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Heart Rhythm Disorders

Microvolt T-Wave Alternans for the Risk Stratification of Ventricular Tachyarrhythmic Events

A Meta-Analysis

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OBJECTIVES The objective of this study was to perform a meta-analysis of the predictive value of microvolt T-wave alternans (MTWA) testing for arrhythmic events in a wide variety of populations.

BACKGROUND Previous studies describing the use of MTWA as a predictor of ventricular tachyarrhythmic events have been limited by small sample sizes and disparate populations.

METHODS Prospective studies of the predictive value of exercise-induced MTWA published between January 1990 and December 2004 were retrieved. Data from each article were abstracted independently by two authors using a standardized protocol. Summary estimates of the predictive value of MTWA were made using a random-effects model.

RESULTS Data were accumulated from 19 studies (2,608 subjects) across a wide range of populations. Overall, the positive predictive value of MTWA for arrhythmic events was 19.3% at an average of 21 months' follow-up (95% confidence interval [CI] 17.7% to 21.0%), the negative predictive value was 97.2% (95% CI 96.5% to 97.9%), and the univariate relative risk of an arrhythmic event was 3.77 (95% CI 2.39 to 5.95). There was no difference in predictive value between ischemic and nonischemic heart failure subgroups. The positive predictive value varied depending on the population of patients studied ($p < 0.0001$).

CONCLUSIONS Microvolt T-wave alternans testing has significant value for the prediction of ventricular tachyarrhythmic events; however, there are significant limitations to its use. The predictive value of MTWA varies significantly depending on the population studied. Careful standardization is needed for what constitutes abnormal MTWA. The incremental prognostic value of MTWA when used with other methods of risk stratification is unclear. (J Am Coll Cardiol 2005;46:75–82) © 2005 by the American College of Cardiology Foundation

The risk stratification of patients for sudden cardiac death (SCD) is a major challenge in clinical medicine. Although we have made advances in the area of risk stratification, it remains troubling that the majority of individuals who die of SCD are among a population not identified by current methods of risk stratification (1). As pointed out by Huikuri et al. (1) and Buxton (2), evidence suggests that ejection fraction (EF) alone lacks sufficient sensitivity and specificity to be a useful single method of risk stratification.

The assessment of microvolt T-wave alternans (MTWA) has been proposed as a method to detect abnormalities in ventricular repolarization that may predict the occurrence of ventricular reentrant arrhythmias (3). Electrical alternans is defined as beat-to-beat changes in the amplitude of the electrocardiogram (ECG) signal. The presence of alternans of the T-wave amplitude at a 0.5 cycle-per-beat periodicity defines T-wave alternans. Measurement of T-wave alternans at the microvolt level was first described by Adam et al. (4). The first clinical description of using MTWA to predict the occurrence of ventricular tachyarrhythmias was performed by Rosenbaum et al. (5). After this description, the methodology of MTWA assessment was standardized (6). With increasing heart rate achieved through atrial pacing, dobutamine, or exercise, sequential ECG cycles are aligned to their QRS complex, and the T-wave amplitude is measured. The beat-to-beat fluctuations in amplitude are spectrally analyzed using a fast Fourier transformation. The presence of significant MTWA is defined as an alternans voltage $\geq 1.9\ \mu V$ 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. Whether or not an indeterminate MTWA assessment should be considered abnormal or excluded altogether remains a methodologic issue (7).

Since its initial description, a number of studies have described the use of MTWA as a predictor of the primary or secondary occurrence of ventricular arrhythmic events. These studies, however, have been limited by small sample sizes and disparate patient populations. We, therefore, performed this systematic review and meta-analysis of MTWA as a predictor of arrhythmic events to clarify the predictive accuracy and usefulness of MTWA for clinical practice.

