Decision Memo for Microvolt T-wave Alternans (CAG-00293R)

Decision Memo

TO:	Administrative File: CAG #00293R1 Reconsideration of Microvolt t-Wave Alternans
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SUBJECT:	Final Decision Memorandum for reconsideration of the NCD on microvolt t-wave alternans testing.
DATE:	May 12, 2008

I. Final Decision

CMS was asked to reconsider our national coverage determination (NCD) on microvolt t-wave alternans (MTWA) diagnostic testing to extend coverage to the modified moving average (MMA) method. CMS' interest in MTWA testing is in the risk stratification of Medicare beneficiaries who may be at risk for sudden cardiac death (SCD) from ventricular arrhythmias and who may be candidates for Medicare coverage for the placement of an implantable cardioverter defibrillator (ICD). The NCD specifically provides for coverage of MTWA using the spectral analysis method and noncovers MTWA using any other method (Section 20.30 Medicare National Coverage Determinations Manual). CMS has determined that there is insufficient evidence to conclude that the MMA method of determining MTWA improves health outcomes for Medicare beneficiaries at risk for sudden cardiac death (SCD) and we therefore find that it is not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act (the Act).

Nationally Covered Indications

Microvolt T-wave Alternans diagnostic testing is covered for the evaluation of patients at risk for SCD only when the spectral analysis method is used.

Nationally Non-Covered Indications

Microvolt T-wave Alternans diagnostic testing is non-covered for the evaluation of patients at risk for SCD if measurement is not performed employing the spectral analysis method.

II. Background

Cardiovascular disease is the leading cause of death in the United States. Sudden cardiac death is estimated to account for 50% of all cardiovascular deaths. There are an estimated 350,000 cases of sudden cardiac death in the U.S. yearly. Of those cases of cardiac arrest occurring outside of a hospital, being resuscitated and reaching the hospital alive, 20% survive to discharge. Of those cases where the individual did not survive to discharge, ventricular tachyarrhythmic events (VTE) are responsible for 75-80% of those deaths.

MTWA testing is a non-invasive diagnostic procedure that detects minute electrical activity in a portion of the electrocardiogram (EKG) known 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 SCD from ventricular arrhythmias. Within groups of patients that may be considered candidates for 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.

CMS currently covers MTWA when it is performed using the spectral analysis method. Spectral analysis is a sensitive mathematical method of measuring and comparing time and EKG signals and these are then used to calculate minute voltage changes and MTWA. Computer software then analyzes these microvolt changes and produces a report to be

interpreted by a physician. The presence of significant MTWA is defined as an alternans voltage ≥1.9 microvolts (V) at 0.5 cycles-per-beat with an alternans ratio ≥3. The absence of MTWA is defined as no evidence of alternans at 0.5 cycles-per-beat when the heart rate is sustained >105 beats/min or within 5 beats/min of maximum predicted heart rate for at least 1 min. Otherwise, MTWA is considered indeterminate. The spectral analytical method requires the patient to be stationary when obtaining the data, thus, this data cannot be acquired with ambulatory ECG monitoring such as Holter monitors.

In the MMA method of measuring t-wave alternans (TWA), electrodes placed on a patient's chest are used to obtain 24 -hour ambulatory EKG recordings using a Holter monitor. These recordings are then analyzed to measure various changes in the t-wave portion of the EKG in the range of one microvolt. Unlike the spectral analysis method, the MMA method does not require that the patient reach a specific monitored heart rate nor does it require the use of specialized electrodes. Software algorithms then analyze these microvolt changes and produce a report to be interpreted by a physician.

III. History of Medicare Coverage

CMS previously reviewed scientific literature and established national coverage of MTWA diagnostic testing using the spectral analysis method. For dates of service on or after March 21, 2006, MTWA is nationally covered for the evaluation of patients at risk for SCD, only when the spectral analysis method is used.

A. Current Request

The request from GE Healthcare asks that CMS reconsider the current NCD, to grant coverage to the MMA method of measuring TWA.

