



# CIGNA MEDICAL COVERAGE POLICY

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Subject **Microvolt T-Wave Alternans**

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## Coverage Policy

**CIGNA covers microvolt T-wave alternans (MTWA) testing as medically necessary to identify the risk of ventricular arrhythmia and sudden cardiac death in an individual who meets criteria for implantable cardioverter defibrillator placement\*.**

**\*Refer to the CIGNA Coverage Policy Implantable Cardioverter Defibrillator (ICD) for additional information.**

**CIGNA does not cover MTWA testing for any other indication because it is considered experimental, investigational or unproven.**

## General Background

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality in the United States. Ventricular tachyarrhythmias are reported to be the most common cause of SCD death. Among individuals at risk for these ventricular arrhythmias and SCD are patients in the post-acute myocardial infarction (MI) period; those with congestive heart failure (CHF), coronary artery disease, or a family history of multiple SCD; and those with hypertensive cardiomyopathy or other types of cardiomyopathy (American Heart Association [AHA], 2010; Gold, Spencer, 2003; Armoundas, et al., 2002; Cohen, 2001; Barron, 2000; Costantini, et al., 2000).

Mortality from a cardiac arrest remains high, which underscores the need for risk stratification techniques to identify patients at high risk for these events and effective interventions that can prevent or abort these events. Although risk stratification techniques have been studied for decades, their current relevance is enhanced by the availability of medical therapies and the implantable cardioverter defibrillator (ICD), which have been shown to reduce both total and SCD mortality in selected high-risk patients. Studies of the ICD showed significant reductions in all-cause and sudden death mortality in certain high-risk cohorts of patients. Two studies in particular are most responsible for the dramatic increase in ICD use for primary prevention. Specifically, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) evaluated patients with symptomatic heart failure (New York Heart Association class II–III) and left ventricular systolic dysfunction, whereas the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) evaluated patients with coronary artery disease and ischemic cardiomyopathy. Both studies showed a benefit of ICD implantation, but appropriate shocks for ventricular tachyarrhythmias were only noted in a few of the patients during 4–5 years of follow-up. This suggests that many patients with current indications for ICD implantation may not benefit from this invasive therapy and that better risk stratification is needed to optimize patient selection for this therapy (Gold, et al., 2008; Goldberger, et al., 2008).

Microvolt T-wave alternans (TWA) or (MTWA) is a noninvasive test of arrhythmia vulnerability. The results of previous observational studies showed that MTWA predicts ICD shocks or arrhythmic events in diverse patient populations, including those with heart failure and ischemic cardiomyopathy. This led to the hypothesis that within groups of patients that may be considered candidates for ICD therapy, a negative MTWA test may be useful in identifying low-risk patients who are unlikely to benefit from, and who may experience worse outcomes from, ICD placement (Gold, et al., 2008, Centers for Medicare & Medicaid Services [CMS], 2008).

The measurement of MTWA during exercise can be challenging since the levels of noise during exercise can exceed the levels of MTWA. However, the use of special multisegment high-resolution electrodes, noise-reduction software, and a spectral method of alternans analysis has reduced noise, enabling reliable measurement of MTWA. Spectral analysis during controlled HR acceleration has been the most widely applied technique to measure TWA (Narayan, 2006; Prystowsky, et al., 2004; Walker, Rosenbaum, 2003; Gold, Spencer, 2003; Armoundas, et al., 2002; Albrecht, et al., 1996).

The amplitude, or magnitude, of TWA is measured in microvolts ( $\mu\text{V}$ ), or MTWA. A value of  $\geq 1.9 \mu\text{V}$  is considered a positive result. The threshold onset HR must be  $< 110$  beats per minute (bpm), and it must be sustained above the HR for the test to be considered positive. In addition to measuring the magnitude of the alternans, this provides a means of establishing the statistical confidence of the alternans measurement. This is determined by measuring the alternans ratio, which is obtained by dividing the noise-corrected alternans voltage by the standard deviation of the noise. This value indicates the number of standard deviations by which the alternans magnitude exceeds the noise level and is positive if it is  $\geq$  three (Gold, Spencer, 2003; Armoundas, et al., 2002; Costantini, et al., 2000).

A limitation of the MTWA test is that it cannot be administered in patients with atrial fibrillation (AF). Other relative contraindications to testing include frequent atrial or ventricular ectopy, paced (ventricular) rhythm, inability to achieve a HR  $> 105$  bpm and adverse reaction to skin electrodes. In addition, for patients in whom the noise level cannot be reduced appropriately or in those with frequent premature ventricular contractions, these factors may mask true alternans or create false alternans. As a result of these problems, approximately 15–40% of MTWA test results are indeterminate (Verrier, et al., 2003; Gold, Spencer, 2003; Armoundas, et al., 2002; Costantini, et al., 2000).

A positive MTWA test is one of many risk factors that have been investigated for primary prevention with an ICD. Other noninvasive tests have been proposed to identify patients at high risk for developing ventricular arrhythmias. These include calculation of left ventricular ejection fraction (LVEF) using echocardiography, ambulatory monitoring to identify ventricular ectopy, signal-averaged ECG (SAECG) to identify late potentials, measures of autonomic tone such as heart rate (HR) variability and baroreflex sensitivity, and abnormalities of ventricular repolarization as reflected by QT dispersion. However, these noninvasive tests have limited sensitivity and specificity as well as low predictive value for stratifying patients at risk for SCD (Bloomfield, 2004; Verrier, et al., 2003; Gold, Spencer, 2003; Adachi, et al., 2001; Barron, 2000; Costantini, et al., 2000). Programmed ventricular stimulation during electrophysiologic study is considered a useful predictor of ventricular tachyarrhythmic events (VTEs) in some patients. However, this technique is invasive and expensive, requires a subspecialist cardiologist, and has limited effectiveness (Gold, et al., 2000).

