Despite recent advances in the prevention and treatment of cardiovascular disease, sudden cardiac death (SCD) still accounts for ≈50% of all cardiovascular deaths in developed countries, thus accounting for a significant proportion of annual death worldwide.1 Reduction of the incidence of SCD in developed countries, thus accounting for a significant proportion of annual death worldwide.1 Reduction of the incidence of SCD depends on identification of those at most risk. In the present review we will concentrate on the challenges of risk stratification for SCD in chronic heart failure (CHF). We evaluate the utility of microvolt T-wave alternans (MTWA) as a tool for predicting SCD and consider whether MTWA is currently a valid means of selecting which patients should, or should not, receive an implantable cardioverter-defibrillator (ICD).

Prevention of Sudden Cardiac Death

Until recently, attempts to prevent SCD relied on pharmacological therapy. β-Blockers,2 angiotensin-converting enzyme inhibitors,3 angiotensin receptor blockers4 and aldosterone antagonists5 modestly reduce the risk of SCD in patients with CHF and after myocardial infarction (MI), whereas antiarrhythmic therapy has largely failed.6 Despite such treatments, these patients remained at high risk until the advent of the ICD. Although ICDs have further reduced the risk of SCD, they are expensive and can be associated with significant morbidity; therefore, precisely targeting their use is crucial. Implantation of ICDs for secondary prevention is clear. Prior sustained ventricular arrhythmia confers high risk and the benefit/risk balance is clearly favorable.7 Also, the secondary prevention population is relatively small and readily identified, thus the financial costs are not insurmountable.

Primary prevention ICD therapy is an entirely different scenario. Large, randomized controlled trials have shown a mortality benefit with ICDs in patients with a low left ventricular ejection fraction (LVEF) and a history of MI or CHF.6,8 However, 2 major concerns have restricted implementation of this strategy. First, although analyses have suggested an acceptable cost-effectiveness profile,9 the immediate cost of implanting devices in this large population is enormous and the workload would exceed the capacity of most cardiology services. Second, the available evidence suggests that selection on the basis of LVEF alone is inefficient. For example, in the largest and longest published trial, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 79% of patients in the ICD arm did not use their device. In other words, in this landmark study many patients who did not require an ICD received one. The absolute risk reduction in the group randomized to ICD implantation was modest (7.2% over 5 years).6 This suggests that there is room for better definition of the target population and underscores the need for improved risk stratification to achieve substantial mortality benefit without prohibitive cost or the morbidity related to unnecessary device implantation.

In patients with CHF, QRS prolongation is associated with a poor prognosis, but whether this relates to an increased risk of SCD is unclear,10 and patients with a narrow QRS remain at high risk.6,11 Similarly, the presence of nonsustained VT does not specifically predict SCD in CHF.12 Other markers of arrhythmic risk, such as signal-averaged ECG, QT dispersion, and heart rate variability are limited by low sensitivity.1

Recently, MTWA testing has been advocated as a predictor of ventricular arrhythmias in potential candidates for primary prevention ICD therapy. Indeed, the Centers for Medicare and Medicaid Services have recently approved its reimbursement for the evaluation of patients at risk of SCD, stating: “Within patient groups that may be considered candidates for ICD therapy, a negative MTWA test may be useful in identifying low-risk patients who are unlikely to benefit from, and who may experience worse outcomes from, ICD placement.”13

Microvolt T-Wave Alternans

T-wave alternans describes beat-to-beat fluctuations in T-wave morphology, which have been anecdotally associated with the onset of ventricular fibrillation (VF). Experimental work has suggested that T-wave alternans is caused by cellular repolarization alternans, which can cause dynamic instability in cardiac repolarization and predispose to VF.14 In initial clinical studies, MTWA during atrial pacing was associated with an increased risk of ventricular arrhythmia.15 MTWA testing is now performed during submaximal exercise, using a commercially available system (CH2000 or HearTwave II, Cambridge Heart, Bedford, Mass). A series of
beats recorded at a stable heart rate are aligned and the amplitude of each T-wave at the same time with respect to the QRS complex is plotted. These data then undergo spectral analysis, which determines the magnitude of T-wave fluctuation occurring on alternate beats. If sufficient alternans is sustained at heart rates > 110 bpm, the test is positive. Absence of alternans at 110 bpm constitutes a negative test. A test satisfying neither set of criteria is classified as indeterminate. The system presents the data, along with an automated classification, as shown in the Figure. Atrial fibrillation (AF) precludes MTWA testing by this method as unequal R-R intervals confound the frequency analysis. MTWA can also be determined with time-domain methods, which are applicable to Holter data and AF. Although this technology has been evaluated during pacing, no prospective data are available regarding the prognostic value of Holter-based MTWA testing.

