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CLINICAL RESEARCH | Clinical Trial

The ABCD (Alternans Before Cardioverter Defibrillator) Trial

Strategies Using T-Wave Alternans to Improve Efficiency of Sudden Cardiac Death Prevention

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Objectives Because risk stratification with electrophysiological study (EPS) improves efficiency but is invasive, we sought to determine whether noninvasive microvolt T-wave alternans (MTWA) testing could identify patients who benefit from implantable cardioverter-defibrillators (ICDs) as well as EPS.

Background Prevention of sudden cardiac death on the basis of left ventricular ejection fraction (LVEF) alone is inefficient, because most ICDs never deliver therapy.

Methods The ABCD (Alternans Before Cardioverter Defibrillator) trial is a multicenter prospective study that enrolled patients with ischemic cardiomyopathy (LVEF ≤0.40) and nonsustained ventricular tachycardia. All patients underwent MTWA and EPS. ICDs were mandated if either test was positive.

Results Of 566 patients followed for a median of 1.9 years, 39 (7.5%) met the primary end point of appropriate ICD discharge or sudden death at 1 year. As hypothesized, primary analysis showed that MTWA achieved 1-year positive (9%) and negative (95%) predictive values that were comparable to EPS (11% and 95%, respectively). In addition, secondary analysis showed that at the pre-specified 1-year end point, event rates were significantly higher in patients with both a positive MTWA-directed strategy (hazard ratio: 2.1, $p = 0.03$) and a positive EPS-directed strategy (hazard ratio: 2.4, $p = 0.007$). Moreover, the event rate in patients with both negative MTWA test and EPS was lower than in those with 2 positive tests (2% vs. 12%; $p = 0.017$).

Conclusions The ABCD study is the first trial to use MTWA to guide prophylactic ICD insertion. Risk stratification strategies using noninvasive MTWA versus invasive EPS are comparable at 1 year and complementary when applied in combination. Strategies employing MTWA, EPS, or both might identify subsets of patients least likely to benefit from ICD insertion. (Study to Compare TWA Test and EPS Test for Predicting Patients at Risk for Life-Threatening Heart Rhythms [ABCD Study]; NCT00187291) (J Am Coll Cardiol 2009;53:471–9) © 2009 by the American College of Cardiology Foundation

Primary prevention trials using risk stratification with electrophysiological study (EPS) to identify patients at high risk for sudden cardiac death (SCD) have demonstrated significant reductions in mortality after implantable cardioverter-defibrillator (ICD) insertion (1,2). Despite the high therapeutic efficiency (4 ICDs/life saved) of this approach, concerns were raised that a negative EPS was not sufficient

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evidence to avoid ICD insertion (3). Moreover, it is impractical to screen all patients at risk for SCD with EPS, because it is invasive, expensive, and requires specialized technology and personnel. Recent randomized trials that selected patients for ICD insertion on the basis of reduced left ventricular ejection fraction (LVEF) alone (4,5) also

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Abbreviations and Acronyms

ATP = antitachycardia pacing
EPS = electrophysiological study
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
MTWA = microvolt T-wave alternans
NPV = negative predictive value
NSVT = nonsustained ventricular tachycardia
PPV = positive predictive value
SCD = sudden cardiac death

demonstrated an improvement in mortality rates but did so with relatively low therapeutic efficiency (15 to 17 ICDs/life saved). Consequently, although guidelines recommend prophylactic ICDs in most patients with LVEF ≤0.35, the majority of inserted ICDs never deliver therapy (6). Concerns regarding device complications, including worsening heart failure, inappropriate shocks, and device recalls, and the impact on health care costs (7) have also prompted a re-examination of this strategy (8).

Electrophysiological markers that, unlike LVEF, more directly reflect arrhythmia substrates might better identify patients who benefit from ICD insertion. In fact, when EPS is used in addition to low LVEF to risk-stratify patients, the cost effectiveness and mortality reduction of ICDs double (9). Recently, microvolt T-wave alternans (MTWA), a subtle beat-to-beat oscillation in the electrocardiogram's T-wave amplitude, which has been linked to an arrhythmogenic mechanism (10), has emerged as a promising noninvasive method for predicting SCD (11–13). Its high negative predictive value (NPV) (12,14) is particularly attractive for use in primary prevention of SCD. Therefore, the ABCD (Alternans Before Cardioverter Defibrillator) trial was designed to test the hypothesis that, in patients with coronary disease and a low LVEF, a noninvasive MTWA test would perform at least as well as an invasive EPS in determining the risk of SCD. In addition, we hypothesized that strategies incorporating a noninvasive MTWA test, either alone or in combination with EPS, would better identify patients likely to benefit from ICD insertion compared with using LVEF alone.