Textbook literature regarding TWA states: "Microvolt-level TWA testing is a promising technique that appears to be an effective, noninvasive predictor of risk for ventricular arrhythmias and sudden death in published studies. This test appears to be comparable to invasive electrophysiologic testing but needs to be assessed in controlled clinical trials to determine whether management based on TWA findings improves the survival of patients at risk for life-threatening ventricular arrhythmias" (Hamill, 2007). Many patients who undergo ICD implantation for primary prevention never require an appropriate shock. Therefore, MTWA may be useful for identifying patients at negligible risk and can forego ICD implantation (Pelosi, et al. 2007).

### **U.S. Food and Drug Administration (FDA)**

The Microvolt T-Wave Alternans Test™ is processed thru the HearTwave® II Cardiac Diagnostic System (Cambridge Heart, Inc., Bedford, MA). The HearTwave II Cardiac Diagnostic System received 510(k) clearance in April 2005 from the FDA (FDA, 2005). The equivalent device is the CH 2000 Cardiac Diagnostic System (Cambridge Heart, Inc., Bedford, MA).

The FDA indications for use states, "The HearTwave II Cardiac Diagnostic System is intended for the recording of electrocardiograms, vector cardiograms and measurement of Microvolt T-Wave Alternans\* at rest and during ECG stress testing. The presence of Microvolt T-wave Alternans as measured by the HearTwave II Cardiac Diagnostic System in patients with known, suspected or at risk of ventricular tachyarrhythmia predicts increased risk of a cardiac event (ventricular tachyarrhythmia or sudden death). The HearTwave II Cardiac Diagnostic System should be used only as an adjunct to clinical history and the results of other non-invasive and/or invasive tests" (FDA, 2005).

### **Literature Review**

Several studies have been published in the peer-reviewed medical literature that evaluate MTWA as a predictor of ventricular arrhythmias and SCD. The studies are international in scope and evaluated MTWA for a wide variety of patient indications, including nonischemic and idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, arterial hypertension, Brugada syndrome, CHF, coronary artery disease, and post-acute MI. Several studies compared MTWA to electrophysiological testing and other, more conventional parameters for arrhythmia risk stratification. Most were prospective studies, including some that were controlled. Some studies used electrophysiologic testing (e.g., programmed ventricular stimulation) as the reference standard for defining vulnerability to arrhythmia. Other comparative, noninvasive tests for determining arrhythmic risk used in some studies were signal-averaged ECG, LVEF, baroreflex sensitivity, 24-hour ECG monitoring, and HR variability.

There is some evidence indicating that MTWA testing, either alone or in combination with other noninvasive tests, may be a sensitive predictor of ventricular arrhythmias and sudden cardiac death (SCD) in certain groups of potentially at-risk patients. There is evidence that MTWA testing has excellent negative predictive value for ventricular arrhythmias in patients with reduced systolic function. The absence of MTWA carries a 3% risk of arrhythmic events during follow-up of one to two years. Negative MTWA testing will be useful for identifying individuals who may not require implantable cardioverter defibrillator (ICD) placement.

### **The Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) Study**

In the multicenter prospective MASTER study, Chow et al. (2008) studied whether MTWA predicts VTEs in post-myocardial infarction patients with LVEF  $\leq$  30%. Previous studies have established MTWA as a predictor for total and arrhythmic mortality, but its ability to identify ICD recipients most likely to experience VTEs remains uncertain. Patients were eligible if they met MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) indications for device implant. All patients underwent MTWA testing followed by ICD implantation, with pre-specified programming to minimize the likelihood of therapies for non-life-threatening ventricular tachyarrhythmic events. Minimum follow-up was two years with annual MTWA testing. Initially indeterminate MTWA tests were repeated. Analyses were conducted on 575 patients. The primary end point for the trial was a ventricular tachyarrhythmic event defined as SCD or an appropriate ICD discharge. The final distribution of MTWA results were: MTWA positive in 293 (51%), MTWA negative in 214 (37%), and indeterminate in 68 patients (12%). Over an average follow-up of 2.1 years, there were 70 ventricular tachyarrhythmic events. A VTEs occurred in 48 of 361 (13%, 6.3%/year) MTWA non-negative and 22 of 214 (10%, 5.0%/year) MTWA negative patients. A non-negative MTWA test result was not associated with VTEs (hazard ratio: 1.26; 95% confidence interval: 0.76– 2.09;  $p=0.37$ ), although total mortality was significantly increased (hazard ratio: 2.04;

95% confidence interval: 1.10–3.78;  $p=0.02$ ). The reported main limitation of this study is the use of ICD treatment for VT/ventricular fibrillation as a surrogate for SCD.

### **Heart Failure and Systolic Dysfunction-(Substudy of the Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT])**

In the prospective substudy of the randomized SCD-HeFT trial, Gold et al. (2008) studied whether MTWA is a risk stratifier in a subgroup of the SCD-HeFT cohort. In the MTWA substudy, 490 SCD-HeFT patients were enrolled at 37 clinical sites. A total of 146 patients were randomized to amiodarone drug therapy, 178 to placebo therapy and 166 to ICD implantation. The primary endpoint was SCD, a sustained ventricular tachyarrhythmia or an appropriate ICD discharge. Patients were followed for a median of 30 months. MTWA results were classified as negative (22%), positive (37%), or indeterminate (41%). No significant difference in event rates was found between any MTWA category. The authors reported that MTWA testing did not predict arrhythmic events or mortality and should not be used to make clinical decisions about ICD therapy among patients who meet SCD-HeFT criteria for ICD implantation.

