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Can microvolt T-wave alternans testing reduce unnecessary defibrillator implantation?

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SUMMARY

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have established that patients with a reduced ejection fraction gain an overall mortality benefit from prophylactic implantable cardioverter-defibrillator therapy. Only a small proportion of the patients in these studies, however, have received life-saving therapy from the defibrillator. Because defibrillator therapy is invasive and expensive, patients with a low ejection fraction would benefit from effective risk stratification so that defibrillator therapy was used only in those at significant risk. In this review, we analyze prospective clinical trials that have evaluated microvolt T-wave alternans (MTWA) testing as a predictor of ventricular tachyarrhythmic events in populations of patients similar to those studied in MADIT II or SCD-HeFT; that is, patients with a reduced ejection fraction who were not selected on the basis of a history of ventricular tachyarrhythmias. In these studies, the average annual rate of fatal and nonfatal ventricular tachyarrhythmic events among the patients who tested negative for MTWA was around 1%. This rate is so low that it is unlikely that such patients would benefit from implantable cardioverter-defibrillator therapy. The mortality, moreover, was lower among MTWA-negative patients who did not receive implantable defibrillators than that observed in the MADIT II and SCD-HeFT patients who received implantable cardioverter-defibrillators. In response, patients with a low ejection fraction who are being considered for implantable cardioverter-defibrillator therapy should undergo MTWA testing as part of their evaluation.

KEYWORDS alternans, implantable cardioverter-defibrillator, primary prevention, sudden cardiac death

REVIEW CRITERIA

All articles were found by performing a literature search on the MEDLINE database. The major search terms that were used were: "alternans", "multicenter unsustained tachycardia trial", "MADIT", "DINAMIT" and "SCD-HeFT". All identified articles were published in English and were not limited by the year of publication. The full-text articles were retrieved from either electronic libraries or the medical libraries at our respective institutions.

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INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) have had a major impact on the treatment of ventricular tachyarrhythmias. Initially, physicians used ICDs primarily to treat patients who had survived cardiac arrest or who had had an episode of documented sustained ventricular tachycardia. The majority of patients who die from sudden cardiac death, however, have not experienced such an event. Thus, physicians have sought to use ICDs prophylactically for the primary prevention of sudden cardiac death in patients who have not had a previous sustained ventricular tachyarrhythmic event. Primary prevention therapy requires some form of risk stratification to identify suitable candidates.

Until the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) results were published in 2002,[1] the primary diagnostic tool for risk stratification in this context was the invasive electrophysiology study (EPS). This technique involves electrical stimulation of the ventricle, through catheters inserted into the patient's heart, in an attempt to induce sustained ventricular tachyarrhythmia. The Multicenter Unsustained Tachycardia Trial (MUSTT),[2] however, demonstrated that, in patients who had previous myocardial infarction, a left-ventricular ejection fraction of 0.40 or less and unsustained ventricular tachycardia, an EPS was a poor predictor of sustained ventricular tachyarrhythmic events. When patients who had positive EPS results were compared with those who had negative EPS results—none of whom were receiving specific antiarrhythmic therapy—a hazard ratio of only 1.4 was reported for sustained ventricular tachyarrhythmic events. In particular, patients who tested negative on EPS still had an annual event rate (λ) of 5.5%. In this paper, λ is used to compare trials with different durations of follow-up. It is derived from data in the reported trials by setting the actuarial event-free survival (S), at the end of the specified follow-up period (T), according to the following formula: $S(T) = e^{-\lambda T}$. In Table 1, the hazard ratio

Table 1 Comparison of annual spontaneous ventricular tachyarrhythmic event rates observed in prospective natural history microvolt T-wave alternans studies.[a]

Study	Population	Number of patients	Follow-up (months)	Annual ventricular tachyarrhythmic event rate		Hazard ratio
				MTWA-positive (%)	MTWA-negative (%)	
Klingenheben *et al.*[20]	CHF (prior MI and DCM)	107	18	16	0	∞
Hohnloser *et al.*[21]	DCM	137	18	17	4	4
Kitamura *et al.*[22]	DCM	83	21	16	2	9
Adachi *et al*.[23]	DCM	82	40	11	1	12
Grimm *et al*.[24]	DCM, LVEF ≤0.45	263	72	3	2	1.5
Ikeda *et al*.[25]	Prior MI	102	13	30	2	16
Ikeda *et al.*[26]	Prior MI	834	24	4[b]	0.5[b]	8
Hohnloser *et al.*[27]	Prior MI, LVEF ≤0.30	129	24	9[b] 19	0[b] 3	∞ 6
Chow *et al.*[28]	Prior MI, LVEF ≤0.30	203	18	8	1	6
All	—	1,811	—	8.4[c]	1.2[c]	7

