Decision Memo

TO: Administrative File: CAG #00293
Microvolt T-wave Alternans Testing

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SUBJECT: Decision Memorandum for Microvolt T-wave Alternans Testing

DATE: March 21, 2006

I. Decision

CMS has determined that there is sufficient evidence to conclude that Microvolt T-wave Alternans (MTWA) diagnostic testing is reasonable and necessary for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used, and CMS is issuing the following national coverage determination (NCD) for this indication.

Microvolt T-wave Alternans (MTWA) diagnostic testing is covered for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used.

II. Background

Cardiovascular disease is the single most common cause of death in the United States. Sudden cardiac death (SCD) is estimated to account for approximately 50% of all cardiovascular deaths. This represents an estimated 350,000 cases per year and only about 20% of these patients survive to hospital discharge. Ventricular tachyarrhythmic events (VTE) are the mechanism responsible for 75-80% of these deaths (Huikuri, 2001).

Microvolt T-wave Alternans (MTWA) testing is a non-invasive diagnostic test that detects minute electrical activity in a portion of the electrocardiogram (EKG) know as the T-wave. Published articles in medical journals have proposed that MTWA testing has a role in the risk stratification of patients who may be at risk for sudden cardiac death (SCD) from ventricular arrhythmias.

Within patient groups that may be considered candidates for implantable cardioverter defibrillator (ICD) therapy, published literature indicates that 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.

The test is performed by placing high-resolution electrodes, designed to reduce electrical interference, on a patient's chest prior to a period of controlled exercise. These electrodes detect tiny beat-to-beat changes, on the order of one-millionth of volt, in the EKG T-wave. Spectral analysis is used to calculate these minute voltage changes. Spectral analysis is a sensitive mathematical method of measuring and comparing time and the electrocardiogram signals. Software then analyzes these microvolt changes and produces a report to be interpreted by a physician.

In a January 27, 2005 final decision memorandum for ICDs, CMS stated:

"We do strongly encourage the inclusion of MTWA is subsequent clinical trials, registries and other data collection protocols in order to further evaluate this promising risk-stratification technology and will work with the stakeholders involved in the subsequent data collection systems to include this information. CMS will continue to support these studies that collect this type of information."

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). MTWA may be eligible for coverage under the Social Security Act section 1861(s)(3) "other diagnostic tests".

CMS does not currently have an NCD on MTWA testing. Coverage is at local Medicare contractor discretion.

IV. Timeline of Recent Activities

July 5, 2005 July 7, 2005	CMS meets with the requestor, Cambridge Heart. CMS opens an NCD to evaluate the use of MTWA testing in the Medicare population. CMS begins a national coverage determination review in response to an external request. A 30-day public comment period is opened.
August 5, 2005	Public comment period closes. CMS completes the posting of public comments to the coverage website.
December 21, 2005	Draft decision memorandum posted. A second 30-day public comment period is opened.
February 21, 2006	Second public comment period closes. CMS completes the posting of these public comments to the coverage website.

V. FDA Status

The Food and Drug Administration (FDA) has cleared Heartwave™ alternans devices, along with various software packages used to perform MTWA testing, through the 510(k) clearance process. Clearance was obtained on July 16, 2002 (K022152) and November 17, 2002 (K03564).

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. Improved net health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

A detailed account of the methodological principles of study design that agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public

comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. The evidence reviewed to date in this decision memorandum includes the published medical literature on pertinent clinical trials of MTWA.

B. Discussion of Evidence Reviewed

1. Questions

1. Is the quality of evidence adequate to conclude that MTWA testing can improve net health outcomes and is reasonable and necessary for Medicare patients who are candidates for ICD placement?

2. *If the evidence is adequate to conclude that MTWA testing can improve net health outcomes, what characteristics of the test method, the pathologic condition, or the patient can satisfactorily predict an improved health outcome?*

2. External technology assessments

We did not request an external technology assessment (TA) on this issue. CMS reviewed a TA published in October 2005 by the National Blue Cross and Blue Shield Association's Technology Evaluation Center (BCBSA TEC) entitled "Microvolt T-wave alternans testing to risk stratify patients being considered for ICD therapy for primary prevention of sudden death". That assessment concluded that MTWA did not meet BCBSA TEC criteria for coverage. The committee felt that the evidence was insufficient to permit conclusions regarding the effect on health outcomes, the evidence was insufficient to determine whether the use of MTWA improved net health outcomes or whether it is as beneficial as any established alternatives, and the use of MTWA to improve outcomes in the investigational setting had not been established.

3. Internal technology assessments

Literature search methods

The reviewed evidence was gathered from: 1) articles submitted by the requestor; 2) an existing technology assessment, and 3) a literature search of the PubMed database.

To support their request for coverage, the requestor submitted a listing of 1028 citations on a compact disc entitled "Publications and Abstracts: Clinical Compendium". These citations included articles on technical feasibility, mathematical models, animal studies, pediatric populations, pharmacologic interventions, and applications of MTWA for other than the requested indication (e.g., hypertension, cardiac pacing). Along with the list of 1028 citations was a separate "Table of Contents" of recent publications relevant to the coverage request. From this list, CMS excluded poster presentations, oral presentations, editorials, review articles, studies that did not specifically address MTWA as a risk stratifier for patients eligible for ICD treatment, and those lacking sufficiently detailed information on study design or discussion of results. From this "Table of Contents", and following a discussion with the requestor, 12 of the submitted articles were considered for review. Bibliographies of these publications were reviewed to identify additional relevant articles.