Predictive Value of MTWA

The studies that have assessed the predictive value of MTWA testing during exercise are summarized in Table 1.

Known or Suspected Arrhythmia

In a population of 313 patients referred for cardiac electrophysiological study (EPS), MTWA predicted the occurrence of ventricular tachyarrhythmic events (VTE) (ie, SCD, VF, sustained ventricular tachycardia (VT), or appropriate ICD therapy) better than EPS (relative risk, 10.9 versus 7.1). However, this was a heterogeneous population; some patients were referred after cardiac arrest and others for assessment of supraventricular tachycardia.

Myocardial Infarction

Three studies have investigated the prognostic utility of MTWA after MI regardless of LVEF. Only 1 study has suggested that MTWA may predict SCD. This study enrolled 850 consecutive patients late after MI (mean, 2.7 months post-MI). MTWA was found to predict SCD or resuscitated VF, although the event rate was only 3%. The proportion of patients prescribed a β-blocker was low (30%). Two other studies suggested that MTWA is not prognostically useful after MI. In 1 study, 140 consecutive patients were investigated in the first 30 days after MI. Only 3 end points (death/VTE) accrued over 15 months of follow-up and MTWA did not predict events. The second study examined the predictive value of MTWA for all-cause death in 323 consecutive patients early after MI (mean, 8 days post-MI). Of these, only 56 (17%) patients were MTWA-positive. None of the 26 deaths occurred in this group. Notably, these patients were evaluated while receiving optimal medical therapy (including a β-blocker in 97%). In a cohort of 1041 patients with preserved LVEF after MI (mean, 48 days post-MI), a positive MTWA test did predict VTE, although the number of end points was extremely low (18 over 32 months).

Two small studies have specifically selected patients who meet Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II entry criteria (previous MI, LVEF ≤30% without prior VF/VT) from other cohorts. In 129 such patients, none of the 12 who experienced SCD or resuscitated VF were in the MTWA-negative group. In a subgroup analysis of a larger study, 177 patients who meet MADIT-II criteria had MTWA tests classified as abnormal (positive/indeterminate, 68%), or normal (negative, 32%). The hazard ratio associated with an abnormal test (4.8; 95% CI, 1.1 to 20.7) was only adjusted for QRS duration and so does not reflect incremental prognostic value.

In short, the evidence for the use of MTWA in risk stratification after MI is not robust. The negative predictive value (NPV) may be high in selected patients, but the results are conflicting in more representative cohorts and, in MADIT-II patients, the incremental prognostic value is untested. Preliminary results are now available from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II study. In 575 MADIT-II eligible patients undergoing ICD implantation, an abnormal MTWA test did not predict the combined end point of arrhythmic death and ICD discharge.

Ischemic Left Ventricular Systolic Dysfunction

Three studies have examined the prognostic value of MTWA in patients with ischemic left ventricular systolic dysfunction (LVSD). The first study performed MTWA testing in 144 nonconsecutive patients referred for EPS. The cohort was divided into primary (n = 88) and secondary (n = 56) prevention subgroups, and 111 patients received an ICD. A positive MTWA test did not predict the primary end point (death/VTE) in the primary prevention subgroup.
The authors analyzed positive and indeterminate tests together and separately, addressed cause-specific death as a secondary end point, and performed a more extensive multivariable analysis than has been seen in other studies. However, the follow-up was relatively short (mean, 18±10 months) and the event rate (n=99) was arguably low for a population of this kind, limiting the power of the study. A nonnegative MTWA test independently predicted all-cause mortality (hazard ratio, 2.24; 95% CI, 1.34 to 3.75) and arrhythmic mortality (hazard ratio, 2.29; 95% CI, 1.0 to 5.24) in the whole population. However, when positive and indeterminate results were analyzed separately, positive results did not predict arrhythmic death, whereas indeterminate results predicted both all-cause and arrhythmic death. Therefore, indeterminate