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram
EF = ejection fraction
ICD = implantable cardioverter-defibrillator
MI = myocardial infarction
MTWA = microvolt T-wave alternans
NPV = negative predictive value
PPV = positive predictive value
RR = relative risk
SCD = sudden cardiac death
VF = ventricular fibrillation
VT = ventricular tachycardia

METHODS

Study selection. We performed a literature search using the PubMed and Cochrane databases to identify articles published between January 1990 and December 2004 of the predictive value of exercise-induced MTWA in humans. The following medical subject heading search terms were used: prospective studies, follow-up studies, predictive value of tests, arrhythmia, sudden death, ventricular tachycardia, ventricular fibrillation. In addition, we used the search term T-wave alternans. The search was restricted to English language literature and human subjects. The date limits were chosen because MTWA testing was not in clinical use before 1994. A second search of articles published by authors identified in the initial search and a review of the bibliographies of all articles were performed to identify additional articles for review.

Studies were included if they met the following criteria: 1) were prospective cohort studies of >10 human subjects who underwent exercise-induced MTWA testing for the prediction of SCD or ventricular arrhythmias; 2) provided primary data on results of MTWA and of clinical outcomes, including SCD, cardiac death, ventricular arrhythmias, and/or implantable cardioverter-defibrillator (ICD) shock; 3) provided clear definition of normal or abnormal MTWA testing; and 4) had a follow-up time of six months or longer.

Two investigators (A.G. and R.S.) independently reviewed the titles and abstracts of these articles and excluded those that clearly did not meet the inclusion criteria. A consensus was reached on which articles should be completely reviewed for potential inclusion in this study.

Data abstraction. Two investigators (A.G. and R.S.) independently reviewed potential articles blinded to the author, journal, and institution. Data for each article were abstracted, including inclusion criteria, study design, patient characteristics (number, mean age, percent men, population of patients), selection criteria (including inclusion/exclusion criteria), details of MTWA assessment (including definition of abnormal test), end points of the study, average follow-up, raw data when provided, and reported findings, including positive predictive value (PPV) and negative predictive value (NPV), relative risk (RR), or hazard ratios of future cardiac events. Results were stratified by definition of abnormal MTWA (including or excluding indeterminate MTWA) when provided.

A quality analysis was performed based on the following assessment of the articles: 1) whether follow-up was complete for >90% of the cohort, 2) whether adjudication of outcomes was blinded to the results of MTWA testing, and 3) whether a multivariate analysis using other standard predictors of ventricular arrhythmic events performed was used. A study was considered at least of fair quality if it fulfilled the criteria for >90% follow-up. A study was considered good if one of the other two criteria was met.

Statistical analysis. The outcomes of each study were presented as PPV, NPV, and univariate RR with confidence intervals (CIs) of MTWA for the prediction of ventricular arrhythmic events at follow-up. Because of the inconsistent use of the definition of abnormal MTWA (including or excluding indeterminate MTWA), outcomes for each study were stratified by this definition. Studies that assessed MTWA and outcomes in different patient populations were presented individually for each patient population.

Summary estimates of the predictive value of ventricular arrhythmic events were made using the DerSimonian and Laird (8) meta-analytic statistical method, which is based on a random effects model. For consistency in the definition of abnormal MTWA, summary estimates were calculated defining abnormal MTWA excluding indeterminate MTWA tests, which was available for all the included studies. A sensitivity analysis based on the definition of an abnormal test (including or excluding indeterminate test as abnormal) was performed on the studies that provided these data to see whether this would affect the predictive value of the test. Subgroup summary estimates were calculated based on patient population (heart failure, ischemic heart failure, nonischemic heart failure, post-myocardial infarction [MI]), history of arrhythmic events (primary vs. secondary prevention), and quality of study (excluding fair quality studies).

A test for homogeneity using the Mantel-Haenszel (9) method was performed for all summary estimates to evaluate the uniformity of findings across studies. A p value <0.10 was considered statistically significant to reject the null hypothesis of the test of homogeneity. Publication bias was assessed using a funnel plot and the correlation coefficient, Kendall's tau, comparing sample size to RR (10).