The limits of our PubMed search excluded non-English articles, studies with fewer than 10 cases, and those not involving human subjects. The search terms used were:

- T-wave alternans, arrhythmia
- T-wave alternans, ventricular
- T-wave alternans, implantable cardioverter defibrillator (ICD)
- T-wave alternans, cardiac defibrillator (ICD)
- T-wave alternans, (MADIT) II
- T-wave alternans, sudden cardiac death
- T-wave alternans, ejection
- T-wave alternans, infarction

- T-wave alternans, cardiomyopathy
- T-wave alternans, primary prevention

From the initial PubMed yield, CMS then applied the same exclusion criteria described above. Using these terms and exceptions, CMS did not identify any additional articles to those supplied by the requestor.

Evidence Review

A number of studies evaluating the effectiveness of MWTA have been found in the medical literature. These include studies evaluating MWTA in patients with ischemic cardiomyopathies, non-ischemic dilated cardiomyopathies, as well as in patients with mixed cardiomyopathies. Endpoints studied include morbidity, mortality (e.g., sudden cardiac deaths, VTE, as well as quality of life measures. Evaluations ranged from single prospective studies to systematic reviews (meta-analysis and article reviews).

Gehi and associates recently performed a meta-analysis evaluating the use of MTWA in determining risk stratification of VTE across a wide range of patient populations (Gehi, Stein, Metz, Gomes, 2005). Using PubMed and Cochrane databases to identify published articles performed between January 1990 and December 2004, 19 prospective studies, which included 2,608 subjects, were found which met the following inclusion criteria: 1) prospective cohort studies of greater than 10 subjects who underwent exercise induced MTWA testing for the prediction of SCD or ventricular arrhythmias; 2) provided primary data on results of MTWA and of clinical outcomes including SCD, cardiac death, ventricular arrhythmias, and/or implantable cardioverter defibrillator (ICD) shock; 3) provided clear definition of normal or abnormal MTWA testing; and 4) had a follow-up time of six months or longer. Outcomes of each study were presented as Positive Predictive Value (PPV), Negative Predictive Value (NPV), and univariate Relative Risk (RR) with Confidence Intervals (CIs) of MTWA for the prediction of ventricular arrhythmic events at follow up.

Study sample sizes ranged from 16 to 834 participants. The mean age of the subjects in the 19 studies ranged from 25 to 64 years, and the average follow-up was 21 months. There was a wide range of subject populations including congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, post myocardial infarction (MI), athletes, and healthy subjects. Mean ejection fraction (EF) of study participants ranged from 23 to 71. After excluding all subjects with indeterminate MTWA test, the PPV at follow-up ranged from 0% to 67%, while the NPV ranged from 71 to 100%. The RR for having a cardiac event ranged from 0.85 to infinity.

For the 19 studies the summary PPV during the 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%), and the univariate RR was 3.77 (95% CI 2.39 to 5.95). The study found that the presence of significant MTWA predicted nearly a four-fold risk of VTE compared to the absence of significant MTWA. The absence of MTWA carries a 3% risk of arrhythmic events during an average 21 months of follow-up. The study also revealed that there was no significant difference in PPV, NPV, or RR of MTWA testing between subjects with ischemic and non-ischemic CHF, as well as no significant difference in the NPV or RR of MTWA testing between CHF and post-MI subjects.

Three studies performed a multivariate Cox regression analysis to determine the independent predictive value of commonly used tests for risk stratification of arrhythmic events. In these three studies, MTWA was independently predictive of arrhythmic events.

In Gehi's assessment of all the articles included in the analysis, none of the studies were of poor quality, testing revealed appropriate heterogeneity, and no evidence of publication bias was found. In this review MTWA was absent in 25% to 54% of subjects, which the author felt was a significant portion of subjects.

Gehi noted that there were some limitations of this meta-analysis including, insufficient data in the multivariate analysis to determine the incremental prognostic value of MWTA independent of other predictors of arrhythmic events, the endpoints of the individual studies used in the summary calculations were variable, most of the subjects included in these studies were primarily men (making the results difficult to generalize to females), and the inconsistency in the exclusion of subjects using beta-blockers or anti-arrhythmic medications.

One of the first clinical studies that was able to demonstrate that electrical alternans was a marker for vulnerability for ventricular arrhythmias was performed by Rosenbaum and associates (Rosenbaum, Jackson, Smith, Garan, Ruskin, Cohen, 1994). The study consisted of 83 consecutive patients who were sent for diagnostic electrophysiologic studies and who met entry criteria (excluded if atrial pacing was not possible; if a permanent pacemaker had been previously implanted; or if excessive ventricular ectopic beats were present). Baseline measurements of electrical alternans were compared with the results of baseline electrophysiologic testing in each patient, along with the relation of electrical alternans to arrhythmia-free survival. Of the 83 patients that entered the study, 17 were excluded from the survival analysis because anti-arrhythmic drug therapy was initiated or changed during the follow-up period.

Of the 66 patients followed for up to 20 months, 13 had arrhythmic events (5 of the events were SCD, the remainders were ventricular arrhythmias). The level of T-wave alternans was significantly greater in patients who had arrhythmic events than in patients without events. This study also revealed that two independent predictors of inducible ventricular arrhythmias were repolarization alternans (ST-segment or T-wave alternans), and impaired left ventricular function. Further studies using multivariate analysis showed that repolarization alternans identified underlying electrical instability, independent of structural heart disease.

