Evidence regarding clinical use of microvolt T-wave alternans

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BACKGROUND Microvolt T-wave alternans (MTWA) testing in many studies has proven to be a highly accurate predictor of ventricular tachyarrhythmic events (VTEs) in patients with risk factors for sudden cardiac death (SCD) but without a prior history of sustained VTEs (primary prevention patients). In some recent studies involving primary prevention patients with prophylactically implanted cardioverter-defibrillators (ICDs), MTWA has not performed as well.

OBJECTIVE This study examined the hypothesis that MTWA is an accurate predictor of VTEs in primary prevention patients without implanted ICDs, but not of appropriate ICD therapy in such patients with implanted ICDs.

METHODS This study identified prospective clinical trials evaluating MTWA measured using the spectral analytic method in primary prevention populations and analyzed studies in which: (1) few patients had implanted ICDs and as a result none or a small fraction (<15%) of the reported end point VTEs were appropriate ICD therapies (low ICD group), or (2) many of the patients had implanted ICDs and the majority of the reported end point VTEs were appropriate ICD therapies (high ICD group).

RESULTS In the low ICD group comprising 3,682 patients, the hazard ratio associated with a nonnegative versus negative MTWA test was 13.6 (95% confidence interval [CI] 8.5 to 30.4) and the annual event rate among the MTWA-negative patients was 0.3% (95% CI: 0.1% to 0.5%). In contrast, in the high ICD group comprising 2,234 patients, the hazard ratio was only 1.6 (95% CI: 1.2 to 2.1) and the annual event rate among the MTWA-negative patients was elevated to 5.4% (95% CI: 4.1% to 6.7%). In support of these findings, we analyzed published data from the Multicenter Automatic Defibrillator Trial II (MADIT II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), and determined that in those trials only 32% of patients who received appropriate ICD therapy averted an SCD.

CONCLUSION This study found that MTWA testing using the spectral analytic method provides an accurate means of predicting VTEs in primary prevention patients without implanted ICDs; in particular, the event rate is very low among such patients with a negative MTWA test. In prospective trials of ICD therapy, the number of patients receiving appropriate ICD therapy greatly exceeds the number of patients who avert SCD as a result of ICD therapy. In trials involving patients with implanted ICDs, these excess appropriate ICD therapies seem to distribute randomly between MTWA-negative and MTWA-nonnegative patients, obscuring the predictive accuracy of MTWA for SCD. Appropriate ICD therapy is an unreliable surrogate endpoint for SCD.

KEYWORDS Arrhythmia; Sudden cardiac death; Cardiac arrest; ICD; T-wave alternans; Surrogate end point; Ventricular tachyarrhythmic event; Primary prevention (Heart Rhythm 2009;6:S36–S44) © 2009 Published by Elsevier Inc. on behalf of Heart Rhythm Society.

Introduction

Microvolt T-wave alternans (MTWA) testing using the analytic spectral method is a noninvasive means of stratifying patients for the risk of sudden cardiac death (SCD). Many studies conducted in patients without implanted cardioverter-defibrillators (ICDs) have found MTWA to be a highly accurate risk stratifier and, in particular, have found that the rate of ventricular tachyarrhythmic events (VTEs) among patients who test MTWA negative is exceedingly low,1–7 suggesting that ICD therapy may not benefit such patients.8 As a result, MTWA has been proposed as a means of guiding ICD therapy in patients with risk factors for SCD but without a prior history of sustained VTEs (primary prevention patients).

With the advent of the Multicenter Automatic Defibrillator Trial II (MADIT II)9 and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)10 trials, clinical guidelines have recommended prophylactic ICD implantation in patients with left ventricular dysfunction and no prior history of VTEs. As a result, a number of recent clinical trials conducted to evaluate MTWA testing have involved patients with prophylactically implanted ICDs.11–15 Such trials have generally used appropriate ICD therapy as the predominant component of the VTE end point. Appropriate ICD therapy is defined as an ICD therapy deemed to be appro-
pigraphic based on expert review of the stored electrogram recorded immediately before the delivery of ICD therapy. MTWA testing has tended to not perform as well in these latter trials involving patients with implanted ICDs.