RESULTS

An initial literature search using the previously mentioned search terms identified 2,853 potential articles for inclusion in this study. After reviewing and eliminating clearly ineligible studies by review of titles and abstracts, 27 articles were identified for full review (5,11–36). A search of the literature of each author and a review of the bibliographies of these articles identified an additional four articles for review (37–40). From these 31 articles, 14 were eliminated

from the meta-analysis: five studies were not prospective (12,16,19,35,38), five studies did not use primary data (21,22,27,29,34), two studies assessed pacing-induced T-wave alternans (5,25), one study had less than six months of follow-up (18), and one study did not provide enough primary data (31). An attempt was made to contact the author of the study that did not provide enough data (31). From the remaining 17 studies, two studies that provided independent data on two different patient populations were separated in the analysis (15,32), which yielded a total of 19 studies in this meta-analysis. Of these 19 studies, eight provided outcomes for participants with indeterminate MTWA, allowing us to calculate the predictive value of abnormal MTWA including or excluding indeterminate MTWA.

The 19 prospective studies of MTWA (Table 1) included 2,608 subjects. The mean age of the study participants ranged from 25 to 64 years. The average follow-up was 21 months. The mean percentage of men ranged from 68 to 100. There was a wide range of subject populations, including congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, post-MI, athletes, and healthy subjects. The mean EF of the study participants ranged from 23 to 71. Several of the studies included only subjects with a history of SCD, ventricular fibrillation (VF), and ventricular tachycardia (VT). Several of the studies included only subjects who were referred for an electrophysiologic study (indications included SCD, VF, VT, non-sustained VT, syncope, and palpitations).

Results of the individual studies are presented in Table 2. Positive predictive value at follow-up ranged from 0% to 67%, NPV ranged from 71% to 100%, and RR for having a cardiac event ranged from 0.85 to ∞. In two studies, there were no events at follow-up such that an RR of events could not be calculated (23,32). All results presented exclude subjects with indeterminate MTWA tests.

Summary estimates of the PPV, NPV, and univariate RR of MTWA for arrhythmic events, excluding indeterminate MTWA, in the 19 studies included in the meta-analysis are presented in Table 3. The summary PPV during the average 21-month follow-up was 19.3% (95% CI 17.7% to 21.0%), NPV was 97.2% (95% CI 96.5% to 97.9%), and the univariate RR was 3.77 (95% CI 2.39 to 5.95).

Summary estimates of the PPV, NPV, and univariate RR for arrhythmic events in several subgroup populations also are presented in Table 3. In the subgroup of subjects with CHF (ischemic or nonischemic), the summary PPV during the average 18 months' follow-up was 25.5% (95% CI 22.7% to 28.3%), NPV was 93.8% (95% CI 92.3% to 95.4%), and the univariate RR was 2.51 (95% CI 1.71 to 3.65) (Fig. 1). There was no significant difference in the PPV, NPV, or RR of MTWA testing between subjects with ischemic and non-ischemic CHF ($p > 0.10$) (Table 3). In subjects after MI, the summary PPV during the average 18 months' follow-up was 6.0% (95% CI 4.5% to 7.4%), NPV was 99.4% (95% CI 98.9% to 99.9%), and the univariate RR was 4.74 (95% CI 1.11 to 20.19) (Fig. 2). There was no significant difference in the NPV or RR of MTWA testing between CHF and post-MI subjects ($p > 0.10$). However, abnormal MTWA had a significantly higher PPV for arrhythmic events at an average 18 months' follow-up in subjects with CHF compared with post-MI (25.5% vs. 6.0%, $p < 0.0001$).