Subsequent studies have confirmed the role of T-wave alternans as a predictor for VTEs. Gold and associates compared T-wave alternans, signal-averaged electrocardiography (SAE), and programmed ventricular stimulation for arrhythmia risk stratification in patients undergoing electrophysiologic studies (Gold, Bloomfield, Anderson, El-Sherif, Wilber, et al. 2000). This study was initiated because the authors felt that accurate identification of patients at increased risk for sustained ventricular arrhythmias was critical to prevent sudden cardiac death. They felt that T-wave alternans correlated with arrhythmia vulnerability, but at that point in time, SAE and programmed ventricular stimulation were more commonly used for risk stratification of this condition. This prospective, multicenter study consisted of 313 participants who underwent diagnostic electrophysiologic studies for T-wave alternans testing using a spectral analysis algorithm. Programmed ventricular stimulation as well as signal averaged electrocardiography were also performed. The primary endpoint was the occurrence of a VTE, while secondary endpoints included a VTE or all-cause mortality. Based on the Kaplan Meier survival analysis as the primary endpoint, MTWA predicted events with a RR of 10.9 compared to RR of 7.1 and 4.5 as predicted by programmed ventricular stimulation, and SAE respectively. The RR for secondary endpoints were 13.9, 4.7 and 3.3 respectively also. When comparing statistical performance of the noninvasive test to predict the results of programmed ventricular stimulation during electrophysiological testing, MTWA and SAE resulted in the following:

	Sensitivity	Specificity	PPV	NPV	RR	p-value
MTWA	77.8%	72.5%	42.9%	92.5%	5.7	<0.0001
SAE	55.6%	83.3%	46.9%	87.5%	3.8	<0.0001

To assess the independent predictors of clinical events, a multivariate analysis was performed based on 11 of the clinical parameters. MTWA was identified as the only independent predictor of cardiac events. Compared to SAE, MTWA was a more sensitive predictor of the induction of a sustained VT during programmed ventricular stimulation, as well as a better discriminator of VTEs or death.

Hohnloser and colleagues also evaluated MTWA's usefulness in predicting VTEs in patients with dilated cardiomyopathies (Hohnloser, Klingenheben, Bloomfield, Dabbous, Cohen, 2003). This study used consecutive patients referred to a heart failure clinic for management of their condition, or to the electrophysiologic laboratory for evaluation of symptomatic arrhythmias. Inclusion criteria for the study included a diagnosis of dilated cardiomyopathy, no intercurrent illnesses limiting life expectancy, and the presence of sinus rhythm at initial presentation. Risk stratification was performed at entry, and assessment included determination of left ventricular ejection fraction (LVEF), heart rate variability, mean 24-hour RR interval, presence of non-sustained VT (NSVT), baroreflex sensitivity (BRS), and analysis of signal-averaged electrocardiography (SAE). Patients at high risk were defined by: LVEF $\leq$35%; mean RR $\leq$700 ms; HR variability; standard deviation of normal-to-normal intervals $\leq$70 ms (SDNN); and BRS $\leq$3.0 ms/mm Hg. An intraventricular conduction defect (IVCD) was defined as a QRS duration of $\geq$ 120 ms. Endpoints included sudden cardiac death (SCD), cardiac arrest due to VF, hemodynamically unstable VT or VF.

A total of 137 patients with non-ischemic dilated cardiomyopathy were included in the study (31 females, and 106 males with a mean age of 55). At study entry 37 patients (27%) had been fitted with an ICD because of prior history of cardiac arrest, documented sustained VT, syncope, or for prophylactic reasons. Patients were followed for 18 months. MTWA, using a spectral analysis algorithm, was positive in 66 patients (48%), negative in 34 patients (25%), and indeterminate in 37 (27%). A multivariate analysis was performed looking at the outcomes of the various risks stratification methods. Results of the analysis revealed that MTWA was the only independent statistical predictor of arrhythmic events (X^2 of 3.87). In patients with ICDs versus those without ICDs, the number of persons with positive MTWA test was 23 (62%) versus 43 (43%), and the number with a negative MTWA test results was 5 (14%) versus 29 (29%) (both numbers were statistically significant), and the number with indeterminate test was 9 (24%) versus 28 (28%) which was not statistically significant. The author concluded that the study demonstrated that MTWA positive patients are at particularly high risk for VTEs. Limitations of the study noted by the authors included a high number of patients enrolled in the study after receiving an ICD, and only including hemodynamically unstable VTEs as endpoints in these ICD recipients.

	Sensitivity	Specificity	PPV	NPV	RR	p-value
MTWA	87%	37%	22%	94%	3.4	<0.0001
SAE	47%	63%	17%	88%	1.4	<0.0001
LVEF$\leq$ 35%	80%	21%	15%	86%	1.0	

A number of other studies have evaluated the use of MTWA in patients with dilated cardiomyopathies. Kitamura and colleagues prospectively followed 104 patients with dilated cardiomyopathy (mean age 52 years) to

determine the prognostic value of onset heart rate (OHR) in MTWA (using a spectral analysis algorithm) in patients with non-ischemic dilated cardiomyopathy (Kitamura, Ohnishi, Okajima, Ishida et al. 2002). All patients were in sinus rhythm and dilated cardiomyopathy was clinically diagnosed according to the criteria recommended by the World Health Organization and the National Heart, Lung, and Blood Institute. To define the high risk subgroup, MTWA positive patients were categorized according to a predetermined cut-off point of OHR for MTWA of ≤100 beats/min which represented the division between the two groups (group A consisted of patients with OHR ≤100 beats/min and group B with 100 < OHR ≤110). MTWA negative patients were designated group C. Conventional markers including left ventricular end-diastolic diameter (LVDd) left ventricular ejection fraction (LVEF), non-sustained ventricular tachycardia (NSVT), SAE were used for comparison purposes. Endpoints included sudden cardiac death (SCD), or documented SVT/VF. Forty-six of the patients (44%) were MTWA positive, while 37 (36%) were MTWA negative. The remainder 21 (20%) were MTWA indeterminate. After excluding patients for poor electrocardiogram recordings, only 83 patients remained in the study. Of the 46 MTWA positive patients, 24 were categorized in group A, while 22 were in group B. Both groups were comparable in terms of heart rate, and the OHR of MTWA was not significantly correlated with LVEF (r=0.025). There were 9 cardiac events in group A, and 2 cardiac events in group B. Only 1 cardiac event occurred in group C. Further analysis revealed that the determination of OHR in combination with MTWA could identify the high risk subgroup among the 83 patients with dilated cardiomyopathy. Using multivariate Cox hazard analysis, the study revealed that MTWA with OHR ≤100 beats/min and left LVEF were the only independent predictors of arrhythmic events.