It had been assumed that, in patients with implanted ICDs, appropriate ICD therapy would be a reliable surrogate end point for SCD. Recent analyses of ICD trials have concluded that appropriate ICD therapies in the ICD arms of the studies exceeded sudden deaths in the control arms by a factor of 2 to 3. These analyses raise questions about the suitability of appropriate ICD therapy as a surrogate end point for SCD in clinical trials.

In this article, we analyze clinical trials conducted to evaluate MTWA as a predictor of VTEs in primary prevention patients. We compare trials in which few patients had implanted ICDs (and therefore in which VTE end point events included none or few occurrences of appropriate ICD therapy) with trials in which many patients had implanted ICDs, thus appropriate ICD therapies comprised the majority of the VTE end points. We also analyze data from the MADIT II and SCD-HeFT trials to determine what fraction of the reported appropriate ICD therapies in those studies terminated VTEs that would have been lethal had no ICD been implanted to elucidate the findings from the analyses of the MTWA studies.

**Methods**

**Identification of clinical trials**

On November 17, 2007, we conducted a PubMed online search for journal publications that included the word alternans in the title and were published after 1993. From this list, we identified prospective clinical trials in which MTWA was measured using the spectral analytic method, involved at least 100 patients with a significant risk factor for SCD but not selected on the basis of a known history of sustained VTEs, and had a mean follow-up period of at least 12 months. We excluded studies that included patients who underwent MTWA testing earlier than 14 days after a recent myocardial infarction (MI). One study was excluded because it reported on a subset of patients reported in a later publication. We also included in our analysis data from recent major studies presented at national meetings (Alterans Before Cardioverter Defibrillator [ABCD], SCD-HeFT substudy, and Microvolt T-Wave Alternans Testing for Risk Stratification of Post-MI Patients [MASTER I]) that had not yet been published in journal articles. We defined the low ICD group to include trials identified above that reported VTE end points in which appropriate ICD therapy events accounted for none or a small fraction (≤15%) of the reported VTE end points; few patients in these studies had implanted ICDs. We defined the high ICD group to include trials identified above that reported VTE end points in which appropriate ICD therapies constituted the majority of the reported VTE end point events. In these studies, VTE was generally defined as arrhythmic/sudden death, nonfatal sustained ventricular arrhythmias, or appropriate ICD therapy.

**Statistical analysis**

To compare end point data across studies with different follow-up periods, event data were converted to annual event rates (AERs). The annual event rate, $\lambda$, was computed from the equation $S = e^{-\lambda T}$ where $S$ is the survival value at time $T$. $S$ and $T$ were determined either: (1) from the published survival curves (resulting from Kaplan-Meier or Cox analyses) by measuring $S$ at the maximum displayed survival time, $T$, or (2) from published data that reported the fraction, $F$, of patients in each subgroup who had sustained end point events during follow-up and setting $S = 1 - F$ and $T$ to the mean reported follow-up period. The hazard ratio (HR) for 2 subgroups was obtained by computing the ratio of the derived AERs.

For each subgroup in each study, we assumed that the occurrence of end point events followed time-dependent binomial statistics and used Bayes theorem to obtain the posterior probability distribution for $S$ conditional on $n$, $p(S/n)$, where $n = (1 - S_{exp})N$, $S_{exp}$ is the experimentally measured value of $S$, and $N$ is the initial total number of subjects:

$$p(S/n) = (N + 1)C(N,n)(1 - S)^nS^{N-n}$$

Here $C(N,n)$ denotes a binomial coefficient. The mean and standard deviation of each AER were obtained from the analytically calculated moments of $\ln(S)$. Weighting factors proportional to the reciprocal of the variances of corresponding AERs in different studies were used to obtain the minimum variance estimate of the cumulative AER. Confidence intervals of the cumulative AERs and their ratios were computed numerically, assuming that the cumulative AER estimates were normally distributed. Differences in cumulative AERs were considered statistically significant based on a 2-sided value of $P < .05$. Cumulative left ventricular ejection fractions (LVEFs) were calculated by weighting reported LVEFs by the number of patients in each study.

The exponential survival model used here assumes that individual subjects have a constant probability per unit time of experiencing an end point event and is the simplest standard model to use to combine data from different studies with different follow-up periods. The results of the analysis should not be very sensitive to the exponential assumption, especially because the survival curves in most of the studies seem at least approximately exponential in shape.