Summary estimates of MTWA for predicting arrhythmic

Table 1. Characteristics of 19 Prospective Studies of Microvolt T-Wave Alternans

Author (Ref.)	Total (n)	Mean Age (yrs)	Men (%)	Population	Mean EF (%)	End Point	History of Arrhythmic Event?	Average Follow-Up (months)	Quality
Hohnloser et al. (11)	62	60	81	ICD recipients	36	ICD event	Yes	15	Good
Hennersdorf et al. (15)	16	44	68	Nonischemic CHF	55.6	VT/VF	Yes	6	Fair
Hennersdorf et al. (15)	44	49	70	Nonischemic CHF	59.5	VT/VF	No	6	Fair
Klingenheben et al. (26)	107	56	80	CHF	28	SCD/VT/VF	No	21	Good
Adachi et al. (36)	64	53	81	Non-ischemic CHF	NA	SCD/VT/VF	No	24	Good
Schwab et al. (39)	104	60	76	Post-MI	56	SCD/VT/VF	No	15	Fair
Tapaneinen et al. (40)	246	62	72	Post-MI	45	Cardiac death	No	14	Good
Sakabe et al. (13)	30	53	91	Non-ischemic CHF	33	VT	No	13	Fair
Sakabe et al. (14)	41	54	80	CHF	48	VT/VF	Yes	13	Good
Ikeda et al. (28)	834	63	84	Post-MI	51	SCD/VF	No	25	Good
Kitamura et al. (37)	83	52	81	Nonischemic CHF	NA	SCD/VT/VF	No	21	Good
Grimm et al. (23)	110	45	69	Healthy	71	SCD/VT/VF	No	32	Good
Grimm et al. (24)	263	48	73	Nonischemic CHF	30	SCD/VT/VF	No	52	Good
Hohnloser et al. (29)	137	55	77	Nonischemic CHF	29	SCD/VT/VF	Yes*	15	Good
Sarzi Braga et al. (17)	46	59	89	CHF	29	Cardiac death	No	19	Fair
Rashba et al. (20)	144	64	81	Ischemic CHF	28	SCD/VT/VF/ICD shock	Yes	17	Good
Furlanello et al. (32)	48	25	100	Healthy	NA	Syncope/VT	No	36	Good
Furlanello et al. (32)	52	28	90	Athletic heart	NA	Syncope/VT	Yes	25	Good
Bloomfield et al. (33)	177	61	85	Ischemic CHF	23	Death	No	20	Good

*A total of 24% of subjects had a history of an arrhythmic event in this study

CHF = congestive heart failure; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NA = not available; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2. Results of 19 Prospective Studies of Microvolt T-Wave Alternans

Author (Ref.)	PPV (%) (95% CI)	NPV (%) (95% CI)	RR (95% CI)
Hohnloser et al. (11)	67 (55–79)	73 (62–84)	2.5 (0.35–17.75)
Hennersdorf et al. (15)	30 (8–52)	100 (100–100)	4.45 (0.27–73.81)
Hennersdorf et al. (15)	0 (0–0)	100 (100–100)	∞
Klingenheben et al. (26)	21 (12–30)	100 (100–100)	∞
Adachi et al. (36)	30 (19–41)	97 (93–100)	10.2 (1.37–75.89)
Schwab et al. (39)	4 (0–7)	99 (96–100)	2.66 (0.29–24.51)
Tapaneiner et al. (40)	0 (0–0)	99 (98–100)	0.85 (0.04–20.51)
Sakabe et al. (13)	54 (36–72)	100 (100–100)	∞
Sakabe et al. (14)	67 (52–81)	71 (57–85)	2.16 (1.02–4.58)
Ikeda et al. (28)	7 (5–9)	100 (99–100)	11.4 (3.4–37.9)
Kitamura et al. (37)	23 (15–33)	97 (94–100)	8.8 (1.2–65.4)
Grimm et al. (23)	0 (0–0)	100 (100–100)	*
Grimm et al. (24)	13 (9–18)	90 (86–94)	1.3 (0.59–2.90)
Hohnloser et al. (29)	22 (14–30)	94 (90–99)	3.44 (0.03–459.0)
Sarzi Braga et al. (17)	29 (15–44)	100 (100–100)	∞
Rashba et al. (20)	40 (31–49)	84 (77–91)	2.2 (1.1–4.7)
Furlanello et al. (32)	0 (0–0)	100 (100–100)	*
Furlanello et al. (32)	57 (43–71)	100 (100–100)	∞
Bloomfield et al. (33)	14 (8–21)	96 (93–100)	3.55 (0.89–14.11)