### **Predictive Value of MTWA in the General Population**

In a cohort study, Nieminen et al. (2007) tested the hypothesis that TWA predicts mortality in a general population of patients referred for a clinical exercise test. A total of 1037 patients with a clinically indicated exercise test and with technically successful ECG data during a bicycle ergometer test were included in the study. Digital ECGs were recorded and TWA was analyzed continuously with the time-domain modified moving average method. The maximum TWA value at HR, 125 bpm was derived and its capacity to stratify risk for all-cause death, cardiovascular death, and sudden cardiac death (SCD) was tested. During a follow-up of  $44 \pm 7$  months, 59 patients died; 34 were due to cardiovascular causes and 20 were due to SCD. In multivariate analysis after adjustment for age, sex, use of beta blockers, functional class, maximal HR during exercise, previous MI, and other common coronary risk factors, the relative risk of  $TWA \geq 65$  mV for SCD was 7.4 (95% confidence interval [CI], 2.8–19.4;  $p<0.001$ ), for cardiovascular mortality 6.0 (95% CI, 2.8–12.8;  $p<0.001$ ), and for all-cause mortality 3.3 (95% CI, 1.8–6.3;  $p<0.001$ ). The study limitations that may prevent the generalization of the present results include the definition of SCD. The authors reported using death within 24 hours after the onset of symptoms as a definition for SCD. It is possible that some of these deaths are not due to ventricular tachyarrhythmia. TWA was a strong predictor of cardiovascular mortality but did not predict well the noncardiac deaths, showing that the occurrence of TWA during exercise reflects abnormal cardiac electrical or mechanical function predisposing to cardiac death. Another limitation is that no information on changes in parameters affecting mortality risk (e.g., smoking, lifestyles, and medication) was available during the follow-up.

### **Congestive Heart Failure and Nonischemic Left Ventricular Dysfunction**

In the Microvolt T-Wave Alternans in Patients with Heart Failure (ALPHA) study, studied the prognostic value of TWA in New York Heart Association (NYHA) functional Class II/III patients with nonischemic cardiomyopathy and  $LVEF \leq 40\%$  on optimal medical therapy. In this multicenter prospective observational study, 446 patients were enrolled and followed up for 18–24 months. The primary end point was the combination of cardiac death and life-threatening arrhythmias; secondary end points were total mortality and the combination of arrhythmic death and life-threatening arrhythmias. Patients with abnormal TWA (65%) compared with normal TWA (35%) tests were older ( $60 \pm 13$  years versus  $57 \pm 12$  years), were more frequently in NYHA functional Class III (22% versus 19%), and had a modestly lower LVEF ( $29 \pm 7\%$  versus  $31 \pm 7\%$ ). Primary end point rates in patients with abnormal and normal TWA tests were 6.5% (95% CI 4.5%–9.4%) and 1.6% (95% CI 0.6%–4.4%), respectively. Unadjusted and adjusted hazard ratios were 4.0 (95% CI 1.4%–11.4%;  $p=0.002$ ) and 3.2 (95% CI 1.1%–9.2%;  $p=0.013$ ), respectively. Hazard ratios for total mortality and for arrhythmic death and life-threatening arrhythmias were 4.6 ( $p=0.002$ ) and 5.5 ( $p=0.004$ ), respectively; 18-month negative predictive values for the three end points ranged between 97.3%–98.6%. The authors reported that the results of the present study suggest that TWA may be effectively used to identify a subgroup of patients who are likely to have little benefit from ICD therapy despite heart failure and left ventricular dysfunction although additional studies are needed.

### **Nonsustained VT and/or Syncope**

In a prospective observational study, Cantillon et al. (2007) evaluated the utility of TWA in predicting arrhythmia-free survival in patients with  $LVEF \leq 35\%$  among patients who underwent both electrophysiology study (EPS) and TWA for SCD risk-stratification. The study included a total of 286 patients with an  $LVEF \leq 35\%$  who underwent TWA and EPS owing to nonsustained VT and/or syncope. Positive and indeterminate TWA results were grouped as non-negative. The primary end point was arrhythmia-free survival; the secondary end point was all-cause mortality. The patients were followed for a mean of 38 months. There was no significant

difference between the TWA-negative (n=90; 31%) and non-negative (n=196; 69%) groups with respect to ICD implant rates (54% versus 64%, respectively; p=0.95) or etiology of cardiomyopathy (ischemic: 73% versus 76%; p=0.71). The Kaplan-Meier curves demonstrated improved arrhythmia-free survival in TWA-negative patients (81% versus 66% at two years; p<0.001), including in both ischemic (79% versus 64% at two years; p=0.004) and nonischemic (88% versus 71% at two years; p=0.015) subgroups. Total mortality was lower in the TWA-negative group (10% versus 18% at two years; p=0.04). The negative predictive value of TWA for (two-year) total mortality was 90%, and 83% for EPS. The authors reported that their study used an atrial pacing protocol while the comparative earlier studies used a treadmill TWA protocol. Differences in autonomic tone, incidence of excessive artifact leading to an indeterminate result, and the ability to reach and maintain a sufficient HR might differ between the two protocols.

