



Assessment  
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# Microvolt T-Wave Alternans Testing to Risk-Stratify Patients Being Considered for ICD Therapy for Primary Prevention of Sudden Death

## Executive Summary

### Background

This Assessment evaluates the evidence on the use of microvolt T-wave alternans (MTWA) testing to risk-stratify patients who are candidates for an implantable cardioverter-defibrillator (ICD). MTWA is proposed as a noninvasive means to predict the likelihood of subsequent ventricular tachyarrhythmic events (VTE, e.g., sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation). For example, in the study population in the “Multicenter Automatic Defibrillator Implantation Trial II” (MADIT II), the number-needed-to-treat (NNT) to avoid one death over a 20-month period was 17.9. Thus, negative MTWA results might identify a subgroup of patients who could safely forego or defer ICD implantation because they are at low risk of fatal VTE.

It is also possible that if used in patients not currently eligible for an ICD, abnormal MTWA results might identify a subgroup of patients at high risk who could potentially benefit from an ICD. However, the clinical evidence for this indication is too sparse to merit review in this Assessment.

### Objective

This Assessment examines evidence to compare outcomes of selecting patients for ICD placement for primary prevention of sudden death with and without MTWA. There are no noninvasive alternative tests, other than left-ventricular ejection fraction (LVEF), considered conventional alternatives.

### Search Strategy

MEDLINE® search (via PubMed) through March 2007; also, pertinent abstracts presented at the 2006 American Heart Association Scientific Sessions were included.

### Selection Criteria

Because of lack of direct clinical trial evidence supporting MTWA, observational studies that provided indirect evidence were selected. Studies that reported death and arrhythmic events in patients who were otherwise eligible for ICD therapy but tested MTWA negative were selected. Studies that might inform the question of what level of risk of death or arrhythmic event precludes benefit from ICD therapy were also selected.

### Main Results

Three studies were identified that evaluated MTWA in patients eligible for ICD therapy. The first study followed 177 patients (57 MTWA negative) over an average of 20 months for all-cause mortality. The second selected ICD-eligible patients from 2 previously published studies (35 total MTWA-negative subjects) and followed them over 2 years for sudden cardiac death or cardiac arrest. The third studied 768 patients who would be eligible for ICD therapy and followed them over a mean of 18 months for

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all-cause mortality and cause-specific mortality. Of these 768 patients, however, over half had ICD therapy, and thus only 376 patients (124 MTWA negative) could be assessed for natural history.

Although MTWA testing did risk-stratify patients in these studies, those with negative tests still had arrhythmic events and deaths. All-cause mortality for patients testing MTWA negative varied from 3.8% to 12.5% over 2 years, which was lower than for patients testing MTWA non-negative. Various arrhythmic event outcomes also varied between studies. Arrhythmic events varied from 0% to 5.7% over 2 years in MTWA-negative patients, depending on the specific outcome studied.

In trying to address at what level of risk ICD therapy for primary prevention would cause more harm than benefit, one study was found that explicitly modeled this question. Using death and event rates derived from the previously described 3 studies, the study showed greater benefit of ICD therapy in MTWA non-negative patients (i.e., those with positive or uninterpretable test results), but also found benefit in MTWA-negative patients. Although such a modeling study is not definitive evidence supportive or against efficacy, it suggests that under reasonable assumptions of the predictive capability of MTWA tests, clinical use of the test to determine ICD placement may not improve health outcomes.

Of further concern, analysis of SCD-HeFT data presented in abstract form at the 2006 American Heart Association Scientific Sessions found that MTWA results were not predictive of the primary endpoint of sudden cardiac death, sustained ventricular arrhythmia, or appropriate ICD discharge.

#### **Author's Conclusions and Comments**

Given the lack of randomized clinical trials, the argument for use of MTWA testing to select patients who might not benefit from ICD therapy rests on two types of information—knowledge of the natural history of persons with MTWA-negative tests, and knowledge of the degree of risk that would confer no benefit from ICD therapy. The knowledge base for both issues is insufficient. Only 3 studies of modest size evaluated outcomes of MTWA-negative subjects who were eligible for ICD placement for primary prevention. Due to the modest number of studies, there is still some uncertainty regarding the outcomes of such patients. Whether these 3 studies actually represent the same population eligible for ICD placement is uncertain. The high negative predictive value for MTWA-negative tests derived from other populations may not generalize to the population eligible for ICD placement. Furthermore, even though MTWA testing is predictive of outcome, it is uncertain if the level of risk is low enough such that ICD therapy is of no benefit. One published decision analysis suggests that ICD therapy is still of net benefit to MTWA-negative patients. Finally, lack of randomized clinical trial evidence precludes any expansion of ICD therapy to a group of newly identified patients who have positive or indeterminate MTWA tests.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether microvolt T-wave alternans testing for risk-stratifying patients being considered for ICD therapy for primary prevention of sudden death meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

#### **1. The technology must have final approval from the appropriate governmental bodies.**

Microvolt T-wave alternans (MTWA) testing may be performed using a commercially available system called the Heartwave™ Alternans Processing System marketed by Cambridge Heart, Inc. This system received 510(k) clearances on November 17, 2002 (K03564) and July 16, 2002 (K022152).

#### **2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The evidence is insufficient. Three observational studies of ICD-eligible patients with negative MTWA tests are relatively small. Although the test does stratify risk in these studies, the absolute risk of events remains uncertain. Furthermore, it is uncertain how low a level of risk precludes benefit from ICD therapy.