*No arrhythmic events at follow-up.
CI = confidence interval; NA = not available; NPV = negative predictive value; PPV = positive predictive value; RR = relative risk.

events in subjects with and without a history of arrhythmic events (primary or secondary events) are presented in Table 4. In the subgroup with a history of arrhythmic events, the summary PPV at an average of 15 months' follow-up was 51.0% (95% CI 45.1% to 56.9%), NPV was 86.0% (95% CI 82.0% to 90.1%), and the univariate RR was 2.45 (95% CI 1.53 to 3.95). In the subgroup with no history of arrhythmic events, the summary PPV at an average of 22 months' follow-up was 15.4% (95% CI 13.8% to 17.0%), NPV was 98.1% (95% CI 97.5% to 98.7%), and the univariate RR was 4.07 (95% CI 2.35 to 7.06). In the subgroup of subjects with CHF and no history of arrhythmic events, the summary PPV at an average 22 months' follow-up was 20.9% (95% CI 17.8% to 24.0%), NPV was 96.3% (95% CI 94.8% to 97.7%), and the univariate RR was 3.81 (95% CI 1.86 to 7.82). In the subgroup of subjects post-MI with no history of arrhythmic events, the summary PPV at an average 18 months' follow-up was 6.0% (95% CI 4.5% to 7.4%), NPV was 99.4% (95% CI 98.9% to 99.9%), and the univariate RR was 4.74 (95% CI 1.11 to 20.19). There was no significant differences in the NPV or RR of MTWA testing between these subgroups ($p > 0.10$). However, the PPV for arrhythmic events at follow-up of MTWA was significantly different in these subgroups (51.0% vs. 20.9% vs. 6.0%, $p < 0.0001$; Fig. 3).

Three studies performed a multivariate Cox regression analysis to determine the independent predictive value of several commonly used tests for risk stratification of arrhythmic events including MTWA (Table 5) (28,36,37). In these three studies, MTWA was independently predictive of arrhythmic events in adjusted analysis. A sensitivity analysis of the summary estimates from the eight studies which included outcomes for subjects with indeterminate MTWA demonstrated no significant difference in whether or not indeterminate MTWA was included in the definition of an abnormal test ($p > 0.05$).

None of the 19 studies were of poor quality. We found no difference in the summary estimates of the PPV, NPV, or RR of MTWA when excluding fair quality studies ($p > 0.10$). The Mantel-Haenszel test for homogeneity was >0.10 for all summary estimates such that the combined studies were always homogeneous. Using a funnel plot and the correlation coefficient Kendall's tau, we found no

Table 3. Summary Estimates of PPV, NPV, and Univariate RR in 19 Prospective Studies of Microvolt T-Wave Alternans for the Prediction of Cardiac Arrhythmic Events

Summary Estimates	PPV (%) (95% CI)	NPV (%) (95% CI)	RR (95% CI)	Average Follow-Up (months)	No. Studies
All studies	19.3 (17.7 to 21.0)	97.2 (96.5 to 97.9)	3.77 (2.39 to 5.94)	21	19
Subgroups					
CHF	25.5 (22.7 to 28.3)	93.8 (92.3 to 95.4)	2.51 (1.71 to 3.65)	18	12
Ischemic CHF	29.7 (23.5 to 35.8)	91.6 (87.8 to 95.3)	2.42 (1.30 to 4.50)	19	2
Non-ischemic CHF	21.3 (17.8 to 24.7)	95.2 (93.5 to 97.0)	3.67 (1.50 to 8.96)	20	7
Post-MI	6.0 (4.5 to 7.4)	99.4 (98.9 to 99.9)	4.74 (1.11 to 20.19)	18	3

CHF = congestive heart failure; CI = confidence interval; MI = myocardial infarction; other abbreviations as in Table 2.