### **Ischemic Left Ventricular Systolic Dysfunction**

In a multicenter prospective cohort study, Chow et al. (2006) studied if MTWA is an independent predictor of mortality in patients with ischemic cardiomyopathy. The 768 enrolled patients had ischemic cardiomyopathy with LVEF  $\leq$  35% and no prior history of ventricular arrhythmia. A positive MTWA test was defined as sustained alternans with an onset HR of  $\leq$  110 beats/min. A negative MTWA test was defined as the absence of criteria for a positive test with a maximum HR of  $\geq$  105 beats/min. All other tests were classified as indeterminate. During statistical analysis, indeterminate and positive tests were classified as non-negative. A total of 514 (67%) of the patients had a non-negative MTWA test. A non-negative test was associated with a higher risk for all-cause and arrhythmic mortality but not for nonarrhythmic mortality. Additionally, a non-negative MTWA test was associated with a higher risk for all-cause mortality in patients with ejection fractions  $\leq$  30% and after excluding those with indeterminate MTWA tests.

In a follow-up study, Chow et al. (2007a) evaluated whether ICDs have different mortality benefits among patients with ischemic cardiomyopathy who screen negative and non-negative (i.e., positive and indeterminate) for MTWA. The primary end point was all-cause mortality and appropriate ICD shocks. The mean follow-up was 27 months. A total of 392 of the 768 patients received ICDs. After multivariable adjustment, ICDs were associated with lower all-cause mortality in MTWA non-negative patients largely due to a reduction in arrhythmic mortality. Only 75 of the MTWA negative group received an ICD. The authors reported that a larger study may have found a benefit with ICD therapy in the MTWA negative group, although prior studies have shown that patients who test MTWA negative have much lower arrhythmic event rates. This is a prospective cohort study, not a randomized study evaluating the benefit of ICD therapy based on MTWA status.

Chan et al. (2008) studied the prognostic utility of MTWA in predicting all-cause mortality and life-threatening arrhythmias over three years. The cohort of patients was from the previous Chow et al. (2006) study. The authors reported that the prognostic utility of MTWA screening in patients with ischemic cardiomyopathy did not diminish after one year of follow-up. Patients with nonnegative MTWA tests continued to have a greater than two-fold increased risk of all-cause mortality and arrhythmic events in their second, and potentially third year, of follow-up. The authors reported that these findings need further validation but they suggest rescreening with MTWA may not need to be performed more frequently than one every two years.

### **Left Ventricular Systolic Dysfunction Irrespective of Etiology**

Bloomfield et al. (2006) conducted a large prospective, multicenter study supported by the National Institutes of Health to test the hypothesis that in patients with either ischemic heart disease or nonischemic cardiomyopathy and LVEF  $\leq$  40%, an abnormal MTWA would be associated with an increased risk of death and non-fatal arrhythmia events, while a normal MTWA would be associated with a favorable prognosis. Patients were excluded for AF, unstable coronary artery disease, or NYHA functional class IV heart failure. Participants underwent an MTWA test and were followed for two years. The primary outcomes were nonfatal sustained ventricular arrhythmias or all-cause mortality. Since previous studies have shown that positive and indeterminate MTWA tests have similar events rates, all comparisons in this analysis were made between patients with normal (negative) and abnormal (positive or indeterminate) MTWA tests. In two years of follow-up, four events occurred in the 189 patients with a normal MTWA test. Forty-seven events occurred in the group with an abnormal MTWA test. Abnormal MTWA tests comprise positive tests (n=162, two-year event rate 12.3%) and indeterminate tests (n=198, two-year event rate 17.5%). The survival rate was 97.5% for those patients with left ventricular dysfunction classified as a low risk by a normal MTWA test.

In a systematic review and meta-analysis, van der Avoort et al. (2009) evaluated MTWA as a predictor of mortality and severe arrhythmic events in patients with severe left-ventricular dysfunction and no history of

previous arrhythmic event. The primary outcome was a composite of mortality and severe arrhythmias. No randomized controlled trials were identified. A total of 8 published cohort studies involving a total of 1,946 patients, including 332 positive, 656 negative, 84 indeterminate, and 874 non-negative (which includes both positive and indeterminate tests) MTWA test results were reported. The risk of mortality or severe arrhythmic events was higher in patients with a positive MTWA compared to a negative test). Similar results were obtained when comparing non-negative MTWA to a negative test. The authors concluded that “although the body of evidence is far from ideal, MTWA appears to predict mortality and severe arrhythmias occurring within one to two years in patients with left-ventricular dysfunction and no previous history of ventricular arrhythmias. Patients with positive or indeterminate tests are at higher risk of mortality and severe arrhythmic events than patients with negative MTWA, potentially aiding the identification of patients most likely to benefit from prophylactic ICD implantation and thereby perhaps improving the cost-effectiveness of this therapy. There remains a need to examine MTWA in well-conducted randomized controlled trials as well as the ability of MTWA to predict long-term outcomes. While awaiting further quality studies, physicians and policy makers may wish to consider MTWA to help identify patients in the greatest need of aggressive primary prevention and ICD implantation.”

### **Post-MI and Left Ventricular Systolic Dysfunction**

In a multicenter, prospective observational study, Huikuri et al. (2009) evaluated whether risk stratification tests can predict serious arrhythmic events after acute myocardial infarction (AMI) in patients with reduced left ventricular ejection fraction (LVEF  $\leq$  0.40). A total of 312 individuals from 10 European centers with a mean LVEF of 31+6% were included in the study. Heart rate variability/turbulence, ambient arrhythmias, signal-averaged electrocardiogram (SAECG), T-wave alternans, and programmed electrical stimulation (PES) were performed six weeks after AMI. The primary endpoint was ECG-documented ventricular fibrillation or symptomatic sustained VT. To document these arrhythmic events, the patients received an implantable ECG loop-recorder. Exercise tests and MTWA analysis were performed at six weeks post-AMI. There were 25 primary endpoints during the follow-up of two years. The strongest predictors of primary endpoint were measures of heart rate variability. Induction of sustained monomorphic VT during PES also predicted the primary endpoint. The authors reported that MTWA did not confirm its clinical benefit early after the AMI.