There are no clinical trials of ICD therapy in patients not currently eligible for ICD therapy who have been selected using MTWA testing. Thus, there is no evidence for using MTWA to expand the pool of patients eligible for ICD placement.

- 3. The technology must improve the net health outcome, and
- 4. The technology must be as beneficial as any established alternatives.

The evidence is insufficient to determine whether the use of MTWA improves net health outcome or whether it is as beneficial as any established alternatives.

- 5. The improvement must be attainable outside the investigational settings.

Whether the use of MTWA improves health outcomes is not established in the investigational settings.

Therefore, the use of microvolt T-wave alternans testing for risk-stratifying patients being considered for implantable cardioverter-defibrillator therapy for primary prevention of sudden death does not meet the TEC criteria.

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## Assessment Objective

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This Assessment evaluates the evidence on the use of microvolt T-wave alternans (MTWA) testing to risk-stratify patients who are candidates for an implantable cardioverter-defibrillator (ICD). MTWA is proposed as a noninvasive means to predict the likelihood of subsequent ventricular tachyarrhythmic events (VTE, e.g., sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation). For example, in the study population in the “Multicenter Automatic Defibrillator Implantation Trial II” (MADIT II), the number-needed-to-treat (NNT) to avoid one death over a 20-month period was 17.9. Thus, negative MTWA results might identify a subgroup of patients who could safely forego or defer ICD implantation because they are at low risk of fatal VTE.

It is also possible that if used in patients not currently eligible for an ICD, abnormal MTWA results might identify a subgroup of patients at high risk who could potentially benefit from an ICD. However, the clinical evidence for this indication is too sparse to merit review in this Assessment.

The use of ICD therapy for primary prevention of sudden death from ventricular tachyarrhythmia has been evaluated in a 2005 TEC Assessment “Use of Implantable Cardioverter-Defibrillators for Prevention of Sudden Death in Patients at High Risk for Ventricular Arrhythmia” (Vol. 19, No. 19). Specific criteria defining patient populations that have met TEC criteria for ICD placement are discussed in the prior TEC Assessment. The most important criterion is a threshold value for left-ventricular ejection fraction (LVEF). LVEF values of 30% and 35% were used as threshold values for entry into clinical trials of ICD therapy for primary prevention.

## Background

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### Microvolt T-Wave Alternans

Microvolt T-wave alternans (MTWA) refers to small beat-to-beat variability in T-wave amplitude. A routine electrocardiogram (ECG) cannot detect these small fluctuations, and thus this test requires specialized sensors to detect fluctuations combined with computer algorithms to evaluate the results. MTWA is a provocative test requiring gradual elevation of

the heart rate to above 110 beats per minute—typically through exercise. During exercise, sequential ECG cycles are aligned with the QRS complex along with measurement of T-wave amplitude. Beat-to-beat fluctuations in T-wave amplitude are then analyzed using consecutive measurements with a fast Fourier transformation. Because MTWA can be obscured by artifacts, including wandering baseline and noise, careful skin preparation and test conduct is required. However, the test can be performed in conjunction with an exercise tolerance stress test. Results are reported as the number of standard deviations by which the peak signal of the T-wave exceeds the background noise. This number is referred to as the “alternans ratio.” An alternans ratio of 3 or greater is typically considered a positive result, an absent alternans ratio negative, and other results indeterminate (Klingenheben and Hohnloser 2002; Bloomfield et al. 2002a).

Short-term reproducibility has been reported among patients derived from at least two different clinical populations. In one study, 22 of 35 patients with congestive heart failure had two determinant tests over 15 minutes (Bloomfield et al. 2002b). Results were concordant in 82% (kappa 0.58 or a moderate level of agreement). Turitto et al. (2002) examined reproducibility over 4 hours among 42 patients undergoing electrophysiological testing. Concordant results were obtained in 39 of 42 patients (93%).

### MTWA as a Risk Predictor of Sudden Death or Arrhythmias

The presence of MTWA has been investigated as a risk factor for fatal arrhythmias and sudden cardiac death in numerous studies in patients with a history of myocardial infarction, congestive heart failure, or cardiomyopathy. The evidence is quite consistent in showing an association between MTWA and arrhythmic events. Gehi et al. (2005) in a meta-analysis of 19 studies evaluating 2,608 subjects found an association between MTWA and arrhythmic events in almost all studies. The summary positive predictive value for arrhythmic events was 19.3% and the summary negative predictive value for arrhythmic events was 97.2%. Table A of the Appendix is a summary of studies TEC identified in its prior Assessment of MTWA. Almost every study showed an association between MTWA result and the outcome measured in the study. Although all studies show such an association, it is important to note that the strength of the association and diagnostic

test characteristics calculated from the studies all vary considerably. The summary negative predictive value calculated from the meta-analysis by Gehi et al. (2005) may not be applicable to specific patient groups under consideration. The population of interest to this Assessment is patients who are candidates for ICD for primary prevention.

