Evidence regarding clinical use of microvolt T-wave alternans

State-of-the-Art Lecture: Evidence Regarding Clinical Use of Microvolt T-Wave Alternans

Short Title: **Accuracy of Microvolt T-Wave Alternans Testing**

Stefan H. Hohnloser, MD,[*] Takanori Ikeda, MD,[†] Richard J. Cohen, MD, PhD[‡]

From the [*]Division of Cardiology, Department of Medicine, J. W. Goethe University, Frankfurt, Germany, [†]2nd Department of Internal Medicine, Kyorin University, Tokyo, Japan, and the [‡]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts

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Correspondence
Stefan H. Hohnloser, MD, FHRS
Division of Cardiology, Department of Medicine, J. W. Goethe University
Theodor-Stern-Kai 7 Bldg 23
Frankfurt, 60590, GERMANY
Telephone: 49-69-6301-7404
Fax: 49-69-6301-7017
Email: Hohnloser@em.uni-frankfurt.de

Abstract and Key Words

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 ICDs, MTWA has not performed as well.

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

METHODS We 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 endpoint VTEs were AICDTs (Low ICD Group) or (2) many of the patients had implanted ICDs and the majority of the reported endpoint VTEs were AICDTs (High ICD Group).

RESULTS In the Low ICD Group comprising 3,682 patients the hazard ratio associated with a non-negative vs negative MTWA test was 13.6 [8.5 30.4] (brackets denote 95% confidence interval) and the annual event rate (AER) among the MTWA negatives patients was 0.3% [0.1% 0.5%]. In contrast, in the High ICD Group comprising 2,234 patients the hazard ratio was only 1.6 [1.2 2.1] and the AER among the MTWA negative patients was elevated to 5.4% [4.1% 6.7%]. In support of these findings we analyzed published data from the MADIT II and SCD-

HeFT trials and determined that in those trials only 32% of patients who received AICDT averted a SCD.

CONCLUSION 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 AICDT greatly exceeds the number of patients who avert SCD as a result of ICD therapy. In trials involving patients with implanted ICDs these *excess* AICDTs appear to distribute randomly between MTWA negative and non-negative patients obscuring the predictive accuracy of MTWA for SCD. AICDT is an unreliable surrogate endpoint for SCD.

KEY WORDS Arrhythmia; Sudden cardiac death; Cardiac arrest; ICD; T-wave alternans; Surrogate endpoint; Ventricular tachyarrhythmic event; Primary prevention

ABBREVIATIONS MTWA, microvolt T-wave alternans; VTE, ventricular tachyarrhythmic event; SCD, sudden cardiac death; ICD, implantable cardioverter defibrillator; AICDT, appropriate ICD therapy; AER, annual event rate; CA, cardiac arrest; HR, hazard ratio.

Introduction

Microvolt T-wave alternans (MTWA) testing using the analytic spectral method is a non-invasive means of stratifying patients for the risk of sudden cardiac death (SCD). Many studies conducted in patients without implanted 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 implantable cardioverter defibrillator (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 MADIT II[9] and 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 utilized *appropriate* ICD therapy (AICDT) as the predominant component of the VTE endpoint. AICDT is defined as an ICD therapy deemed to be appropriate based upon expert review of the stored electrogram recorded immediately prior to 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, AICDT would be a reliable surrogate for sudden cardiac death. Recent analyses of ICD trials[16, 17] have concluded that AICDTs in the ICD arms of the studies exceeded sudden deaths in the control arms by a factor of two to three. These analyses raise questions about the suitability of AICDT as a surrogate endpoint for SCD in clinical trials[18].

In this paper 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 endpoint events included none or few occurrences of AICDT) with trials in which many patients had implanted ICDs and thus AICDTs comprised the majority of the VTE endpoints. We also analyze data from the MADIT II[9] and SCD-HeFT[10] trials to determine what fraction of the reported AICDTs in those studies terminated VTEs that would have been lethal had no ICD been implanted in order 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 which 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 sudden cardiac death 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 which included patients who underwent MTWA testing earlier than 14 days after a recent myocardial infarction (MI). One study[19] 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 (ABCD[14], SCD-HeFT substudy[15], and MASTER I[13]) which had not yet been published in journal articles. We defined the Low ICD Group to include trials identified above which reported VTE endpoints in which AICDT events accounted for none or a small fraction (≤ 15%) of the reported VTE endpoints –

few patients in these studies had implanted ICDs. We defined the High ICD Group to include trials identified above which reported VTE endpoints in which AICDTs constituted the majority of the reported VTE endpoint events.

