Clinical Dossier

Microvolt T-Wave Alternans (MTWA) Diagnostic Testing by the Modified Moving Average (MMA) Method

Contents:
I. Executive Summary
II. MMA Method in Comparison to Spectral Method
III. Published Studies Validating MTWA by MMA Identified in Medicare’s 2008 National Coverage Decision (CAG-00293R)
IV. Studies Validating MTWA by MMA Published Since Medicare’s 2008 National Coverage Decision (CAG-00293R)
V. Concluding Statements

I. Executive Summary

- MTWA is a beat-to-beat variation in the morphology and amplitude of the ST segment and T wave of the electrocardiogram (ECG) that can serve as an indicator of risk for sudden cardiac death (SCD). It reflects a repolarization abnormality that is a manifestation of underlying myocardial pathology that places the patient at risk for life-threatening ventricular arrhythmias.

- MTWA analysis is a non-invasive diagnostic test that measures this pattern. MTWA analysis by both the Spectral and MMA Methods has received FDA clearance. These methods are mathematical algorithms that assess the same electrocardiographic phenomenon.

- The MMA algorithm is suitable for use both in standard ambulatory recordings and in routine, symptom-limited exercise testing. Because it does not require patients to reach a target heart rate, MMA analysis can be performed in the flow of routine clinical assessment while patients remain on beta-blockers and other chronic medications and as well as in patients who are unable to exercise. The MMA Method analyzes recordings from standard precordial leads, retains ECG morphology, and provides a unique “template” tool that allows physicians to verify the automated MTWA value, thereby minimizing the potential for false positive results. MMA does not require special electrodes because noise rejection is accomplished by signal processing. The low indeterminate test result rate of 3-5% for MMA analysis is composed largely of cases with technically inadequate recordings.

- By contrast, the Spectral Method algorithm is employed in exercise tests, during pacing, or with infused chronotropic drugs that raise and stabilize patients’ heart rates to a target 105-110 beats/min range. It has been reported that in 20-40% of cases, the Spectral Method provides indeterminate test results; in 51% of these indeterminate readings, the finding is due to patients’ inability to reach the target heart rate (1). This target heart rate range can require washout of therapies such as beta-adrenergic blockade, which lower
heart rate, so that patients’ test condition differs from their followup condition, thereby affecting long-term prediction (2). It also necessitates running a separate protocol and requires specialized electrodes. The Spectral Method reports the computed MTWA value but is unable to display the ECG morphology.

- The body of evidence pertinent to MMA is significantly more robust than when Medicare last considered this issue in 2008. Six peer-reviewed prospective full-cohort clinical studies have been published since that time, which evaluated >3,700 patients of multiple ethnicities, age ranges, and a variety of baseline cardiovascular characteristics (Tables 1 and 2). These studies reported that MMA analysis of MTWA generated hazard ratios of 4.4-22.6 for SCD across a variety of clinical cohorts in multivariate analyses that corrected for known cardiovascular risk factors including left ventricular ejection fraction, the current marker for implantable cardioverter-defibrillator (ICD) use. Thus, MMA analysis provides information regarding SCD risk that is in addition to what may be learned from left ventricular ejection fraction in terms of likelihood of benefitting from ICD implantation. The studies included patients in the Medicare age group both with and without left ventricular dysfunction. These hazard ratios are similar to those generated with the Spectral Method. The negative predictive values of MMA-based MTWA ranged from 96% to 99%, also equivalent to the Spectral Method. All MMA-based MTWA studies have demonstrated that MMA-based MTWA is predictive.

- The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (4) recommended MTWA analysis in two settings:
  - “5.2.3. Ambulatory Electrocardiography Recommendations, Class I (“Procedure should be performed”): Ambulatory ECG is indicated when there is a need to clarify the diagnosis by detecting arrhythmias, QT-interval changes, T-wave alternans (TWA), or ST changes, to evaluate risk, or to judge therapy. (Level of Evidence: A)”
  - “5.2.4. Electrocardiographic Techniques and Measurements Recommendations, Class IIa (“It is reasonable to perform procedure”): It is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias. (Level of Evidence: A)”

- The 2008 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific statement on noninvasive risk stratification techniques for identifying patients at risk for SCD (5) stated:
  - “A moderate amount of data suggest that T-wave alternans may be useful for risk stratification for SCD. Further information will be required to determine how to implement this test in clinical practice.”
In 2011, a consensus guideline from the International Society for Holter and Noninvasive Electrocardiology (1), written by authors who are international experts on both Spectral and MMA Methods, stated:

- “Predictivity of TWA analysis by the MMA Method has been demonstrated in 4,800 patients, including those with coronary artery disease, recent or old myocardial infarction, congestive heart failure, or cardiomyopathy.”
- “MMA-based TWA studies with ambulatory ECG recordings and exercise support the concept that TWA represents a continuum of risk with higher TWA levels indicating greater risk.”
- “Hazard ratios generated by the Spectral and MMA Methods are similar, whether in the same population (6), or in studies overall.”
- “Overall, our assessment is that it is reasonable to consider TWA evaluation whenever there is suspicion of vulnerability to lethal cardiac arrhythmias.”
- This statement is endorsed by several cardiology societies including: International Society for Holter and Noninvasive Electrocardiology, Japanese Circulation Society, the Computers in Cardiology Working Group on e-Cardiology of the European Society of Cardiology, and the European Cardiac Arrhythmia Society.

MTWA analysis by MMA has been standardized for clinical practice with cutoffs based on the patient’s pre-test probability of SCD based on prospective studies. Quantification of MTWA magnitude by MMA allows determination of levels of SCD risk, which is important for gauging urgency of therapy and for identifying higher- and lower-risk individuals.

Overall, extensive clinical evidence accumulated over the past decade indicates that the MMA Method provides at least equivalent predictivity for SCD as does the currently reimbursed Spectral Method, which received earlier approval from Center for Medicare & Medicaid Services as a diagnostic test to stratify Medicare beneficiaries’ risk of SCD. The equivalent diagnostic capacity of the methods is supported by the MTWA consensus paper (1) as well as by the body of clinical information gathered during the 5 years since the 2008 coverage decision.