[a]All these studies were performed in patients with a history of ischemic or nonischemic heart disease and a reduced ejection fraction, who were not selected on the basis of a history of ventricular tachyarrhythmias. [b]Sudden cardiac death and cardiac arrest endpoints only; all other entries include sudden cardiac death, cardiac arrest and sustained ventricular tachycardia endpoints. [c]These composite annual event rates represent the averages of the annual event rates in each of the trials weighted by the number of patients in each trial. The Hohnloser *et al.*[27] study in MADIT II-type patients is excluded from the composite rate calculation because the patients from this study were all drawn from the Klingenheben *et al.*[20] and Ikeda *et al.*[26] studies, which are already included in the composite rate calculation. CHF, congestive heart failure; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MTWA, microvolt T-wave alternans.

is calculated as the ratio of the values of λ for microvolt T-wave alternans (MTWA)-positive versus MTWA-negative groups.

MADIT II and SCD-HeFT[3] were the two landmark studies that established the usefulness of ICD therapy for the primary prevention of sudden cardiac death in patients who did not undergo risk stratification by means of EPS. These studies led the US Center for Medicare and Medicaid Services to approve Medicare reimbursement for ICD therapy in the population groups included in the trials. MADIT II and SCD-HeFT evaluated the efficacy of ICD therapy in patients who had left-ventricular dysfunction without a history of sustained ventricular tachyarrhythmia. MADIT II addressed ICD use in patients with previous myocardial infarction and a left ventricular ejection fraction of 0.30 or lower, whereas SCD-HeFT addressed this therapy in patients with a left ventricular ejection fraction of 0.35 or lower who had NYHA class II or III heart failure on an ischemic or nonischemic basis. Both studies demonstrated a small but statistically significant reduction in all-cause mortality with ICD use (Table 2).

The treatment of all individuals in the US who would be eligible for an ICD according to the MADIT-II and SCD-HeFT inclusion criteria would involve more than 1 million implantations per year. The American Heart Association estimates that there are 550,000 new cases of clinical heart failure annually in the US.[4] Less than half of all individuals with severe ventricular dysfunction, however, have clinical heart failure.[5] Thus, the estimated incidence of severe ventricular dysfunction is around 1 million individuals per year in the US. If the cost of this procedure, including follow-up care, is estimated to be US$40,000,[6] full implementation of this program would cost $40 billion annually, adding substantial cost to the health-care system.

In addition, as the absolute reduction in annual mortality in the MADIT II and SCD-HeFT populations was only a few percent (4.0% and 2.5%, respectively), only a very small proportion of the proposed ICDs would deliver life-saving therapy in a given year (e.g. in SCD-HeFT, only 5.1% of ICDs fired appropriately on an annual basis, leading to a 2.5% absolute reduction in annual mortality).[3] The patients in whom the ICD never discharges are subject to the morbidity and mortality risks associated with ICD implantation, but never receive any benefit. These risks include wound infection, inappropriate shocks,

Table 2 Comparison of the annual all-cause mortality rates between patients in the SCD-HeFT and MADIT II trials, and those in prospective natural history microvolt T-wave alternans studies.

Study	Population	Number of patients	Follow-up (months)	Annual mortality (%)	
Prospective ICD studies				**No ICD**	**ICD**
MADIT II[1]	Prior MI, LVEF ≤0.30	1,232	20	13.2	9.2
SCD-HeFT[3]	CHF, LVEF ≤0.35	2,521	60	9.0	6.5
All	—	3,753	—	10.4	7.4
Prospective MTWA studies in non-ICD patients				**Entire population**	**MTWA negative**
Bloomfield *et al.*[18]	Prior MI, LVEF ≤0.30	177	24	7	2
Hohnloser *et al.*[27]	Prior MI, LVEF ≤0.30	129	24	10	7
Costantini *et al.*[29]	DCM, LVEF ≤0.40	282	24	3	0
Grimm *et al.*[24]	DCM, LVEF ≤0.45	263	72	4	2
All	—	851	—	5.3	2.0