B. Benefit Category

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) and §1861(s) (Definition of Medical and Other Health Services) of the Act. MTWA using the MMA method is considered to be within the following benefit category: other diagnostic tests, §1861(s)(3) of the Act. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

August 17, 2007	CMS accepts a formal request for reconsideration of the NCD Manual Section 20.30 to include the MMA method of determining MTWA. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
September 16, 2007	The initial 30 day public comment period ended. Thirteen comments were received.
February 14,2008	Proposed decision posted
March 15, 2008	The second 30 day public comment period ended. Twenty-six comments were received.

V. FDA Status

The Food and Drug Administration (FDA) has cleared GE Medical's MTWA devices, along with various software packages used to perform MTWA testing, through the 510(k) clearance process. Clearance was obtained on December 3, 2002 (K023380) and October 30, 2003 (K032513).

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 health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based 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 comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review. The evidence reviewed, which supports the basis for this coverage determination, is the published medical literature on pertinent clinical trials of the MMA method for measuring MTWA. We reviewed the information to determine if it improves health outcomes for patients at high risk of SCD with specific consideration of patients who may receive ICDs.

B. Discussion of Evidence Reviewed

1. Question

Is the evidence adequate to conclude that MTWA testing using the MMA method improves health outcomes for Medicare beneficiaries who are candidates for ICD placement?

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this issue.

3. Internal technology assessment

The reviewed evidence was gathered from articles submitted by the requestor and a literature search of the PubMed database.

To support its request for coverage, the requestor initially submitted 11 referenced articles. The requestor subsequently submitted 21 additional references. During the initial comment period, four more articles were reviewed. The references included articles on technical or methodological feasibility; unpublished articles; non-clinical study articles; articles in which the MMA method was mentioned but not reported; and applications of MTWA for other than the requested indication (e.g., hypertension, cardiac pacing, or mental stress). From these references, CMS excluded and did not consider unpublished articles, oral presentations, editorials, review articles, studies that did not specifically address MTWA as a risk stratifier for patients eligible for ICD treatment, and those references, which lacked sufficient detailed information on study design or discussion of results.

Literature search methods

The search terms used by CMS 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, Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)
- T-wave alternans, sudden cardiac death (SCD)
- T-wave alternans, ejection
- T-wave alternans, infarction
- T-wave alternans, cardiomyopathy
- T-wave alternans, primary prevention

From the PubMed search results, CMS then excluded non-English language articles, studies with fewer than 10 cases and those not involving human subjects. Using these terms and exceptions, CMS did not identify any articles in addition to those provided by the requestor.

Nieminen, et al. (July, 2007) studied indigenous Finnish subjects in one geographic area of Finland as a part of the Finnish Cardiovascular Study. They tested the hypothesis that TWA predicts mortality in a general population of patients referred for a clinical exercise test. According to the authors, a total of 1037 consecutive patients (673 men and 364 women) gave consent and were enrolled. The reported “mean age ± SD” [standard deviation] was 58 ± 13 years, which indicates that approximately 26-27% of the subjects were 65 years of age or older. Subjects who came for any reason) in a clinically indicated exercise test at a particular Finnish university hospital between October 2001 and January 2003 and had a technically successful EKG were included in the study.

The authors report that the patients given the exercise test had one or more of the following characteristics: coronary heart disease (CHD) (46%); arrhythmia during exercise (18%); need to be evaluated for work capacity (19%); need to be checked for adequacy of CHD treatment (24%); or need for an exercise profile prior to an invasive operation (13%) or after an MI (10%).

Ninety-six percent of the tests were successful according to the authors. Digital EKGs were recorded and MTWA results were analyzed continuously with the time-domain MMA method. The maximum MTWA value at a heart rate (HR) of 125 beats per minute (BPM) was derived and its ability to stratify risk was tested for the following outcomes: all-cause death; cardiovascular death; and SCD. There were no data on persons who already had an implanted ICD or persons who had already been selected to receive an ICD.