**Results**

**Predictive accuracy of MTWA testing**

Tables 1 and 2 show data from prospective trials conducted to evaluate the predictive accuracy of MTWA testing measured using the spectral analytic method in patients with a significant risk factor for SCD but not selected on the basis of a known prior history of sustained VTEs. The trials presented in these tables all reported VTE end points. Table 1 shows data from the low ICD group of MTWA trials in which few patients had implanted ICDs and ≤15% of the reported VTEs were Appropriate Implantable Cardioverter
Table 1  Annual VTE event rates from MTWA trials in low ICD group

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Mean LVEF (%)</th>
<th>Patient No.</th>
<th>Arrhythmic end point</th>
<th>ICDs reported implanted at baseline/follow-up (%)</th>
<th>AICDTs reported as percent of VTE end points</th>
<th>Nonnegative AER (%) [95% CI]</th>
<th>Nonnegative AER (%) [95% CI]</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klingeneheb et al., 2000</td>
<td>CHF</td>
<td>28</td>
<td>107</td>
<td>SCD, CA</td>
<td>Pos</td>
<td>0.00[15.7]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ikeda et al., 2002</td>
<td>Prior MI</td>
<td>50</td>
<td>834</td>
<td>SCD, CA</td>
<td>Pos</td>
<td>0.2[3.6]</td>
<td></td>
<td></td>
<td>16.5</td>
</tr>
<tr>
<td>Kitamura et al., 2002</td>
<td>DCM</td>
<td>37</td>
<td>104</td>
<td>SCD, CA</td>
<td>Pos</td>
<td>1.6[15.6]</td>
<td></td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td>Grimm et al., 2003</td>
<td>DCM, LVEF ≤ 45%</td>
<td>30</td>
<td>263</td>
<td>SCD, CA</td>
<td>Pos + Ind</td>
<td>2.1[4.1]</td>
<td></td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>Hohnlos et al., 2003</td>
<td>CAD LVEF ≤ 30%</td>
<td>25.5</td>
<td>129</td>
<td>SCD, CA</td>
<td>No ICD</td>
<td>0.0[8.4]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloomfield et al., 2006</td>
<td>No ICD subset</td>
<td>25</td>
<td>549</td>
<td>SCD</td>
<td>Pos + Ind</td>
<td>0.4[NR]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chow et al., 2006</td>
<td>CAD LVEF ≤ 35%</td>
<td>28.3</td>
<td>376</td>
<td>SCD</td>
<td>No ICD</td>
<td>2.3[7.9]</td>
<td></td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Ikeda et al., 2006</td>
<td>Prior MI LVEF &gt; 40%</td>
<td>55</td>
<td>1,003</td>
<td>SCD</td>
<td>Pos</td>
<td>0.2[3.5]</td>
<td></td>
<td></td>
<td>23.1</td>
</tr>
<tr>
<td>ALPHA, 2007</td>
<td>DCM LVEF ≤ 40%</td>
<td>29.5</td>
<td>446</td>
<td>SCD, CA</td>
<td>Pos + Ind</td>
<td>0.9[4.8]</td>
<td></td>
<td></td>
<td>5.1</td>
</tr>
<tr>
<td>Cumulative</td>
<td>All</td>
<td>40.5</td>
<td>3,682</td>
<td>SCD, CA</td>
<td>Pos</td>
<td>0.3[1.0–0.5]</td>
<td>4.4*[3.7–5.1]</td>
<td>13.6[8.5–30.4]</td>
<td></td>
</tr>
<tr>
<td>Cumulative</td>
<td>Mean LVEF &lt; 30%</td>
<td>27.4</td>
<td>1,478</td>
<td>SCD</td>
<td>Pos</td>
<td>1.2[0.5–2.0]</td>
<td>6.3*[4.5–8.0]</td>
<td>5.2[2.9–13.8]</td>
<td></td>
</tr>
<tr>
<td>Cumulative</td>
<td>Only SCD, CA End points</td>
<td>43.9</td>
<td>2,762</td>
<td>SCD, CA</td>
<td>Pos</td>
<td>0.3[0.1–0.5]</td>
<td>4.1*[3.1–5.1]</td>
<td>15.3[8.5–46.1]</td>
<td></td>
</tr>
</tbody>
</table>

