Microvolt T-Wave Alternans Distinguishes Between Patients Likely and Patients Not Likely to Benefit From Implanted Cardiac Defibrillator Therapy

A Solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Conundrum

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Background—In 2003, the Centers for Medicaid and Medicare Services recommended QRS duration as a means to identify MADIT II–like patients suitable for implanted cardiac defibrillator (ICD) therapy. We compared the ability of microvolt T-wave alternans and QRS duration to identify groups at high and low risk of dying among heart failure patients who met MADIT II criteria for ICD prophylaxis.

Methods and Results—Patients with MADIT II characteristics and sinus rhythm had a microvolt T-wave alternans exercise test and a 12-lead ECG. Our primary end point was 2-year all-cause mortality. Of 177 MADIT II–like patients, 32% had a QRS duration >120 ms, and 68% had an abnormal (positive or indeterminate) microvolt T-wave alternans test. During an average follow-up of 20±6 months, 20 patients died. We compared patients with an abnormal microvolt T-wave alternans test to those with a normal (negative) test, and patients with a QRS >120 ms with those with a QRS ≤120 ms; the hazard ratios for 2-year mortality were 4.8 (P=0.020) and 1.5 (P=0.367), respectively. The actuarial mortality rate was substantially lower among patients with a normal microvolt T-wave alternans test (3.8%; 95% confidence interval: 0, 9.0) than the mortality rate in patients with a narrow QRS (12.0%; 95% confidence interval: 5.6, 18.5). The corresponding false-negative rates are 3.5% and 10.2%, respectively.

Conclusion—Among MADIT II–like patients, a microvolt T-wave alternans test is better than QRS duration at identifying a high-risk group and also better at identifying a low-risk group unlikely to benefit from ICD therapy. (Circulation. 2004;110:1885-1889.)

Key Words: heart failure ■ coronary disease ■ death, sudden ■ heart arrest ■ defibrillation

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II showed that patients with prior myocardial infarction and a left ventricular ejection fraction ≤0.30 who were randomized to implanted cardiac defibrillator (ICD) therapy had an improved survival rate compared with those patients randomized to conventional medical therapy.1 The absolute mortality reduction in MADIT II was 5.6% over an average of 20 months of follow-up. Consensus panels have accepted the scientific validity of the MADIT II results but have recognized the need for better methods of risk stratification.2 In addition, many patients, physicians, health-care insurers, and regulators have recognized not only the potential economic burden but also the potential adverse effects of implanting cardiac defibrillators in all patients who meet the MADIT II criteria.3,4 On the basis of its analysis of the MADIT II data, the Centers for Medicaid and Medicare Services (CMS) published in June 2003 its intent to issue a National Coverage Decision indicating that “there is adequate evidence to conclude that an ICD is reasonable and necessary in patients with prior myocardial infarction, an ejection fraction ≤0.30, and a QRS duration >120 ms.”5 This decision effectively limits prophylactic treatment with an ICD to the one third of MADIT II patients with a QRS >120 ms. It is not clear, however, that patients with a QRS duration ≤120 ms truly represent a low-risk group; methods to select patients for ICD therapy...
treatment should minimize the fraction of high-risk patients left unprotected.6

Microvolt T-wave alternans (MTWA) has the ability to identify patients at high risk for sudden cardiac death. In studies in animals7 and humans,8–12 MTWA is strongly associated with an increased risk of reentrant ventricular tachyarrhythmias and sudden cardiac death. Notably, a number of small studies in patients with heart failure have demonstrated that a normal MTWA test is associated with an extremely low mortality rate.9 We are conducting a multicenter, prospective study of the prognostic significance of MTWA in patients with left ventricular dysfunction. Although the main study includes patients with nonischemic cardiomyopathies, this report analyzes a subgroup of patients who have ischemic heart disease and an ejection fraction ≤0.30 and who meet other MADIT II criteria (>1 month after a myocardial infarction and >3 months after coronary revascularization) to determine whether MTWA is superior to QRS duration for selecting a high-risk group likely to benefit from ICD prophylaxis and for excluding a low-risk group unlikely to benefit from ICD prophylaxis.