During a follow-up period of 44 ± 7 months (mean ± SD), 59 patients died—34 due to cardiovascular causes and 25 from other causes. Of the 34, 20 were due to SCD. Multivariate analysis was performed after adjustment for age, sex, use of -blockers, functional class, maximal HR during exercise, previous myocardial infarction, and other common coronary risk factors. The relative risk associated with a positive MTWA (65 mV cutoff) for SCD was 7.4 (95% CI, 2.8–19.4; $p < 0.001$); for cardiovascular mortality was 6.0 (95% CI, 2.8–12.8; $p < 0.001$), and for all-cause mortality was 3.3 (95% CI, 1.8–6.3; $p < 0.001$). At cutoff points of 65 mV and 46 mV, the PPV (positive predictive value - the percentage of true positives in all persons testing positive) was 8% and 3.7% respectively and the NPV (negative predictive value - the percentage of true negatives in all persons testing negative) was 98.6% and 98.7% respectively for SCD. The authors concluded that time-domain MTWA analysis powerfully predicts mortality in a general population undergoing a clinical exercise test.

Verrier, et al. (2003) used a nested case-control method to analyze 15 cases and 29 controls from the large ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction, 1991-1994) study, matched for sex, age, site of MI, left ventricular ejection fraction (LVEF), thrombolysis, and beta blocker therapy. The 15 cases were selected from the 27 cases with cardiac arrest due to documented ventricular fibrillation or arrhythmic death. The authors report that the remaining 12 potential cases were excluded for a variety of reasons, but state that the clinical characteristics of the excluded subjects did not differ significantly from the included cases. Peak MTWA values were reported by one blinded investigator for a single 15 second period at three predetermined time intervals, i.e., 15 second intervals beginning with maximum heart rate, 8:00 AM and maximum ST segment deviation, separately. They used the Wilcoxon rank sum test to compare the MMA method of measuring MTWA means between cases and controls at three predetermined time intervals. They *a priori* defined high MTWA as being > the 75th percentile among the controls. The authors report that MTWA magnitude was similar at baseline in cases and controls, but that mean MTWA in microvolts was significantly higher in cases than controls at maximum heart rate and at 8:00 AM in lead V_5. There was a similar but nonsignificant trend in V_1. The mean maximum MTWA during maximum ST segment deviation was similar in cases and controls in both leads. Odds ratios for cardiac arrest or sudden death due to arrhythmia were increased for cases versus controls at maximum heart rate and at 8:00 AM.

Cox, et al. (2006) studied MTWA simultaneously using spectral analysis and the MMA method during pacing (< 110 beats/min) in 41 patients. The authors stated that the 41 patients had no prior sustained ventricular arrhythmias, and were referred for risk stratification. Patients were age 67 ± 9 years and 85% had coronary disease. Thirty nine of 41 patients were male. They measured MTWA during ventricular (ventricular + atrial) pacing, although comparisons with 'traditional' atrial pacing again found concordance. Over 542 ± 311 days follow-up, there were 11 deaths or sustained ventricular arrhythmias ('events').

Positive spectral analysis MTWA (1.9 µV) predicted patients with ventricular arrhythmia events from those without events ($p = 0.02$). Receiver-operating characteristics for the MMA method of measuring MTWA showed that the cutpoint of 10.75 µV was optimal for the combined endpoint. Kaplan-Meier analysis using this cutpoint trended to predict events ($p = 0.06$), while the MMA method of measuring MTWA combined with spectral analysis MTWA predicted events ($p = 0.01$) the authors stated. This study is small and limited to males (=95%). It employed a composite clinical endpoint instead of the endpoint of sustained arrhythmias or sudden cardiac arrest. The MMA method of MTWA measurement in Nearing's (2002) article defining the MMA method at a HR of somewhere around 150 beats in animals and potentially 120 beats/min in humans, was tested at 110 in this study.