#### **Prevention of Sudden Death with ICD**

The potential utility of a risk factor for sudden death comes acutely into focus with knowledge derived from major clinical trials evaluating the effectiveness of ICD for primary prevention of sudden death. Sudden death is a common cause of death in patients with heart failure. Thus, patients with sufficient severity of heart failure have been enrolled in clinical trials of ICD therapy. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) (Moss et al. 2002) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (Bardy et al. 2005) established the effectiveness of ICD for primary prevention of sudden death using LVEF as the major entry criterion into the studies. In the MADIT II study, patients with prior myocardial infarction (MI) who had a LVEF of  $\leq 50\%$  were eligible for ICD implantation. In SCD-HeFT, patients with class II or III symptoms who had LVEF of  $\leq 35\%$  were eligible for ICD implantation. Unlike prior clinical trials of ICD implantation, no history of arrhythmia or prior testing for susceptibility was required.

With clinical trial evidence showing that patients with LVEF  $\leq 35\%$  benefit from ICD therapy, a test that stratifies risk could provide useful information to select patients. Among patients who are considered candidates for ICD therapy by having sufficiently low LVEF, does MTWA identify a low-risk subgroup of these patients who actually receive no benefit or net harm from ICD therapy? Ideally, this question would be answered by randomized clinical trials, where MTWA is used as a selection or stratification criterion in such trials. It could be demonstrated directly whether MTWA identifies subgroups of patients that do or do not benefit from ICD therapy.

In the absence of clinical trials, it is necessary to make an indirect argument regarding the utility of MTWA. The body of evidence supporting that MTWA as a predictive risk factor for arrhythmic events is consistent across many studies evaluating many different kinds of patients and using many different types of

outcome events. The critical issue, however, is whether MTWA has specific characteristics as a predictor of risk that make it clinically useful for a specific indication. Studies that include patients ineligible for ICD therapy cannot really address the issue at hand, because the event rates and hazard ratios may not reflect the higher risk of patients who have depressed LVEF. Data on the association of MTWA and events using either hazard ratios or diagnostic test characteristics is actually not relevant to the question either, beyond reconfirming that MTWA is a risk factor. For the question of whether MTWA can identify a subgroup of patients currently eligible for ICD therapy who actually would not benefit, the following information is needed:

- Does T-wave alternans risk-stratify patients eligible for ICD therapy?
- What is the risk of arrhythmia or other adverse outcome among patients eligible for ICD therapy who have a negative MTWA test?
- Is this risk consistent with no benefit or harm if ICD therapy is used?

**FDA Status.** Microvolt T-wave alternans testing may be performed using a commercially available system called the Heartwave™ Alternans Processing System marketed by Cambridge Heart, Inc. This system received 510(k) clearances on November 17, 2002 (K03564) and July 16, 2002 (K022152).

**Medicare Coverage Policy.** In April 2006, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination statement on MTWA. The statement declared that within patient groups that may be considered candidates for ICD therapy, published literature indicates that a negative MTWA test may be useful in identifying patients who are unlikely to benefit from, and who may experience worse outcomes from ICD placement.

## **Methods**

### **Search Methods**

MEDLINE® was searched (via PubMed) through March 2007 to identify all articles pertaining to microvolt T-wave alternans testing. The key terms “T-wave” AND “alternans” were

used. The following search limits were applied: English-language reports, human subjects, and publication type (randomized, controlled trial; controlled trial; review, meta-analysis, editorial). A text search was conducted for unindexed items. Additionally, the Cochrane Library was searched in a similar fashion. In addition, the manufacturer of MTWA was contacted and shared additional information. Also, pertinent abstracts presented at the 2006 American Heart Association Scientific Sessions were also included.

### Study Selection

Study selection was designed in order to answer the questions outlined in the background section of this report. Studies were sought of ICD eligible patients who underwent MTWA testing and were followed for arrhythmic events or all-cause mortality.

Studies were required to meet all the following criteria in order to be included in the review of evidence:

- Used MTWA performed with a commercially available device and according to stress protocol.
- Applied MTWA and prospectively observed subjects for relevant clinical endpoints (e.g., ventricular tachyarrhythmic events, sudden cardiac death, cardiac death, or mortality).
- Reported event rates stratified by MTWA results or Kaplan-Meier analysis.
- Reported results for patients currently eligible for ICD placement for primary prevention, principally, LVEF  $\leq 35\%$ .
- Published in English as a full-length, peer-reviewed journal article or with sufficient information about study design, methods, and results.

Single case reports were excluded. Selected abstracts were included as supplemental information.

Given the lack of clinical trials, there is no direct evidence regarding what level of risk would be consistent with no benefit or harm associated with ICD therapy. One study was found that explicitly modeled the outcomes of a strategy of medically managing patients with negative MTWA tests versus placing ICDs in all patients. This study, by Chan et al. (2006), used estimates from the same 3 studies included in this Assessment that calculated event rates in ICD-eligible patients.

### Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on November 2, 2006. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the table(s) and text where appropriate. There were no studies that would change the conclusions of this Assessment.

## Formulation of the Assessment

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### Patient Indications

Patients who are eligible for ICD placement for primary prevention of sudden death

### Technologies to be Compared

There is currently no conventional noninvasive test currently being used to select patients for ICD placement other than measurement of LVEF. Use of MTWA would be compared to not using MTWA in selecting patients for ICD placement. Thus, use of MTWA would result in only a portion of currently eligible patients receiving ICD therapy.