Methods
The epidemiological study from which the present sample is drawn was conducted at 11 clinical centers in the United States. The institutional review board at each clinical center approved the protocol, and consent was obtained from all patients before their enrollment. The first patient was enrolled in November 1996 and the last in March 2003. Patients were eligible to participate in our epidemiological study if they were at least 18 years of age, had a left ventricular ejection fraction ≤0.40, had no history of a prior arrhythmic event, and were able to provide informed consent. Because MTWA can only be measured during a stable atrial rhythm, patients who had persistent atrial fibrillation or flutter or required ventricular pacing at the time of MTWA testing were excluded. Patients with unstable coronary artery disease or New York Heart Association functional class IV heart failure and those who were unable to exercise on a bicycle or treadmill were also excluded from the study. For this analysis, we selected the subset of patients who also met MADIT II criteria for ICD prophylaxis. During the baseline visit, a complete medical history and a 24-hour Holter ECG recording were obtained.

MTWA Testing
Patients had a MTWA exercise test (bicycle or treadmill) while taking their regular cardiovascular medications, including β-blockers. Careful skin preparation, including mild abrasion and high-resolution electrodes (High-Res, Cambridge Heart, Inc), was performed to minimize noise. Electrocardiographic leads were placed at the standard 12-lead positions and in an orthogonal X,Y,Z configuration. Measurements were made with the CH2000 system or a HeartWave device (Cambridge Heart, Inc) and utilized a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude. The MTWA test was automatically interpreted by the Alternans Report Classifier (Version D10) according to previously described criteria.13 Because previous studies showed that positive and indeterminate MTWA tests have similar mortality rates, all comparisons in this analysis were made between patients with normal (negative) and abnormal (positive or indeterminate) MTWA tests.

QRS Measurement
In the majority of patients, the QRS was measured electronically with the use of computerized ECG systems. If an automated analysis of QRS interval was not available, the ECG was printed out at 50 mm/s paper speed, and the QRS was measured manually with calipers by 2 individuals who were unaware of the clinical information or outcome of the patients. A third individual reviewed a random sample of the ECGs as well as all ECGs for which the 2 primary reviewers had discrepant values for QRS duration.

Follow-Up
The first scheduled follow-up visit occurred 1 month after the alternans test. After that, patients were followed up at 4-month intervals. Follow-up visits focused on reviewing patients’ interim medical and cardiovascular drug histories.

End Points
We used all-cause mortality as the end point for this analysis because it was the end point used in MADIT II.

Statistical Analyses
We classified MTWA tests as normal (negative) or abnormal (positive or indeterminate) and dichotomized QRS duration as ≤120 ms or as >120 ms. Kaplan-Meier curves were used to describe the survival experience for each MTWA and QRS duration group. The log-rank test was used to test the equality of the survival distributions for each risk predictor. Actuarial 24-month mortality was used to describe the outcome of patients classified by the different risk predictors. Cox proportional hazards regression was used to estimate the hazard ratio for mortality for the 2 risk predictors. Cox models were also used to estimate the hazard ratio for MTWA status and QRS duration adjusted for the other. The significance of each risk predictor adjusting for the other was assessed with likelihood ratio tests. All statistical tests were 2 tailed and used an α level of 0.05.

Results
Our study enrolled 587 patients, but 38 of these subsequently had a postenrollment exclusion (patients who consented to be in the study but withdrew or died before MTWA testing). Of the 549 evaluable patients, 177 had ischemic heart disease and an ejection fraction ≤0.30 and also met other MADIT II criteria. Follow-up was available for 99.4% of these patients, and mean follow-up duration was 20±6 months.

The clinical characteristics of the MADIT II–like patients are listed in Table 1. QRS duration was >120 ms in 32% of patients, and the MTWA test was abnormal in 68% of patients. The 2-year actuarial mortality rates for patients with positive and indeterminate MTWA tests were similar (14.5% and 20.1%, respectively).

For all 177 MADIT II–like patients, the actuarial 2-year mortality rate was 13.2%. We analyzed the difference in mortality between the 2 MTWA groups and between the 2 QRS duration groups (Figure, Table 2). According to log-rank tests, the 2-year actuarial mortality rate for patients with abnormal MTWA (17.8%) was significantly greater than for patients with normal MTWA (3.8%, P=0.020, hazard ratio 4.8). However, the mortality rate for patients with a QRS duration >120 ms (15.9%) was not significantly different than for patients with a QRS duration ≤120 ms (12.0%, P=0.367, hazard ratio 1.5).