Statistical Analysis

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

For each subgroup in each study we assumed that the occurrence of endpoint events follow 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:

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

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 two-sided $p < 0.05$.

Cumulative left ventricular ejection fractions (LVEFs) were calculated by weighting reported LVEFs by the number of patients in each study.

Results

Predictive Accuracy of MTWA Testing

Tables 1 and 2 display 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 ventricular tachyarrhythmic event (VTE) endpoints. Table 1 displays data from the Low ICD Group of MTWA trials in which few patients had implanted ICDs and ≤ 15% of the reported VTEs were AICDTs. Among the 3,682 patients enrolled in these studies, the cumulative AER among MTWA negative patients was 0.3% [0.1% 0.5%] and among MTWA non-negative patients was 4.4% [3.7% 5.1%] (HR for MTWA non-negative versus negative, 13.6 [8.5 30.4]). Here brackets denote 95% confidence interval. In the subset of studies including patients with a mean LVEF < 0.30, the corresponding cumulative AERs were 1.2% [0.5% 2.0%] and 6.3% [4.5% 8.0%] (HR, 5.2 [2.9 13.8]). In subset of studies which included only SCD and cardiac arrest (CA) - but not non-fatal sustained ventricular tachyarrhythmia - as an endpoint, the cumulative AERs were 0.3% [0.1% 0.5%] among the MTWA negative patients and 4.1% [3.1% 5.1%] among the MTWA non-negative patients (HR, 15.3 [8.5 46.1]). In the Low ICD Group and each of the presented subsets, the MTWA negative

versus non-negative cumulative AERs are significantly different ($p < 0.0001$) 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 endpoint events. Among the 2,234 patients in these trials, the AERs were 5.4% [4.1% 6.7%] among the MTWA negative patients and 8.5% [7.5% 9.6%] among the MTWA non-negative patients (HR, 1.6 [1.2 2.1]). While in the High ICD Group the hazard ratio narrows substantially compared to the hazard ratio in the Low ICD Group (and each of the presented subsets), the hazard ratio remains significantly greater than unity. The MTWA negative and non-negative 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 illustrates the values of the cumulative AERs in MTWA negative and non-negative patients, as well as the associated hazard ratio, 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 [2.0 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 which reported total mortality endpoint 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 above analysis of MTWA trials demonstrates 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 endpoint involved a low or high fraction of AICDTs. In the Low ICD Group, involving patients primarily without implanted ICDs, the hazard ratio was 13.6 for annual VTE rates in MTWA non-negative compared to MTWA negative patients (hazard ratio was 5.2 in studies in which the mean LVEF < 0.30). The hazard ratio increases to 15.3 when only SCD and CA, but not non-lethal sustained VTEs, are included in the endpoint. In contrast, in patients in the High ICD Group, the hazard ratio falls 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 endpoint. 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 demonstrate that in MADIT II[9] and SCD-HeFT[10] only 1 in 3.1 patients (32%) who received AICDT averted a SCD that would have occurred in the absence of ICD implantation. This result is consistent with 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[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[17]. Whatever the mechanism, the large excess of the number of patients receiving AICDT over the number of patients averting SCD indicates that AICDT is an unreliable surrogate for a SCD endpoint in clinical trials[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 appears that MTWA does not predict the *excess* AICDTs. When AICDT is used as an endpoint in a clinical trial, these excess AICDTs appear to play the role of statistical noise being randomly distributed as endpoint events among the MTWA negative and non-negative 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 endpoints for SCD. Daubert[20] found that in MADIT II[9] that ICD therapy for fast VT/VF with rates > 240 bpm occurred at the same frequency in ICD patients as excess mortality occurred in patients without ICDs. A rate > 240 bpm 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 bpm might be a candidate surrogate endpoint for SCD in patients with ICDs even if the threshold is set at a lower rate. Such an endpoint 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 above, such an endpoint would still result in excess AICDTs and remain a poor surrogate for SCD.