	Sensitivity	Specificity	PPV	NPV	RR
MTWA	91.7%	50.7%	23.9%	97.3%	8.8
SAE	41.7%	78.9%	25%	88.9%	2.3
LVEF≤ 35%	66.7%	66.2%	25%	92.2%	3.2

Adachi and associates also studied the use of MTWA as a risk stratification tool in patients with dilated cardiomyopathy (Adachi, Ohnishi, Yokoyama 2001). This study consisted of 82 consecutive patients with a diagnosis of non-ischemic dilated cardiomyopathy that were referred for electrophysiologic studies. MTWA testing was performed, as well as left ventricular end-diameter (LVDd), left ventricular ejection fraction (LVEF), signal-average ECG (SAECG), 24 hour Holter monitoring for non-sustained VT (NSVT), as well as QT dispersion (QTd) for comparison purposes. Endpoints included sudden cardiac death (SCD), documented SVT, or resuscitated VF. The follow-up period lasted for 24 months. In this study, 37% of participants were MTWA positive, 41% were MTWA negative, and the remaining 22% were indeterminate. The percentage of patients with MTWA in the arrhythmic events group (group A) was significantly larger than that in the non-event group (group B) (90% versus 39%). When evaluating MTWA and other predictor markers for event-free survival, the following matrix is created:

	Sensitivity	Specificity	PPV	NPV	RR	p-values
MTWA	90%	61%	30%	97%	10.2	0.0029
SAE	40%	80%	27%	88%	2.2	0.1783
LVEF≤ 35%	70%	80%	39%	93%	6.0	0.0013

A multivariate Cox regression analysis revealed that a combination of an LVEF of ≤35% along with MTWA positivity were the only statistically significant independent risk factors for VTEs. None of the patients who were MTWA negative and who had an LVEF>35% experienced arrhythmic events. The author did note that small sample size, as well as the exclusion of patients from the study due to atrial fibrillation, were some limitations of this study.

Momiyama and associates evaluated MTWA using a spectral analysis algorithm as a marker of high risk in patients with hypertrophic cardiomyopathy (HCM), comparing 14 patients with HCM to 9 normal controls (Momiyama, Hartikainen, Nagayoshi, Albrecht et al. 1997). Risk stratification for VTEs had been made prior to the study based on an adverse family history, the detection of VT on ambulatory electrocardiogram monitoring, and the finding of paced ventricular electrograms. Of the 14 patients with HCM, 7 were classified as high risk for VTEs, while the other 7 were determined to be of low risk. Nine healthy volunteers made up the control group. There were no significant differences in age or gender in the 3 groups. MTWA voltage was used as a measure (defined as >1.9μV during a period of >250 betas with a HR >100 beats/min), while VTEs, and sudden cardiac death (SCD) were chosen as endpoints. The results of the alternans analysis revealed that the alternans voltage was significantly higher in the high-risk group than in the low-risk and control groups (2.8+/-1.7 vs 0.6+/-0.5). In the high-risk group, the median alternans ratio was also significantly greater than in the low-risk group as well as the control group (3.9 vs 0.6 and 0.3). Of the 7 high-risk participants, 5 (71%) showed significant MTWA voltage (3.7+/-1.0), whereas none of the 7 low-risk patients or the 9 control subjects had MTWA 1.9μV. Of particular note, the study documented that all 4 patients with sustained VT or abnormal paced ventricular electrograms exhibited MTWA. Limitations of the study included small sample size, the inability to elucidate the quantitative relationship between MTWA, and the inhomogeneity of intramyocardial conduction assessed by electrophysiologic testing because it was performed in only 6 of 14 patients.

A number of studies have evaluated the usefulness of MTWA as a predictor of cardiac events after a myocardial infarction (MI). Ikeda and associates used a combined assessment of MTWA and other predictive test to predict arrhythmias after myocardial infarction (Ikeda, Sakata, Takami, Kondo et al. 2000), and later with other collaborators Ikeda used MTWA as a predictor for sudden cardiac death after myocardial infarction (Ikeda, Saito, Tanno, Shimizu, 2000). In the first study, 102 consecutive patients with an acute MI were followed longitudinally, comparing MTWA, late potentials (LP) by SAE, and ejection fractions (EF) for the detection of arrhythmic events (LP as determined by SAE, and left ventricular ejection fraction have been used to identify patients at risk for the development of ventricular arrhythmias). Documentation of spontaneous ventricular arrhythmic events was uses as an endpoint in this study. The follow-up period for the study was 13 months. The results of the study revealed that MTWA was present in 50 patients (49%), while LP was present in 21 patients (21%) and an ejection fraction of less than 40% in 28 patients (27%). Using predictive values as well as a univariate Cox regression to predict events, the following accuracy measures were obtained for the three diagnostic measures:

	Sensitivity	Specificity	PPV	NPV	RH	p-value
MTWA	93%	59%	28%	98%	16.8	0.006
LP	53%	85%	38%	91%	5.7	0.0008
EF	60%	78%	32%	92%	4.7	0.004

The authors concluded that because of the high values for sensitivity as well as negative predictive value, MTWA could be used as a tool for screening patients for various serious ventricular arrhythmias after a myocardial infarction. The author notes that some limitations of the study include the fact that patients with a very low EF (<20%) were excluded from the study. Also the results may not be applicable to patients with significant accounts of ventricular ectopy or abnormal heart rate variability.