Notably, the 2-year actuarial mortality rate was substantially lower among patients with a normal MTWA test (3.8% 95% confidence interval: 0.0, 9.0) than among patients with a narrow QRS (12.0%; 95% confidence interval: 5.6, 18.5), corresponding to false-negative rates of 3.5% and 10.2%, respectively. In other words, when trying to reassure patients with ischemic heart disease and severe left ventricular dysfunction that they may not require ICD therapy, a physician
can say that there is a 95% chance that the 2-year mortality risk of a patient with a normal MTWA test is <9.0%, compared with a 95% chance that the 2-year mortality is <18.5% for patients with a QRS duration ≤120 ms. Among the 118 patients with a QRS duration of ≤120 ms (patients who would not qualify for ICD reimbursement on the basis of the current CMS guidelines), 12 died (12.0% actuarial 2-year mortality) and all but one had abnormal MTWA tests. Remarkably, patients with a normal T-wave alternans test and an ejection fraction ≤0.30 had a lower 2-year actuarial mortality rate than patients with an abnormal MTWA test and an ejection fraction between 0.31 and 0.40 (3.8% versus 9.2%, respectively). A QRS duration >120 ms was weakly associated with MTWA status (odds ratio 1.7, \(P = 0.15\)). In a multivariate Cox model, MTWA remained a strong predictor of mortality (hazard ratio 4.7, \(P = 0.012\)) after adjusting for QRS duration. QRS duration did not add significantly to prognostic information provided by T-wave alternans.

### Discussion

In our analysis of patients who fit the MADIT II criteria, patients with an abnormal MTWA exercise test had a substantially increased risk of dying, with a 2-year actuarial mortality rate of 17.8%, whereas patients with a normal MTWA test had a low 2-year actuarial mortality rate of 3.8%.

The results of this study are consistent with a retrospective meta-analysis\(^4\) of 2 observational studies that included patients without known prior sustained ventricular tachyarrhythmias.\(^9,12\) This meta-analysis reported the results of MTWA testing in 129 patients who were identified from

#### TABLE 1. Baseline Clinical Characteristics of the 177 Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 ± 9.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>85</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.23 ± 0.06</td>
</tr>
<tr>
<td>QRS duration &gt;120 ms†</td>
<td>32</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td></td>
</tr>
<tr>
<td>No prior heart failure</td>
<td>16</td>
</tr>
<tr>
<td>I</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>47</td>
</tr>
<tr>
<td>III</td>
<td>26</td>
</tr>
<tr>
<td>Prior admission for heart failure</td>
<td>60</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34</td>
</tr>
<tr>
<td>Mean time after myocardial infarction, y</td>
<td>5.6 ± 5.7</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft surgery</td>
<td>53</td>
</tr>
</tbody>
</table>

#### TABLE 2. Comparison of MTWA and QRS Duration

<table>
<thead>
<tr>
<th>Measure</th>
<th>MTWA</th>
<th>QRS Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actuarial mortality, %</td>
<td>Abnormal*</td>
<td>17.8</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>3.8</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>4.8 (1.1, 20.7)</td>
</tr>
<tr>
<td>(95% confidence interval)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P)‡</td>
<td></td>
<td>0.020</td>
</tr>
<tr>
<td>Classified as low risk, %</td>
<td></td>
<td>32.2</td>
</tr>
<tr>
<td>False-negative rate, %</td>
<td></td>
<td>3.5</td>
</tr>
</tbody>
</table>

*For QRS duration, abnormal is >120 ms.
†Confidence intervals for the hazard ratios are based on Cox model estimates of the log hazard ratio and its standard error.
‡\(P\) values are based on log-rank tests.
the 2 studies that fit the MADIT II selection criteria (ischemic heart disease, ejection fraction $\leq 0.30$). At 2 years’ follow-up, no sudden cardiac death or cardiac arrest was seen among patients with a normal MTWA test, compared with an event rate of 15.6% among the remaining patients with an abnormal MTWA test. The additional data from the present study more than double the published experience of MTWA in this MADIT II subgroup of patients and use all-cause mortality as the end point for a direct comparison with MADIT II (because all-cause mortality was the primary end point in MADIT II). Taken together, the data from our study and the data from The Lancet meta-analysis indicate that MTWA testing is highly effective for identifying patients who will not experience sustained ventricular tachyarrhythmias during follow-up. In addition, the present study not only adds a more representative sample of this population of heart failure patients (because it included patients from 11 geographically distinct centers, including community-based cardiology practices), but also adds data on QRS duration in addition to MTWA, allowing for an analysis of the outcome of patients based on the current CMS guidelines.