Methods

Patient population. Patients were enrolled from 43 centers in the U.S., Germany, and Israel. Follow-up ended on June 30, 2006. Patients were eligible if they were ≥18 years old, had LVEF ≤0.40 attributable to ischemic heart disease, and had nonsustained ventricular tachycardia (NSVT). Ischemic heart disease was documented by a prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting or by angina with either a positive stress test or a ≥50% occlusion of any coronary artery by angiography. The LVEF was documented within 6 months of enrollment by echocardiography, radionuclide, or contrast ventriculography. The NSVT was documented by 24-h ambulatory recording within 6 months of enrollment and was defined as in prior trials (15). Patients were excluded if they had unstable coronary artery disease, New York Heart Association functional class IV heart failure, prior cardiac arrest, sustained ventricular arrhythmia, or unexplained syncope; were within 28 days of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention; had permanent atrial fibrillation; or were taking an antiarrhythmic drug at baseline. All patients underwent MTWA testing and EPS within 28 days of each other.

MTWA testing and analysis. The MTWA was measured with the spectral method by a graded exercise protocol. High-resolution electrocardiographic leads (Cambridge Heart, Inc., Bedford, Massachusetts) were placed in the standard 12-lead positions and in the X, Y, and Z orthogonal configuration. Beta-blocker drugs were withheld for ≥24 h before the MTWA test. The MTWA tests were interpreted with previously described criteria (16) by an independent core laboratory blinded to clinical outcomes and the EPS results.

The primary analysis compared an "MTWA-directed" strategy to "EPS-directed" strategy in predicting arrhythmic events. The "MTWA-directed" strategy was defined as positive ("high risk") either if the MTWA test was positive or if the MTWA test was indeterminate and the EPS was positive. The "MTWA-directed" strategy was defined as negative ("low risk") if the MTWA test was negative or if the MTWA test was indeterminate and the EPS was negative. This was intended to simulate a strategy where all patients with reduced LVEF are screened noninvasively with an MTWA test and undergo additional risk stratification with EPS only if the MTWA test were indeterminate. Pre-specified secondary analyses were performed with the standard definition of MTWA positivity (excluding from analysis patients with indeterminate results) and a previously validated definition (17) of patients with positive or indeterminate MTWA as "MTWA-abnormal" and those with negative MTWA as "MTWA-normal."

Electrophysiological testing and analysis. The EPS was performed and analyzed with established methods (15). Briefly, programmed ventricular stimulation used single, double, and triple extra-stimuli from 2 right ventricular sites with minimum premature coupling interval of 180 ms. The protocol was terminated if sustained monomorphic ventricular tachycardia or ventricular fibrillation was induced. An independent core laboratory blinded to patient outcomes and to the results of the MTWA tests interpreted all EPS. An EPS was positive (and therefore the "EPS-directed" strategy was positive) if sustained monomorphic ventricular tachycardia was induced at a cycle length faster than 500 ms, lasting at least 30 s or causing hemodynamic compromise, or if ventricular fibrillation or polymorphic ventricular tachycardia was induced by 1 or 2 extra-stimuli. Otherwise, the EPS (and therefore the "EPS-directed" strategy) was negative.

ICD insertion and programming. An ICD insertion was mandated in all patients with either positive MTWA or EPS. Although strongly encouraged, ICD insertion was left to the discretion of the investigators in patients with both

negative MTWA and EPS or an indeterminate MTWA test and a negative EPS. The ICD programming was pre-specified for detection of ventricular tachyarrhythmias (single zone) exceeding 171 beats/min, with "shock only" therapy at maximal outputs.

Follow-up and study end points. The follow-up period began immediately after the MTWA test and the EPS were both completed. Patients were followed at 6-month intervals for up to 2 years. If ICD therapy was delivered, the patient was scheduled as quickly as possible to document the event.

The primary end point was defined a priori as either the first appropriate ICD discharge or SCD (as defined by the Hinkle-Thaler classification) (18), at 1 year of follow-up. An independent events committee, blinded to the results of the MTWA test and EPS, reviewed the clinical history, electrocardiographic, and ICD data to assure appropriate classification of an event as an end point.

Study design and statistical analysis. Because the main objective of the ABCD trial was to prove that a noninvasive strategy of risk stratification for SCD was equal to (rather than superior to) an invasive one, we chose a noninferiority study design. The study was designed to prospectively evaluate whether the positive predictive value (PPV) and NPV of MTWA-directed ICD insertion was noninferior to that of EPS at 1 year of follow-up. The noninferiority cut-point was defined as 10% for the PPV and NPV hypotheses. A 2-step statistical model was employed to estimate the power of the study with bootstrap methods. A 10% loss to follow-up was taken into account for the purpose of calculating sample size. With 538 patients, the power for the primary hypotheses was >95% at the 5% significance level.