In a second study, Ikeda and associates again assessed T-wave alternans as a predictor for sudden cardiac death after an MI (Ikeda, Saito, Tanno, Shimizu, Watanabi, Ohnishi, et al. 2002). This was a prospective study that recruited 850 consecutive MI patients. Most of the participants (90%) underwent MTWA testing within 2 to 10 weeks of the acute MI. In addition to MTWA, other prognostic indices used to predict sudden death included ventricular late potentials (LP), and 40% left ventricular ejection fraction (EF). Primary endpoints were prospectively defined as sudden cardiac death (SCD), as well as VTE. Secondary endpoints included sustained tachycardia. During the study a number of participants died from non-arrhythmic causes. For the remaining 834 patients, the mean follow-up period was 25 months. A total of 67 patients (8%) had arrhythmic events (either primary or secondary endpoints). Of these patients, 3% reached 1 of the primary endpoints, 12 died suddenly, and 13 had resuscitated VF while for secondary endpoints, 5% had sustained VT. MTWA was positive in 36% of participants, indeterminate in 12% and negative in 52% of participants. LP was positive, and an abnormal EF was found in 18% of participants, and LP was negative and the EF was normal in remaining 82% of participants. Of the 11 risk indices (e.g., gender, age, CABG, antiarrhythmic drug therapy, successful percutaneous coronary intervention, LP, MTWA, EF), univariate analysis revealed that MTWA predicted primary endpoints with a relative hazard ratio of 11.4, while the remainder risk indices had relative risk ratios varying between 6.6 and 3.2. Using multivariate Cox regression, only MTWA and EF were found to be significantly associated with primary endpoints. MTWA has the highest sensitivity and NPV than either EF alone, or combined MTWA and EF.

	Sensitivity	Specificity	PPV	NPV	RH	p-value
MTWA	92%	83%	7%	99%	11.4	0.0001
EF	56%	83%	9%	98%	6.6	0.0001
MTWA/EF	52%	92%	18%	98%	11.9	0.0001
	50%	84%	10%	98%	5.2	0.0002

The authors concluded that MTWA and abnormal left ventricular ejection fraction were significant predictors of sudden cardiac death or VF, where as LP by signal-averaged electrocardiography and other prognostic indices failed to predict subsequent risk in this large series of infarction survivors. One of the limitations of the study mentioned by the authors is not including heart rate variability as a study variable. In both studies, a spectral analysis algorithm was used as a protocol for MTWA testing.

Because of the association between VTEs and cardiac mortality, implanted cardiac defibrillators have been used in patients at high risk of this condition. In 2003, CMS recommended using QRS duration as a means to identify Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)-like patients suitable for implanted cardiac defibrillators (ICD) therapy. Bloomfield and associates compared the ability of MTWA (using a spectral analysis algorithm) and QRS duration to identify groups at high risk and low risk of dying among heart failure patients who met the MADIT II criteria for ICD prophylaxis (Bloomfield, Steinman, Namerow, Parides, Davidenko, Kaufman, et al. 2004). The study enrolled 549 subjects, of whom 177 had ischemic heart disease and an ejection fraction of $\leq$ 30 percent, and also met other MADIT II criteria (> than 1 month after a myocardial infarction, and > 3 months after coronary revascularization). MTWA testing as well as QRS testing was performed on each participant, and all-cause mortality was used as an endpoint. Based on the results of these test, participants were placed in 1 of 4 groups: MTWA normal; MTWA abnormal; QRS < 120 ms; QRS >120 ms. The results of the study

revealed the following: 32% of the MADIT II-like patients had a QRS duration of >120 ms, and the MTWA test was abnormal in 68% of the patients. The 2-year actuarial mortality rates for patients with positive and indeterminate MTWA test were similar (14.5% and 20.1% respectively). For all 177 MADIT II-like patients, the 2-year actuarial mortality rate was 13.2%. When analyzing the difference in mortality between the 2 MTWA groups and the 2 QRS groups, the 2-year actuarial mortality rate was substantially lower among patients with normal MTWA test (3.8%), than among patients with a narrow QRS duration (12%), corresponding to false negative rates of 3.5% and 10.2% respectively (see below). A QRS duration >120 ms was weakly associated with MTWA status (OR 1.7, p=0.15). In a multivariate Cox model, MTWA remained a strong predictor of mortality after adjusting for QRS duration (hazard ratio 4.7, p=0.012).

Measure	MTWA	QRS Duration
Actuarial Mortality%		
Abnormal	17.8	15.9
Normal	3.8	12.0
Hazard Ratio	4.8	1.5
Classified as low risk (%)	32.2	68.2
False-negative rate (%)	3.5	10.2

The data from this study indicates that MTWA is a better than QRS duration in identifying high-risk patients among those with ischemic heart disease and left ventricular ejection fraction of $\leq$ 30% who fit MADIT II criteria.

Cohen also investigated the usefulness of MTWA in stratifying risk of the MADIT II population (Cohen, 2004). He prospectively evaluated nine studies done previously which had evaluated MTWA's role in predicting occurrence of VTE. These studies included a variety of patient populations (patients referred for electrophysiologic studies, patients with CHF, patients with dilated cardiomyopathies, and patients with myocardial infarctions), as well as a number of differing follow up periods (ranged from 13 to 72 months). The results of the analysis revealed that relative risk (RR) varied between 1.4 to 16.8 indicating that MTWA was an effective non-invasive means of assessing which patients were at high risk and low risk of VTE and sudden cardiac death. Cohen also noted a study performed by Hohnloser and associates that reported on 129 MADIT II type patients drawn from two previously published prospective studies which evaluated the use of MTWA as a predictor of VTEs (Hohnloser, Ikeda, Bloomfield, Dabbous, Cohen, 2003). These patient had previously had myocardial infarctions as well as ejection fractions < than 30%. This evaluation consisted of 87 patients that were taken from the Ikeda and colleagues study (Ikeda, Saito, Tanno, et al. 2002); while 42 participants were taken from the Klingenhaben and colleagues study (Klingenheben, Zabel, D'Agostino, Cohen, Hohnloser 2000). The primary endpoint of the study was sudden cardiac death. Sub-group analysis revealed that in this population at 24 months of follow up, there was a 15.6% rate of cardiac arrest and sudden cardiac death among participants that tested positive or indeterminate for MTWA, compared with no events among patients that tested negative for MTWA.