Data from indicated studies. The Nonnegative column indicates whether in the indicated study a nonnegative MTWA test result was defined as a positive MTWA test result, or either a positive or an indeterminate MTWA test result. Columns labeled ICDs reported implanted at baseline/follow-up (%) and AICDTs reported as percent of VTE end points refer to patients identified in Population column if this represents a subset of all patients reported in study. The Bloomfield et al., 2006 study reported a combined mortality plus nonfatal sustained VTE end point. However, the study reported that the only arrhythmic event, in the subset of MTWA-negative patients who did not receive ICDs either at enrollment or during follow-up, was 1 sudden cardiac death; we obtained the number of patients in this subset from the study database. Chow et al., 2006 reported separately the results for patients with and without ICDs; the results for the non-ICD patients are reported here. The Hohnloser et al., 2003 data are not included in the cumulative statistics because patients in this study were drawn from Klingeneheb et al., 2000, and Ikeda et al., 2002.

AER = annual event rate; CA = cardiac arrest; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; DCM = nonischemic dilated cardiomyopathy; Ind = indeterminate MTWA test result; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Nonnegative = a nonnegative MTWA test result; NR = not reported; Pos = positive MTWA test result; Negative = negative MTWA test result; SCD = sudden cardiac death; SusVT = sustained ventricular tachycardia; VF = ventricular fibrillation; VTE = ventricular tachyarrhythmic events.

*Cumulative AER different from entry immediately to its left at the (P < .0001) significance level.
Defibrillator Therapies (AICDTs). Among the 3,682 patients enrolled in these studies, the cumulative AER among MTWA-negative patients was 0.3% (95% confidence interval [CI]: 0.1% to 0.5%) and among MTWA nonnegative patients was 4.4% (95% CI: 3.7% to 5.1%); HR for MTWA nonnegative versus negative, 13.6 (95% CI: 8.5 to 30.4).

In the subset of studies including patients with a mean LVEF <0.30, the corresponding cumulative AERs were 1.2% (95% CI: 0.5% to 2.0%) and 6.3% (95% CI: 4.5% to 8.0%), HR 5.2 (95% CI: 2.9 to 13.8). In the subset of studies that included only SCD and cardiac arrest (CA), but not nonfatal sustained ventricular tachyarrhythmia, as an end point, the cumulative AERs were 0.3% (95% CI: 0.1% to 0.5%) among the MTWA negative patients and 4.1% (95% CI: 3.1% to 5.1%) among the MTWA nonnegative patients; HR 15.3 (95% CI: 8.5 to 46.1). In the low ICD group and each of the presented subsets, the MTWA negative versus nonnegative cumulative AERs are significantly different (P <.0001) and the HRs all significantly exceed one.

In contrast, in Table 2 we present the AERs from the high ICD group of MTWA trials, in which many patients had implanted ICDs and AICDT comprised the majority of the end point events. Among the 2,234 patients in these trials, the AERs were 5.4% (95% CI: 4.1% to 6.7%) among the MTWA negative patients and 8.5% (95% CI: 7.5% to 9.6%) among the MTWA nonnegative patients; HR 1.6 (95% CI: 1.2 to 2.1). Although in the high ICD group the HR narrows substantially compared with the HR in the low ICD group (and each of the presented subsets), the HR remains significantly greater than unity. The MTWA-negative and MTWA-nonnegative cumulative AERs in the high ICD group are each significantly greater than the corresponding values for the low ICD group (and each of the presented subsets). Figure 1 shows the values of the cumulative AERs in MTWA-negative and MTWA-nonnegative

![Figure 1](image-url)
patients, as well as the associated HR, in the low and high ICD groups.

In Table 3, we calculate from analysis of published data the ratio of the annual rate of AICDT to the annual rate of ICD-mediated reduction in mortality in the MADIT II and SCD-HeFT trials. This ratio is 3.1 (95% CI: 2.0 to 6.3). The ratio implies that only 1 in 3.1 patients (32%) who received AICDT in MADIT II and SCD-HeFT averted a sudden death that would have occurred in the absence of ICD implantation.