### Health Outcomes

The health outcomes of interest are morbidity, mortality, and quality of life. While total mortality is the most appropriate outcome for evaluating efficacy of ICD therapy, it is generally accepted that ICD therapy works by treating VTE, thereby preventing sudden cardiac death. A diagnostic test to predict the risk of subsequent VTE with high reliability could be useful determining whether or not ICD placement is appropriate. This is of particular interest where MTWA might be used to determine when an ICD may not be beneficial among patients who would otherwise be eligible. However, it is difficult to know how low the level of risk needs to be in order for an ICD not to be beneficial. Any rate above zero could be harmful to the patient if an ICD is not used. On the other hand, ICD therapy has known risks. Without direct evidence from clinical trials, one can only speculate. One possible method to determine benefit or harm is to model the risk of harm from untreated low risk versus the benefit or harm of ICD therapy.

**Specific Assessment Questions**

Does an MTWA test stratify risk among patients eligible for ICD therapy?

What is the rate of arrhythmic events or mortality among patients otherwise eligible for ICD therapy who have a negative MTWA test?

What is the rate of arrhythmic events or mortality that is consistent with no benefit or harm when using ICD therapy?

**Review of Evidence****Does an MTWA test stratify risk among patients eligible for ICD therapy? and****What is the rate of arrhythmic events or mortality among patients otherwise eligible for ICD therapy who have a negative MTWA test?**

Three studies evaluated MTWA in patients that would be eligible for ICD therapy (Tables 1 and 2). These 3 studies provide evidence for the first two Assessment questions. Bloomfield et al. (2004) followed 177 patients over an average of 20 months for all-cause mortality. Hohnloser et al. (2003a) selected ICD-eligible patients from 2 previously published studies and followed them over 2 years for sudden cardiac death or cardiac arrest. Chow et al. (2006) studied 768 patients who would be eligible for ICD therapy and followed them over a mean of 18 months for all-cause mortality and cause-specific mortality. Of these 768 patients, however, over half had ICD therapy, and thus, only 376 patients can be assessed for natural history.

In the study by Bloomfield et al. (2004), patients were enrolled from 11 clinical centers who had LVEF  $\leq 0.40$ . The publication represents a subset of patients who would have met MADIT II criteria for ICD therapy. Patients were followed up at 4-month intervals, and mean follow-up duration was  $20 \pm 6$  months. For those with a negative MTWA test, the actuarial 2-year mortality rate was 3.8% (Table 3). For those with non-negative MTWA test, the actuarial 2-year mortality rate was 17.8%.

In the study by Hohnloser et al. (2003a), patients who met MADIT II criteria were pooled from 2 previously published studies. Eighty-seven out of 850 patients in a study by Ikeda et al. (2002) and 42 out of 107 patients

in a study by Klingenhoben et al. (2000) met MADIT II criteria and were pooled in the analysis. The study reported all-cause mortality, rates of sudden cardiac death or cardiac arrest, and rates of ventricular tachyarrhythmic events. For all-cause mortality estimated at 2 years, those with negative MTWA tests had a mortality rate of 12.5%, whereas those with non-negative MTWA tests had a mortality rate of 21.4%. For the primary outcome of sudden death or cardiac arrest, those with negative MTWA tests had a 0% rate, and those with non-negative MTWA tests had a 15.6% rate. For the secondary outcome of all ventricular arrhythmic events, those with a negative MTWA test had a 5.7% rate, and those with non-negative tests had a 31.1% rate (Table 3).

In the study by Chow et al. (2006), 768 consecutive patients with ischemic cardiomyopathy (LVEF  $\leq 35\%$ ) and no prior history of ventricular arrhythmia were followed for a mean of 18 months. Over half of the patients underwent ICD therapy, and thus, their event rates are not comparable to the other studies. Only the 376 patients who had only medical therapy are reported here. Thus, these data might be biased by selection of those who chose to have ICD therapy. In examining descriptive characteristics of the patients in the study, it appears that the MTWA-negative patients who did not receive ICD compared to the MTWA-negative patients who did receive ICD had less-severe congestive heart failure (mean LVEF 0.293 vs. 0.269).

Actuarial outcome rates were only reported in graphical form in which rates at specific time points could not be estimated with any precision. Only total deaths divided by total numbers of patients at the end of the follow-up are reported. This rate should be roughly similar to the actuarial mortality at the time of mean follow-up. At 18 months' mean follow-up, the all-cause mortality rate was 8.4% in MTWA-negative patients, and 21.8% in MTWA non-negative patients. For arrhythmic deaths, the rate was 3.4% in MTWA-negative patients, and 11.2% in MTWA non-negative patients.

Thus, all three studies demonstrate that the risk of arrhythmic events is higher among persons with MTWA-positive or indeterminate findings than those with MTWA-negative tests. The risk ratios appear to be consistent with numerous other studies evaluating various clinical populations. However the size of the risk ratio and the absolute risk of events in the

**Table 1.** Description of Studies of ICD-eligible Patients Undergoing MTWA Testing

Study	Population description	n	Mean Follow-up	Outcomes
Bloomfield et al. (2004)	Ischemic heart disease, LVEF <0.30, met other MADIT II criteria	177	20 months	Actuarial 2-year mortality rate
Hohnloser et al. (2003a)	Selected out of 2 prior published studies, ischemic heart disease, LVEF <0.30	129	16.6 months	Actuarial 2-year rate of sudden death or cardiac death, or all ventricular tachyarrhythmic events
Chow et al. (2006)	Ischemic heart disease, LVEF <0.35, no prior arrhythmia	376 (no ICD)	18 months	All-cause mortality, arrhythmic deaths