II. MMA Method in Comparison to Spectral Method:

A. Analytical Principles

The Spectral Method employs the Fast Fourier Transform and utilizes specialized electrodes to minimize noise to detect microvolt levels of TWA; this approach requires measuring MTWA during target-heart rate exercise or at rest.

The time-domain MMA algorithm achieves the same demonstrated level of accuracy using standard electrodes by applying the noise-rejection principle of recursive averaging and is thereby suited to measure MTWA during ambulatory ECG monitoring or symptom-limited exercise testing or at rest. The algorithm continuously streams odd and even beats into separate bins and creates median complexes for each bin (Fig. 1). These complexes are then superimposed, and the maximum difference between the odd and even median complexes at any point within the JT segment is averaged for every 10 to 15 seconds and reported as the MTWA.
value (Fig. 2). The moving average allows control of the influence of new incoming beats on the median complexes with an adjustable update factor, that is, the fraction of morphology change that an incoming beat can contribute. The recommended rapid update factor of one-eighth provides greater sensitivity and capacity to detect transient but clinically important surges in MTWA than one-sixteenth or one-thirtysecond. Noise measurements are in part derived from the mismatch of the even or odd median complexes outside the JT segment. The algorithm excludes extrasystoles, noisy beats, and the beats preceding them and filters out effects of noise, movement, and respiration. The inherent noise-rejection features of the MMA design have been enhanced by GE Healthcare’s proprietary algorithms such as Finite Residual Filter and Cubic Spline, which further minimize artifact and reduce the potential for false positive readings, as described in the FDA clearance document.

Fig. 1: Flow chart of the major components of the Modified Moving Average Method of microvolt T-wave alternans analysis. (Reprinted with permission from American College of Cardiology Foundation from reference 1.)
Fig. 2: Precordial (V4) ECG rhythm strip (left) and high-resolution template of QRS-aligned complexes (right) during routine exercise testing from a patient with coronary artery disease from the Finnish Cardiovascular Study (FINCAVAS). The template of superimposed beats illustrates microvolt T-wave alternans (MTWA) as a separation between ST-T segments in A and B beats. MTWA magnitude = 106 μV. Sec = second. mV = millivolt. (Reprinted with permission from American College of Cardiology Foundation from reference 1.)

B. MMA’s QRS-Aligned MTWA Templates Facilitate Overreading and Verification
A unique design feature of the MMA Method is the generation and display of high-resolution QRS-aligned templates of superimposed ECG complexes, which are available for analysis of both ambulatory ECGs and exercise stress test ECGs (Fig. 2, right panel). These templates permit the operator to inspect the ECGs and to verify the MTWA pattern and its magnitude, validating the automated analyses, thereby minimizing the potential for false positive results due to noise or movement artifacts.

C. Classification of MMA-Based MTWA Test Results
MTWA represents a continuum of risk, and higher levels indicate greater risk. MTWA levels >60 μV during routine exercise testing and ambulatory ECG monitoring indicate severely elevated risk for SCD and/or cardiovascular mortality (7-9). In patients during the early post-myocardial infarction (post-MI) phase with or without heart failure, an MTWA level >47 μV also predicted SCD (10-13). Each 20 μV of MTWA increases risk of cardiovascular and SCD by 55 and 58%, respectively (14). Quantitative assessment of MTWA level, which is standard for MMA analysis, may add to its prognostic value beyond qualitative categorization of a test as “positive,” “negative,” or “indeterminate.” For many clinical measures, such as blood pressure, cholesterol levels, left ventricular ejection fraction, and others, knowing an individual patient’s values within a range can be important in evaluating urgency of intervention and effectiveness of therapy. Essentially, quantification of MTWA level by MMA enables this technology to fulfill the contemporary need to develop methods for personalized medical care.

D. Importance and Implications of Testing Patients on Chronic Medications
Because beta-adrenergic blocking agents, which are in widespread use in the population of interest, inhibit the heart rate response to exercise, their use can limit the capacity of certain patients to achieve a target heart rate of 105-110 beats/min, which is required for MTWA testing with the Spectral Method. Inability to reach this heart rate accounts for 51% of indeterminate test results with this method (2). Washout of beta-blockers represents one approach to MTWA testing in these patients. However, because beta-blockers are antifibrillatory, their withdrawal and later resumption can interfere with predictivity, especially as it has been shown that beta-blockers can convert a positive to negative test in 17% to 50% of cases (15-17). Chan and
colleagues (3) noted in a meta-analysis that a common element in the nonpredictive Spectral Method studies, including patients with and without ICDs, was washout of beta-adrenergic blocking agents at the time of the test, with resumption of the medication after testing. Of the nine studies enrolling 3,939 patients reviewed in this meta-analysis, the effect of washout of beta-adrenergic blockade was to decrease the predictive power by nearly 4-fold, as indicated by a reduction in hazard ratios from 5.39 (2.68-10.84, p <0.001) to 1.40 (95% CI: 1.06-1.84, p = 0.02).

As mentioned above, the MMA Method does not require achieving a target heart rate to make an MTWA measurement. Accordingly, it has not been necessary to withdraw beta-blockade therapy to perform MMA-based MTWA testing during routine exercise or ambulatory ECG monitoring. The >5,200 patients tested with MMA-based MTWA were all evaluated on chronic medications, consistent with current guidelines (1), and all studies have been predictive (Table 1). Thus, medical therapy does not disrupt prediction by MMA.