MTWA in Non-Ischemic Dilated Cardiomyopathy Patients

In Table 1 three studies present data exclusively on patients with non-ischemic dilated cardiomyopathy. The results of Kitamura[3] (104 patients) and ALPHA[7] (446 patients), with hazard ratios of 10.0 and 5.1, are well within the range of results obtained in patients with ischemic heart disease. Also, Bloomfield[5] (549 patients), using a mixed endpoint of non-fatal sustained ventricular arrhythmias and all cause mortality, reported no difference in the predictive accuracy of MTWA in ischemic and non-ischemic patients. However, Table 1 reports a hazard ratio of only 1.9 for the Grimm[21] (263 patients) study of non-ischemic dilated cardiomyopathy patients. This study, while it is included in the summary statistics, appears to be an outlier. One possible explanation for MTWA performance in Grimm[21] compared to the other studies of MTWA in DCM patients might be that in Grimm beta-blockers were withheld for at least 24 hours prior to MTWA testing while 74% of patients took beta-blockers during follow-up. In contrast in ALPHA[7], Kitamura[3], and Bloomfield[5] were not withheld prior to MTWA testing. It is known that beta-blockers both reduce the incidence of ventricular tachyarrhythmias and – particularly in patients with non-ischemic cardiomyopathy - suppress MTWA[22, 23]. Thus, in Grimm[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 because they cannot achieve the minimum heart rate of 105 bpm, 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 bpm can do so upon repeating the exercise test after a short rest period.)

Benefit of ICD Therapy in MTWA Non-Negative versus Negative Patients

ICD therapy is associated with its own morbidity and mortality including infection, lead breakage, inappropriate shocks, perforation, device and lead recalls[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[24]. The cumulative complication rate for ICDs has been reported as 31% over 46 months of follow-up[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 demonstrated that ICD therapy provides a mortality benefit in patients with an annual risk of SCD or CA even remotely as low as one percent or less. Thus there is no clinical evidence that patients without a prior history of sustained ventricular arrhythmias and a negative MTWA test benefit from ICD therapy. The DINAMIT[26] study demonstrated that ICD therapy was associated with a significant increase in non-arrhythmic mortality of 2.6% per year ($p = 0.02$), suggesting that ICD therapy may have an adverse effect on total mortality in a patient population with an annual arrhythmic mortality of less than 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[9] and SCD-HeFT[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 that 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 to 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*, 2007[27] conducted a prospective non-randomized 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 non-negative patients was associated with a 55% reduction in all-cause mortality ($p < 0.003$), 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 US, 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 two million primary prevention patients may qualify for reimbursable ICD therapy. However, only approximately 100,000 ICDs per year are being implanted 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 non-invasive means of assessing risk of SCD a 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 non-negative test 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] demonstrated 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 publication[30] 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 where LVEF had been measured, only thirty percent 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/her LVEF measured. Thus, this study would suggest that patients with LVEF ≤ 0.35 comprise a small minority of all SCDs – at most thirty percent but likely a substantially lower fraction. Thus, since the substantial majority of SCDs appear 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 test MTWA negative should be considered for annual testing. The myocardial substrate may evolve over time and MTWA as a non-invasive test can be used to monitor changes in arrhythmic susceptibility. In patients with LVEF ≤ 0.35 a positive or indeterminate MTWA test indicate a high level of risk[32], whereas in patients with higher LVEF only a positive test appears 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 appear to distribute randomly between MTWA negative and non-negative patients obscuring the predictive accuracy of MTWA for SCD. AICDT is an unreliable surrogate endpoint for SCD.

There is no evidence that ICD therapy provides a mortality benefit for primary prevention patients with a negative MTWA test. In patients with ischemic heart disease and LVEF ≤ 0.35, there is evidence that ICD therapy provides a substantial mortality benefit for MTWA positive or 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 sudden cardiac death but with LVEF > 0.35, should undergo further evaluation for preventative therapy. Because the substantial majority of SCDs occur in LVEF > 0.35 patients[31], substantial progress in reduction of SCD will only be possible when the high risk patients in this group are identified and treated prophylactically.

References

1. Klingenheben T, Zabel M, D'Agostino RB, et al. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet.* Aug 19 2000;356(9230):651-652.

2. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol.* Jan 1 2002;89(1):79-82.

3. Kitamura H, Ohnishi Y, Okajima K, et al. Onset heart rate of microvolt-level T-wave alternans provides clinical and prognostic value in nonischemic dilated cardiomyopathy. *J Am Coll Cardiol.* Jan 16 2002;39(2):295-300.

4. Hohnloser SH, Ikeda T, Bloomfield DM, et al. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *Lancet.* Jul 12 2003;362(9378):125-126.

5. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol.* Jan 17 2006;47(2):456-463.

6. Ikeda T, Yoshino H, Sugi K, et al. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. *J Am Coll Cardiol.* Dec 5 2006;48(11):2268-2274.

7. Salerno-Uriarte JA, De Ferrari GM, Klersy C, et al. Prognostic value of T-wave alternans in patients with heart failure due to nonischemic cardiomyopathy: results of the ALPHA Study. *J Am Coll Cardiol.* Nov 6 2007;50(19):1896-1904.

8. Armoundas AA, Hohnloser SH, Ikeda T, et al. Can microvolt T-wave alternans testing reduce unnecessary defibrillator implantation? *Nat Clin Pract Cardiovasc Med.* Oct 2005;2(10):522-528.

9. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* Mar 21 2002;346(12):877-883.

10. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* Jan 20 2005;352(3):225-237.

11. Cantillon DJ, Stein KM, Markowitz SM, et al. Predictive value of microvolt T-wave alternans in patients with left ventricular dysfunction. *J Am Coll Cardiol.* Jul 10 2007;50(2):166-173.

12. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol.* May 2 2006;47(9):1820-1827.

13. Chow T, Kereiakes DJ, Onufer J, et al. Late-Breaking Clinical Trials Abstract: Primary Results From the Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients (MASTER I) Trial. *Circulation.* 2007;116(22):2631.

14. Costantini O, Rosenbaum DS, Hohnloser SH, et al. Late-Breaking Clinical Trials Abstract: The Alternans Before Cardioverter Defibrillator (ABCD) Trial: A Noninvasive

Strategy for Primary Prevention of Sudden Cardiac Death Using T-Wave Alternans. *Circulation.* November 28, 2006 2006;114(22):2426.

15. Gold MR, Ensley D, Chilson D, et al. Abstract 2113: T-Wave Alternans SCD HeFT Study: Primary Endpoint Analysis. *Circulation.* 2006;114:II_428-II_429.

16. Ellenbogen KA, Levine JH, Berger RD, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation.* Feb 14 2006;113(6):776-782.

17. Germano JJ, Reynolds M, Essebag V, et al. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol.* Apr 15 2006;97(8):1255-1261.

18. Connolly SJ. Use and misuse of surrogate outcomes in arrhythmia trials. *Circulation.* Feb 14 2006;113(6):764-766.

19. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation.* Oct 5 2004;110(14):1885-1889.

20. Daubert JP, Wilber DJ, Lin A, et al. Abstract 1786: ICD Therapy for Fast Ventricular Tachycardia or Ventricular Fibrillation is a Surrogate Endpoint for Mortality in MADIT II. *American Heart Association Scientific Sessions*; 2003.

21. Grimm W, Christ M, Bach J, et al. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. *Circulation.* Dec 9 2003;108(23):2883-2891.

22. Klingenheben T, Gronefeld G, Li YG, et al. Effect of metoprolol and d,l-sotalol on microvolt-level T-wave alternans. Results of a prospective, double-blind, randomized study. *J Am Coll Cardiol.* Dec 2001;38(7):2013-2019.

23. Murata M, Harada M, Shimizu A, et al. Effect of long-term beta-blocker therapy on microvolt-level T-wave alternans in association with the improvement of the cardiac sympathetic nervous system and systolic function in patients with non-ischemic heart disease. *Circ J.* Oct 2003;67(10):821-825.

24. Reynolds MR, Cohen DJ, Kugelmass AD, et al. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol.* Jun 20 2006;47(12):2493-2497.

25. Alter P, Waldhans S, Plachta E, et al. Complications of implantable cardioverter defibrillator therapy in 440 consecutive patients. *Pacing Clin Electrophysiol.* Sep 2005;28(9):926-932.

26. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* Dec 9 2004;351(24):2481-2488.

27. Chow T, Kereiakes DJ, Bartone C, et al. Microvolt T-wave alternans identifies patients with ischemic cardiomyopathy who benefit from implantable cardioverter-defibrillator therapy. *J Am Coll Cardiol.* Jan 2 2007;49(1):50-58.

28. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* Feb 6 2007;115(5):e69-171.

29. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation.* Dec 13 2005;112(24):3738-3744.

30. Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive Risk Assessment Early After a Myocardial Infarction. *J Am Coll Cardiol.* . 2007;50(24):2275-2284.

31. Stecker EC, Vickers C, Waltz J, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol.* Mar 21 2006;47(6):1161-1166.

32. Kaufman ES, Bloomfield DM, Steinman RC, et al. "Indeterminate" microvolt T-wave alternans tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol.* Oct 3 2006;48(7):1399-1404.

33. Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation.* Dec 21 2004;110(25):3760-3765.

Table 1

Annual VTE Event Rates from MTWA Trials in Low ICD Group

Study	Patient Population	Mean LVEF (%)	Patient Number	Arrhythmic Endpoint	ICDs Reported Implanted at Baseline (%)	AICDTs Reported as Percent of VTE Endpoints	Non-Neg	Neg AER (%)	Non-Neg AER (%)	HR
Klingenheben et al, 2000[1]	CHF	28	107	SCD, CA SusVT	0	0	Pos	0.00	15.7	∞
Ikeda *et al*, 2002[2]	Prior MI	50	834	SCD, CA	0	0	Pos	0.2	3.6	16.5
Kitamura *et al*, 2002[3]	DCM	37	104	SCD, CA SusVT	0	0	Pos	1.6	15.6	10.0
Grimm *et al*, 2003[21]	DCM, LVEF ≤ 45%	30	263	SCD, CA SusVT	0	0	Pos + Ind	2.1	4.1	1.9
Hohnloser *et al*, 2003[4]	CAD LVEF ≤ 30%	25.5	129	SCD, CA	0	0	Pos + Ind	0.0	8.4	∞
Bloomfield *et al*, 2006[5]	LVEF ≤ 40% No ICD subset	25	549	SCD	0	0	Pos + Ind	0.4	NR	
Chow *et al*, 2006[12]	CAD LVEF ≤ 35% No ICD subset	28.3	376	SCD	0	0	Pos + Ind	2.3	7.9	3.5
Ikeda *et al*, 2006[6]	Prior MI LVEF > 40%	55	1003	SCD, CA	0	0	Pos	0.2	3.5	23.1
ALPHA, 2007[7]	DCM LVEF ≤ 40%	29.5	446	SCD, CA SusVT	0	15	Pos + Ind	0.9	4.8	5.1
Cumulative	**All**	**40.5**	**3682**					**0.3 [0.1 0.5]**	**4.4** [3.7 5.1]**	**13.6 [8.5 30.4]**
Cumulative	**Mean LVEF < 30%**	**27.4**	**1478**					**1.2 [0.5 2.0]**	**6.3** [4.5 8.0]**	**5.2 [2.9 13.8]**
Cumulative	**Only SCD, CA Endpoints**	**43.9**	**2762**					**0.3 [0.1 0.5]**	**4.1** [3.1 5.1]**	**15.3 [8.5 46.1]**

Data drawn from indicated studies. The *Non-Neg* column indicates whether in the indicated study a non-negative 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 (%)* and *AICDTs Reported as Percent of VTE Endpoints* refer to patients identified in *Population* column if this represents a subset of all patients reported in study. The Bloomfield *et al*, 2006[5] study reported a combined mortality plus non-fatal sustained VTE endpoint. 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 one sudden cardiac death; we obtained the number of patients in this subset from the study database. Chow *et al*, 2006[12] 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[4] data are not included in the cumulative statistics because patients in this study were drawn from Klingenheben *et al*, 2000[1] and Ikeda *et al*, 2002[2]. Abbreviations: AER, annual event rate; CA, cardiac arrest; CAD, coronary artery disease; CHF, congestive heart failure; DCM, non-ischemic dilated cardiomyopathy; Ind, indeterminate MTWA test result; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Non-Neg, a non-negative MTWA test result; NR, not reported; Pos, positive MTWA test result; Neg, negative MTWA test result; SCD, sudden cardiac death; SusVT, sustained ventricular tachycardia; VF, ventricular fibrillation; [], 95% confidence interval; * (**), cumulative AER different from entry immediately to its left at the $p < 0.001$ ($p < 0.0001$) significance level.