Bloomfield et al. (2004) compared the ability of MTWA and QRS duration to identify groups at high and low risk of dying among heart failure patients who met Multicenter Automatic Defibrillator Implantation Trial (MADIT) II criteria for implantable cardioverter defibrillator (ICD) prophylaxis. The MADIT II showed that patients with prior MI and a LVEF  $\leq$  30% who were randomized to ICD therapy had an improved survival rate compared to those patients randomized to conventional medical therapy. The Centers for Medicare & Medicaid Services (CMS) analyzed MADIT II data and in June 2003 published its intent to issue a National Coverage Decision indicating there is adequate evidence to conclude that an ICD is reasonable and necessary in patients with prior MI, an ejection fraction  $\leq$  0.30, and a QRS duration  $>$  120 milliseconds (ms). The CMS decision prompted the study by Bloomfield and colleagues. Five hundred and forty-nine patients were evaluated, with 177 meeting criteria. The mean patient follow-up was 20 months, and the primary outcome was all-cause mortality. Of 177 MADIT II-like patients, 32% had a QRS duration  $>$  120 ms, and 68% had an abnormal (positive or indeterminate) MTWA test. During an average follow-up of 20  $\pm$  6 months, 20 patients died. The authors compared patients with an abnormal MTWA test to those with a normal (negative) test, and patients with a QRS  $>$  120 ms to those with a QRS  $\leq$  120 ms; the hazard ratios for two-year mortality were 4.8 (p=0.020) and 1.5 (p=0.367), respectively. The actuarial mortality rate was substantially lower among patients with a normal MTWA test (3.8%; 95%CI: 0, 9.0) than the mortality rate in patients with a narrow QRS (12.0%; 95% CI: 5.6, 18.5). The corresponding false-negative rates are 3.5% and 10.2%, respectively. The authors reported that among MADIT II-like patients, a MTWA test is better than QRS duration at identifying a high-risk group and also better at identifying a low-risk group unlikely to benefit from ICD therapy. These conclusions are consistent with the retrospective meta-analysis by Hohnloser et al. (2003b).

Hohnloser et al. (2003b) analyzed pooled data from two prior studies on MTWA testing in patients with a prior MI and reduced LVEF (Klingenheben, et al., 2000; Ikeda, et al., 2002) to evaluate the utility of the test in determining which patients would not benefit from ICD therapy. The risk of SCD or cardiac arrest during a two-year follow-up was significantly reduced in patients who were MTWA-negative compared to patients who tested positive or indeterminate. Similarly, the risk of a composite end point consisting of sustained ventricular arrhythmias, sudden death, and cardiac arrest was significantly reduced in MTWA-negative patients compared to those who tested positive or indeterminate. Therefore, the authors suggested that patients who test negative for MTWA might not benefit from prophylactic ICD implantation and that those who tested positive or indeterminate might be appropriate candidates. These findings require confirmation in larger, well-designed

trials. Limitations of this study included a small sample size and lack of data on drug therapy, which can affect MTWA test results.

### **Post-MI**

In a multicenter cohort study in Japan, Ikeda et al. (2006) evaluated the predictive power of MTWA in patients with preserved LVEF after MI. There is little information available about the prognostic value of risk stratification markers in this population. A total of 1041 post-MI patients with an LVEF  $\geq 40\%$  (average  $55 \pm 10\%$ ) were enrolled in this study. MTWA testing was performed an average of 48 days after acute MI, and 10 other risk variables were also evaluated. The end points were SCD or life-threatening arrhythmic events. During an average follow-up of 32 months, 38 patients (3.7%) died of nonarrhythmic causes and were not considered for analysis. Of the 1003 remaining patients, 18 (1.8%) reached an end point. MTWA was positive in 169 patients (17%), negative in 747 (74%), and indeterminate in 87 (9%). A positive MTWA test, nonsustained VT, and ventricular late potentials were predictors of events, and percutaneous coronary intervention decreased the risk rate. On multivariate analysis, a positive MTWA test was the most significant predictor. This marker had the highest sensitivity and negative predictive value for events. The authors reported that “in patients with preserved cardiac function, the incidence of indeterminate results of MTWA is low, and a positive test result is associated with arrhythmic events. MTWA could be used for risk stratification in this low-risk population.” One reported limitation of this study is that the clinical outcome of patients may be influenced by the accompanying post-MI therapy. The low rate of beta-blocker use may influence the results in terms of risk stratification. In Western countries, beta-blockers are considered mainstay in post-MI therapy with high beneficial impact on prognosis. Japanese patients exhibit a threefold greater incidence than Caucasian patients of coronary spasm after acetylcholine. The Japanese guidelines for diagnosis and treatment of cardiovascular disease state that a physician may not use beta-blockers when coronary spasm is suspected as the cause of acute coronary syndrome. The authors reported that the results of their study may not be transferable to post-MI cohorts in Western countries.