In the proposed Decision Memorandum, we did not review the REFINE study by Exner, et al. (2007), however, this study was published recently. It sought to determine whether combined assessment of autonomic tone plus cardiac electrical substrate identified most patients at risk of serious events after myocardial infarction (MI) and to compare assessment at 2 to 4 weeks versus 10 to 14 weeks after MI. To identify most patients at risk of serious events after MI they evaluated 322 patients with studies such as ejection fraction (EF), heart rate turbulence (HRT) and T-wave alternans (TWA). The primary outcome was cardiac death or resuscitated cardiac arrest. All cause mortality and fatal or nonfatal cardiac arrest were secondary outcomes. The authors found that the mean EF significantly increased over the initial 8 weeks after MI. Testing 2 to 4 weeks after MI did not reliably identify patients at risk, whereas testing at 10 to 14 weeks did. Results from the testing at 10-14 weeks, but not at 2-4 weeks, independently determined a statistically significant higher hazard ratio on TWA testing (both spectral and MMA per personal communication with Dr. Exner) in those subjects with a positive test as compared to the others. The 20% of patients with impaired HRT, abnormal exercise TWA, and an EF < 50% beyond 8 weeks post-MI had a 5.2 times (2.4, 11.3, $p < 0.001$) higher adjusted risk of the primary outcome. This combination identified 52% of those at risk, with good positive (23%; 95% CI 17% to 26%) and negative (95%; 95% CI 93% to 97%) accuracy. The authors concluded that impaired HRT, abnormal TWA and an EF < 50% beyond 8 weeks after MI reliably identify patients at risk of serious events.

We also note that new evidence potentially casts doubt on the usefulness of MTWA testing. The MASTER 1 trial is designed to evaluate MTWA testing for risk stratification for life threatening VTEs among post-MI patients with impaired ejection fraction undergoing ICD implantation. (See: Clinicaltrials.gov Identifier NCT00305240.) In a

presentation by Dr. Theodore Chow at the American Heart Association Annual Scientific Session, Orlando, Florida, November 2007, the following abstract was reported.

Among post-MI patients with impaired EF undergoing ICD implantation, risk stratification using MTWA was not associated with difference in prediction of life-threatening ventricular tachyarrhythmic events.

Additionally,

Non-negative MTWA associated with higher risk of death, but not specifically arrhythmic death, suggesting positive MTWA test may just identify cohort of sicker patients, as evidenced by increase in baseline risk.

The full report of MASTER 1 still has not been published as we write this final decision memorandum. We anticipate reviewing these data more fully as part of our ongoing interest in this topic.

4. MedCAC

A Medicare Evidence Development and Coverage Advisory Committee (MedCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

No evidence-based guidelines are available for MTWA using the MMA method for patients who are candidates for ICD placement.

6. Professional Society Position Statements

The Heart Rhythm Society submitted a letter during the initial comment period that did not support coverage of MTWA using the MMA method for the requested indications. No references were cited in this letter. During this second 30 day comment period, the American College of Cardiology and America's Health Insurance Plans also submitted letters that did not support the coverage of MTWA using the MMA method for the requested indications. No references were cited in either letter.

7. Expert Opinion

We did not solicit any expert opinions on the use of MTWA using the MMA method.

8. Public Comments

Initial Comment Period: August 17, 2007 – September 17, 2007

Timely public comments are summarized below:

CMS received a total of thirteen comments during the first public comment period. Ten out of the thirteen comments stated that there was insufficient evidence to expand coverage to the MMA method. Two of these ten individuals cited specific research studies within their comments. Of the remaining three commenters, one felt that MTWA should be required prior to ICD placement but did not address the question as it relates to the MMA method versus spectral analysis. One commenter was in favor of coverage but indicated that randomized trials are needed to determine if either method can guide ICD therapy. The last commenter indicated that the MMA method was effective for risk stratification and should be covered nationally; however, this commenter is from the same organization as the entity that requested the reconsideration.

Second Comment Period: February 14, 2008 – March 15, 2008

Timely public comments are summarized below:

During the second comment period, 26 timely comments were received. The majority of the comments primarily fell into two broad categories: those in favor of expanding coverage and those who supported the proposed decision that the current policy remains unchanged. Another comment discussed various aspects of the technology without rendering an opinion about the policy itself. While we appreciate some commenters' reports of personal experiences, we must accord it less evidentiary weight than evidence from more methodologically rigorous clinical trials. The comments and CMS' responses are summarized below:

<u>Comments in favor of expansion of the current policy:</u>

There were 17 commenters who felt that the current policy should be expanded to include the MMA method. These commenters cite the recently published REFINE study by Exner, studies by Nieminen and Verrier and an unpublished study by Stein. An analysis of the REFINE study is included in this decision memorandum. An analysis of the study by Stein is not included because it has not yet been published as we write this decision memorandum.