Table 2

Annual VTE Event Rates from MTWA Trials in High ICD Group

Study	Patient Population	Mean LVEF (%)	Patient Number	Arrhythmic Endpoint	ICDs Reported Implanted at Baseline (%)	AICDTs Reported as Percent of VTE Endpoints	Non-Neg	Neg AER (%)	Non-Neg AER (%)	HR
ABCD, 2006[14]	CAD, LVEF ≤0.40 NSVT	28	566	SCD, AICDT	>50†	85	Pos or Ind	5.1	9.4	1.8
Chow *et al*, 2006[12]	CAD, LVEF ≤ 0.35 ICD subset	26	317	SCD, AICDT	100	65	Pos or Ind	4.6	7.8	1.7
SCD-HeFT Substudy, 2006[15]	CHF LVEF ≤ 0.35	25	490	SCD, SusVT, AICDT	~50†	>50†	Pos	4.2	8.2	1.9
Cantillon *et al*, 2006[11]	LVEF ≤ 0.35, NSVT or Syncope	26	286	SCD, SusVT, AICDT	61%	>50†	Pos or Ind	10.5	20.8	2.0
MASTER I, 2007[13]	CAD LVEF ≤ 0.30	24	575	SCD, AICDT	100	96	Pos or Ind	5.2	6.8	1.3
Cumulative		**25.8**	**2,234**					**5.4 [4.1 6.7]**	**8.5* [7.5 9.6]**	**1.6 [1.2 2.1]**

Data drawn from indicated studies. Chow et al, 2006[12] reported separately the results for patients with and without ICDs; the results for the ICD patients are reported here. Columns labeled *ICDs Reported Implanted at Baseline (%)* and *AICDTs Reported as Percent of VTE Endpoints* refer to patients identified in *Population* column if this represents a subset of all patients reported in study. † indicates values not explicitly reported, but confidently estimated from other reported information. Abbreviations: AICDT, appropriate ICD therapy; NSVT, non-sustained ventricular tachycardia. Other abbreviations as in Table 1.

Table 3

Ratio of Annual Rate of *Appropriate* ICD Therapy to Annual Rate of ICD Mediated Reduction in Mortality

Study	Number of Patients	Annual Rate of *Appropriate* ICD Therapy (%)	Annual Rate of ICD Mediated Reduction in Mortality (%)	Ratio
MADIT II, 2002[9, 33]	1232	15.3	4.1	3.8
SCD-HeFT, 2004[10]	1676	6.2	2.1	2.9
Cumulative	**2908**	**7.5 [6.7 8.4]**	**2.4 [1.2 3.7]**	**3.1 [2.0 6.3]**

Annual Rate of Appropriate ICD Therapy represents the annual rate of increase in the number of patients having had AICDT. *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 SCD-HeFT trial excludes amiodarone arm.

Table 4

Annual Mortality Rates in 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

				Annual Mortality (%)	
Study	**Population**	**Number of Patients**	**Mean LVEF (%)**	**No ICD**	**ICD**
MADIT II, 2002[8, 9]	Prior MI, LVEF ≤ 0.30	1,232	23	13.2	9.2
SCD-HeFT, 2004[8, 10]	CHF, LVEF ≤ 0.35	1,676	25	9.0	6.8
All		**2,908**	**24.2**	**9.5 [8.6 10.5]**	**7.3* [6.5 8.1]**
Study	**Population**	**Number of Patients**	**Mean LVEF (%)**	**Entire Population**	**MTWA Negative**
Hohnloser *et al*, 2003[4]	CAD, LVEF ≤ 0.30	129	25.5	10.4	6.7
Bloomfield *et a*l, 2006[5]	LVEF ≤ 0.40	549	25	4.5	0.6
Chow et al, 2006[12]	CAD, LVEF ≤ 0.35, No ICD	376	28.3	11.2	5.8
ALPHA, 2007[7]	DCM, LVEF ≤ 0.40	446	29.5	3.9	1.3
Cumulative		**1500**	**27.2**	**5.4 [4.5 6.4]**	**1.7** [0.8 2.6]**