In Table 4, we present mortality rates in the MADIT II and SCD-HeFT trials and in MTWA trials involving predominantly patients without implanted ICDs in which the mean LVEF <0.30 and that reported total mortality end point data. In the non-ICD arm of the MADIT II and SCD-HeFT trials, the annual mortality rate was 9.5%. In the entire population of the MTWA trials presented here, the annual mortality rate was 5.4%. In the ICD arm of the MADIT II and SCD-HeFT trials, the annual mortality rate was 7.3%. In the MTWA-negative patients in the corresponding MTWA trials, the annual mortality rate was only 1.7%. The annual mortality rate among MTWA-negative patients who predominantly did not receive ICDs was significantly lower, by a factor of 4.3, than among patients in MADIT II and SCD-HeFT who did receive ICD therapy.

Discussion

Predictive accuracy of MTWA

The previous analysis of MTWA trials shows that there is a substantial and consistent difference in the reported VTE predictive accuracy of MTWA testing performed using the spectral analytic method in trials in which the end point involved a low or high fraction of AICDTs. In the low ICD group, involving patients primarily without implanted ICDs, the HR was 13.6 for annual VTE rates in MTWA-nonnegative compared with MTWA-negative patients (HR was 5.2 in studies in which the mean LVEF <0.30). The HR increases to 15.3 when only SCD and CA, but not nonlethal sustained VTEs, are included in the end point. In contrast, in patients in the high ICD group, the HR decreases to 1.6. Similarly, the annual VTE rate in the low ICD group is only 0.3% (1.2% in studies in which mean LVEF <0.30); the annual VTE is 0.3% when only SCD and CA are included in the end point. In contrast, the annual VTE rate among MTWA-negative patients is 5.4% in the high ICD group, greater by an order of magnitude.

In our analysis, we also show that in MADIT II and SCD-HeFT only 1 in 3.1 patients (32%) who received AICDT averted an SCD that would have occurred in the absence of ICD implantation. This result is consistent with

### Table 3  Ratio of annual rate of appropriate ICD therapy to annual rate of ICD-mediated reduction in mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No. patients</th>
<th>Annual rate of appropriate ICD therapy (%)</th>
<th>Annual rate of ICD-mediated reduction in mortality (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT II, 2002</td>
<td>1,232</td>
<td>15.3</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td>SCD-HeFT, 2004</td>
<td>1,676</td>
<td>6.2</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Cumulative</td>
<td>2,908</td>
<td>7.5 [95% CI: 6.7–8.4]</td>
<td>2.4 [95% CI: 1.2–3.7]</td>
<td>3.1 [95% CI: 2.0–6.3]</td>
</tr>
</tbody>
</table>

The annual rate of appropriate ICD therapy represents the probability per unit time of an individual in the specified study sustaining an appropriate ICD therapy event. Annual rate of ICD-mediated reduction in mortality was obtained by computing the difference in the annual mortality event rates between the non-ICD and ICD arms of each study (see Table 4). Number of patients in the SCD-HeFT trial excludes the amiodarone arm. Abbreviations as in Table 1.

### Table 4  Annual mortality rates in the MADIT II and SCD-HeFT trials and in MTWA trials reporting total mortality in which mean LVEF <30% and involving patients predominantly without implanted ICDs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. patients</th>
<th>Mean LVEF (%)</th>
<th>Annual mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT II, 2002</td>
<td>Prior MI, LVEF ≤ 0.30</td>
<td>1,232</td>
<td>23</td>
<td>13.2</td>
</tr>
<tr>
<td>SCD-HeFT, 2004</td>
<td>CHF, LVEF ≤ 0.35</td>
<td>1,676</td>
<td>25</td>
<td>9.0</td>
</tr>
<tr>
<td>Cumulative</td>
<td>All</td>
<td>2,908</td>
<td>24.2</td>
<td>9.5 [95% CI: 8.6–10.5]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. patients</th>
<th>Mean LVEF (%)</th>
<th>Annual mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hohnloser et al., 2003</td>
<td>CAD, LVEF ≤ 0.30</td>
<td>129</td>
<td>25.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Bloomfield et al., 2006</td>
<td>LVEF ≤ 0.40</td>
<td>549</td>
<td>25</td>
<td>4.5</td>
</tr>
<tr>
<td>Chow et al., 2006</td>
<td>CAD, LVEF ≤ 0.35, no ICD</td>
<td>376</td>
<td>28.3</td>
<td>11.2</td>
</tr>
<tr>
<td>ALPHA, 2007</td>
<td>DCM, LVEF ≤ 0.40</td>
<td>446</td>
<td>29.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Cumulative</td>
<td>1,500</td>
<td>27.2</td>
<td>5.4 [95% CI: 4.5–6.4]</td>
<td>1.7** [95% CI: 0.8–2.6]</td>
</tr>
</tbody>
</table>