**Table 2.** All-Cause Mortality in Studies of ICD-Eligible Patients Undergoing MTWA Testing

Study (n)	% of Subjects MTWA Negative	Mortality Outcome	Rate in MTWA-negative	Rate in MTWA non-negative
Bloomfield et al. (2004) n=177	32	2-year actuarial all-cause mortality	3.8%	17.8%
Hohnloser et al. (2003a) n=129	27	2-year actuarial all-cause mortality	12.5%	21.4%
Chow et al. (2006) n=376	33*	Total deaths over 18 months' mean follow-up	8.4%	21.8%

\*Number calculated from full sample size of 768, since sample of 376 is subset of patients who did not undergo ICD placement

**Table 3.** Arrhythmic Outcome Rates in Studies of ICD-Eligible Patients Undergoing MTWA Testing

Study/n	% of Subjects MTWA Negative	Arrhythmic Outcome	Rate in MTWA-negative	Rate in MTWA non-negative
Hohnloser et al. (2003a) n=129	27	2-year actuarial rate of sudden cardiac death or arrest	0%	15.6%
		2-year actuarial rate of all ventricular tachyarrhythmic events	5.7%	31.1%
Chow et al. (2006) n=376	33*	Arrhythmic deaths over 18 months' mean follow-up	3.4%	11.2%

MTWA non-negative groups are not really relevant to the question at hand. The absolute risk of events in the MTWA-negative group, which is the group that might avoid ICD therapy, is critical.

The Bloomfield et al. (2004) study reports the lowest all-cause mortality rate of the 3 studies. The estimated 2-year mortality of 3.8% was less than one-third that of Hohnloser et al. (2003a). The mortality in the Bloomfield et al. (2004) study was also probably much lower than the study by Chow et al. (2006), which only reports mortality at a mean follow-up of 18 months. The rates of arrhythmic events also varied between the studies. This variation could be due to unmeasured differences in patients between the studies despite claiming to select MADIT II-type patients, and the relatively small numbers of patients who tested MTWA negative (35 in Hohnloser et al., 124 in Chow et al., and 57 in Bloomfield et al.). Although the sample sizes of the studies were sufficient to show a significant difference in outcome rates between MTWA-negative and MTWA non-negative patients, there is still uncertainty in the absolute rate of outcomes.

It cannot be certain that the patients in these studies are indeed similar to MADIT II patients. For example, the higher-risk MTWA non-negative patients in the study of Bloomfield et al. (2004) had an all-cause 2-year mortality of 17.8%. The mortality rate in the medically treated group in the MADIT II trial was 19.8% over a mean follow-up of 20 months. This indicates that the subjects in Bloomfield et al. (2004) were at lower risk overall than those in the MADIT II trial, and the reported all-cause mortality rate of 3.8% may not apply. In the study by Chow et al. (2006), selection of certain subjects to ICD therapy may bias estimates of mortality.

**What is the rate of arrhythmic events or mortality that is consistent with no benefit or harm when using ICD therapy?**

Given that MTWA-negative patients are at some degree of risk of death or arrhythmic events, the question is whether that degree of risk is consistent with no benefit or harm of ICD therapy. At some low level of risk, the harms of ICD therapy may balance out the benefit of preventing a low risk of sudden death. Since no direct clinical trial evidence exists, it may be possible to model the benefits and harms of ICD therapy as a function of the risk of sudden death.

Such a modeling study was published by Chan et al. (2006). In this study, the outcomes and costs associated with 2 clinical strategies were modeled. In one strategy, all patients eligible for ICD therapy as selected by MADIT II received ICD therapy. In the other strategy, patients who tested MTWA negative were managed medically, and only patients testing non-negative (i.e., positive or uninterpretable test results) received ICD therapy. Incremental outcomes and costs were compared between the two strategies using standard decision analytic methods.

Central to the model are the estimates of all-cause mortality and sudden death mortality according to patients' MTWA test results. Chan et al. (2006) cites the 3 previously discussed studies as the source of these estimates and used the following values in the analysis, which should correspond roughly to the results cited in the studies mentioned in the prior section of this Assessment (Table 4). These model estimates seem to be consistent with the observational data indicating lower risk of total mortality and sudden cardiac death mortality in those who test MTWA negative.

**Table 4.** Selected Model Estimates from Chan et al. (2006)

MTWA test result	Mortality rate without ICD, % per year
Negative	5.3% total mortality 2.7% sudden cardiac death mortality 2.6% other mortality
Non-negative	12.5% total mortality 6.4% sudden cardiac death mortality 6.1% other mortality

The results of the study showed that maximum quantity of quality-adjusted life was obtained with the strategy of treating all patients with ICD regardless of MTWA result. Although 83% of the potential benefit was achieved by implanting ICDs in the 67% of patients who were MTWA non-negative, there was additional benefit in implanting ICDs in all patients.

The results of this modeling study suggest that, using estimates derived from the 3 studies cited from the first part of this section, using MTWA to select patients who should not receive ICD implant results in worse health outcomes. Although the patients who test MTWA negative are at lower risk and receive less benefit from ICD therapy, they do achieve some net benefit in quality-adjusted survival. At least from the estimates used in the Chan analysis, MTWA does not identify a sufficiently low-risk population that the benefit of ICD therapy is outweighed by the harm of ICD therapy.