Grimm and colleagues evaluated a number of variables which were felt important in determining arrhythmia risk stratification for patients with dilated cardiomyopathy (Grimm, Christ, Bach, Müller, Maisch 2003). These factors included left ventricular ejection fraction and size by echocardiography, heart rate variability, baroreflex sensitivity, SAE, arrhythmias on Holter ECG, QTc, and MTWA using a spectral analysis algorithm. Of the 463 screen patients with IDC, 343 were enrolled, and of this number 263 patients with sinus rhythm. During the 52 month follow-up period, major arrhythmias were observed in 46 patients (13%), including sudden cardiac death in 23 patients. A total of 49 patients (14%) died during follow-up, and 10 patients (3%), underwent heart transplantation.

Major arrhythmic events occurred in 38 (14%) of the 263 patients with sinus rhythm at study entry. Univariate analysis revealed that left ventricular ejection fraction and diameter, non-sustained VT, and frequent ventricular premature beats on a 24-hour Holter ECG, and indeterminate MTWA were statistically associated with arrhythmic events during follow up. But multivariate analysis revealed only left ventricular ejection fraction was a significant predictor of major events during follow-up, with a relative risk of 2.28 per 10% reduction of ejection fraction. Multivariate analysis also revealed that left ventricular ejection fraction was a significant predictor of transplantation-free survival, with a relative risk of 2.51 per 10% decrease in ejection fraction. And for the 10% of patients with ICDs and atrial fibrillation at the entry to the study, multivariate analysis again revealed that left ventricular ejection fraction and the lack of beta-blockers were significant predictors of major arrhythmic events. Based on the multivariate analysis, MTWA was not found to be statistically associated with arrhythmic risk stratification.

Grimm does note discrepancies in results when compared to other studies evaluating the usefulness of MTWA. He attributes differing results due to a differences in methods and patient populations. In contrast to this study, other studies have used smaller patient populations as well as other studies allowing patients with sustained VT or VF. Also, Grimm notes that other studies most of the arrhythmic events during follow-up occurred in patients who had already received an ICD before study entry because of a history of sustained VT or cardiac arrest. The author did note some limitations of this study included fact that the use of beta-blockers was non-uniform and

that many patients did not receive beta-blockers at the entry of the study. He also noted that even though this was a large study that included patients with Idiopathic cardiomyopathy for risk stratification, the number of events in the MACAS study may still be too small to exclude moderate relations of some of the variables tested to outcome with certainty.

Modified Moving Average (MMA) technique for determining MTWA

A review of the literature failed to reveal any large studies using this technique to detect MTWA. One commenter provided us with two articles on the use of MMA for MTWA detection. One of the articles submitted was by Nearing et al. (Nearing, Verrier, 2002), which describes the use of MMA analysis of MTWA to predict ventricular fibrillation in 12 mongrel dogs. Another study submitted by the commenter used a methodological framework to study principles of MTWA analysis (Martinez, Olmos, 2005). This article only presented a methodological overview of the different approaches to MTWA analysis. No information about study design, sample size, inclusion/exclusion criteria, or results was supplied.

Included in the bibliography of the latter article were two others studies which used MMA as a means of predicting MTWA. In the first article the authors evaluated the effects of acute mental stress and exercises on MTWA in patients with implantable cardioverter defibrillators (Kop et al. 2004). This study did not use MMA as a determinant of MTWA which would predispose patients to ventricular tachyarrhythmic events. The second study used the MMA analysis to assess risk of cardiac arrest or arrhythmia in postmyocardial infarction patients (Verrier, Nearing, La Rovere et al. 2003). The authors used the MMA analysis to measure MTWA magnitude in 24-hour ambulatory electrocardiogram recordings from the Autonomic Tone and Reflexes after Myocardial Infarction study (ATRAMI), a prospective study of 1,284 post MI patients. Using a nested case-control approach with 44 total subjects, cases were defined as patients who experienced cardiac arrest due to documented ventricular fibrillation or arrhythmic deaths during the follow up period. Researchers analyzed 15 cases and 29 controls matched for sex, age, site of MI, left ventricular ejection fraction, use of thrombolytics, and beta-blocker therapy. The study was able to demonstrate that 4 to 7 fold higher odds of life-threatening arrhythmias were predicted by MTWA using MMA. We were able to communicate with the primary author, who supplied us with results using measures of accuracy (sensitivity, specificity, positive and negative predictive values) commonly used by those authors who had reported results on the use of spectral analysis to assess MTWA.

The author of the latter article also submitted other studies using MMA to assess MTWA. One study evaluated psychological effects on repolarization, and its impact on hemodynamic factors (Lampert, Shusterman, Burg et. al. 2005). The study consisted of 33 subjects with ICDs and a history of ventricular arrhythmia who underwent ambulatory ECG monitoring during a laboratory mental stress protocol. The study revealed that MTWA increased from 22 at baseline to 29 during mental stress. But limitations of this study include the lack of a control group, as well as small sample size. Another study submitted by the author assessed the degree of association between MMA and spectral analysis in assessing MTWA (Hosteler, Xue, Young et al. 2004). The study revealed a high degree of correlation between the two technologies (between .92 and .99), but 22 data sets from ECG stress test, and 17 data sets from European Society of Cardiology (ESC) ST-T database were used. No head-to-head comparisons in the clinical setting were performed. A final study submitted by the author attempted to improve MTWA measurement quality by reducing noise and artifact (Kaiser, Findeis, Young 2004). Simulated ECGs with differing MTWA values, Holter ECGs from the ESC ST-T database, and exercise ECGs were used as data sources. The study did reveal a high sensitivity and specificity when compared to exercise ECGs and Holter ECGs, but did note that despite the improved acceptance and rejection capability for noise and artifact, noise related false positive MTWA values could not be completely eliminated.