An important corollary to this experience with beta-adrenergic blockade is that the MTWA level reflects the effects of medications on arrhythmia vulnerability, allowing it potentially to help guide medical therapy, thereby reducing the number of ICD implantations, as was suggested in a review of all classes of antiarrhythmic therapy (18) as well as in the MTWA consensus paper (1).
III. Published Studies Validating MTWA by MMA Identified in Medicare’s 2008 Coverage Decision (CAG-00293R 2008)


<table>
<thead>
<tr>
<th>Summary of Study Objective/Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>This was the first study assessing MMA-based MTWA in 24-hour ambulatory ECGs in post-myocardial infarction (post-MI) patients with moderately depressed left ventricular ejection fraction (LVEF). A nested case-control approach was employed. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study was a 25-center prospective study of 1,248 post-MI patients conducted in the US, Europe, and Japan. MMA-based MTWA was analyzed in ambulatory ECG records obtained 6-28 days following myocardial infarction from 15 ATRAMI patients, who during 21±8 months of follow-up experienced cardiac arrest due to ventricular fibrillation or arrhythmic death. These data were compared in a blinded prospective manner with MMA-based MTWA obtained 6-28 days after myocardial infarction from 29 controls in the ATRAMI study, who did not experience cardiac death and were matched for sex, age, site of MI, LVEF, thrombolysis and beta-blockade treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There were no statistically significant differences in baseline characteristics between the cardiac arrest patients and controls: Mean ages were 60±2.1 and 62±1.4 years, LVEF was 42±3.6% and 41±2.2%.</td>
</tr>
<tr>
<td>• MTWA was reported as the maximum 15-second value at a) maximum heart rate; b) 8:00 AM; c) maximum ST-segment deviation:</td>
</tr>
<tr>
<td>o At maximum heart rate, a MTWA &gt;75th percentile of MTWA in survivors was associated with 4.2-fold higher odds for cardiac arrest or arrhythmic death (p=0.04) when measured in lead V1, and 7.9-fold higher odds (p=0.005) when measured in lead V5.</td>
</tr>
<tr>
<td>o At 8:00 AM readings, MTWA levels &gt;75th percentile of MTWA in survivors were associated with a 5.0-fold higher odds of cardiac arrest or arrhythmic death (p=0.02) in lead V1 and 4.2 odds in lead V5 (p=0.04).</td>
</tr>
<tr>
<td>o During maximum ST-segment deviation, MTWA levels &gt;75th percentile of MTWA in survivors were not associated with higher odds of cardiac arrest or arrhythmic death in either lead V1 or V5. The maximum ST-segment deviations did not differ among cases and controls, indicating that myocardial ischemia does not predict lethal arrhythmia.</td>
</tr>
<tr>
<td>• MTWA assessment using MMA analysis in routine ambulatory ECGs provided risk stratification in a relatively low-risk post-MI population.</td>
</tr>
<tr>
<td>• This study established 47µV, derived as 75th percentile of MTWA level in survivors/controls, as a cutpoint for MTWA studies with the MMA Method.</td>
</tr>
</tbody>
</table>

**Summary of Study Objective/Patient Population**

This prospective full-cohort investigation was conducted as part of the Finnish Cardiovascular Study (FINCAVAS), which had as an original goal to investigate the predictive capacity of MTWA (19). Data collection began in 2001. To date, the study had enrolled a total of 1037 consecutive patients (mean age 58 yrs, 673 men, 364 women) who were referred for a clinically indicated exercise test. The main indications for the exercise test were diagnosis of coronary heart disease (46%), vulnerability to arrhythmia during exercise (18%), evaluation of work capacity (19%) adequacy of the coronary heart disease treatment (24%), preoperative exercise test profile prior to an invasive surgery (13%) and evaluation following myocardial infarction (MI) (10%); some patients had more than one indication; baseline patient characteristics were provided (Tables 1, 2 in reference 11). Enrollment rate was high. Indeterminate rate was 3.4% and due to technical recording failures. The MTWA values were calculated using time-domain MMA analysis during the entire exercise test from rest to recovery using all standard leads (I, II, III, aVR, aVL, aVF, and precordial leads V1–V6). The maximum MTWA value at heart rates <125 beats/min was derived. SCD was defined as a cardiac death within 24 hours after the onset of symptoms.

**Summary of Results**

- During a follow-up of 44±7 months, 59 patients died; 34 deaths were due to cardiovascular causes and 20 were due to SCD. In multivariate analysis after adjustment for age, sex, use of beta-blockers, functional class, maximal heart rate during exercise, previous myocardial infarction, and other common coronary risk factors, MMA-derived MTWA at an optimized cutpoint of ≥65 μV exhibited significant predictive strength:
  - Hazard ratios comparing cases to survivors (controls) 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).
- Negative Predictive Value (NPV) for cardiovascular death was 97.6 and for SCD was 98.6.
- The investigators also found that the 47-μV cutpoint derived in the ATRAMI study (10) provided a high level of predictivity. For SCD, the hazard ratio was 2.9 (1.2-7.1, p = 0.02) and negative predictive value (NPV) was 98.7; for cardiovascular mortality, the hazard ratio was 2.6 (1.3–5.1, p = 0.01) and the NPV was 97.6.
- Thus, MMA-based MTWA analysis powerfully predicts SCD and cardiovascular mortality in a population undergoing a clinical exercise test.
- This study established 65μV as a cutpoint for MTWA studies with the MMA Method.
- It also established the suitability of precordial leads for MMA-based MTWA analysis.
### III.c. Exner et al, Journal of the American College of Cardiology 2007 (6)

**Summary of Study Objective/Patient Population**

The REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) full-cohort study was a prospective six-center Canadian study of patients with moderately depressed left ventricular function after myocardial infarction. This study sought to determine whether several measures of autonomic tone plus MTWA by both the Spectral and MMA Methods could identify most patients at risk of serious events after myocardial infarction. The primary outcome was cardiac death or resuscitated cardiac arrest. Of the 752 patients who met criteria, 322 patients were recruited. Characteristics of remaining patients were similar to recruits (Table 1 in reference 6). Recruits had an ejection fraction (EF) <50% in the initial week after myocardial infarction and were followed for a median of 47 months.

**Summary of Results**

- Abnormal MTWA tested at 10-14 weeks post-myocardial infarction by both the Spectral and MMA Methods reliably identified patients at increased risk:
  - MTWA during Exercise by Spectral Method, hazard ratio = 2.75 (95% CI: 1.08-7.02 p=0.034).
  - MTWA on post-exercise ambulatory ECGs by MMA Method, hazard ratio = 2.94 (95% CI: 1.10-7.87 p=0.031).
  - Combined analysis with heart rate turbulence, a measure of baroreceptor function, improved risk assessment further, as MMA-based MTWA reached hazard ratio of 6.22 (2.88–13.42, p<0.001).
  - These data provide evidence of the equivalence of the Spectral and MMA Methods in predicting cardiac death or resuscitated cardiac arrest.