A multivariate analysis in MADIT II showed that QRS duration $>120$ ms was an independent predictor of death, with a hazard ratio of 1.90 (95% confidence interval 1.14 to 3.14, $P=0.013$). Establishing a QRS duration $>120$ ms as an independent predictor of death, however, does not ensure that patients with a normal QRS duration are not at increased risk of dying. On the contrary, in MADIT II, patients with QRS duration $\leq 120$ ms had a 2-year mortality rate of 14%, a finding confirmed by our study. Notably, in our study, MTWA classified as high risk those patients with a normal QRS duration who died during follow-up. These data indicate that MTWA is much better than QRS duration for identifying high-risk patients among those with ischemic heart disease and left ventricular ejection fraction $\leq 0.30$. MTWA also is much more effective than QRS duration at identifying low-risk patients who are not likely to benefit from an ICD (Table 2). In our study, there were just 2 deaths within the first 2 years of follow-up among patients with a normal MTWA test.

For years, electrophysiological testing was considered the “gold standard” for identifying high-risk patients who would benefit from implantation of an ICD. Electrophysiological testing was not performed routinely as part of either MADIT II or the present study because of several important limitations: First, in the Multicenter UnSustained Tachycardia Trial (MUSTT), two thirds of patients did not have inducible VT during an electrophysiological study but had a 12% 2-year arrhythmic event rate. This high false-negative rate is a limitation of electrophysiological testing in patients with ischemic cardiomyopathy. Second, electrophysiological testing is invasive, expensive, done in a hospital setting, and therefore cumbersome as a screening tool. These concerns led directly to MADIT II, which attempted to identify high-risk patients by using only a simple noninvasive test, left ventricular ejection fraction. Like the determination of ejection fraction, MTWA can be done routinely in a doctor’s office by using modifications of currently available exercise testing equipment and is relatively inexpensive.

MADIT II unleashed a controversy about selection of patients for ICD prophylaxis. Unquestionably, MADIT II established a survival benefit for prophylactic ICDs in patients with ischemic heart disease and an ejection fraction $\leq 0.30$. However, the absolute risk reduction in MADIT II was 5.6% over an average follow-up of 20 months. Accordingly, 18 ICDs must be implanted to save 1 life, and this modest benefit is offset by ICD-related adverse events. Previous studies demonstrate that ICD therapy decreases quality of life as a result of a variety of problems. In addition, society must bear the economic burden for treating so many patients who will not use their ICDs. It would be ideal to identify a subset of MADIT II–like patients unlikely to experience sustained ventricular tachyarrhythmias to spare them an ICD implantation. The CMS decision to use QRS duration $>120$ ms to identify high-risk patients reduces the fraction who get ICDs to about one third of the total MADIT II group, but it fails to treat a substantial number of patients who would benefit from ICD prophylaxis. If, instead of QRS duration, MTWA testing were used to exclude a low-risk subset of the MADIT II population, about two thirds of patients would get ICD therapy, but those who did not would have minimal risk of experiencing ICD-preventable death. If this strategy were used, among the patients with an abnormal MTWA test, only 7 ICDs would have to be implanted to save 1 life.

**Conclusion**

Compared with QRS duration, an abnormal MTWA test is a stronger predictor of death in patients with ischemic heart disease and left ventricular dysfunction who fit MADIT II criteria. More importantly, MTWA can better identify a group of patients not likely to benefit from ICD therapy.

**Appendix**

The following people participated in this study (asterisks indicate principal investigators).


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National Institutes of Health, Bethesda, Md; a grant from the Doris Duke Charitable Foundation; and a grant from Cambridge Heart, Inc, Bedford, Mass. This article was written with the use of data from version 2.0 of The MTWA in CHF database.

Disclosure
Dr Bloomfield has received research support from Cambridge Heart, Inc, has been an investigator in other clinical trials of T-wave alternans sponsored by Cambridge Heart, Inc, has been an occasional consultant to Cambridge Heart, Inc, and has been on the Speakers Bureau for Cambridge Heart, Inc. Dr Bloomfield does not hold any position with Cambridge Heart, Inc. Dr Bloomfield currently works for Merck Research Laboratories but continues to be an Adjunct Associate Professor of Medicine at Columbia University.

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