### Table 1. Prospective Observational Studies of MTWA Testing*

<table>
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<th>Population/Study</th>
<th>N</th>
<th>Mean Age, y</th>
<th>Mean LVEF, %</th>
<th>Prior VA, %</th>
<th>Pretest β-Blocker Stopped?</th>
<th>MTWA Result (%)</th>
<th>Primary End Point</th>
<th>Predictive Value</th>
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</table>

VA indicates ventricular arrhythmia; FU, follow-up; RR, relative risk; HR, hazard ratio; PPV, positive predictive value; NA, not available; NS, nonsignificant; and ACM, all-cause mortality.
*Published studies only.
†Multivariable HR/RR.
‡VTE including ICD discharge.
§Excluded from predictive analysis.
rather than positive tests accounted for the majority of the predictive value for arrhythmia, which counters the proposition that MTWA identifies a specific proarrhythmic substrate.

The Alternans Before Cardioverter Defibrillator (ABCD) study recruited 566 patients with ischemic LVSD and non-sustained VT and compared the ability of MTWA and EPS to predict VTE. Preliminary results show that the 1-year event rate was lowest when both tests were negative (2.3%), highest when both were abnormal (12.6%), and intermediate when only 1 test was abnormal (MTWA nonnegative, 5%; EPS abnormal, 7.5%). Use of an ICD (shock or pacing) accounted for the majority (55 of 65) of end points. However, ICD implantation was not mandated if both tests were normal, and so patients in this group (n=99) may have been less likely to reach an end point. Furthermore, because ICD therapies occur more frequently than SCD in patients without ICDs, a significant proportion of the end points in this study may have been attributable to subclinical arrhythmias.

Left Ventricular Systolic Dysfunction Irrespective of Etiology

One study recruited 549 patients with LVSD, including patients with ischemic (n=267) and nonischemic (n=282) cardiomyopathy. The primary end point was a composite of death and VTE. Over 20 months, there were 2 deaths and 2 ICD discharges in the normal MTWA group (n=189) compared with 38 deaths and 9 ICD discharges in the abnormal group (n=360) (the proportion with an ICD in each group was the same). After multivariable adjustment, an abnormal MTWA test was associated with an increased risk of VTE.

Nonischemic Left Ventricular Systolic Dysfunction

Three studies have examined the prognostic utility of MTWA in nonischemic cardiomyopathy. The first study performed MTWA testing in 104 patients and concluded that a positive MTWA test was independently associated with VTE. However, this study has many limitations. The number of end points was very small (n=12), as was the sample size, limiting the multivariable analysis. Many screened patients were ineligible because of AF, but no information was given regarding their number or characteristics. No patient was prescribed an angiotensin-converting enzyme inhibitor or β-blocker before entry into the study (ie, MTWA testing was carried out on suboptimal medical therapy). The second study recruited 137 patients and compared MTWA with other arrhythmic markers. MTWA was the only independent predictor of VTE after a mean follow-up of 14 months. However, the multivariable model did not include age or LVEF. The cohort included patients with an ICD (27%), mostly for prior VF/VT, and 11 of 18 end points occurred in those patients. This limits extrapolation of these results to a primary prevention population. The largest study (n=263) excluded patients with prior VF/VT and had a longer duration of follow-up (52 months). A positive MTWA test was not associated with the occurrence of VTE.

The available evidence does not suggest that MTWA is a reliable indicator of arrhythmia in patients who have nonischemic LVSD. There appears to be little to recommend a strategy of using MTWA in this population to determine which patients should have an ICD.

Symptomatic Heart Failure With Low LVEF

The evidence, such as it is, for the prognostic utility of MTWA in LVSD cannot simply be extrapolated to patients with symptomatic CHF, which is a clinically distinct entity. Three small studies (n=73, n=46, n=107) have assessed the predictive value of MTWA testing in patients with low ejection fraction heart failure. On initial review these studies suggest that MTWA predicts clinical outcome in this population. However, they do have several limitations beyond their size.

The first selected 73 patients with New York Heart Association II CHF after excluding those with LVEF ≤20% “because of high risk of death.” An additional 17 patients were excluded after indeterminate MTWA testing, leaving a small and highly selected group in which a positive MTWA test was associated with an increased risk of VTE over 17 months. In another study, of 46 patients with New York Heart Association II/III CHF, MTWA predicted cardiac death (n=7) but not SCD (n=1). In the third study, of 107 patients with CHF, none of the 13 end points occurred in MTWA-negative patients and MTWA was the only independent predictor of VTE. However, the multivariable adjustment included only 7 arrhythmia markers.