### **Indeterminate MTWA Testing**

MTWA tests are classified as negative, positive, or indeterminate. About 20–40% of MTWA tests are indeterminate due to patient or technical factors. Kaufman et al. (2006) evaluated the hypothesis that an indeterminate MTWA test, when due to patient factors (i.e., ectopy, unsustained MTWA, or low exercise HR), has prognostic significance similar to a positive MTWA test. A total of 549 participants were included in the study. Exclusions included unstable angina, class IV heart failure, AF, or prior sustained ventricular arrhythmia. Patients in sinus rhythm with LVEF  $\leq 40\%$  underwent MTWA exercise tests, analyzed with the spectral method and classified by a computerized interpretation algorithm. The primary end point was all-cause mortality or documented non-fatal sustained ventricular arrhythmia (SVA). Follow-up was completed at one month after the MTWA test and every four months thereafter. A positive MTWA test was classified as  $\geq$  one minute of MTWA with an onset at a HR  $\leq 110$  beats/min that sustained as long as HR remained above the patient-specific onset HR. A test was classified as negative if sustained MTWA was not present at an onset HR  $\leq 110$  beats/minute and if there was a  $\geq$  one min at HR  $\geq 105$  beats/min in sinus rhythm with noise level  $< 2\mu\text{V}$  and ectopy  $< 10\%$ . Otherwise, an MTWA test was classified as indeterminate and could be caused by patient or technical factors. Patient factors included failure to maintain HR between 105–110 beats/min for  $\geq$  one minute, unsustained MTWA, or excessive ectopy during exercise. Technical factors included a noisy recording or a rapid rise in HR through the target exercise HR range of 105–110 beats/min. The authors noted that the number of technically indeterminate tests can be reduced by immediately repeating the test. Indeterminate tests were reviewed jointly by two readers blinded to subsequent events to determine the primary reason for indeterminacy. The patients' mean age was 56, and 71% were male; 49% had ischemic cardiomyopathy. The mean ejection fraction was 25%, and about 80% of the patients were receiving beta blockers. There were a total of 40 deaths and 11 non-fatal SVA. Most (94%) of the indeterminate results were due to patient factors. The two-year rate for death or SVA was 17.8% in patients with an indeterminate MTWA test compared to 12.3% in those with a positive test. The authors stated their findings suggest “that both positive and indeterminate MTWA test results indicate high risk and only patients with a negative MTWA test are low risk and therefore unlikely to benefit from ICD prophylaxis.” These findings are similar to the study by Chan et al. (2007).

### **Medical Therapy and Predictive Value of MTWA**

Chan et al. (2010) conducted a meta-analysis of the predictive value of MTWA screening for ventricular arrhythmic events in primary prevention patients with left ventricular dysfunction and examined whether results differed depending upon whether beta-blocker use was withheld prior to MTWA testing. Prospective studies that evaluated whether MTWA predicted ventricular arrhythmic events published between January 1980 and

September 2008 were included. Nine studies involving 3939 patients were identified. Overall, an abnormal MTWA (positive and indeterminate) test was associated with an almost two-fold increased risk for arrhythmic events ( $p=0.002$ ). However, significant heterogeneity across studies was observed ( $p=0.024$ ). In the four studies in which beta blocker therapy was not withheld prior to MTWA assessment, an abnormal MTWA test was associated with a five-fold increased risk for arrhythmic events ( $p<0.001$ ) and was robust to sensitivity analyses. In contrast, the association was much weaker in those studies where the use of beta-blocker therapy was withheld prior to MTWA testing ( $p=0.02$ ). The authors report that in primary prevention patients with left ventricular dysfunction, the predictive power of MTWA varied widely, based on whether beta-blocker therapy was withheld prior to its assessment. This observation may explain the inconsistent results of MTWA studies in this population.

In a prospective study, Zacks et al. (2007) evaluated 387 patients to evaluate whether oral beta-blocker use within 24 hours of MTWA influences yield and predictive value of MTWA and EPS. The mean age of the patients was 67 years. The patients had coronary artery disease,  $LVEF \leq 40\%$ , and nonsustained VT. All the patients had EPS and were followed for a mean of 2.8 years. Patients who were referred to the EPS laboratory who were not receiving beta-blockers ( $n=62$ ) remained off beta-blockers for the EPS and MTWA testing. Those who were receiving beta-blockers ( $n=325$ ) continued on the beta-blocker for the EPS and MTWA testing. Patients were considered to be off beta-blockers if they had not received the drug for at least 24 hours before the EPA and MTWA testing. There were no significant differences between the patients on beta-blockers and the patients off beta-blockers with regard to age, sex, LVEF, QRS duration, and ICD implantation. The authors reported there was no difference in EPS (31 [50%] inducible off beta-blockers versus 166 [51%] on beta-blockers) or TWA (26 [42%] positive, 17 [27%] indeterminate off beta-blockers versus 136 [42%] positive, 81 [25%] indeterminate on beta-blockers). Beta-blocker use within 24 hours of testing did not affect the predictive value of MTWA or EPS for overall or two-year event-free survival. The limitation of this study is the low number of arrhythmic events despite the overall population size. Additionally, patients were considered to be on beta-blockers regardless of dose and were considered to be off beta-blocker therapy even if only for the 24 hours preceding EPS.

#### **Heart Rate and MTWA Testing for Ventricular Arrhythmias**

In a single-center prospective analysis ( $n=248$ ), Tanno et al. (2004) conducted a study to determine whether patients with TWA at low HRs have increased vulnerability to ventricular tachyarrhythmias. Subjects with a mean age of  $59 \pm 17$  years underwent electrophysiological study from 1997–2000. TWA recording was made in sinus rhythm and at atrial pacing rates of 90, 100, 110, and 120 bpm with the Cambridge Heart CH2000 system. Alternans voltage ( $V_{alt}$ ) was measured when the alternans ratio was  $> three$  for a period of  $> one$  minute in VM, X, Y, Z, or two adjacent precordial leads. Study end point was the first appearance of VT, ventricular fibrillation (VF), appropriate implantable cardioverter-defibrillator therapy with pacing or shocks, or SCD. During the  $37 \pm 12$ -month follow-up period, 22 patients had sustained VT, and five patients died of SCD. In patients with  $> 1.9$ - $\mu V$   $V_{alt}$  at rates of 90, 100, and 110 bpm, the incidence of VT/VF/SCD was 56%, 28%, and 18%, respectively.  $V_{alt}$  of  $> 2.9$   $\mu V$  at a HR of 90 bpm had a 70% positive predictive value for VT/VF/SCD. However, when  $V_{alt}$  was  $< 0.9$   $\mu V$  at a rate of 120 bpm, negative predictive value was 100%. The authors reported that patients with TWA at relatively low HRs are susceptible to ventricular tachyarrhythmias.