One commenter stated that based on the REFINE study, spectral analysis and the MMA method were likely measuring similar things. Another commenter also felt that both the spectral analysis method and the MMA method could be viewed as two ways of getting to the same goal. However, this comment focused on the manner in which the EKG signal should be acquired for useful clinical testing. Another commenter, although supportive of expansion of the current policy, also noted that there are some challenges with the MMA method. This commenter's focus was more on the use of MTWA, in general, rather than either the spectral method or the MMA method.

Response:

These commenters have essentially proposed an alternative interpretation of the body of evidence on SA TWA testing. We believe that this alternative is not as consistent with the body of evidence compared to our own interpretation. We note that our interpretation is supported by other public commenters as well as several professional societies. Many of

the comments in favor of the policy expansion were submitted by the requestor, associates of the requestor and authors of the articles who have studied MTWA using the MMA method. Most of these comments point to the REFINE study as justification for policy expansion. We do not consider unpublished articles in making our decision, as the public would thus be denied the opportunity to see the evidence we have reviewed. The details of our decision, including an analysis of the REFINE study, are included below in this final decision memorandum. We summarize them here in the comment section for the convenience of the reader.

In our previous analysis in the proposed decision memorandum, we did not discuss the REFINE article by Exner, et al., because it had not yet been published; it has since been published. We note that the REFINE data suggest that MTWA, independent of specified other factors, may help predict those persons with a prior MI who may have a subsequent sudden cardiac death or cardiac arrest. This study is not described as an RCT. Of the 752 subjects (eligible participants) who could have been included in this series (we are unable to determine if these were consecutively enrolled subjects or not) only 322 got serial testing. The exclusion of over half of the eligible subjects creates significant, questions as to the ultimate validity of the results.

As we discuss in Appendix A, evidence from methodologically rigorous clinical trials provides greater confidence that the results of those trials actually support the conclusions claimed by the authors. Methodologic rigor minimizes bias and confounding which are among the factors that reduce such confidence. Expert opinion, while it can be informative, is inherently unable to provide comparable methodologic rigor. CMS will review new data as part of our routine analysis of additional evidence.

The follow-up period is four years on average and the TWA testing done at 10-14 weeks post MI demonstrates a barely statistically significant increased hazard for subsequent sudden cardiac death or cardiac arrest. We have personal communication from the author, Dr. Exner, stating that both the MMA and the SA methods were used for measuring TWA. He communicated to us that what he referred to in his paper as the Holter TWA method is really a method based on the Nearing, et al., (2002) MMA method. The Nearing method study makes no reference to Holter. Exner describes in his REFINE paper that, due to lack of prior Holter TWA data (MMA), MMA TWA was calculated based on 32 heart beats on Holter high resolution recordings collected immediately after the spectral recording. This is apparently an arbitrary method and has not been validated to our knowledge.

Consistent test criteria are important characteristics of diagnostic tests. It is plainly and inherently challenging to claim that a single test result would appropriately be interpreted as positive by one physician and negative by another. Such a scenario logically casts doubt on the ability of the test to provide clinically useful information.

Comments in support of the current policy:

There were eight commenters in support of continuing the current policy. These commenters cite insufficient evidence for a change in the current CMS policy regardless of the recently published REFINE study and the Stein article which is anticipated to soon be published. Some commenters also cite preliminary findings of the MASTER trial as justification for their comments. However, an analysis of the MASTER trial is not included since it has not been published as of the date of the posting of this decision memo.

Response:

CMS appreciates the supportive comments. Some of these comments were received from those who have ownership or interest in the spectral analysis method. Others have either authored articles utilizing the spectral analysis method or provided comments based on personal experience. Additionally, three of these commenters represent professional societies with a vast number of constituents. These commenters also make references to the MASTER trial. As noted before, the results of the MASTER trial have not been published as of the date of the posting of this final decision.

Other comment:

One individual commented about particular filtering or noise detection issues in the spectral and time domain methods. This individual did not cite specific studies. However, this commenter did not render an opinion to expand the current policy or in support of the current policy.

Response:

We appreciate the commenter’s thoughts on the technical aspects of these tests.