CHF, congestive heart failure; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT II, Multicenter Automatic Defibrillator Implantation Trial II; MI, myocardial infarction; MTWA, microvolt T-wave alternans; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

lead breakage, cardiac perforation, device failure and vascular complications.[7]

Of the other primary prevention trials that did not use EPS for risk stratification, not all found that ICDs conferred a mortality benefit. For instance, the Coronary Artery Bypass Graft Patch (CABG-Patch) trial[8] involved patients who were undergoing coronary artery bypass grafting surgery, whose left ventricular ejection fraction was lower than 0.36 and who had abnormal signal-averaged electrocardiograms. ICDs conferred no significant mortality benefit. In addition, the Defibrillator In Acute Myocardial Infarction Trial (DINAMIT)[9] showed that in patients who had recently had a myocardial infarction, with a left ventricular ejection fraction of 0.35 or lower and impaired autonomic function, ICD therapy was associated with no significant change in overall mortality: a decrease of 2.0% in the annual rate of arrhythmic mortality was balanced by an increase of 2.6% in the annual rate of nonarrhythmic mortality. The different outcomes of the CABG-Patch trial and DINAMIT to those of the MADIT II and SCD-HeFT might be attributed, in part, to the different populations of patients involved. Notably, in the DINAMIT, however, the altered arrhythmic and nonarrhythmic mortality rates persisted for 4 years, and, therefore, were not attributable to deaths occurring during the immediate postinfarction period.

The purpose of this review is to evaluate whether existing clinical data support the use of MTWA testing as a means of identifying patients with left ventricular dysfunction who are at low risk of sudden cardiac death and thus unlikely to benefit from primary prevention using ICDs. If successful, such an approach would result in a reduction in the number of unnecessary ICD implantations, and the associated morbidity and mortality risks, as well as a substantial reduction in health-care expenditure.

MICROVOLT T-WAVE ALTERNANS

T-wave alternans, which involves an 'ababab…' pattern of variation in T-wave morphology in sequential beats, is a phenomenon that has been recognized for around 100 years.[10] Computer simulations have suggested that T-wave alternans is associated with the development of re-entrant arrhythmias.[11] The technique of measuring MTWA was developed to detect fluctuations in T-wave morphology at levels far below that which can be observed on visual inspection of the electrocardiogram (Figure 1).[12] In initial animal trials[12,13] and human studies conducted in high-risk patients,[12,14,15] MTWA was shown to be an accurate predictor of susceptibility to sustained ventricular tachyarrhythmic events.

Currently, MTWA testing is an established noninvasive clinical technique for assessing susceptibility to ventricular tachyarrhythmia events that lead to cardiac arrest and sudden cardiac death. The presence of MTWA is believed to be related to alternation in action-potential

duration in localized regions of the ventricular myocardium. This feature gives rise to localized delayed recovery on an alternate-beat basis. The resulting spatial dispersion of recovery leads to the fractionation of depolarization wave fronts and the development of re-entry (Figure 2).[16] T-wave alternans is highly heart-rate-dependent and, therefore, MTWA is usually measured while the heart rate is elevated for several minutes by means of exercise, cardiac pacing or pharmacologic stress (e.g. dobutamine with or without atropine). In order to achieve adequate noise reduction during MTWA testing, multi-electrode noise-reducing sensors are used to record the electrocardiographic signals in the most widely used commercial system (CH 2000 or Heartwave®, both from Cambridge Heart Inc., Bedford, MA). This system uses specialized, signal-processing algorithms to process the electrocardiographic signals in order to determine the amplitude of the alternans and whether it is statistically significantly higher than the background noise. An MTWA test can be conducted by a trained technician in about 30 min, including preparation of the patient.