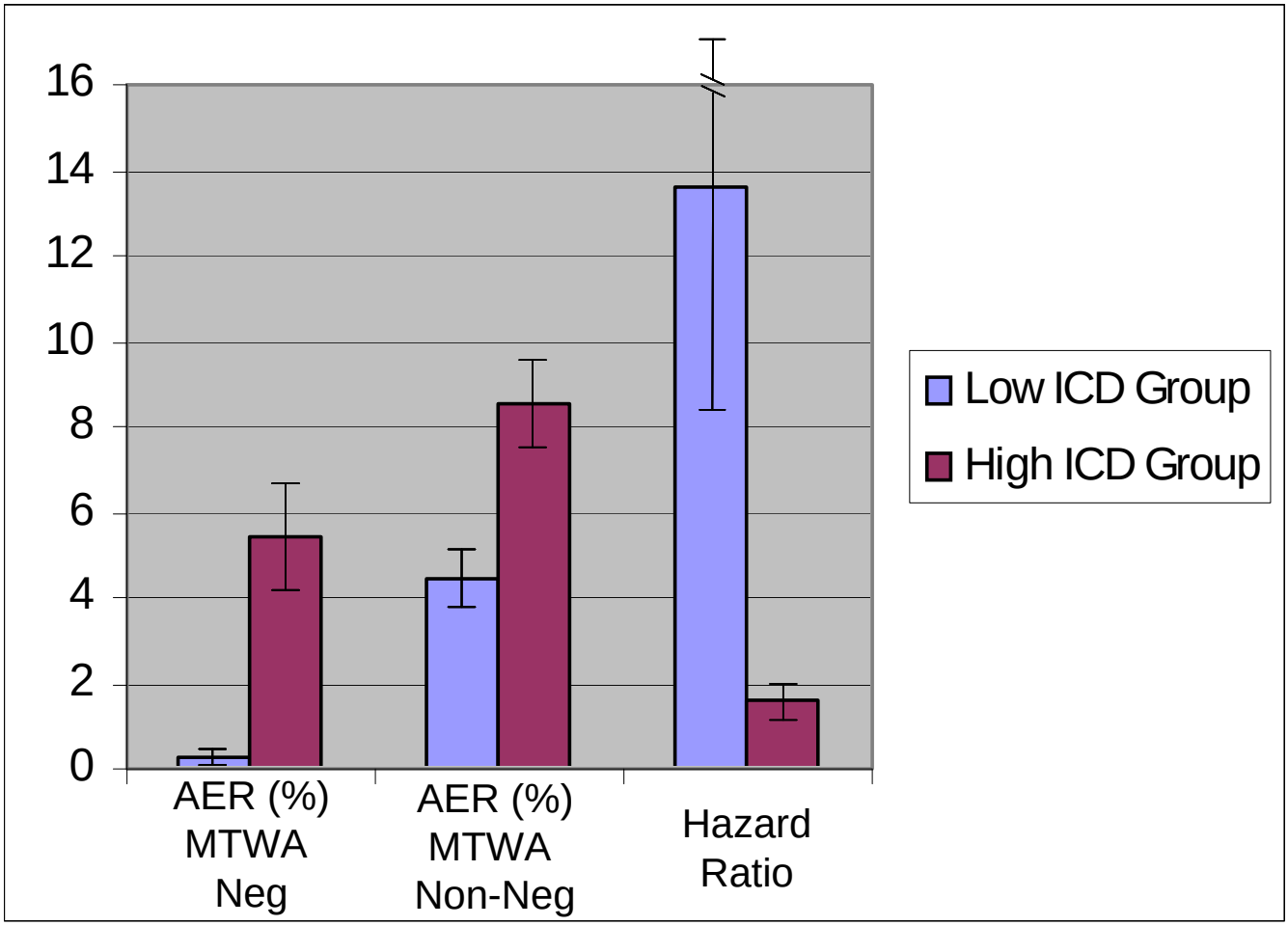
Number of patients in SCD-HeFT trial excludes amiodarone arm. For abbreviations see preceding tables.