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 by Medicare (§1869(f)(1)(B) of the Act). 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.” See §1862(a)(1)(A)of the Act. This section presents the agency’s evaluation of the evidence considered and conclusions reached for the assessment

A diagnostic test is not expected to directly change health outcomes. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such

actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. Thus, in the case of MTWA we expect that the evidence base would demonstrate changes in patient outcomes by informing physician decisions to determine which beneficiaries may need an ICD and which do not. The Medicare regulations at 42 CFR 410.32(a) state in part, "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." In this instance we focus on evidence to determine if MTWA testing by the MMA method correctly stratifies Medicare beneficiaries' risk for SCD and thus informs the treating physicians' decision to recommend or not recommend ICD placement.

Question

Is the evidence adequate to conclude that MTWA testing using the MMA method improves health outcomes for Medicare beneficiaries who are candidates for ICD placement?

Analysis

Extensive clinical research has revealed that patients with symptoms of, or at risk for, life threatening arrhythmias and who also test positive for TWA have a higher risk for subsequent development of sudden cardiac events including sudden death. Those who test negative for TWA have a lower risk. However, many patients have indeterminate results. MTWA using a spectral analysis algorithm, as a stratification tool, may help to identify individual patients from high risk populations (e.g., those with ischemic and nonischemic cardiomyopathy, dilated cardiomyopathy, post myocardial infarction, MADIT II-type, or SCD-HeFT-type) who are actually at low-risk for SCD and who thus may be able to avoid ICD placement. CMS has previously determined that it is possible to classify those patients who test positive or indeterminate for MTWA (i.e., those more likely to benefit from ICD implantation), and those who test negative for MTWA (i.e., those less likely to benefit from ICD implantation) using the SA method. This determination was made based on the evidence available at that time for the SA method.

The question before us may be addressed either by independent demonstration of a clinical benefit of the MMA method of measuring MTWA or by demonstration of substantial comparability of the MMA and SA methods of measuring MTWA. Most of the evidence we reviewed focused on the former method.

Although one additional study was recently published, the relevant evidence base for the MMA method algorithm is still comparatively sparse. We are concerned that the narrow subject populations in the trials limit the generalizability of study results to Medicare beneficiaries. Other methodologic limitations characterizing this literature include small sample sizes (Lampert, Shusterman, Burg et. al. 2005; Verrier, Nearing, La Rovere et al. 2003, Kop et al 2004), the use of simulations or non-clinical outcome measures (Nearing, Huang, Verrier, 2002, Nearing, Verrier, 2001, Martinez, Olmos, 2005; Shusterman, Goldberg, London, 2004,), and the lack of control groups (Lampert, Shusterman, Burg et al. 2005). Other studies focused on MMA TWA to measure non-cardiac indications such as mental stress (Kop et al 2004, Lampert, Shusterman, Burg et al. 2005). The 2005 article by Verrier, et al., is an expert opinion, so we assigned it less weight than the clinical trials that we reviewed. While expert opinion can be informative it is inherently unable to provide sufficient methodologic rigor for confident conclusions about scientific evidence. An analysis of the REFINE study is discussed below.

With respect to the comparison between MMA and SA, results of the 2003 study by Verrier, et al., suggest that the clinical diagnostic information provided by the MMA method is comparable in some respects to that provided by SA. Though the ATRAMI study from which the study data were later drawn was prospective and included 1284 post-myocardial infarction patients, the Verrier study only examined 15 cases and 29 controls, using data that was originally collected for a purpose other than MTWA testing. The limitations of this small sample size and limited study design, along with very large, and thus, imprecise confidence intervals, lead us to assign lesser weight to its conclusions.

The Nieminen study has a much larger sample size, with 1037 participants. A strength of the study is that approximately 26% of its subjects were 65 years or older and therefore of Medicare age. Without explanation, the authors chose to apply the MMA method to a standard EKG instead of a Holter monitor. We are not aware of any advantages or disadvantages of such application. Many participants (over 1000) underwent exercise stress tests and the test had good negative predictive value for certain MMA method cutoff points. The reported follow-up time of 44 ± 7 months is of sufficient duration.

We will describe in detail our reservations about the Nieminen study.