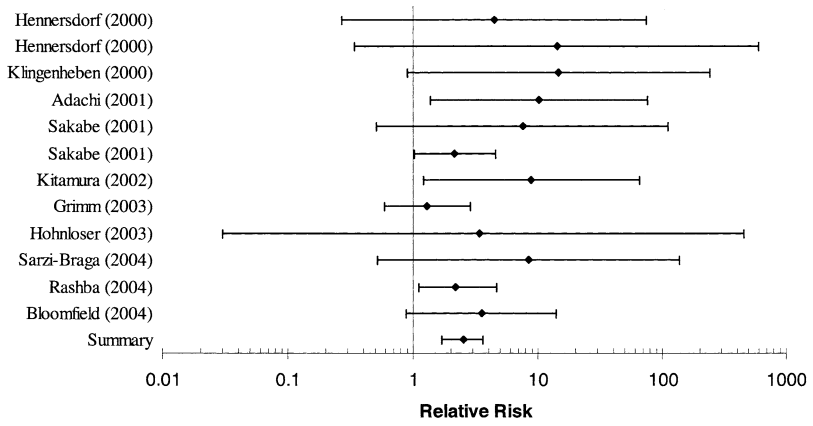

Figure 1. Summary estimate of the relative risk of abnormal microvolt T-wave alternans in subjects with congestive heart failure.

evidence of publication bias in this meta-analysis ($p = 0.159$).

DISCUSSION

We conducted the first meta-analysis of MTWA as a predictor of arrhythmic events in a wide variety of patient populations, accumulating prospective data on more than 2,600 subjects. Overall, we have found that the presence of significant MTWA predicted a nearly four-fold risk of a ventricular arrhythmic event compared with the absence of significant MTWA. The absence of MTWA carries a 3% risk of arrhythmic events during an average of 21 months' follow-up. The presence of MTWA predicts a ventricular arrhythmic event in 19% of subjects during an average of 21 months' follow-up. We found no difference in the predictive value of MTWA between patients with ischemic and nonischemic CHF. We found that the PPV of MTWA depends significantly on the population being studied. In the three studies that performed a multivariate analysis of commonly used methods of risk stratification, MTWA remained significantly predictive of events after adjustment for the predictive value of other methods, including EF. When comparing studies that provided outcomes data classifying abnormal MTWA as including or excluding indeterminate MTWA, we found no difference in the overall PPV, NPV, or RR of abnormal MTWA.

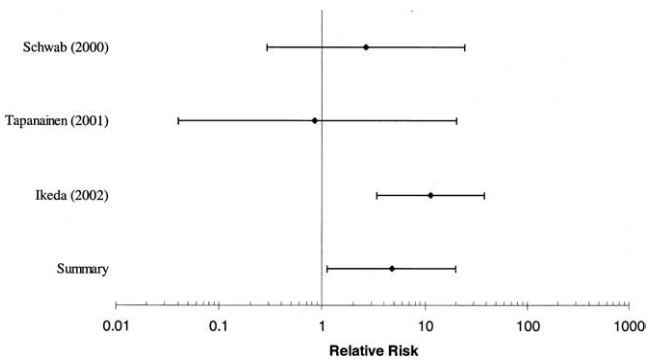

Figure 2. Summary estimate of the relative risk of abnormal microvolt T-wave alternans in subjects after myocardial infarction.

Bailey et al. (41), in a meta-analysis, studied the testing characteristics of several other methods of risk stratification for arrhythmic events, including EF, ambulatory ECG, heart rate variability, signal-averaged ECG, and electrophysiologic study. The predictive value of these methods varied with PPV, ranging from 13.3% to 25.8% at an average of two years of follow-up, NPV ranging from 94.52% to 96.12%, and univariate RR ranging from 2.9 to 6.6 with no particular test having exceptional predictive value compared with the others. We found MTWA to have similar testing characteristics to these previous methods of risk stratification, suggesting that MTWA should be considered at least equivalent in its prognostic value.