Figure Legends

Figure 1. Cumulative annual event rates (AERs) for MTWA negative and MTWA non-negative patients, and associated hazard ratio, in the Low and High ICD Groups. Bars indicate 95% confidence intervals.

Figure 2. Clinical algorithm for use of MTWA in evaluating primary prevention patients.

Figure 1


16
14
12
10
8
6
4
2
0
AER (%) MTWA Neg
AER (%) MTWA Non-Neg
Hazard Ratio
Low ICD Group
High ICD Group

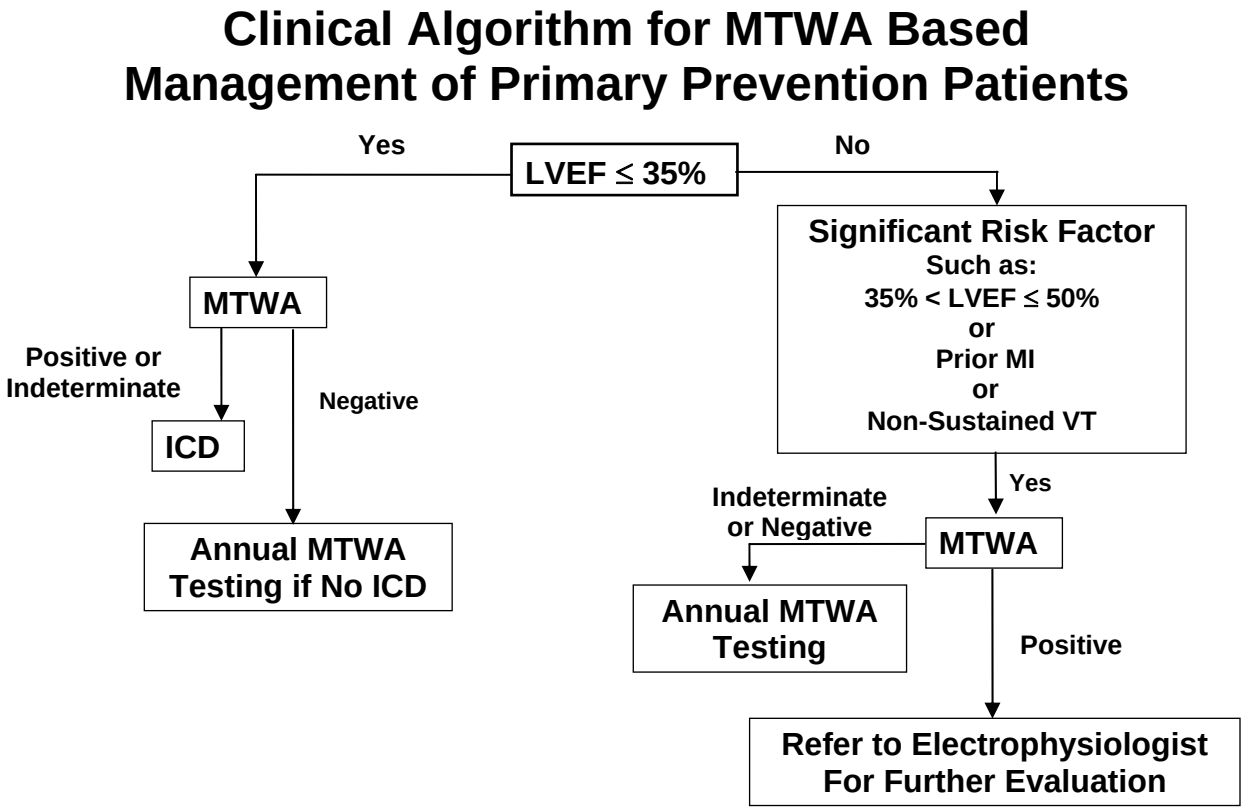

Clinical Algorithm for MTWA Based Management of Primary Prevention Patients
LVEF ≤ 35%
Yes
No
MTWA
Positive or Indeterminate
ICD
Negative
Annual MTWA Testing if No ICD
Significant Risk Factor
Such as:
35% < LVEF ≤ 50%
or
Prior MI
or
Non-Sustained VT
Yes
Indeterminate or Negative
MTWA
Annual MTWA Testing
Positive
Refer to Electrophysiologist For Further Evaluation

Figure 2