Decision models are not definitive proof of comparative efficacy of treatment strategies, however. Results are dependent on the quality of the supporting evidence and the accuracy of the model. Nonetheless, the Chan model clearly illustrates that it is not sufficient to simply demonstrate that a particular test or risk factor is strongly predictive of outcomes. The Chan analysis finds that although MTWA discriminates between a higher- and a lower-risk group, the lower-risk group still benefits, although to a lesser degree, from ICD therapy.

#### **Abstracts Presented at the 2006 American Heart Association Scientific Sessions**

At the most recent American Heart Association meetings in November 2006, there were several presentations on use of MTWA to risk-stratify patients. Most of these studies have not yet been published.

Gold and Bardy presented an analysis of MTWA testing among 490 patients enrolled in the SCD-HeFT trial. MTWA test results were not predictive of the primary endpoint of sudden cardiac death, sustained ventricular arrhythmia or appropriate ICD discharge.

Chan and Chow presented an analysis based on the same patients as the study reviewed in this Assessment by Chow et al. (2006). Since some of the total of 768 patients received ICDs, they were able to perform an observational analysis comparing outcomes of ICD placement

by MTWA results. Propensity scores were calculated for ICD implantation in order to minimize confounding. Among patients with non-negative MTWA tests, ICD placement was associated with lower all-cause mortality (hazard ratio 0.45, 95% CI: 0.27–0.76). Among MTWA-negative patients, there was less benefit that was not statistically significant (hazard ratio 0.85, 95% CI: 0.33–2.20). The difference in hazard ratio was statistically significant with a p value for interaction of 0.04. This analysis has since been published in full in a peer-reviewed publication (Chow et al. 2007). An accompanying editorial (Russo and Marchlinski 2007) states, “On the basis of the results of the current study [Chow et al. 2007], MWTA [sic] appears promising in predicting patients who might be most likely and least likely to benefit from ICD therapy,” however, “Because of limitations of the current cohort study, subsequent validation in larger cohort studies or future randomized studies is definitely needed before MTWA can be used routinely as a screening test to determine the need for prophylactic ICD insertion.”

Costantini et al. presented initial results of the ABCD trial, which was a comparison of MTWA and electrophysiologic testing (EPS) in predicting arrhythmic events in patients receiving ICDs. The principal research question of this trial may not be of relevance to this TEC Assessment, as EPS testing is not considered as an accepted comparator test. However, the study does allow a calculation of event rates among patients with different MTWA test results. Using an endpoint of arrhythmic death or appropriate ICD shock, MTWA non-negative patients had an event rate at 1 year of 9%, and MTWA-negative patients had an event rate of 5%. These predictive capabilities were equivalent to EPS testing.

A more thorough evaluation of these studies awaits their publication in peer-reviewed journals. The study by Gold and Bardy is concerning because unlike most other studies of MTWA testing, this is a large study that shows no predictive capability of MTWA testing, and it was done on the population in which ICD placement has been shown to be effective. The ABCD trial simply adds to prior literature which shows that MTWA testing stratifies risk of sudden death, approximately in the range that has been shown in prior studies. The study by Chan and Chow is an attempt to actually demonstrate differential treatment effectiveness according to MTWA results. However, patients

were not randomly assigned to ICD placement or medical therapy. Confounding can potentially affect the results of an observational study, even if appropriate statistical techniques are used. The results are consistent with a differential effect of ICD therapy, but are not consistent with no benefit from ICD therapy in MTWA-negative patients. The hazard ratio of 0.85 had an extremely wide confidence interval, consistent with a 3-fold reduction in mortality associated with ICD therapy.

### **Summary of Application of the Technology Evaluation Criteria**

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether microvolt T-wave alternans testing for risk-stratifying patients being considered for ICD therapy for primary prevention of sudden death meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

#### **1. The technology must have final approval from the appropriate governmental bodies.**

Microvolt T-wave alternans (MTWA) testing may be performed using a commercially available system called the Heartwave™ Alternans Processing System marketed by Cambridge Heart, Inc. This system received 510(k) clearances on November 17, 2002 (K03564) and July 16, 2002 (K022152).

#### **2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The evidence is insufficient. Three observational studies of ICD-eligible patients with negative MTWA tests are relatively small. Although the test does stratify risk in these studies, the absolute risk of events remains uncertain. Furthermore, it is uncertain how low a level of risk precludes benefit from ICD therapy.

There are no clinical trials of ICD therapy in patients not currently eligible for ICD therapy who have been selected using MTWA testing. Thus, there is no evidence for using MTWA to expand the pool of patients eligible for ICD placement.

#### **3. The technology must improve the net health outcome, and**

#### **4. The technology must be as beneficial as any established alternatives.**

The evidence is insufficient to determine whether the use of MTWA improves net health outcome or whether it is as beneficial as any established alternatives.

#### **5. The improvement must be attainable outside the investigational settings.**

Whether the use of MTWA improves health outcomes is not established in the investigational settings.

Therefore, the use of microvolt T-wave alternans testing for risk-stratifying patients being considered for implantable cardioverter-defibrillator therapy for primary prevention of sudden death does not meet the TEC criteria.