Number of patients in the SCD-HeFT trial excludes the amiodarone arm. Abbreviations as in Table 1.

*P <0.001.

**P <0.0001.
the reports of other investigators, who have also found that the number of AICDTs greatly exceeds the ICD-mediated reduction in deaths in clinical ICD trials.\textsuperscript{16,17} One explanation for the excess number of AICDTs is that ICDs treat arrhythmias that would have self-terminated had no ICD been implanted. Another possible explanation is that ICDs are themselves arrhythmogenic and induce arrhythmias that they then end up treating.\textsuperscript{17} Whatever the mechanism, the large excess of the number of patients receiving AICDT over the number of patients averted SCD indicates that AICDT is an unreliable surrogate for an SCD end point in clinical trials.\textsuperscript{18} The large number of patients studied in clinical trials involving predominantly non-ICD patients have shown that MTWA as measured by the spectral analytic method is a highly accurate predictor of spontaneous VTEs, in particular SCD and CA. In contrast, it seems that MTWA does not predict the excess AICDTs. When AICDT is used as an end point in a clinical trial, these excess AICDTs seem to play the role of statistical noise being randomly distributed as end point events among the MTWA-negative and MTWA-nonnegative subgroups.

It should be mentioned that there is variation in the thresholds set for triggering AICDT across different trials (and even within trials), which may lead one to speculate that AICDTs triggered at higher set thresholds might constitute more suitable surrogate end points for SCD. Dauber et al.\textsuperscript{20} found that in MADIT II\textsuperscript{9} ICD therapy for fast VT/VF with rates >240 beats/min occurred at the same frequency in ICD patients as excess mortality occurred in patients without ICDs. A rate >240 beats/min far exceeds what has been deemed clinically acceptable in terms of a threshold for triggering AICDT therapy. However, occurrence of VT/VF with a heart rate >240 beats/min might be a candidate surrogate end point for SCD in patients with ICDs even if the threshold is set at a lower rate. Such an end point would be a reliable surrogate for SCD only if rate is the primary factor in determining the lethality of a tachyarrhythmia. Also, if the mechanism for the excess AICDTs is an arrhythmogenic effect of the ICD itself, as discussed earlier, such an end point would still result in excess AICDTs and remain a poor surrogate for SCD.

**MTWA in non-ischemic dilated cardiomyopathy patients**

In Table 1, 3 studies are presented with data exclusively on patients with nonischemic dilated cardiomyopathy. The results of Kitamura et al.\textsuperscript{3} (104 patients) and ALPHA\textsuperscript{7} (446 patients), with HRs of 10.0 and 5.1, are well within the range of results obtained in patients with ischemic heart disease. Also, Bloomfield et al.\textsuperscript{5} (549 patients), using a mixed end point of nonfatal sustained ventricular arrhythmias and all-cause mortality, reported no difference in the predictive accuracy of MTWA in ischemic and nonischemic patients. However, Table 1 reports an HR of only 1.9 for the Grimm et al.\textsuperscript{21} (263 patients) study of nonischemic dilated cardiomyopathy patients. This study, although it is included in the summary statistics, seems to be an outlier. One possible explanation for MTWA performance in the study by Grimm et al.\textsuperscript{21} compared with the other studies of MTWA in DCM patients might be that beta-blockers were withheld for at least 24 h before MTWA testing, whereas 74\% of patients took beta-blockers during follow-up. In contrast, in ALPHA\textsuperscript{7}, Kitamura et al.\textsuperscript{3} and Bloomfield et al.\textsuperscript{5} they were not withheld before MTWA testing. It is known that beta-blockers both reduce the incidence of ventricular tachyarrhythmias and, particularly in patients with nonischemic cardiomyopathy, suppress MTWA.\textsuperscript{22,23} Thus, in the study by Grimm et al.\textsuperscript{21} it is possible that the withdrawal of beta-blockers acutely increased the incidence of MTWA without concomitantly increasing VTEs during follow-up because these same patients were taking beta-blockers during follow-up. The results of these studies suggest that it may be advisable to perform MTWA tests in patients while they are on the same pharmacologic regimen as they will be on during follow-up. Only if patients have an indeterminate test result because they cannot achieve the minimum heart rate of 105 beats/min would it be advised to withdraw beta-blockers to the extent needed for the patient to achieve this heart rate. (Of note, many patients who on initial exercise testing cannot achieve a heart rate of 105 beats/min can do so upon repeating the exercise test after a short rest period.)