These studies are small, appear to be highly selected, and lack proper multivariable adjustment. Their limited relevance to real-life populations with CHF is exemplified by the mean ages of the patients enrolled (64 years, 59 years, and 56 years, respectively). The average age of unselected heart failure populations is 75 years.

Results are now available from 2 larger studies of MTWA in CHF. The Microvolt T-Wave Alternans in Patients with Heart Failure (ALPHA) study recruited 446 patients with nonischemic cardiomyopathy (LVEF≤40%) and stable New York Heart Association II/III CHF on optimal medical therapy. A nonnegative MTWA test was associated with an increased risk of cardiac death or VTE over 18 to 24 months. However, these patients were older, more symptomatic, and had a lower mean LVEF, imbalances that highlight the need for careful multivariable adjustment in such studies. In the SCD-HeFT T-wave alternans substudy, MTWA testing was performed in 490 patients with LVEF ≤35% and New York Heart Association II/III CHF; 41% of tests were indeterminate and over 35 months there was no difference in the rate of VTE between MTWA groups for patients who received either ICD or placebo. These studies are larger than those published so far and their contradictory results mean that doubt remains regarding the value of MTWA for predicting arrhythmic risk in CHF.

Unresolved Issues in MTWA Testing

Does MTWA Have Incremental Prognostic Value?

There are few data regarding the true incremental prognostic value of MTWA testing because of the lack of detailed multivariable analysis undertaken in the studies to date (Table 2). A number of powerful predictors of outcome in CHF have recently been identified, including plasma B-type natriuret-
ic peptide (BNP) levels, which have an established prognostic significance in CHF with reduced LVEF. BNP has also been found to be an independent predictor of SCD. The prognostic value of MTWA testing has not been compared with that of BNP. It is certainly conceivable that a low BNP could confer as good a prognosis as a negative MTWA test. If this were the case, then the cost and small risk to the patient associated with MTWA testing would be unjustified. Although some may argue that BNP is not suitable for risk stratification because it varies over relatively short time scales, it should be noted that there is no evidence regarding the reproducibility of MTWA results over time scales greater than a few hours.

Atrial Fibrillation
MTWA exercise testing cannot be performed in patients with AF. Only 2 studies have reported the proportion of screened patients ineligible because of AF (23% and 22%). In MADIT-II, 9% of patients had AF, and in populations with CHF, 25% to 30% have concurrent AF. If sufficient evidence was accrued to allow MTWA to be used to identify appropriate candidates for ICD therapy in populations with sinus rhythm, attention should remain on alternative strategies in the large population ineligible for testing.

Inability to Exercise
Tapanainen et al reported that 15% of 379 consecutive MI patients in sinus rhythm could not exercise due to comorbidity or physical frailty. Although a positive MTWA test failed to predict all-cause mortality, inability to exercise was found to be an independent predictor of death (relative risk, 5.62; 95% CI, 1.76 to 15.99). Implementation of a risk-stratification tool that requires exercise is likely to be problematic in CHF, where the incidence of frailty and comorbidity is high.

Medical Therapy
Despite the fact that pharmacological therapy can reduce SCD, in only 1 of the studies described is optimal medical therapy mandated. In 1 post-MI study and 2 CHF studies, fewer than half of patients were prescribed a β-blocker. Many studies discontinued β-blockers for at least 24 hours to reduce indeterminate tests. However, as acute β-blockade reduces MTWA magnitude, in some cases converting a positive to a negative test, omission of β-blockers may not only reduce the number of indeterminate tests but may also increase the number of positive tests. We would argue that MTWA testing is only clinically valuable if shown to be independently predictive of outcome in patients on optimal tolerated medical therapy, including a β-blocker.