### III.d. Cox et al, Pacing and Clinical Electrophysiology 2007 (20)

This study of 41 patients comparing the Spectral and MMA Methods employed customized rather than commercial software for MMA and thus is not relevant to the current application.
IV. Studies Validating MTWA by MMA Published Since Medicare’s 2008 National Coverage Decision (CAG-00293R)


Summary of Study Objective/Patient Population

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a United States prospective randomized controlled trial involving 6,632 acute post-myocardial infarction (post-MI) patients with left ventricular dysfunction, who are thus representative of patients in whom ICD implantation is considered. Patients were randomized to treatment with eplerenone or placebo and none of the patients had received an ICD. In the ambulatory ECG substudy of EPHESUS, 493 patients had pre-randomization 24-hour ambulatory ECG recordings obtained between 2 and 10 days post-MI. MMA-based MTWA was analyzed in a nested case-control design from the 46 patients in the substudy who, during 16.4 months of follow-up, died of cardiovascular causes, including 18 SCDs. These data were compared with MMA-based MTWA findings in 92 ambulatory ECG substudy patients who were alive at the end of the follow-up and were matched based on age, gender, and presence of diabetes. The primary goal of this study was to determine if the MTWA cutpoint of 47 μV derived in the ATRAMI MTWA substudy (10) predicted SCD in post-MI patients with left ventricular dysfunction.

Summary of Results

- MTWA in either precordial lead V1 or V3 was higher for patients with SCD (P ≤ 0.05) versus survivors or patients who died of non-SCD causes.
- MTWA ≥ 47 μV in precordial lead V1 was associated with relative risk (RR) = 5.2 (P = 0.002) and in V3 with RR = 5.5 (P < 0.001) for SCD.
- The optimized cutpoints for MTWA were ≥ 43 μV in V1 and ≥ 47 μV in V3.
- MTWA greater than the optimal cutpoint in either lead was associated with RR = 7.1 (P < 0.001) for SCD, with 11 out of 18 patients dying of SCD (Fig. 3).
- There was no difference in the number of patients with SCD who received active therapy with eplerenone or received placebo, suggesting that the findings were not affected by subsequent therapy.
- Ambulatory ECG-based MTWA measured with MMA is a powerful predictor of SCD in high-risk post-MI patients with left ventricular dysfunction.
- This study validated 47 μV as a cutpoint for MTWA studies with the MMA Method.

Fig. 3: Cox regression analysis for MTWA above optimal cutpoint in either lead V₁ or V₃ as a predictor of SCD. (Reprinted with permission from Wiley from Stein et al, reference 12.)
The objective of this study was to evaluate the utility of MTWA in the immediate post-exercise period to identify and validate cutpoints for the MMA Method. This study utilized the data from the 322 participants in the REFINE study (6) to define a 60-μV cutpoint for validation in the 681 patients with coronary artery disease in FINCAVAS (11). This analysis employed the sensitive 1/8 update factor for MMA-based MTWA, as recommended.

Summary of Results

- A linear relationship between the magnitude of MTWA and the risk of cardiovascular death was identified (Fig. 4). Patients with MTWA >60 μV experienced the greatest incidence of cardiovascular and total mortality, whereas those with MTWA 20 to 59 μV had an intermediate risk of these outcomes.
- In the validation cohort of FINCAVAS patients with coronary artery disease, MMA-based MTWA ≥60μV had a hazard ratio for SCD of 3.1 (95% CI: 1.3-7.4; p=0.01) and for cardiovascular death of 2.6 (1.1-6.0, p=0.05) with a negative predictive value of 95%.
- The 60-μV MMA cutpoint is a more specific marker of risk and may be better suited for use in low-risk populations.
- The 20-μV MMA cutpoint provides a sensitive marker of risk and may be most applicable in settings where patient risk is already elevated as reflected by abnormalities in other markers.
- This study supported 60 μV as a cutpoint for MTWA analysis by the MMA Method.

Fig. 4: Rates of cardiovascular death (orange) and total mortality (blue) at 4 years, by quintile of microvolt T-wave alternans (MTWA) using the Modified Moving Average (MMA) Method. (Reprinted with permission from American College of Cardiology Foundation from reference 7.)
Summary of Study Objective/Patient Population

This prospective full-cohort study conducted in Japan evaluated 295 consecutive patients with left ventricular dysfunction (left ventricular ejection fraction <40%), who are representative of patients in whom ICD implantation is considered. Patients were divided into two groups: those with ischemic or non-ischemic cardiomyopathy. MMA-based MTWA was obtained from routine 24-hour ambulatory ECG recordings. The maximum MTWA at heart rates \(\leq 120\) bpm in either lead V5 or V1 was defined as positive when voltage was \(\geq 65\) μV. Consecutive patients (N=312) were evaluated for the study and 17 were excluded because of inability to perform data analysis due to paroxysmal atrial fibrillation, supraventricular tachycardia, or frequent extrasystoles. Patients were followed at 2- to 4-week intervals during a follow-up period of 390±212 days. The primary end-point was prospectively defined as cardiac mortality or appropriate ICD therapy.