#### **CHF and Left Ventricular Systolic Dysfunction**

In a prospective study of patients with ischemic or idiopathic CHF, the majority tested positive for MTWA, and the incidence of cardiac death was significantly higher in MTWA-positive patients than in MTWA-negative patients (Sarzi, et al., 2004); however, maximum amount of oxygen consumption ( $VO_2$  max) was the strongest risk factor for cardiac death. While MTWA testing alone had high sensitivity and a high negative predictive value, the  $VO_2$  max test alone had higher diagnostic accuracy for cardiac death. The combination of  $VO_2$  max and MTWA testing was superior to any single test or combination of tests. This study lacked blind assessment of results, and results may not be generalizable to other CHF patient populations.

In a cross-sectional study of patients with idiopathic hypertrophic cardiomyopathy, the prevalence of nonsustained VT was significantly higher in patients who were MTWA-positive compared to patients who tested negative (Kuroda, et al., 2002). The MTWA test was more sensitive than findings of QT dispersion or late potentials for predicting future arrhythmias. Furthermore, examination of endomyocardial biopsy specimens showed that MTWA-positive patients were more likely to have histopathological signs of ventricular damage.

#### **MTWA Compared with Electrophysiological Study (EPS)**

Costantini et al. (2009) studied whether MTWA testing could identify patients who benefit from ICDs as well as EPS. The ABCD (Alternans Before Cardioverter Defibrillator) trial is a multicenter prospective study that enrolled patients with ischemic cardiomyopathy (LVEF  $\leq$  0.40) and nonsustained VT. All patients underwent MTWA and EPS. ICDs were mandated if either test was positive. Of 566 patients followed for a median of 1.9 years, 39 (7.5%) met the primary end point of appropriate ICD discharge or sudden death at one year. As hypothesized, primary analysis showed that MTWA achieved one year positive (9%) and negative (95%) predictive values that were comparable to EPS (11% and 95%, respectively). In addition, secondary analysis showed that at the pre-specified one year end point, event rates were significantly higher in patients with both a positive MTWA-directed strategy (hazard ratio: 2.1,  $p=0.03$ ) and a positive EPS-directed strategy (hazard ratio: 2.4,  $p=0.007$ ). Moreover, the event rate in patients with both negative MTWA test and EPS was lower than in those with two positive tests (2% versus 12%;  $p=0.017$ ). A limitation of this trial is the actual overall event rate for the end point of ICD discharges or SCD was only 7.5% and 14% at one and two years, respectively. The low event rate reduced the power of the study to prove the primary hypothesis, because it could have masked the detection of differences in PPV and NPV between EPS and MTWA. The authors reported that in the end, the clinician must consider which strategy is most appropriate for each individual patient, depending on comorbidities, potential risk of ICD insertion itself, willingness of the patient to undergo insertion, and the risk of SCD weighed against the competing risk of nonsudden or noncardiac death.

### **Brugada Syndrome**

Ikeda, et al. (2001) reported negative findings in a study comparing MTWA to two other noninvasive tests for detecting arrhythmic events, late potentials and QT-interval dispersion, in patients with Brugada syndrome, an electrical disease in an otherwise structurally normal heart, and age- and gender-matched normal controls. In multivariate analysis, only late potentials had a significant correlation with the occurrence of life-threatening arrhythmic events, whereas MTWA and QT-interval dispersion did not. This was a case-control study and so a temporal relationship between occurrence of arrhythmic events and presence of potential risk stratifiers, such as late potentials, MTWA, and QT-interval dispersion, could not be determined.

### **Combining MTWA with Other Testing**

In a prospective study ( $n=322$ ), Exner et al. (2007) reported that they conducted the first prospective study to assess the combined assessment of autonomic tone including HR turbulence, cardiac electrical substrate including TWA, and ejection fraction ( $< 50\%$ ) to identify patients at risk of serious events after a MI. The authors reported that impaired HR turbulence plus abnormal TWA measured at 10–14 weeks after a MI best identified patients at risk. This combination predicted a higher risk of cardiac death or cardiac arrest, a higher risk of death from any cause, and a higher risk of fatal or nonfatal cardiac arrest

Two studies reported that MTWA combined with another test (e.g., LVEF or late potentials) was a better predictor of arrhythmic events than MTWA alone (Ikeda, et al., 2000; Adachi, et al., 2001). Study limitations included small sample size and exclusion from analysis of patients with indeterminate (i.e., neither positive nor negative) MTWA results.