For a positive result, the MTWA test must detect sustained alternans; that is, alternans that meets amplitude and statistical significance criteria, and is consistently present above an onset heart rate of 110 beats/min or less (Figure 3). For a test to be negative, it must not qualify to be classified as positive and there must be at least 1 min of data collected at a heart rate of 105 beats/min or higher without significant alternans. Tests that do not qualify as either positive or negative are classified as indeterminate.[17]

MTWA testing was originally introduced with the primary goal of being used as a positive predictor to identify patients who are at increased risk of sudden cardiac death, so that they can be referred for EPS and ICD therapy. MTWA testing was shown to be highly predictive of spontaneous ventricular tachyarrhythmia events, with a predictive accuracy that compared favorably with that of invasive EPS.[14,15]

MADIT-II and SCD-HeFT subsequently demonstrated that ICD therapy resulted in an overall reduction in mortality, in a broad population of patients with left ventricular dysfunction who underwent no further risk stratification. As discussed above, however, most patients did not benefit, because only a small proportion of the implanted devices provided life-saving therapy each year. Thus, with the advent of these trials, the major question facing physicians treating similar populations shifted from which patients should receive an ICD to which, if any, should not receive an ICD.[8] Consequently, because of the highly negative predictive accuracy of MTWA for the occurrence of sustained ventricular tachyarrhythmic events, physicians have focused on its potential use as a noninvasive negative predictor to identify which

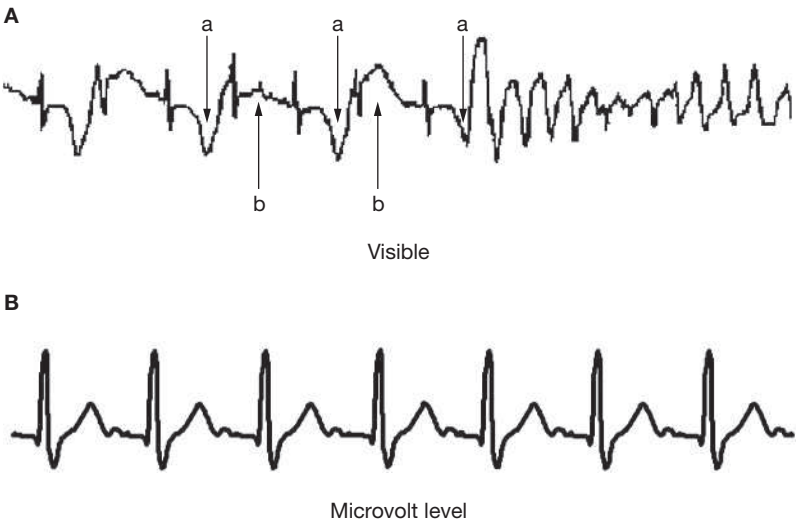

Figure 1 Visible and microvolt T-wave alternans. (**A**) Visible T-wave alternans, showing 'ababa …' pattern, preceding the onset of ventricular fibrillation. Reproduced with permission from reference 30 © (1992) Massachusetts Medical Society. (**B**) Microvolt T-wave alternans is not apparent on visual inspection of the electrocardiogram.

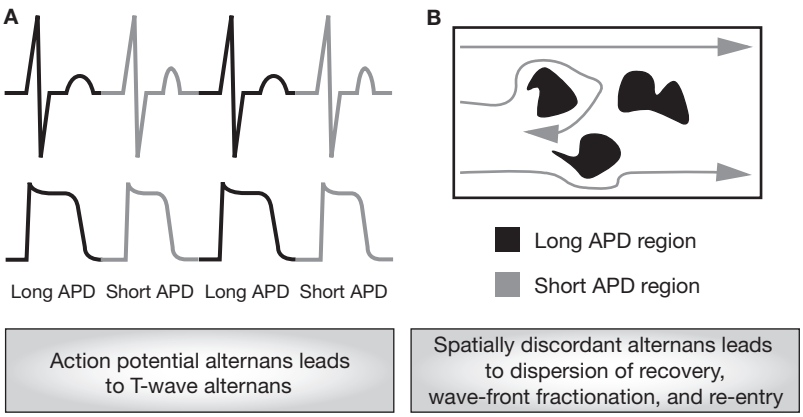

Figure 2 Mechanisms by which T-wave alternans is involved in the development of arrhythmias. (**A**) Localized action-potential alternans is manifested as T-wave alternans on the surface electrocardiogram. (**B**) Localized regions of tissue exhibiting action-potential alternans are associated with delayed recovery on an every-other-beat basis. These tissue islands of delayed recovery can lead to the fractionation of depolarization wave fronts and the development of re-entry. APD, action-potential duration.