Summary of Results

- Mean age = 66, 72% male, 41% New York Heart Association (NYHA) class III or IV, mean left ventricular ejection fraction = 34%.
- Follow-up was completed in 100% of study patients.
- 27 (9.2%) patients reached the primary end-point of cardiac mortality: 5 suffered witnessed SCD, 9 died of congestive heart failure, 12 patients died of cardiac complications, including frequent ventricular/atrial arrhythmias and congestive heart failure; 1 patient received appropriate ICD defibrillation.
- Primary endpoint was reached in 38% of patients who were MTWA positive and 3% who were MTWA negative.
- MMA-based MTWA >65 μV was associated with cardiovascular mortality with a hazard ratio of 15.9 (95% CI, 6.7–37.8, \(P <0.0001\)) after univariate analysis.
- MMA-based MTWA had a hazard ratio of 17.1 (95% CI, 6.3–46.6, \(P <0.0001\)) for cardiovascular mortality after multivariate Cox proportional hazards analysis to correct for significant variables.
- MMA-based MTWA had hazard ratio of 22.6 (95% CI, 2.6–193.7, \(P <0.005\)) for witnessed SCD.
- Hazard ratio for patients in the ischemic group with MMA-based MTWA >65 μV was 19.0 (95% CI, 6.7–54.2, \(P <0.0001\)) and for patients in the nonischemic group was 12.3 (95% CI, 2.6–58.1, \(P = 0.002\)) (Fig. 5).
- The negative predictive values for cardiac death were: 97.1 for the entire study population, 97.1 for the ischemic group, and 97.2 for the non-ischemic group.

Fig. 5: Event-free curves for cardiac mortality using maximal voltage of MMA-based MTWA [time domain (TD)-TWA] from 24-hour ambulatory ECGs in ischemic (A) and nonischemic (B) study subgroups. (Reprinted with permission from Heart Rhythm Society from reference 21.)
### Summary of Study Objective/Patient Population

This study examined whether quantification of MTWA measurement enhances its capacity to evaluate risk. This full-cohort analysis of the FINCAVAS study prospectively enrolled 2,119 consecutive patients with a clinically indicated exercise test. MMA-based MTWA was analyzed from precordial leads and the results were grouped in increments of 10 μV. This study enlarged the cohort of patients reported earlier in Nieminen et al 2007 (11). Indications for testing included coronary heart disease (45%), palpitations (21%), work capacity (18%), adequacy of coronary heart disease treatment (16%), preoperative medical evaluation (13%), and following myocardial infarction (8%). Patients could have more than one indication.

### Summary of Results

- During a follow-up of 47.1 months, 126 patients died: 62 were cardiovascular deaths, and 33 of these deaths were sudden.
  - During routine, symptom-limited exercise, hazard ratios for cardiovascular mortality were significant when MMA-based MTWA was ≥50 μV.
- The highest hazard ratio for cardiovascular death (6.4, p = 0.002) was reached at MTWA ≥90 μV.
- SCD was strongly predicted by MTWA ≥60 μV, with a hazard ratio of 4.6 (p=0.002).
- Quantification of MMA-based MTWA enhances its capacity for determination of the risk for cardiovascular mortality and SCD in low-risk populations.
- This study established 60 μV as a cutpoint for MTWA studies with the MMA Method.

#### IV.e. Leino et al, Heart Rhythm 2009 (9)

### Summary of Study Objective/Patient Population

This study continued the full-cohort, prospective evaluation of FINCAVAS with additional enrollment compared to Nieminen et al 2007 (11) and Minkkinen et al 2009 (8). The autonomic nervous system parameter of heart rate recovery was included in this analysis of 1,972 consecutive patients.

### Summary of Results

- During a follow-up of 48 months, 116 patients died and 55 deaths were for cardiovascular causes.
- In multivariable Cox analysis after adjustment for common coronary risk factors:
  - MMA-based MTWA ≥60 μV during exercise yielded relative risk of 5.8 for cardiovascular mortality (p<0.01).
  - The combination of MMA-based MTWA ≥60 μV during exercise with heart rate recovery <18 bpm improved risk assessment for cardiovascular mortality to a relative risk of 12.3 (p<0.01).
- Prediction of risk by MMA-based MTWA and heart rate recovery, both singly and in combination, exceeded standard cardiovascular risk factors.
This study was a retrospective analysis of 63 consecutive patients who underwent MMA-based MTWA and heart rate turbulence at a single center in Japan. Patients were divided into 3 groups: 21 control patients without organic heart disease, including patients studied by 24-hour ambulatory ECGs for palpitations with a normal study; 21 patients with recent myocardial infarction (MI) complicated by ventricular tachycardia (VT), who received an ICD; and 21 patients with older myocardial infarction without ventricular arrhythmia or ICD. Both groups of patients with myocardial infarction exhibited depressed left ventricular ejection fraction and are thus representative of patients in whom ICD implantation is considered. Ambulatory ECG recordings were performed at 1–3 months after the MI.

Summary of Results

- After 72 months, total mortality was highest among patients with previous MI and VT compared with the control group and the post-MI group without VT.
- Among the 3 groups, MMA-based MTWA $\geq 65 \mu V$ and impaired heart rate turbulence were observed most frequently in the post-myocardial infarction patients with VT ($p<0.05$).
- MMA-based MTWA $>65 \mu V$ yielded an odds ratio of 6.1 (1.1–34.0, $p=0.041$) for life-threatening ventricular arrhythmias after adjustment for common cardiac risk factors.
Summary of Study Objective/Patient Population

The Cardiovascular Health Study is a United States based National Institutes of Health sponsored longitudinal study to identify risk factors that relate to the onset and course of coronary heart disease and stroke in 5,201 men and a women 65 years and older. This population directly reflects the group of interest to Medicaid & Medicare Services. A nested case-control study was conducted in the 1,649 Cardiovascular Health Study participants with at least 18 hours of analyzable ambulatory ECG data. Of this group, 49 (3%) died of SCD during the 14-year follow-up. MMA-based MTWA identified patients who experienced SCD as compared with matched controls in the Cardiovascular Health Study population who did not experience SCD (Fig. 6).

Summary of Results

- Odds ratio of MTWA $\geq 37$ $\mu$V in lead V5 for SCD was 4.8 ($p<0.009$).

**Fig. 6**: Age-adjusted survival curves for SCD for participants with MMA-based MTWA above and below the cutpoint of 37 $\mu$V in precordial lead V5. (Reprinted with permission from Elsevier from reference 23.)
**IV.h. Leino et al, Heart Rhythm 2011 (14)**

**Summary of Study Objective/Patient Population**
This prospective full-cohort study continued the evaluation of the FINCAVAS presented by Nieminen et al 2007 (11), Minkkinen et al 2009 (8), and Leino et al 2009 (9). This analysis reported on 3,598 consecutive patients.