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# Appendix

**Table A.** MTWA Studies on Various Populations that Are Not Wholly ICD Eligible

Study	n	Endpoint	MTWA Results	Event Rate [95% CI] p value	f/u (mean)	Event-free Survival Kaplan Meier 1-year	Event-free Survival Kaplan Meier 2-year	Event-free Survival Kaplan Meier 3-year	Event-free Survival Kaplan Meier 5-year	Sub-groups	Hazard Ratio (95% CI) p value
Rashba 2004 U Maryland U South Carolina	144	Death (n=14) Sust VT/VF (n=10) Approp ICD shocks (n=26) Prevalence = 35%	MTWA + 70 (49%) MTWA ? 36 (25%) MTWA - 38 (26%)	40% 25% 16%	17 mos.	70%	50%			36% 0% LVEF 30-40%	HR=2.2 (1.1, 4.7) P=0.3
Tanno 2004 Tokyo, Japan	248	SCD (n=5) Sustained VT/VF or Approp ICD shock (n=22) Prevalence = 11%	MTWA + 23% MTWA ? 23% MTWA - 44%	NR	45 mos.			75% 99% p=0.0001			
Braga 2004 Italy	46	Cardiac death (SCD=1 + non-SCD=6) Prevalence = 15%	MTWA+ 24 (52%) MTWA ? 9 (20%) MTWA - 13 (28%)	7 (29%) 0 (0%) 0 (0%)	19 mos.						
Kirchhof 2004 Muenster Germany	16	(not well specified) Ventricular tachycardia events (n=1) Prevalence = 1/16 = 6% Prevalence = 1/9 pts = 11%	MTWA + 0 (0%) MTWA ? 4 (25%) MTWA - 12 (75%)	0 0 1 (8%)	34 mos.						
Grimm 2003 Marburg Germany	263	SCD Sustained VT/VF (n=38) Prevalence = 14%	MTWA + 137 (52%) MTWA ? 54 (21%) MTWA - 72 (27%)	13% 24% 13%	52 mos.	96%	94%	92%	83%		

**Table A.** MTWA Studies on Various Populations that Are Not Wholly ICD Eligible (cont'd)

Study	n	Endpoint	MTWA Results	Event Rate [95% CI] p value	f/u (mean)	Event-free Survival 1-year Kaplan Meier	Event-free Survival 2-year Kaplan Meier	Event-free Survival 3-year Kaplan Meier	Event-free Survival 5-year Kaplan Meier	Sub-groups	Hazard Ratio (95% CI) p value
Hohnloser 2003b Frankfurt Germany	137	Sudden death (n=4) Cardiac arrest Symptomatic VT/VF (n=14) Prevalence = 13%	MTWA + 66 (48%) MTWA ? 37 (27%) MTWA - 34 (25%)	13 (19.6%) 3 (8%), <b>2 (5.9%)</b>	14 mos.	84% 93%					
Ikeda 2002 Tokyo, Japan	834 of 850	SCD (n=12) Resuscitated VF (n=13) Prevalence = 3%	MTWA + 302 (36%) MTWA ? 95 (12%) TWA - 437 (52%)	22 (7%) Excluded <b>2 (1%)</b>	25 mos.	94% 99%	92% 99%			5.9 p=0.007	
Kitamura 2002 Kobe, Japan	104	SCD (n=3) Documented sustained VT/VF (n=9) Prevalence = 12%	MTWA + 46 (44%) Group A1 = 24 (23%) Group B = 22 (21%) MTWA ? 21 (20%) MTWA - 37 (36%)	11 (25%) 9 (25%) 2 (4%) 0 <b>1 (2.7%)</b>	21 mos.	— 72.5% 99%	— 50% 95%	— 50% 91%			8.8 (1.2, 65.4) p<0.0001
Tapanainen 2001 Finland	323 of 379	Primary: Total mortality (n=26) Prevalence = 8%	MTWA + 56 (17%) MTWA ? 46 (14%) MTWA - 144 (45%) MTWA incomplete 133 (35%)	0 (0%) 1 (4%) <b>1 (4%)</b> 24 (18%)	14 mos.	99% (+ or ?) 100% 87%	99% (+ or ?) 100% 63%			<b>Incomplete TWA</b> HR=24.7	
		Secondary: Cardiac death								HR=15	

<sup>1</sup> Group A had onset heart rate (OHR) for TWA (+) of ≤100 bpm and Group B had onset heart rate of 100<OHR≤110 bpm

**Table A.** MTWA Studies on Various Populations that Are Not Wholly ICD Eligible (cont'd)

Study	n	Endpoint	MTWA Results	Event Rate [95% CI] p value	f/u (mean)	Event-free Survival Kaplan Meier 1-year	Event-free Survival Kaplan Meier 2-year	Event-free Survival Kaplan Meier 3-year	Event-free Survival Kaplan Meier 5-year	Sub-groups	Hazard Ratio (95% CI) p value	
Adachi 2001 Kobe, Japan	64 Of 82	SCD (n=1) VTE (n=9) Prevalence = 12%	MTWA + 30 (37%) MTWA ? 18 (22%) MTWA - (34 (41%))	9 (30%) Excluded 1 (3%)	24 mos.	78%	70%	70%				
Gold 2000 Multicenter And (Cambridge Heart website)	?204 of 313	Primary: (n=27) SCD (n=5) Sustained VT/VF Appropriate ICD shock Prevalence = 9%	MTWA + 31% MTWA ? 24% MTWA - 45%	NR NR NR	9.9 mos.	81%				Determinate only: 10.9 (1.7, <∞) p<0.002	MTWA + or ? 9.5 (3.1, <∞)	
Pivotal FDA Multicenter Trial		Secondary: (n=27) Any of above plus all-cause mortality (n=10)				77%				13.9 (3.5, <∞) p<0.001	11.5 (4.0, <∞)	
Ikeda 2000 Tokyo, Japan	102 Of 119	Arrhythmic events (n=15) including symptomatic, sustained VT or VF (but excluding those in first 7 days post MI) Prevalence = 13%	MTWA + 50 (42%) MTWA ? 17 (14%) MTWA - 52 (44%)	14 (28%) Excluded 1 (2%)	13 mos.	70%				Determinate only: 16.8 (2.2, 127) p=0.006		
Klingenheben 2000 Frankfurt Germany	107	SCD (n=7) Sustained VT/VF (n=6) Prevalence = 12%	MTWA + 52 (49%) MTWA ? 22 (21%) MTWA - 33 (31%)	11 (21%) 2 (9%) 0 (0%)	18 mos.	81%					100%	MTWA was only significant predictor p=0.0036