Another commenter mentioned the use of the MMA as a means to measure MTWA, and supplied us with a list of citations which included published articles and abstracts. Most of the citations listed were addressed above (Nearing, Verrier, 2002; Martinez, Olmos, 2005; Kop et al. 2004; Verrier, Nearing, La Rovere et 2003), though an additional study was submitted using 16 adult mongrel dogs to measure MTWA and vulnerability to ventricular fibrillation (Nearing, Huang, Verrier, 1991). As noted above, results of animal studies are not generalizable to the Medicare population. Another citation mentioned by the commenter pertains to the pathophysiological and clinical applications of MTWA (Armoundas, Tomaselli, Esperer, 2002). Though spectral analysis was discussed in this article, there was no specific mention of the MMA technique for MTWA detection (the article mentions several other computerized methods have been applied for detection and quantification of MTWA such as autocorrelation techniques, complex demodulation and autoregression techniques). Also the article fails to mention any specific studies which used the MMA method, the study design, sample size, inclusion/exclusion criteria, or study results. One additional citation mentioned by the commenter compares spectral and time-domain techniques for tracking temporal repolarization instabilities, using simulated signals with changing heart rates, variable levels of MTWA, phase shifts, spurious artifacts, and period-four oscillations, all based on real-life Holter data. (Shusterman, Goldberg 2004). But as noted previously, no information on measures of accuracy (sensitivity, specificity, positive and negative predictors) were provided. No information was provided on study subjects, research design, or pertinent information about clinical comparability, which could help in determining which modality is more useful.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

We did not find published evidence-based guidelines for MTWA.

6. Professional Society Position Statements

There were no published position statements on the use of MTWA as a diagnostic test from the American Heart Association, the American College of Cardiologist, the Heart Rhythm Society, or the American College of Chest Physicians. We did receive comments from several professional societies during the public comment periods, as noted below.

7. Expert Opinion

We have not currently received any expert opinions on the use of MTWA testing for evaluating candidates for ICD placement.

8. Public Comments

During the initial public comment period, CMS received written statements from 28 sources including practicing cardiologists, professors of medicine at various university hospitals, cardiac devices manufacturers, and a summary comment from the requestor. The initial public comments are available for review at: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=165#0707200508072005

During the second public comment period, CMS received written statements from 80 sources, representing a similar cross-section of stakeholders as seen during the first comment period. Comments from the second public comment period are available for review at: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=165#1221200501212006

Comments about the evidence:

Comment:

Four commenters stated that CMS should include the Modified Moving Average (MMA) method of determining MTWA and included references to support their recommendation. An additional four commenters believed CMS should include MMA, but with evidentiary support. Four commenters stated that MMA should not be covered nationally due to a lack of large scale studies.

Response:

A review of the literature failed to reveal any large studies using the MMA technique to detect MTWA. See sections entitled *Modified Moving Average (MMA) technique for determining MTWA* in the Evidence section above and the Analysis section below for a review of the evidence.

Comments about other aspects of the decision memorandum:

Comment:

Among the commenters, 54 stated that MTWA is effective for risk stratification prior to ICD therapy and that the technology should be nationally covered. Of these five stated that MTWA testing should be required prior to ICD implantation. An additional 11 provided general support for the memorandum's determination.

Response:

CMS has determined that there is sufficient evidence to conclude that MTWA diagnostic testing is covered for the evaluation of patients at risk of sudden cardiac death. The test is not required prior to ICD implantation.

Comment:

CMS received a combined comment from the Heart Rhythm Society and the American College of Cardiology. In it, they stated that MTWA may become an important part of patient management, but that the test should not be a prerequisite for determining the appropriateness of ICD therapy. They went on to state that additional prospective studies are needed to identify appropriate uses of MTWA in various populations. CMS received comments from three device manufacturers. One stated that although MTWA appears as a promising technology, the NCD should be delayed until the results of an industry-sponsored clinical study are released in late 2006. Since data are lacking on patients that are greater than 20 months post-test, two device manufacturers believe that additional time is needed to determine the long-term impact of a single negative MTWA test. One party also believes the results of an on-going, industry-sponsored, prospective clinical trial will assist physicians on the use and interpretation of MTWA testing. A third device manufacturer agreed that MTWA testing should not be required prior to ICD therapy, but that CMS should delineate in its decision which patients may or may not be appropriate for MTWA testing.

Response:

We agree that there is not sufficient current evidence to require MTWA testing as a prerequisite for ICD therapy. CMS encourages on-going study of MTWA to further refine this technology and to inform physicians and patients on the best use of MTWA diagnostic testing.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," according to §1862(a)(1)(A) of the Social Security Act. This section presents the agency's evaluation of the evidence considered and the conclusions reached for the assessment questions.

1. Is the quality of evidence adequate to conclude that MTWA testing can improve net health outcomes and is reasonable and necessary for Medicare patients who are candidates for ICD placement?

From the studies used to evaluate this technology, it does appear that the quality of evidence is adequate to conclude that MTWA testing using a spectral analysis algorithm can improve net health outcomes, and is reasonable and necessary for Medicare patients who are candidates for ICD placement. The reviewed literature contains a number of studies evaluating the use of MTWA in a variety of population settings, including subjects with congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, dilated cardiomyopathy, hypertrophic cardiomyopathy, post MI, and in healthy subjects. The material reviewed included not only small prospective studies with a homogenous patient population, but also large systematic reviews with heterogeneous patient populations. Also included in this analysis were studies that looked specifically at MTWA's role as a risk stratification tool in patient populations similar to those in both MADIT II and SCD-HeFT.