**Summary of Results**
- During the 55-month follow-up, 231 patients died; 97 deaths were from cardiovascular causes, and 46 were SCD.
- In Cox analysis after adjustment for common coronary risk factors
  - Each 20-μV increase in MMA-based MTWA in lead V5 multiplied the hazard ratio for cardiovascular mortality by 55% (HR: 1.545 as a continuous variable, p=0.033) and for SCD by 58% (HR: 1.576 as a continuous variable, p< 0.033).
  - Higher MMA-based MTWA values indicate greater cardiovascular mortality and SCD risk, supporting the importance of quantification of MTWA.

**IV.i. Hou et al, Journal of Electrocardiology 2012 (13)**

**Summary of Study Objective/Patient Population**
This prospective full-cohort study enrolled 227 consecutive patients who were monitored with 24-hour ambulatory ECGs within 1-15 days after acute myocardial infarction in a single center in China. MMA-based MTWA was measured and compared with subsequent clinical course. The primary end point was SCD or lethal ventricular arrhythmia. Hazard ratios for MTWA were based on the 47-μV cutpoint determined in the ATRAMI substudy.

**Summary of Results**
- Follow-up of 16±7 months was completed in 100% of patients.
- Univariate Cox regression analyses indicated that MTWA ≥47μV predicted SCD or lethal ventricular arrhythmia with a hazard ratio 15.07 (p<0.0031) after correction for standard risk factors.
- Negative predictive value = 99%.
IV.j. Sulimov et al, Europace 2012 (24)

**Summary of Study Objective/Patient Population**

This prospective full-cohort study enrolled 111 patients with myocardial infarction 60 days to 36 years before entry into the study. The age range was 64.1±10.5 years; left ventricular ejection fraction was 46.6±12.2%. 60 subjects aged 62.5±11.6 years with no cardiovascular disease were also enrolled as controls. MTWA was monitored from ambulatory ECG recordings.

**Summary of Results**

- During the 12-month follow-up, the primary endpoint of SCD was reached by 15 patients and the secondary endpoint of cardiovascular mortality was reached by 8 additional patients. Patients who died of SCD exhibited the highest MTWA levels [92 μV (range 72-213)], significantly higher than patients with non-sudden cardiovascular death [74 μV (70-86)], p<0.05
- 73.3% of patients who died suddenly had MTWA >53.5 μV compared to 35.4% of survivors
- MTWA at the 53.5-μV cutpoint at heart rate of 100 beats/min independently predicted SCD with a relative risk of 5.01 (95% CI, 1.5–17.0, P = 0.005; PPV = 24.4%, NPV = 93.9%; sensitivity = 73.3%, and specificity 64.6%)
- MTWA at heart rate of 100 beats/min predicted SCD with area under the curve (AUC) of 0.643.

IV.k. Ren et al, Cardiovascular Diabetology 2012 (25)

**Summary of Study Objective/Patient Population**

This prospective full-cohort study prospectively enrolled 248 consecutive subjects: 96 without diabetes following myocardial infarction (MI), 77 diabetics following myocardial infarction, and 75 healthy controls. Average age of patients was 66 years. MTWA was monitored from ambulatory ECG recordings at 1 to 3 weeks after hospitalization.

**Summary of Results**

- During followup of 1.6±0.4 years, 10 patients experienced cardiac death including 3 who experienced SCD
- Post-MI patients with diabetes had higher MTWA values than post-MI patients without diabetes (58±21 vs 52±18 μV, p = 0.029); both groups had higher MTWA values than healthy controls (37±13 μV, p<0.05)
- Post-MI patients with diabetes had a higher incidence of MTWA ≥47μV events than post-MI patients without diabetes (59.7% vs 53.1%, p<0.05); incidence of MTWA ≥47μV events was lowest (5.3%) in healthy controls (p<0.05).
- Area under the curve (AUC) for MTWA for cardiovascular mortality was 0.708 (p = 0.021)
### IV.I. Shimada et al, American Journal of Cardiology 2012 (26)

<table>
<thead>
<tr>
<th>Summary of Study Objective/Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>This retrospective study analyzed MTWA in 40 consecutive patients with vasospastic angina (age 59±15 years) and 40 age- and sex-matched control subjects to determine the whether MTWA could identify risk of ventricular tachycardia in patients with vasospastic angina. MTWA was monitored from ambulatory ECGs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maximum MTWA was higher in patients than in controls (68.6±21 vs 34.0±11 μV, p &lt;0.01)</td>
</tr>
<tr>
<td>• Patients with ventricular tachycardia had higher MTWA values than those without ventricular tachycardia (83.0±15 vs 65.9±20 μV, p &lt;0.05)</td>
</tr>
<tr>
<td>• Incidence of MTWA &gt;65 μV was higher in patients than in controls (24 of 40 vs 0 of 40, p &lt;0.01)</td>
</tr>
<tr>
<td>• MTWA was lower in patients taking calcium channel blockers than in subjects not taking these drugs (59.5±21 vs 73.8±18 μV, p &lt;0.05)</td>
</tr>
<tr>
<td>• Odds of developing ventricular tachycardia was increased by 15.5-fold (95% CI, 1.7 to 142.0, p &lt;0.01) in patients with MTWA ≥65 μV</td>
</tr>
</tbody>
</table>

### IV.m. Hoshida et al, Circulation Journal 2012 (27)

<table>
<thead>
<tr>
<th>Summary of Study Objective/Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>This prospective study enrolled 313 consecutive post-myocardial infarction (MI) patients (age 70±12 years) with left ventricular ejection fraction of 47±11%. Ambulatory ECGs were recorded &gt;2 weeks after acute myocardial infarction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The MTWA cutpoint of 65 μV was reached by 4 (14%) of the 28 patients who experienced fatal arrhythmic events and by 10 (4%) of the 285 patients without arrhythmic events, p&lt;0.0312</td>
</tr>
<tr>
<td>• On univariate analysis, MTWA ≥65 μV independently predicted cardiovascular death with a hazard ratio of 3.6 (1.3-10.4, p&lt;0.0174)</td>
</tr>
<tr>
<td>• On multivariate analysis, MTWA ≥65 μV independently predicted fatal arrhythmic events (SCD, ventricular fibrillation, or ventricular tachycardia) with a hazard ratio of 5.8 μV (95% CI 1.6–20.8, P=0.0072)</td>
</tr>
</tbody>
</table>