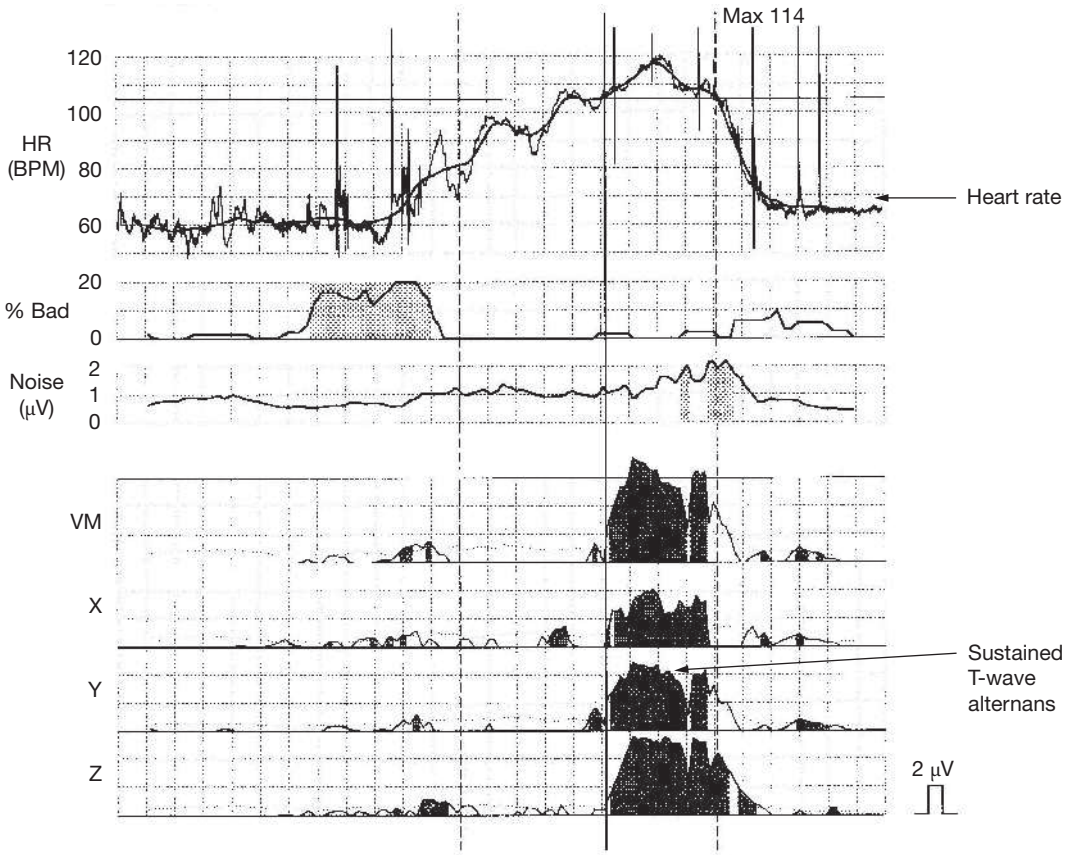

Figure 3 Representative report of microvolt T-wave alternans test. Sustained microvolt T-wave alternans is present with an onset heart rate of around 107 beats/min, resulting in a positive classification. The tracings from top to bottom indicate the following features: heart rate; the proportion of bad beats that could not be used in the analysis; the noise level in the vector-magnitude lead; and the T-wave alternans levels in the Frank orthogonal vector leads. Shading in the vector leads indicates that the alternans is statistically significant compared with the background noise (see Bloomfield *et al*.[17] for methods of interpretation). BPM, beats/min; HR, heart rate; VM, vector magnitude lead; X, Y and Z, Frank orthogonal vector leads.

patients with left ventricular dysfunction might not require ICD therapy.

CLINICAL STUDIES

Tables 1 and 2 present prospective natural history studies that were conducted in populations of patients similar to those studied in MADIT II and SCD-HeFT; that is, patients with a history of ischemic or nonischemic heart disease and a reduced ejection fraction who were not selected on the basis of a history of ventricular tachyarrhythmias. Table 1 presents studies that included an endpoint of sustained ventricular tachyarrhythmic events and Table 2 presents studies that included an endpoint of all-cause mortality. We show the event rates in annual terms, so that studies with different durations of follow-up can be compared. The studies all assessed MTWA, measured on CH 2000 or Heartwave® instrumentation, while the heart rate was elevated by means of exercise, cardiac pacing or pharmacologic stress. The annual overall ventricular tachyarrhythmia event rate among patients who tested negative for MTWA was only 1.2% (Table 1); this rate is so low that ICD therapy may not be warranted in such patients.