Clinically, accepting a 97% NPV, one could sufficiently classify a patient with absent MTWA as "low risk" for arrhythmic events. In our review, MTWA was absent in 25% to 54% of subjects, which was a substantial proportion of subjects. However, when deciding which patients should receive an internal ICD for primary prophylaxis, the PPV of arrhythmic events is more clinically relevant. Overall, the PPV for MTWA at 21 months' follow-up was 19%. When we excluded the patients with a history of arrhythmic events who had a high enough pretest probability to warrant an ICD, the PPV for MTWA decreased to 15%. From this standpoint, MTWA seems no better than the 20% PPV of a low EF reported in the meta-analysis of Bailey et al. (41).

Bailey et al. (41) ultimately suggest that a combination of noninvasive risk stratification tests may be the most feasible strategy to risk stratify a large proportion of patients into high- and low-risk categories. As demonstrated in the studies we reviewed that performed a multivariate analysis (Table 5), MTWA adds incremental prognostic value to other commonly used method of risk stratification. However, the additional absolute prognostic value is not clear from present studies.

It must be emphasized that the predictive value of MTWA testing varies depending on the pretest probability for arrhythmic events of the population being studied (spectrum bias). This variation is demonstrated clearly when comparing the predictive value of MTWA

Table 4. Summary Estimates of PPV, NPV, and Univariate RR in Prospective Studies of Microvolt T-Wave Alternans for the Prediction of Primary versus Secondary Arrhythmic Events

Summary Estimates	PPV (95% CI)	NPV (95% CI)	RR (95% CI)	Average Follow-Up (months)	No. Studies
Secondary event	51.0 (45.1–56.9)	86.0 (82.0–90.1)	2.45 (1.53–3.95)	15	6
Primary event	15.4 (13.8–17.0)	98.1 (97.5–98.7)	4.07 (2.35–7.06)	22	15
CHF, primary event	20.9 (17.8–24.0)	96.3 (94.8–97.7)	3.81 (1.86–7.82)	22	9
Post-MI, primary event	6.0 (4.5–7.4)	99.4 (98.9–99.9)	4.74 (1.11–20.19)	18	3

CI = confidence interval; other abbreviations as in Tables 2 and 3.

testing among subjects post-MI, with CHF, or with a history of ventricular arrhythmias (Table 4, Fig. 3). The interpretation of results from MTWA testing in the individual patient must be integrated with the clinical history of that patient.

Inconsistency remains in current practice as to whether an indeterminate MTWA test should be considered abnormal or excluded altogether. Comparing the predictive value of abnormal MTWA in the eight studies (17,23,24,26,30,32,33,40), which provided outcomes based on the inclusion or exclusion of indeterminate MTWA, we found no significant difference in the predictive value of an abnormal test. Although statistically it seems that including an indeterminate MTWA test as abnormal does not change the predictive accuracy of the test, this does not necessarily indicate that an indeterminate MTWA test should be considered abnormal. Fundamentally, it seems erroneous to consider a test that is, for example, uninterpretable because of noise as clinically relevant. It remains important to develop and study alternative methods of assessing MTWA (e.g., dobutamine-induced) to risk stratify the patients who may have an indeterminate exercise-induced MTWA test (as many as 50% of patients in our review).

There are several strengths of this meta-analysis of MTWA. First, all of the studies were consistent in their definition of the presence, absence, or indeterminacy of significant T-wave alternans based on the current standard of T-wave alternans as developed by Rosenbaum et al. (6). The exception to this was the study of Tapanainen et al. (40), which introduced the concept of T-wave alternans testing incomplete. However, including or excluding the group of patients from this study with an incomplete MTWA test in our meta-analysis did not change the results of the sensitivity analysis. Second, all of the studies were consistent in the use of the CH2000 (Cambridge Heart Inc., Bedford, Massachusetts) device for exercise-induced MTWA testing. Finally, we assessed the value of MTWA testing in a wide variety of patient populations.