### IV.n. Green et al, Pacing and Clinical Electrophysiology 2012 (28)

In this small, likely underpowered study of 19 patients with renal disease requiring dialysis, MTWA did not predict the combined endpoint of cardiovascular events and death, which was reached by 7 patients. The number of cardiovascular events was not stated. MTWA is not expected to predict non-cardiovascular mortality, as it is a measure of cardiac electrical instability. Also, MTWA was measured as mean rather than as peak levels and the automated results were not over-read by reference to the templates; this departure from recommended practice could have introduced errors into the MTWA measurement.
### Summary of Study Objective/Patient Population

Ambulatory ECGs of 48 ST-elevation myocardial infarction (STEMI) patients undergoing successful percutaneous coronary intervention (PCI) were analyzed during the procedure and the following 23 hours.

### Summary of Results

- Maximum MTWA was elevated in patients with (N=22) compared to without (N=26) nonsustained ventricular tachycardia (NSVT) (75.1±6.3 vs. 49.9±3.6μV, p<0.005) during the 22-hour monitoring period.
- With ≥60μV MTWA cutoff, sensitivity for NSVT was 77%; specificity, 73%; positive predictive value, 74%; and negative predictive value, 80%.
- Area under the receiver operator characteristic curve (AUC) was 0.87 for maximum MTWA in predicting NSVT.
## Table 2: Clinical Studies With the Modified Moving Average Method

<table>
<thead>
<tr>
<th>Test Setting</th>
<th>Patient Population</th>
<th>Mean LVEF</th>
<th>Hazard Ratios (95% CI) for TWA; NPV and PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine exercise testing</td>
<td>1,037 consecutive patients referred for routine exercise testing; 56 ± 13 yrs (patients included in Laino et al. [66])</td>
<td>Mostly preserved</td>
<td>6.0 (2.9-12.9) for CV death; 7.4 (2.8-10.4) for SCD at 44 ± 7 yrs for 65-μV TWA cutoff; NPV for CV death = 97.6%, PPV = 12.6% NPV for SCD = 98.6%, PPV = 8.0%</td>
</tr>
<tr>
<td>Minnokas et al. [FINCAVAS] (65)</td>
<td>2,119 consecutive patients referred for routine exercise testing; 57 ± 13 yrs (patients included in Laino et al. [66])</td>
<td>Mostly preserved</td>
<td>4.4 (2.2-9.9) for CV death; 4.4 (1.5-12.7) for SCD at 47 months for 65-μV cutoff; NPV for CV death = 97.4%, PPV = 30.2%</td>
</tr>
<tr>
<td>Laino et al. [FINCAVAS] (66)</td>
<td>3,998 consecutive patients referred for routine exercise testing; 56 ± 13 yrs</td>
<td>Mostly preserved</td>
<td>1.96 (1.150-2.018, p &lt; 0.004) for CV death; 1.58 (1.041-2.412, p &lt; 0.033) for SCD at 55 months per 20 μV TWA in lead V2</td>
</tr>
<tr>
<td>Exercise recovery</td>
<td>Eser et al. [REFINE] (54)</td>
<td>Moderately depressed (38%–48%)</td>
<td>2.94 (1.10–7.87) monitored at 10–14 weeks after event for CV death or nonsustained ventricular tachycardia (primary endpoint); at 12 months, NS when monitored at 2–4 weeks after MI. For primary endpoint for TWA, AUC = 0.52; for combination of TWA + HRR, AUC = 0.71.</td>
</tr>
<tr>
<td></td>
<td>Siwinsky et al. (REFINE, FINCAVAS) (67)</td>
<td>Moderately depressed (38%–48%) and preserved (56%–63%) groups</td>
<td>2.5 (1.1–6.0) for CV death at 48 months for 60-μV cutoff; NPV = 99%, PPV = 1%, AUC for CV mortality = 0.69.</td>
</tr>
<tr>
<td></td>
<td>Laino et al. [FINCAVAS] (68)</td>
<td>Mostly preserved</td>
<td>3.5 (1.6–7.9) for CV death at 48 months for 60-μV cutoff. For CV death for TWA alone, C-statistic = 0.950–0.960; for combination of TWA + HRR, C-statistic = 0.671–0.691.</td>
</tr>
<tr>
<td>Ambulatory ECG monitoring</td>
<td>Vantier et al. [ATRAMI] (69)</td>
<td>Moderately depressed (42 ± 3%)</td>
<td>7.9 (1.9–33.1) for cardiac arrest or nonpenetrating death at 21 months for a prior 75th percentile cutoff (47 μV); patients were monitored at 15 ± 10 days post-MI.</td>
</tr>
<tr>
<td></td>
<td>Stain et al. [EPHESUS] (70)</td>
<td>Depressed (34 ± 5%)</td>
<td>5.5 (2.2–13.6) for SCD at 16 months for 47-μV cutoff; patients were monitored at 2–10 days post-MI. For SCD: AUC = 0.73 for TWA in lead V2 and 0.70 in lead V4 (p &lt; 0.001).</td>
</tr>
<tr>
<td></td>
<td>Sakurai et al. (71)</td>
<td>Depressed (34 ± 6%)</td>
<td>17.4 (6.3–46.6) for CV death; 22.6 (6.3–34.7) for witnessed SCD at 1 yr for 65-μV cutoff; NPV for CV death = 97%; PPV = 37%</td>
</tr>
<tr>
<td></td>
<td>Maeda et al. (72)</td>
<td>Depressed (36%–43%) for post-MI group</td>
<td>6.1 (1.1–24.0) for sustained VT or VF at 6 yrs for 65-μV cutoff</td>
</tr>
<tr>
<td></td>
<td>Stain et al. [CVDI] (73)</td>
<td>Not tested, assumed preserved</td>
<td>4.8 (1.48–15.81) for SCD at 14 yrs</td>
</tr>
<tr>
<td></td>
<td>Hoy et al. (74)</td>
<td>&gt;35% in 201; ≤35% in 18</td>
<td>17.78 (7.75-43.41) for SCD within 10 months for 47-μV cutoff; patients were monitored at 1–15 days post-MI; NPV = 99%; PPV = 17%</td>
</tr>
</tbody>
</table>

This table is based on searches of the published medical data on the terms utilized and attenuation for all clinical studies that reported hazard ratios in published (National Library of Medicine, National Institute of Health, Bethesda Maryland) and Payerbase (Bethesda Massachusetts) databases. Reference lists from these studies and from recent reviews (4-7) were also scanned.