**Table A.** MTWA Studies on Various Populations that Are Not Wholly ICD Eligible (cont'd)

Study	n	Endpoint	MTWA Results	Event Rate [95% CI] p value	f/u (mean)	Event-free Survival Kaplan Meier 1-year	Event-free Survival Kaplan Meier 2-year	Event-free Survival Kaplan Meier 3-year	Event-free Survival Kaplan Meier 5-year	Sub-groups	Hazard Ratio (95% CI) p value
Hohnloser 1998 Frankfurt	62 of 95	Appropriate ICD therapy or shock (n=41) Prevalence = 43%	MTWA + 36 (41%) MTWA ? 16 (18%) MTWA - 26 (30%)	? Excluded ?	14.7 mos.	60%					MTWA and LVEF were only predictors in CAD subgroup
<i>Armoundas 1998<sup>2</sup> Retrospective (overlap with Rosenbaum)</i>	36 f/u of 43	Sudden cardiac death Sustained VT/VF (n=3) Prevalence = 3/36=8%	MTWA + 11 (26%) MTWA ? 0 (0%) MTWA - 32 (74%)	? ? ?	5.7 mos.	55%					16 p<0.0012
Rosenbaum 1994 Cleveland	66 of 83	Sudden cardiac death (n=5) Sustained VT/VF (n=8) Prevalence = 13/66 = 20%	MTWA + 33 ? NR MTWA ? 2 ? NR MTWA - 48 ? NR	? ? ?	20 mos.	60%	19%	94%			9.0 p<0.001, 20 mos.

<sup>2</sup> Armoundas is subgroup report of Rosenbaum 1994

**Abbreviations**

CAD	coronary artery disease
EP	electrophysiologic
ICD	implantable cardioverter-defibrillator
LVEF	left-ventricular ejection fraction
NR	not reported
SCD	sudden cardiac death
VF	ventricular fibrillation
VTE	ventricular tachyarrhythmic events
VT	ventricular tachycardia

**Table B.** Selected MTWA Abstract Reports

Study	n	Study Population Endpoint	MTWA Results	Event Rate	f/u (mean)	Event-free Survival Kaplan Meier 1-year	Event-free Survival Kaplan Meier 2-year	Event-free Survival Kaplan Meier 3-year	Event-free Survival Kaplan Meier 5-year	Subgroups	Hazard Ratio (95% CI) p value
Bloomfield 2005 American College Cardiology and Poster and Bigger 2005 Columbia University, NY	549	Mixed ischemic and nonischemic cardiomyopathy with LVEF ≤40%  Death (n=40) Nonfatal adverse events (n=11)	66% abnormal ? % negative	false negative rate=2%	20 mos.	92% 99%	85% 98%			Poster: At 2 years: MTWA(-) Nonischemic had 0% events Ischemic had 4.8% events	6.5 p<0.001
Costantini 2004 Case Western Reserve and Columbia University	282	Nonischemic dilated cardiomyopathy with LVEF ≤40%  Excluded atrial fibrillation, NYHA class IV, or sustained ventricular tachycardia  All-cause mortality (n=12)	66% abnormal 34% negative	8.6% 0%	16.4 mos.						
Bloomfield 1999 Multicenter	130	Syncope or presyncope patients selected from 337 patients referred for EP testing  VTE (n=7) Sustained VT/VF Appropriate ICD Death (n=2)	38% positive ? % negative		9 mos.	81% 97%					7.1

**Table B.** Selected MTWA Abstract Reports (cont'd)

Study	n	Study Population Endpoint	MTWA Results	Event Rate	f/u (mean)	Event-free Survival Kaplan Meier 1-year	Event-free Survival Kaplan Meier 2-year	Event-free Survival Kaplan Meier 3-year	Event-free Survival Kaplan Meier 5-year	Subgroups	Hazard Ratio (95% CI) p value
Chow 2003 Cincinnati	193 of 203	MADIT-II-like CAD and LVEF ≤30%	50.3% positive 20.2% indeterminate 29.5% negative	9 (9%) 3 (8%) 1 (2%)	12.5 mos.		88.2%				6.0
		Arrhythmic death Resuscitated cardiac arrest Appropriate ICD					98%	18 mos.			

- Abbreviations**
- CAD coronary artery disease
  - EP electrophysiologic
  - ICD implantable cardioverter-defibrillator
  - LVEF left-ventricular ejection fraction
  - NR not reported
  - SCD sudden cardiac death
  - VF ventricular fibrillation
  - VTE ventricular tachyarrhythmic events
  - VT ventricular tachycardia





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