**Benefit of ICD therapy in MTWA-nonnegative versus MTWA-negative patients**

ICD therapy is associated with its own morbidity and mortality, including infection, lead breakage, inappropriate shocks, perforation, and device and lead recalls.\textsuperscript{17} The early complication rate associated with just the ICD implantation procedure itself has been reported to be 11\%, including a mortality rate of 1\%, exclusive of the complications after hospital discharge such as inappropriate shocks and lead breakage.\textsuperscript{24} The cumulative complication rate for ICDs has been reported as 31\% over 46 months of follow-up.\textsuperscript{25} Potentially at-risk primary prevention patients with a negative MTWA test have only a 0.3\% annual risk of SCD and CA (Table 1), suggesting that the risk of ICD therapy may outweigh the benefit in these patients. No clinical trial has ever shown that ICD therapy provides a mortality benefit in patients with an annual risk of SCD or CA even remotely as low as 1\% or less. Thus there is no clinical evidence showing that patients without a prior history of sustained ventricular arrhythmias and a negative MTWA test benefit from ICD therapy. The Defibrillator In Acute Myocardial Infarction Trial (DINAMIT)\textsuperscript{26} study showed that ICD therapy was associated with a significant increase in nonarrhythmic mortality of 2.6\% per year ($P = .02$), suggesting that ICD therapy may have an adverse effect on total mortality in a patient population with an annual arrhythmic mortality of <2.6\%.

Table 4 shows that, in MTWA studies involving patients with LVEF <0.30, the annual total mortality rate was 57\% of that observed in the non-ICD arms of the MADIT II\textsuperscript{9} and SCD-HeFT\textsuperscript{10} trials. An explanation for this observation is
possible referral bias in MADIT II and SCD-HeFT, where physicians referring patients into these treatment trials pre-selected patients they believed would be at higher risk of SCD and thus more likely to benefit from ICD therapy. In the natural history MTWA trials, no therapy was mandated, so there would be little reason to expect a similar referral bias. Of greater interest is the fact that the mortality rate among the MTWA- negative patients presented in Table 4 who predominantly did not receive ICD therapy had a factor of 4.3 lower mortality rate than the patients in MADIT II and SCD-HeFT who did receive ICD therapy. Even if one adjusts for the overall lower mortality rate in the MTWA trials compared with MADIT II and SCD-HeFT, the MTWA-negative patients who predominantly did not receive ICDs still had a 2.4 times lower mortality rate than the MADIT II and SCD-HeFT patients who did receive ICD therapy. This observation further suggests that MTWA patients without a history of sustained VTES may not benefit from ICD therapy.

Chow et al.27 conducted a prospective nonrandomized study of 768 patients with ischemic heart disease and LVEF ≤ 0.35, of whom 51% received ICDs. In this study, the propensity score statistical methodology was used to adjust for factors that affect the decision to implant an ICD. These investigators found that ICD implantation in MTWA-negative patients was associated with a 55% reduction in all-cause mortality (P < .003), but that ICD implantation in an equivalent number of MTWA-negative patients had no statistically significant effect on mortality.

