.78)	0.11		
β-blockers	0.44 (0.16–1.23)	0.12		
ACEI/ARB	1.38 (0.31–6.06)	0.67		
Diuretics	3.06 (0.69–13.47)	0.14		
MTWA non-negative	10.53 (1.39–79.71)	0.02	7.52 (1.01–57.7)	0.05
Presence of an ICD	2.06 (0.75–5.68)	0.16		

NYHA, New York Heart Association. Other abbreviations as in Table 1.

Similar to the LVEF ≤35% subgroup, among those with LVEF 36–40%, survival free of cardiac death was significantly better among those patients who were MTWA negative at all time points assessed: 24 months, 94.1% vs. 0 (P=0.03); 60 months, 80.5% vs. 0 (P<0.01); and 8.0 years, 80.0% vs. 0 (P<0.01). Of note, there were no documented episodes of cardiac death among patients with LVEF 36–40% who were MTWA negative.

In order to determine correlates of overall mortality and cardiac death, we performed multivariate analysis to identify predictors of mortality and cardiac death at 24 months (Table 3). On univariate analysis, increasing age, lower LVEF, presence of CAD and non-negative MTWA status were associated with increased 24-month mortality, whereas use of β-blockers was associated with lower mortality. On multivariate analysis, only MTWA status and β-blocker use were significant predictors of survival at 2 years (Table 3). Predictors of cardiac death at 24 months included older age, lower LVEF and non-negative MTWA status, all 3 of which remained significant on multivariate analysis (Table 3).

Discussion

In this large, real-world cohort, despite a very low percentage of ICDs (13%), patients with LVEF ≤40% and negative MTWA tests had very low rates of all-cause mortality (12.9% at 6.9 years) and cardiac death (2.7% at 8.0 years) during long-term follow-up. These findings highlight the excellent prognosis associated with a negative MTWA test, and suggest that the risk of fatal arrhythmias among MTWA-negative patients may be so low that they are unlikely to benefit from primary prevention ICDs.

MTWA testing has been shown to be a powerful predictor of arrhythmic risk in patients who do not already have an ICD.[3,11] Thus, MTWA testing may serve as a useful tool for predicting which patients may benefit from future ICD therapy. In fact, large prospective studies have shown that MTWA non-negative patients receive a substantial mortality benefit from ICD therapy but MTWA-negative patients receive no benefit.[9,15] One highly consistent finding has been that patients without an implanted ICD who test MTWA negative have a very low rate of arrhythmic events. In a pooled analysis of 2,883 patients without ICDs drawn from multiple studies, patients with LVEF ≤35% and negative MTWA tests had an SCD event rate of only 0.9% per year, suggesting that the risk of VTE/SCD in patients with a negative MTWA test may be too low to benefit from primary prevention ICDs. In this study, the annual cardiac death event rate – which included both sudden and non-sudden deaths – among MTWA-negative patients was also <1% (0.3% at 8 years, 0.7% at 24 months and 0.5% at 60 months). No studies to date have demonstrated a benefit of primary prevention ICD therapy with an annual event rate anywhere near as low as 1%. Furthermore, in multiple studies the mortality rate among patients with a negative MTWA test, who predominantly had not been implanted with ICDs, was approximately 4-fold lower[3] than the mortality rate in similar patients in the ICD arms of the seminal Multicenter Automatic Defibrillator Trial II (MADIT II)[5] and Sudden Cardiac Death in Heart Failure (SCD-HeFT)[4] trials. The data in this study are also consistent with a prior single-center prospective study that utilized MTWA testing for allocation of primary prevention ICD therapy and noted significantly lower rates of all-cause and cardiac mortality among MTWA-negative patients, despite a significantly lower percentage of ICDs.[16] In aggregate, there is a paucity of data to suggest benefit of primary prevention ICD therapy in MTWA-negative patients.