Table 2 compares the annual all-cause mortality rates in MADIT II and SCD-HeFT with the annual all-cause mortality rates among similar patients who underwent MTWA testing. The mean all-cause annual mortality rate of 5.3% among the pooled populations of the four MTWA studies was a factor of 2.0 smaller than the corresponding rate among patients not receiving ICD therapy in MADIT II and

SCD-HeFT (10.4%). The mean annual all-cause mortality rate of 2.0% among MTWA-negative patients was, however, a factor of 3.7 smaller than the annual all-cause mortality rate (7.4%) for MADIT-II or SCD-HeFT patients receiving ICD therapy. These data suggest that the all-cause mortality among MTWA-negative patients who were not treated with ICDs is at least as low as that in similar patients treated with ICDs who did not undergo MTWA-based risk stratification. MTWA-negative patients seem unlikely, therefore, to benefit from ICD therapy.

MTWA is an appropriate risk-stratification tool for patients similar to those studied in MADIT II and SCD-HeFT, because of its excellent negative predictive accuracy—patients who test negative are at very low risk of ventricular tachyarrhythmia events. By contrast, Bloomfield *et al.*[18] demonstrated that QRS width is an ineffective electrocardiographic parameter on which to stratify risk in patients similar to the MADIT-II population, because of the unacceptably high event rate among patients with normal QRS width (6% annual mortality).

CONCLUSIONS

A large body of data indicate that patients with left ventricular dysfunction who are being considered for ICD therapy for the purposes of primary prevention should undergo MTWA testing. Patients who test MTWA negative are at very low risk of ventricular tachyarrhythmia events and sudden cardiac death, are thus unlikely to benefit from and are subject to the risks related to ICD therapy. As the ventricular tachyarrhythmia event rate among such patients is only 1.2% per year, ICDs would have to be implanted in 83 patients at a cost of around $3.3 million to prevent one fatal or nonfatal ventricular tachyarrhythmia event per year during the expected lifetime of the ICD (about 5 years). Thus, from both a medical and an economic perspective, MTWA testing should be used to help guide ICD primary prevention therapy in patients with left ventricular dysfunction.

A negative MTWA test could lead some patients with left ventricular dysfunction and no history of ventricular tachyarrhythmia, in consultation with their physicians, to decide to not receive ICD therapy. Conversely, a non-negative MTWA test might lead some patients who had been previously reluctant to have an ICD implanted, to decide appropriately to receive such therapy.

The studies cited above adequately demonstrate the negative predictive accuracy of MTWA in patients with left ventricular dysfunction. While it might be desirable to conduct a prospective trial with an all-cause mortality endpoint, comparing ICD versus non-ICD therapy in MTWA-negative patients with left ventricular dysfunction, it is unlikely that such a study will ever be performed. Because the sudden cardiac death rate is so low in MTWA-negative patients, such a trial would have to be many times larger than the MADIT-II and SCD-HeFT trials combined, in order to be adequately powered statistically. Of note, no ICD trial to date has demonstrated a mortality benefit for any population with a ventricular tachyarrhythmic event rate even remotely approaching as low as 1.2% per year. The negative predictive accuracy of MTWA is so high that little or no benefit would be expected from combining MTWA with other risk stratifiers, such as signal-averaged electrocardiography[19] or QRS width.[18]

If a negative MTWA test is used as a basis for not implanting an ICD in a patient with left ventricular dysfunction, such an individual might require only conventional medical therapy for their underlying heart disease and follow-up monitoring by means of MTWA testing. One advantage of a noninvasive risk-stratification method, such as MTWA testing, in contrast to an invasive technique such as EPS, is that it can be easily repeated. In this context, the predictive accuracy of MTWA need only be established over a follow-up period corresponding to the interval between repeat tests. Most of the prospective MTWA studies in Table 1 had follow-up periods of between 1 and 2 years; therefore, it would seem reasonable to repeat MTWA testing every 1–2 years.

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Competing interests

RJ Cohen declared competing interests; go to the article online for details. The other authors declared they have no competing interests.

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