**MTWA as a guide to ICD therapy**

In the United States, ICD therapy is generally reimbursed by third-party insurers for patients with symptoms of heart failure with LVEF ≤ 0.35. The American Heart Association estimates that there are 5.2 million patients in the United States with symptomatic heart failure.28 Solomon et al.29 studied 7,599 patients with symptomatic heart failure and found that approximately 44% had LVEF ≤ 0.35. These data suggest that in excess of 2 million primary prevention patients may qualify for reimbursable ICD therapy. However, only approximately 100,000 ICDs per year are undergoing implantation in the United States in this patient population. This suggests that there may be a reluctance to accept ICD therapy for this population among referring physicians and patients. Recent recalls of devices and leads reported prominently in the popular press may have served to reinforce this reluctance.

MTWA testing as an accurate noninvasive means of assessing risk of SCD may serve to identify patients most likely to benefit from ICD therapy. Approximately one-third of the symptomatic patients with LVEF ≤ 0.35 may test MTWA negative.7,12 However, a nonnegative test result in the remaining patients may serve as a specific call to action for the patient and referring physician. As a result, a greater number of appropriate patients may receive ICD therapy. Ikeda et al.6 showed in patients with a prior MI and LVEF > 0.40 that a positive MTWA identified patients at significant risk of SCD. This finding is supported by another recent publication30 in a population with prior MI and mean LVEF of 0.47. Thus, MTWA may play a role in identifying patients with a significant risk factor for SCD but with only moderate left ventricular dysfunction who need further evaluation for possible ICD therapy.

Stecker et al.31 found that LVEF had been measured in only 17% of 714 cases of SCD. In the cases in which LVEF had been measured, only 30% had LVEF ≤ 0.35. One would presume that the lower a patient’s LVEF, the more likely that patient would come to clinical attention and have his or her LVEF measured. Thus, this study would suggest that patients with LVEF ≤ 0.35 comprise a small minority of all SCDs, at most 30% but likely a substantially lower fraction. Thus, because the substantial majority of SCDs seem to occur in patients with LVEF > 0.35, it is critical to identify patients in this latter group who are at significant risk for SCD so that they can be evaluated for preventative therapy.

Figure 2 illustrates a possible clinical algorithm for the use of MTWA in evaluating primary prevention patients. Of note, patients who have risk factors such as LVEF ≤ 0.35 or prior MI and who test MTWA negative should be considered for annual testing. The myocardial substrate may evolve over time, and MTWA as a noninvasive test can be used to monitor changes in arrhythmic susceptibility. In patients with LVEF ≤ 0.35, a positive or indeterminate MTWA test result indicates a high level of risk;32 whereas in patients with higher LVEF only a positive test result seems to indicate elevated risk.6

**Conclusion**

MTWA testing using the spectral analytic method identifies, among non-ICD patients with risk factors for SCD but with no prior history of sustained VTES, a group of patients at very low risk for SCD and a group at elevated risk. In prospective trials of ICD therapy, the number of AICDTs greatly exceeds the number of SCDs prevented as a result of ICD implantation. In trials involving patients with implanted ICDs, these excess AICDTs seem to distribute randomly between MTWA-negative and MTWA-negative patients, obscuring the predictive accuracy of MTWA for SCD. AICDT is an unreliable surrogate end point for SCD.

There is no evidence showing that ICD therapy provides a mortality benefit for primary prevention patients with a negative MTWA test result. In patients with ischemic heart disease and LVEF ≤ 0.35, there is evidence showing that ICD therapy provides a substantial mortality benefit for MTWA-positive or MTWA-indeterminate patients, but not for MTWA-negative patients.27 MTWA testing may serve as a means of guiding ICD therapy to appropriate patients and overcoming the widespread reluctance among patients and referring physicians to accept ICD therapy for appropriate patients. MTWA testing may also provide a means for identifying which patients, with risk factors for SCD but with LVEF > 0.35, should undergo further evaluation for
Clinical Algorithm for MTWA Based Management of Primary Prevention Patients

![Clinical Algorithm](image)

Figure 2  Clinical algorithm for use of MTWA in evaluating primary prevention patients. LVEF = left ventricular ejection fraction; MI = myocardial infarction; VT = ventricular tachycardia; other abbreviations as in Figure 1.

preventative therapy. Because the substantial majority of SCDs occur in patients with LVEF > 0.35, substantial progress in reduction of SCD will only be possible when the high-risk patients in this group are identified and treated prophylactically.

References