ATRAMI = Autonomic Tone and Reflexes after Myocardial Infarction, CHS = Cardiovascular Health Study, CV = Cardiovascular, EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, FINCAVAS = Finnish Cardiovascular Study, HRR = heart rate recovery, NPV = negative predictive value, PPV = positive predictive value; other abbreviations as in Table 1.

(Table reprinted with permission from American College of Cardiology Foundation from reference 1.)
Since September 2011, when the MTWA consensus guideline (1) was published, 5 additional original research studies enrolling a total of 685 patients have appeared relevant to risk stratification for severe arrhythmia, SCD, and cardiovascular mortality (Table 2).

<table>
<thead>
<tr>
<th>First Author (reference number)</th>
<th>Patient Population (Enrollment, Disease, Mean Age)</th>
<th>Mean Left ventricular ejection fraction</th>
<th>Hazard Ratios (95% CI) for MTWA, NVP, and PPV, or AUC at followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulimov et al 2012 (24)</td>
<td>111 post-MI patients, 64.1 yrs</td>
<td>46.6%</td>
<td>5.01 (95% CI 1.5–17.0, P ¼ 0.005) for SCD for MTWA &gt;53.5 μV at heart rate of 100 bpm, NPV = 93.9%; PPV = 24.4%; at 12 months</td>
</tr>
<tr>
<td>Ren et al 2012 (25)</td>
<td>173 consecutive post-MI patients with and without diabetes mellitus, 66 yrs</td>
<td>46%</td>
<td>AUC = 0.708 for cardiac mortality at 1.6 yrs</td>
</tr>
<tr>
<td>Shimada et al 2012 (26)</td>
<td>40 consecutive patients with vasospastic angina, 59 yrs</td>
<td>66%</td>
<td>15.5 (1.7–142.0, p&lt;0.009) for VT for MTWA ≥65 μV at 2.9 yrs</td>
</tr>
<tr>
<td>Hoshida et al 2012 (27)</td>
<td>313 consecutive post-MI patients, 70±12 yrs</td>
<td>48%</td>
<td>5.8 (1.6–20.8) for SCD for MTWA ≥65 μV at 3.3 yrs</td>
</tr>
<tr>
<td>Verrier et al 2013 (29)</td>
<td>48 acute STEMI patients; 61 yrs</td>
<td>51%</td>
<td>AUC = 0.87; NPV = 79%; PPV = 71% for NSVT during or after PCI</td>
</tr>
</tbody>
</table>

Key: AUC = area under the curve; bpm = beats/min; CI = confidence interval; μV = microvolt; NPV = negative predictive value; PCI = percutaneous coronary intervention; post-MI = post-myocardial infarction; PPV = positive predictive value; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; MTWA = microvolt T-wave alternans; VT = ventricular tachycardia; yrs = years.
V. Concluding Statements

Extensive clinical evidence from six prospective full-cohort studies (13,14,21,24,25,27) enrolling >3,800 patients has been accumulated over the past five years demonstrating that MMA-based MTWA assessment is a sound methodology that has clinical utility in identifying patients at risk for SCD who may benefit from medical or device based therapy. In addition, two retrospective studies (12,23) analyzed MMA’s predictivity in existing cohorts that enrolled >2,100 patients using a nested case-control design, which allows statistical significance in large data sets to be tested from representative samples with relatively minor loss in statistical efficiency (http://www.wikidoc.org/index.php/Nested_case-control_study). Based on these investigations, the predictivity of this diagnostic algorithm appears to be at least comparable to that observed with the currently reimbursed Spectral Method. Moreover, multivariate analyses indicated that MMA-based MTWA stratifies SCD risk independent of left ventricular ejection fraction, the current marker for insertion of ICDs, thus providing physicians with information in addition to left ventricular ejection fraction regarding potential benefit from ICD insertion. Risk assessment with MMA-based MTWA is also independent of medications and is accurate in patients with depressed as well as preserved left ventricular ejection fraction.

Furthermore, studies were published that reported MTWA levels for patients with various diseases known to increase risk for cardiovascular mortality. Mean MTWA levels were 58 μV in patients with myocardial infarction and diabetes (25), 71 μV in patients with renal disease requiring hemodialysis (30), and 51-65 μV in patients with sleep apnea (31,32), conditions that are relevant to the CMS population.

The technology has inherent advantages in terms of patient care as the MMA-based MTWA test can be performed either during routine, symptom-limited exercise testing or ambulatory ECG monitoring, from precordial leads with standard electrodes, allowing it to be used in the flow of clinical evaluation. It offers a low indeterminate rate of 3-5% compared to 20-40% indeterminate rate with the Spectral Method (2). Absence of requirement for stabilization or elevation of heart rate to a target level and suitability to be performed while patients are on chronic medications represent major intrinsic advantages. It reports clinically meaningful MTWA values in microvolts, from which greater or lesser risk for SCD can be gauged based on cutpoints established in prospective studies. It retains ECG morphology and provides a unique tool for physicians to visualize MTWA level and verify the automatically generated report. The utility of MMA and specific guidelines for its use are provided in a recent multi-society endorsed consensus guideline statement authored by experts in both the Spectral and MMA Methods (1), which describes and compares the methods. It concludes that the two methods are equivalent in prediction and that “it is reasonable to consider TWA evaluation whenever there is suspicion of vulnerability to lethal cardiac arrhythmias.”
REFERENCES