### **Meta-Analysis**

Gehi et al. (2005) conducted a meta-analysis evaluating the predictive value of MTWA in determining risk stratification of VTEs across a wide variety of subjects ( $n=2608$ ). Nineteen prospective studies met the inclusion criteria: prospective cohort studies of greater than 10 human subjects who underwent exercise-induced MTWA testing for the prediction of SCD or ventricular arrhythmias; provided preliminary data on results of MTWA and of clinical outcomes, including SCD, cardiac death, ventricular arrhythmias, and/or ICD shock; provided a clear definition of normal or abnormal MTWA testing; and had a follow-up time of six months or longer. Subject populations included CHF, ischemic CHF, non-ischemic CHF, post MI, athletes, and healthy subjects. Mean ejection fraction ranged from 23 to 71. Most of the subjects were men. From the 19 studies, the summary positive predictive value (PPV) of MTWA for arrhythmic events during the average 21 months of follow-up was 19.3% (95% CI 17.7% to 21%); the NPV was 97.2% (95% CI 95.5% to 97.9%). The study found that the presence of significant MTWA predicted nearly a fourfold risk of VTE compared to the absence of MTWA. The absence of MTWA carries a 3% risk of arrhythmic events during follow-up. No difference was found in the predictive value between patients with ischemic and nonischemic CHF. The authors conclude that if the MTWA test is negative, the patient would be at low risk for arrhythmic events. If the MTWA test is positive, this would reinforce the decision for ICD placement for primary prophylaxis. There is inconsistency in current medical practice as to whether an indeterminate MTWA test should be considered abnormal or excluded altogether. Of note, there is a significant proportion of indeterminate tests (50% of the patients) in this review. After comparing

the predictive value of abnormal MTWA in the eight studies which provided outcomes based on the inclusion or exclusion of indeterminate MTWA, the authors found no significant difference in the predictive value of an abnormal test, although this does not indicate that an indeterminate MTWA test should be considered abnormal.

### **Professional Societies/Organizations**

In 2009, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published a focused update to the guidelines for the diagnosis and management of heart failure in adults. In the assessment of prognosis section of the guideline the authors reported that, "Routine use of ambulatory electrocardiographic monitoring, T-wave alternans analysis, heart rate variability measurement, and signal-averaged electrocardiography have not been shown to provide incremental value in assessing overall prognosis, although ambulatory electrocardiographic monitoring can be useful in decision making regarding placement of ICDs" (Jessup, et al., 2009).

In 2008, the AHA/American College of Cardiology (ACC) Foundation/Heart Rhythm Society published a scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death. The authors reported that a number of observational cohort studies have been published that suggest that MTWA may work at least as well as electrophysiological testing for prediction of SCD or major arrhythmic events. Recent cohort studies that involved at least 100 patients found that MTWA was associated with substantially increased risk and predicted events as well as or better than other markers, including LVEF, electrophysiological testing, SAECG, baroreceptor sensitivity, and heart rate variability. Furthermore, MTWA predicted risk in patients with coronary artery disease and in patients with dilated cardiomyopathy. In all of these studies, patients not manifesting MTWA were at low risk for SCD. The authors concluded that, "a moderate amount of data suggest that T-wave alternans may be useful for risk stratification for SCD. Further information will be required to determine how to implement this test in clinical practice" (Goldberger, et al., 2008).

The 2008 ACC/AHA performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction does not identify MTWA as a test for the management of patients with ventricular arrhythmias (Krumholz, et al., 2008).

The 2006 ACC/AHA/European Society of Cardiology (ESC) guideline for management of patients with ventricular arrhythmias and the prevention of SCD recommends MTWA with class IIa level of evidence stating, "It is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias. (Level of evidence A)" (Zipes, et al., 2006).

The ACC/AHA practice guideline for the management of patients with ST-elevation MI (STEMI) (Antman, et al., 2004) recommends, "Noninvasive assessment of the risk of ventricular arrhythmias may be considered (including signal averaged ECG, 24-hour ambulatory monitoring, HR variability, micro T-wave alternans, and T-wave variability) in patients recovering from STEMI." In 2009 a focused update was published to this guideline with no update to the previous recommendation (Kushner, et al., 2009).

### **Summary**

Evidence in the published peer-reviewed scientific literature indicates that the presence of microvolt t-wave alternans (MTWA) is associated with increased disease severity and reduced functional status in patients with various types of ischemic and nonischemic heart disease and that ventricular arrhythmias and sudden death are more common in patients who test positive for MTWA. There is also some evidence indicating that MTWA testing, either alone or in combination with other noninvasive tests, may be a sensitive predictor of ventricular arrhythmias and sudden cardiac death (SCD) in certain groups of potentially at-risk patients.

There is evidence that MTWA testing has excellent negative predictive value for ventricular arrhythmias in patients with reduced systolic function. The absence of MTWA carries a 3% risk of arrhythmic events during follow-up of one to two years. Negative MTWA testing will be useful for identifying individuals who may not require implantable cardioverter defibrillator (ICD) placement.

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## **Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT®* Codes	Description
93025	Microvolt T-wave alternans for assessment of ventricular arrhythmias

ICD-9-CM Diagnosis Codes	Description
086.0	Chagas' disease with heart involvement
414.8	Other specified forms of chronic ischemic heart disease
422.91	Idiopathic myocarditis
425.1	Hypertrophic obstructive cardiomyopathy
425.4	Other primary cardiomyopathies
425.9	Secondary cardiomyopathy, unspecified
426.0	Atrioventricular block, complete
426.82	Long QT syndrome
427.1	Paroxysmal ventricular tachycardia
427.41	Ventricular fibrillation
427.5	Cardiac arrest
428.0-428.9	Heart Failure
429.3	Cardiomegaly
746.89	Other specified congenital anomaly of heart
780.2	Syncope and collapse
V12.53	Personal history of sudden cardiac arrest
V49.83	Awaiting organ transplant status

**Experimental/Investigational/Unproven/Not Covered:**

ICD-9-CM Diagnosis Codes	Description
	All other codes

\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	6/15/2008	0143	Microvolt T-Wave Alternans

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