1) The paper does not report the baseline status of the subjects, i.e., coronary heart disease, arrhythmia during exercise, need to be evaluated for work capacity, or need for an exercise profile prior to an invasive operation or after an MI, relative to which ones eventually had SCD or other heart related death. Since these factors are potential confounders, the lack of separate consideration for each one is problematic and clouds the results.

2) The ethnicity of the study population apparently differs sufficiently from the Medicare beneficiary population to limit the generalizability of its conclusions. Though the racial makeup is not mentioned, CMS does not have evidence that Hispanic and African American populations are proportionately represented in this study since over 98% of the

population of Finland is of Finnish (93 + %) or Swedish ethnicity. We note that the ethnic make-up of populations studied in individual trials of the SA method may be similarly narrow; however, this concern is addressed by the greater number of individual trials using that method. Thus, the overall body of evidence for the SA method is derived from a more broadly representative sample.

3) The EF was only determined for approximately 50% of the study population, and we are uncertain as to whom that applies (i.e., which half of the subjects by baseline status). This confounds the analysis.

4) The study does not compare the MMA method of measuring MTWA to SA MTWA. While this is not a requirement, i.e., the requestor can attempt to demonstrate a clinical benefit of the MMA method of measuring MTWA on its own merits; it does limit the potential relevance of evidence regarding spectral analysis to the current question. A comparison might be helpful since the evidence of benefit for the MMA method itself is limited.

5) Cutoff points were determined after the fact rather than prospectively. As in other articles describing critical values for prediction of SCD via the MMA method, there is neither a standard lead nor a standard mV cutoff point. This methodologic limitation, i.e. establishing the test result criteria after-the-fact, does not support a conclusion that this test has predictive value.

6) This study was performed in a more general population undergoing routine exercise testing whereas in this NCD. Medicare's interest in the evidence base of this test is specific to those beneficiaries that would be eligible for Medicare coverage of ICD therapy. CMS is thus interested in populations at higher risk for ventricular arrhythmia events or SCD event specifically who are candidates for ICD implantation. The predictive value of TWA testing in other populations with different risks is not applicable to the population of interest here.

7) According to the study protocol published in 2006 (Nieminen, et al., BMC Cardiovascular Disorders 2006),

The participant pool consists of patients who undergo exercise stress tests at Tampere University Hospital. All the consecutive patients coming in for an exercise stress test and willing to participate in the study have been and will be recruited between October 2001 and December 2007. Our goal is to recruit roughly 5,000 patients. Currently, the research group is actively analyzing the data on the 2,212 patients (1,400 men and 812 women) recruited by the end of 2004.

CMS is unclear about the apparent discrepancy between the 1037 subjects in the 2007 MTWA study under discussion and the availability of much more data at the time the study was published. Are the data on all those patients after the first 1037? Did they change techniques in January 2003, or was there some other change? We also question why the protocol was published in 2006 since the study was to be ongoing from 2001 forward. The protocol for this study does mention t-wave alternans as a goal of measurement to see if it is linked with mortality.

8) The report does not say it was prospectively planned from the outset in 2001. i.e., it appears to have been an afterthought. This is methodologically challenging as we cannot be confident the data that were analyzed were collected in a manner that would minimize bias. It has no control group, which is a significant methodologic weakness as it is therefore not possible to determine that SA TWA testing improves clinically meaningful health outcomes in subjects who were tested, compared to those who were not tested.

9) We are also not told what percent of patients were not willing to participate and how their demographic characteristics compare to those of the 1037 who gave consent; indicating possible mishandling of indeterminate findings and skewing of results.

10) The study reports that 96.6% of 1037 patients had technically successful exercise tests. The study did not report why the other 3.4% were unsuccessful and if they had characteristics that would have changed the outcome. Because there were approximately 35 individuals in this group, this information is important. That is, these individuals may have not completed the stress test successfully for some reason (health or otherwise), which in turn, might affect the findings.

11) This is not a randomized control trial but a consecutive series. Randomization minimizes bias and provides greater confidence that the effects attributed to the intervention are actually a result of the intervention rather than to other factors that were not adequately considered.