A number of diagnostic tools are available for risk assessment. Unfortunately, some of these tools have low diagnostic usefulness. In order for a diagnostic test to be useful, it must be able to demonstrate accuracy and reliability. Commonly used measures of diagnostic accuracy include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Though some of the studies used in this assessment did not include these measures of accuracy, most did. When reviewing these measures of accuracy, MTWA demonstrated superior findings related to sensitivity and NPV when compared to other diagnostic tests used to assess risk of VTEs.

Across a number of population settings, MTWA consistently demonstrates superiority when compared to other diagnostic measures that assess risk of VTEs. Though some of the studies noted some limitations related to methodology as well as research design, these limitations were not enough to invalidate their findings.

We reviewed the BCBSA technology assessment. Both CMS and BCBSA use an evidenced-based medicine approach, based on specific criteria, when assessing the effectiveness of technology. Though both CMS and BCBSA have similar criteria for assessing technology, CMS must also assure that the technology has demonstrated improved net outcomes within the Medicare-eligible population.

Due to the unique characteristics of the Medicare-eligible population (i.e. elderly, and more likely to have multiple co-morbidities), sudden cardiac death has a higher potential to occur as a result of VTE in this population. The potential harms from adverse events are also more likely to occur within this population. Because of these features of the Medicare population, the potential for benefit or harm from ICD placement varies from that of the BCBSA population at large, and plays a prominent role in our decision-making. Indications for ICD placement also differ between the two organizations. Because of the higher potential for VTE occurrence in the Medicare population, and because CMS recognizes VTEs as an indication for ICD placement, CMS feels that the use of MTWA is reasonable and necessary to address problems related to VTE and its adverse consequences.

Based on this analysis, CMS has determined that MTWA is a useful risk stratification tool and can identify which heart patients are at negligible risk of sudden death, and who may therefore be able to avoid ICD implantation and its attendant risks. Studies have demonstrated that ICD implantation does improve survival in patients prone to VTEs. Based on accuracy measures such as sensitivity and NPV, studies have demonstrated that, when it is applied to appropriate target populations, MTWA can identify those patients in which prophylactic ICD implantation is of little benefit, as well as the patient populations in which ICD implantation is beneficial.

However, CMS does not believe that the evidence is sufficient to show that MTWA should be the only diagnostic test for the purpose of stratifying high risk patients of VTE. Physicians may choose to use a variety of other diagnostic testing to elucidate the need for an ICD (e.g., left ventricular ejection fraction, signal-averaged ECG, etc.). Also, we do not believe that the current evidence is sufficient to require that physicians use the results of MTWA testing to select appropriate patients for ICD implantation.

2. If the evidence is adequate to conclude that MTWA testing can improve net health outcomes, what characteristics of the test method, the pathologic condition, or the patient can satisfactorily predict an improved health outcome?

Extensive clinical research has revealed that patients with symptoms of or at risk of life threatening arrhythmias who test positive for T-wave alternans are at a significant risk for subsequent development of sudden cardiac events, including sudden death, while those who test negative are a minimal risk. The use of MTWA using a spectral analysis algorithm as a stratification tool can help to identify patients in high risk population (e.g., those with ischemic and non-ischemic cardiomyopathy, dilated cardiomyopathy, post myocardial infarction, MADIT II-type, or SDC-HeFT-type) who are actually at low-risk for SCD. By applying this diagnostic tool, it is possible to classify those who test positive or indeterminate for MTWA (e.g., those more likely to benefit from ICD implantation), and those who test negative for MTWA (e.g., those less likely to benefit from ICD implantation).

The relevant evidence base for the modified moving average (MMA) algorithm is comparatively small. Animal studies (Kop et al. 2004; Nearing, Huang, Verrier, 1991) do not provide an adequate surrogate for Medicare beneficiaries. Limitations of various published reports on MMA include small sample sizes (Lampert, Shusterman, Burg et. al. 2005; Verrier, Nearing, La Rovere et al. 2003), use of theoretical models, simulations or non-clinical outcome measures (Martinez, Olmos, 2005; Kaiser, Findeis, Young 2004; Shusterman, Goldberg 2004; Armoundas, Tomaselli, Esperer, 2002), and the lack of control groups (Lampert, Shusterman, Burg et al. 2005)

Results of the 2003 study by Verrier, Nearing, La Rovere et al. suggest that the clinical information provided by MMA is comparable in some respects to spectral analysis. Though the sensitivity was moderate, the negative predictive value was equivalent to findings using spectral analysis. Problems associated with this study include small sample size (n =44), limitations of study design (e.g., potential for survivor bias, the possibility that the observed associations are due to the effects of confounding, and baseline measurements may be affected by silent pre-clinical diseases.). In addition, the results also had large confidence intervals, which might indicate imprecision and high variability. The author informed us of an ongoing study employing the use of MMA for MTWA analysis. That study has a much larger sample size, but the study has not been completed yet. We look forward to reviewing it when it has been published in the peer-reviewed medical literature.

In summary, the evidence base supporting the spectral analysis method includes numerous trials that enrolled adequate numbers of human subjects and used patient-relevant clinical outcome endpoints. The evidence base for the MMA method is smaller, and though suggestive of benefit, is not yet convincing. We believe that currently available evidence only supports the use of spectral analysis algorithm for the detection of MTWA.

IX. Conclusion

CMS has determined that there is sufficient evidence to conclude that Microvolt T-wave Alternans (MTWA) diagnostic testing is reasonable and necessary for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used, and CMS is issuing the following national coverage determination (NCD) for this indication.

Microvolt T-wave Alternans (MTWA) diagnostic testing is covered for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used.

Appendices

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