In the present study, despite being implanted with ICDs

nearly 5-fold less frequently, patients with a negative MTWA test had lower rates of all-cause mortality and cardiac death than patients with a positive MTWA test. Although the difference in cardiac death rate was significantly different at all time points surveyed, the difference in survival for all-cause mortality became statistically significant only during long-term follow-up (after 60 months). These findings, however, are consistent with data from randomized clinical trials that demonstrated relatively low annual event rates among primary prevention ICD recipients (approximately 2–5%),[17] suggesting that the benefits of primary prevention ICD therapy take time to accrue. In MADIT II, during the initial phase of the study with a median follow-up of 1.5 years, ICD therapy was associated with an overall survival benefit of only approximately 2 months.[18] During extended follow-up, however, the benefit of ICD therapy continued to accrue over time, resulting in an aggregate 34% relative risk reduction in likelihood of death at 8 years.[18] Similarly, the mortality benefit of ICD therapy also accrued over time in the SCD-HeFT trial, reaching a significant absolute risk reduction of 7.2% at 5 years compared with placebo.[4] Therefore, the present finding that the all-cause mortality difference between MTWA-non-negative and -negative patients became significant only after 60 months is consistent with the time course of benefit of ICD therapy among primary prevention patients. Importantly, the present results remained consistent when the cohort was stratified into subgroups of LVEF ≤35% and LVEF 36–40%.

There is significant impetus to identify patients who are unlikely to benefit from primary prevention ICD implantation. Implantation of ICDs has been associated with an early complication rate of up to 10% and an in-hospital mortality rate of 1% among Medicare beneficiaries,[7] with notable longer-term risks including lead malfunction/recalls and device infection. Perhaps even more importantly, the recently published Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT) study has brought into sharp relief the significant risk of morbidity and mortality associated with inappropriate ICD shocks.[19] In light of these findings, it is particularly important to establish clinical algorithms to identify patients who do not benefit from ICDs and enable them to avoid exposure to the hazards associated with device therapy. Lastly, in recent clinical studies, an average of 39% of patients with LVEF ≤35% tested MTWA negative.[11] Given the burgeoning heart failure epidemic and the rapidly increasing numbers of patients who would be candidates for primary prevention ICD therapy under current criteria,[20] the use of MTWA testing to identify patients who are unlikely to benefit from ICD implantation also has substantial implications for cost containment.[21]

Study Limitations

Several limitations of our study should be noted. First, the centers included in this study were all located in Europe or Japan. In contrast to the USA, where third-party payers generally reimburse for primary prevention ICDs based primarily on LVEF criteria, in other parts of the world, additional metrics are needed to determine which patients will be allocated ICDs. We believe that this provides a unique opportunity to study the impact of MTWA testing on prognosis in a real-world cohort of patients who would all be eligible for ICD implantation under current guidelines. Second, although MTWA testing was performed specifically for the purpose of guiding decisions about ICD implantation, the ultimate decision to implant a device rested with the treating physician. It is conceivable that other clinical variables, beyond LVEF and MTWA, might have affected the decision not to implant an ICD in non-negative patients or to implant an ICD in negative patients, and these other variables may have confounded the present results. Although we cannot rule out such confounding, the primary finding of the present study, that patients with negative MTWA tests, despite a very low percentage of ICDs, have an excellent prognosis, remains notable. Lastly, patients with non-negative MTWA tests had a slightly lower LVEF and were slightly older than MTWA-negative patients. Therefore, the increased event rates, regardless of ICD status, among MTWA-non-negative patients could be regarded as a reflection of older age and worse ventricular function and not necessarily any reflection of MTWA status. The presence of baseline differences in age, LVEF and other clinical variables between MTWA-negative and -non-negative patients has been well documented.[9,11,22] The purpose of the present study, however, was to demonstrate the utility of MTWA testing as a diagnostic test to identify patients with such low risk that they may not benefit from ICDs. Therefore, in as much as MTWA serves as a risk stratification tool, it is entirely conceivable and expected that MTWA-non-negative and -negative patients may differ in baseline covariates and that the MTWA test result essentially serves as a measurable and quantifiable surrogate for those other comorbidities. Furthermore, on multivariate analysis, MTWA status was the only significant predictor of both overall mortality and cardiac death at 24 months.

Conclusions

We present data from a large, real-world cohort of patients with no prior history of sustained ventricular tachyarrhythmia and LVEF ≤40% in whom MTWA testing was prospectively used to guide ICD therapy. MTWA-negative patients, who had a very low rate of ICD implantation, had a significantly lower rate of all-cause mortality and cardiac death during long-term follow-up than MTWA-non-negative patients, the majority of whom received ICDs. The cardiac death rate among patients with a negative MTWA test was substantially lower than in any studies to date that have demonstrated a benefit of primary prevention ICD implantation. The present data suggest that MTWA-negative patients are unlikely to benefit from primary prevention ICD therapy.

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Disclosures

D.M. has served as a consultant to Cambridge Heart. R.J.C. was a consultant and share-owner in Cambridge Heart, which previously manufactured equipment for measuring MTWA but no longer does so. No other conflicts reported.

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