In our previous analysis in the proposed decision memorandum, we did not discuss the REFINE article by Exner, et al., because it had not yet been published; it has since been published. We note that the REFINE data suggest that MTWA, independent of specified other factors, may help predict those persons with a prior MI who may have a subsequent sudden cardiac death or cardiac arrest. This study is not described as an RCT. Of the 752 subjects (eligible participants) who could have been included in this series (we are unable to determine if these were consecutively enrolled subjects or not) only 322 got serial testing. The exclusion of over half of the eligible subjects creates significant, questions as to the ultimate validity of the results. For example, of the 402 that refused testing, we do not know how many deaths or resuscitated cardiac arrests occurred. Reporting of that information might have provided us with better insight into the comparability of those tested and those refusing tests.

The follow-up period is four years on average and the TWA testing done at 10-14 weeks post MI demonstrates a barely statistically significant increased hazard for subsequent sudden cardiac death or cardiac arrest. We have personal

communication from the author, Dr. Exner, stating that both the MMA and the SA methods were used for measuring TWA. He communicated to us that what he referred to in his paper as the Holter TWA method is really a method based on the Nearing, et al., (2002) MMA method. The Nearing method study makes no reference to Holter. Exner describes in his REFINE paper that, due to lack of prior Holter TWA data (MMA), MMA TWA was calculated based on 32 heart beats on Holter high resolution recordings collected immediately after the spectral recording. This is apparently an arbitrary method and has not been validated to our knowledge. We also note that the REFINE study included subjects whose EF was below 50%. This is significantly broader than the population of interest in our review, as Medicare coverage of ICD placement is, except for beneficiaries who have already sustained a near SCD event, predicated on an EF below 35%. Thus we are not confident that the conclusions of the REFINE authors reflect the ability of the MMA method to stratify risk are applicable to the population of interest here.

Consistent testing protocols and criteria for positivity and negativity are important characteristics of diagnostic tests. Test results may vary depending on the manner in which a test was performed. It is plainly and inherently challenging to claim that a single test result would appropriately be interpreted as positive by one physician and negative by another. Such a scenario logically casts doubt on the ability of the test to provide clinically useful information, unless it has an unusually high sensitivity and specificity given the risk involved.

After careful examination CMS finds that the evidence base supporting the MMA method of measuring MTWA remains limited and unconvincing. Proponents of the MMA method claim that its evidence base is as well developed as that of the competing SA method. We disagree, based on our analysis of this body of literature. Public comment is divided on the issue, apparently reflecting the interests of the stakeholders who have allied with one or the other MTWA method. We note the lack of support from the relevant professional societies for expanded coverage at this time. Thus, we find that the evidence is not sufficient for CMS to determine that MTWA via the MMA method improves health outcomes for Medicare beneficiaries who are candidates for ICD placement.

We note that the body of evidence on MTWA continues to grow with new trials in progress and new results being published. For example, CMS anticipates reviewing the full published MASTER 1 report as a part of our ongoing interest in this topic. We agree with the commenters who noted the need for additional trials about this technology, and we believe that this trial and other ongoing trials will be important additions to the evidence base.

IX. Conclusion

CMS was asked to reconsider our national coverage determination (NCD) on microvolt t-wave alternans (MTWA) diagnostic testing to extend coverage to the modified moving average (MMA) method. CMS' interest in MTWA testing is in the risk stratification of Medicare beneficiaries who may be at risk for sudden cardiac death (SCD) from ventricular arrhythmias and who may be candidates for Medicare coverage for the placement of an implantable cardioverter defibrillator (ICD). The NCD specifically provides for coverage of MTWA using the spectral analysis method and noncovers MTWA using any other method (Section 20.30 Medicare National Coverage Determinations Manual). CMS has determined that there is insufficient evidence to conclude that the MMA method of determining MTWA improves health outcomes for Medicare beneficiaries at risk for sudden cardiac death (SCD) and we therefore find that it is not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act (the Act).

Nationally Covered Indications

Microvolt T-wave Alternans diagnostic testing is covered for the evaluation of patients at risk for SCD only when the spectral analysis method is used.

Nationally Non-Covered Indications

Microvolt T-wave Alternans diagnostic testing is non-covered for the evaluation of patients at risk for SCD if measurement is not performed employing the spectral analysis method.

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