Indeterminate Testing
MTWA tests are classified as indeterminate in a defined set of circumstances: if there is significant noise or ectopy, if alternans is unsustained, or if the patient cannot attain a heart rate of 110 bpm for 1 minute. In early studies, indeterminate
MTWA tests were assumed to be of no significance to arrhythmic events and were excluded. However, in the first report by Bloomfield et al, indeterminate MTWA tests accounted for the majority of nonnegative tests and were grouped together with positive tests as abnormal,11 which is now common practice. Table 3 shows outcomes in MTWA-positive and indeterminate groups from studies that have examined all-cause death. In each, the rate of death was higher in the indeterminate group. Clearly, an indeterminate test indicates an unfavorable prognosis, but the nature of this risk is unclear. Only 1 study enrolled a sufficiently large cohort to examine cause-specific death (Table 4). Indeterminate tests accounted for 159 of 514 abnormal MTWA tests and predicted both arrhythmic and nonarrhythmic death, whereas a positive test only predicted all-cause death.24 In another study, the rate of major arrhythmic events was highest in the indeterminate group (24%) compared with the MTWA-positive (13%) or MTWA-negative (10%) groups.28

This raises the possibility that an indeterminate test may actually predict both nonarrhythmic and arrhythmic risk. Although this may seem counterintuitive, it is possible that patients with nonsustained alternans or ectopy on exercise are prone to ventricular arrhythmia. Recent analyses of indeterminate tests concluded that such patients were at high risk, distinct from the tests ruled as indeterminate because of noise, artifact, or a sharp rise in heart rate,42,43 suggesting that the prognostic value of MTWA may be improved by reclassification of indeterminate tests.43

**Extrapolation to Primary Prevention ICD Therapy**

There has been much speculation that MTWA could improve risk stratification for the primary prevention of SCD, and many commentators have argued that the current evidence regarding the favorable prognosis conferred by a negative test is sufficient to justify using MTWA to identify a subgroup of primary prevention ICD candidates who would not benefit.11,44 This could reduce the number of primary prevention implants and thereby reduce the cost of therapy.

However, the current evidence is lacking in many respects. Most of the studies are limited by small sample size or by low event rates, which reduces power, and there is a lack of detailed multivariable analysis. We cannot, at present, extrapolate the prevalence data for a negative test to unselected populations, because the proportion of patients who would be ineligible for testing because of AF or an inability to exercise is unknown. In addition, a high NPV has only been demonstrated over relatively short time scales, and because the arrhythmic substrate changes over time it is likely that serial MTWA testing would be required. The corollary of not implanting in MTWA negative patients would be to implant in all nonnegative patients, including those with indeterminate tests. Given the lack of proven incremental prognostic value of MTWA and the conflicting results in some studies, we have serious doubts regarding the benefit of this strategy and believe that the decision of the Centers for Medicare and Medicaid Services to reimburse for MTWA testing in all potential candidates for ICD implantation is premature. Indeed, the Blue Cross Blue Shield Technology Evaluation Center has not approved MTWA testing for this indication on the basis of insufficient evidence.45

### Improving the Evidence Base for MTWA

Further investigation is required to address the shortcomings and contradictions apparent in the data pertaining to MTWA and arrhythmic risk. A meta-analysis has already been conducted and, although it confirmed the high NPV of MTWA across many smaller studies, it could not address the lack of multivariable adjustment or the unrepresentative nature of the study populations.46

Prospective MTWA testing in all patients undergoing ICD implantation could provide valuable evidence as to whether MTWA can predict arrhythmic events. This may be achievable through the US National ICD Registry, which includes the improvement of risk stratification among its aims.47

In addition, further observational studies should be carried out in well-defined, representative populations. In these studies, multivariable models should be designed carefully to...
test incremental prognostic value over established predictors, and attention should be paid to the characteristics and outcomes of those ineligible for MTWA testing. The possibility that the high NPV of MTWA could be utilized in combination with other markers as part of a risk stratification algorithm should also be explored. A carefully designed trial of MTWA-guided ICD therapy would provide the most robust evidence. In this approach, patients who meet evidence-based criteria for ICD implantation would be assigned to medical therapy only, and such selection would therefore require careful ethical consideration. This is certainly conceivable, given that not all patients who meet the criteria receive an ICD at present. However, to justify such a trial, the evidence derived from observational studies should first be improved.

In conclusion, the evidence for the use of MTWA in risk stratification of patients at risk of SCD is compelling in some aspects, principally its NPV in patients with ischemic LVSD. However, the available evidence is not yet sufficient to allow its extrapolation to routine clinical use in large numbers of patients to determine whether primary prevention ICD implantation is indicated. To plan the most clinically and cost-effective method of SCD prevention, MTWA needs to be investigated in more detail.

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KEY WORDS: death, sudden heart failure, implantable cardioverter-defibrillator, T-wave alternans
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