Study limitations. There are several limitations to this study. First, there were not sufficient data contained in the included multivariate analyses to determine the incremental prognostic value of MTWA independent of other predictors of arrhythmic events, such as EF, signal-averaged ECG, heart rate variability, or electrophysiologic study. Although MTWA seems clinically useful in this meta-analysis, the test may offer little additional predictive value beyond other commonly used clinical predictors. Second, the end points of the individual studies used in the summary calculations were variable (e.g., cardiac death vs. SCD/VT/VF vs. syncope/VT). It may be more clinically applicable for future studies of MTWA to use the end point of cardiac death, as was used in the study of Bloomfield et al. (33) and the study of signal-average ECG of Gomes et al. (42). Third, the subjects in the included studies were primarily men. For this reason, the results of this analysis may not be applicable to the general population. Fourth, there was inconsistency in the exclusion of subjects using beta-blockers or antiarrhythmic agents in the included studies. Because beta-blockers and antiarrhythmic agents can decrease the sensitivity of MTWA (43–45), it is possible that this biased the results of our study. Finally, as with any meta-analysis, its quality is limited by the quality of the included studies. However, eliminating the studies considered to be of lower quality by our quality assessment did not affect the outcomes of our analysis.

Conclusions. We studied the use of MTWA as a predictor of arrhythmic events in a meta-analysis of more than 2,600 subjects. We found that the presence of MTWA predicted a nearly four-fold risk of an event compared with the absence of MTWA. The NPV of MTWA testing was 97%. However, the PPV of MTWA varied from 0% to 51%, depending on the population of subjects studied. Given the challenge of risk stratification for life-threatening arrhyth-

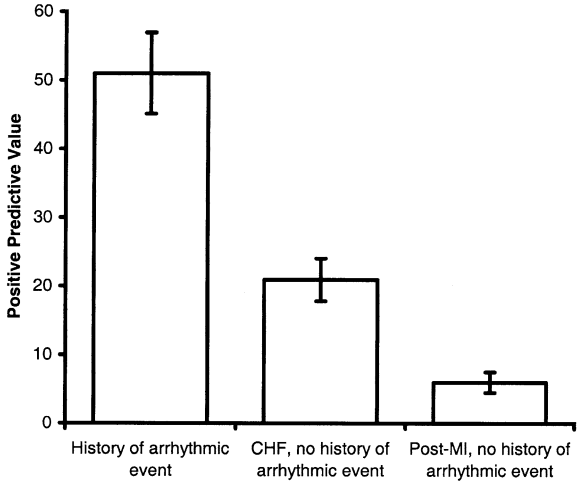

Figure 3. Positive predictive value of abnormal microvolt T-wave alternans in three populations of subjects. CHF = congestive heart failure; MI = myocardial infarction.

Table 5. Multivariate Predictive Value in Three Prospective Studies of Microvolt T-Wave Alternans

Author (Ref.)	Multivariate Predictors	Adjusted RR of MTWA (95% CI)	p Value
Adachi et al. (36)	MTWA, EF, SAEKG, NSVT, LVDd, QTd	NA	<0.05
Ikeda et al. (28)	MTWA, EF, SAEKG, NSVT	5.9 (1.6 to 21.4)	0.007
Kitamura et al. (37)	MTWA, EF, SAEKG, NSVT, LVDd	8.93 (2.38 to 33.52)	0.0001

EF = ejection fraction; LVDd = left ventricular diastolic diameter; MTWA = microvolt T-wave alternans; NA = not available; NSVT = nonsustained ventricular tachycardia; QTd = QT dispersion; SAEKG = signal-averaged electrocardiogram; other abbreviations as in Table 2.

mic events that faces today's cardiologist and the economic implications for today's society, our study helps understand the value and the limitations of MTWA testing. Further study of the combined predictive value of several methods of risk stratification including MTWA with adequate follow-up and appropriate end points is warranted.

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