Clinical characteristics were compared with the *t* test or Pearson chi-square test as appropriate. The PPV and NPV were calculated on the basis of the Kaplan-Meier 1- and 2-year event rates, and a nonparametric bootstrap method was used to calculate standard errors. Sensitivity and specificity were calculated on the basis of actual event rates. Analyses comparing the event rates in the positive and negative groups were done with the log-rank test or Cox proportional hazards model, and when appropriate, the Cox proportional hazards model employed time-dependent covariates to represent the time cut-off at which the EPS or MTWA test was no longer predictive. A 2-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics. After screening 629 patients, 63 were excluded for protocol violations (Fig. 1). The remaining 566 patients were followed for 1.6 ± 0.6 years (median 1.9 years). The clinical characteristics of patients are shown in Table 1. There were no significant differences between patients with positive and negative EPS or between those with a normal MTWA and abnormal MTWA. The MTWA test was positive, negative, and indeterminate in 46%, 29%, and 25%, respectively. The EPS was positive in 40%. Four hundred ninety-four patients (87%) completed at least 1 year of follow-up, and 362 (64%) completed 2 years of follow-up. Patients were categorized into 6 groups on the basis of EPS and MTWA test results (Table 2). Overall, 87% of the total population received ICDs (495 of 566). Nearly all (97%) patients who were either MTWA+ or EPS+ received ICDs, as required by protocol. ICDs were inserted in 67% of patients with a negative or indeterminate MTWA and a negative EPS.

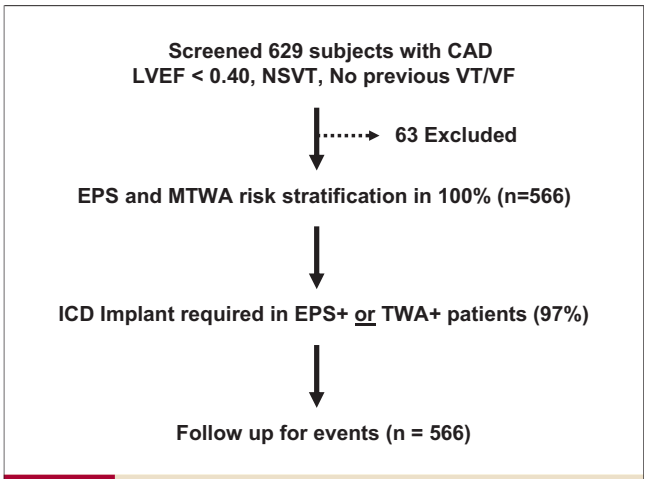

Figure 1 Summary of Study Design

CAD = coronary artery disease; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MTWA = microvolt T-wave alternans; NSVT = nonsustained ventricular tachycardia.

Events. The 1- and 2-year event rates were 7.5% (n = 39) and 14% (n = 65), respectively. Of the 65 patients who met the primary end point, 55 had appropriate ICD discharges (51 shocks and 4 antitachycardia pacing [ATP] therapies) and 10 had SCD (7 of these had inserted ICDs). Although the protocol did not call for ATP therapy, 4 patients were adjudicated by the events committee to have met the primary end point because ATP therapy was delivered for ventricular tachycardia above the rate cutoff specified in the protocol. Therefore, these patients were included in the analyses.

Comparison of noninvasive MTWA with invasive EPS in predicting events. The mean difference in PPV at 1 year between the MTWA- (9.5%) and EPS-directed (11.1%) strategies (Δ in Fig. 2) was 1.6%. Similarly, the mean difference in NPV at 1 year was 0.2% (95.3% for MTWA vs. 95.1% for EPS). Because all differences were within the 10% definition of noninferiority, the MTWA-directed strategy was comparable to an EPS-directed strategy in predicting the occurrence of the primary end point at 1 year (Fig. 2). The sensitivity and specificity of the MTWA-directed strategy was 74% and 44% at 1 year and 66% and 44% at 2 years, respectively. The EPS-directed strategy had

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Table 1 Clinical Characteristics of Patients

Clinical Characteristic	Subjects (n = 566)
Age (yrs)	65.4 ± 10
Sex	
Male	478 (84%)
Female	88 (16%)
NYHA functional class	
I	172 (30%)
II	286 (51%)
III	107 (19%)
Unknown	1 (0.2%)
Mean LVEF	0.28 ± 0.08
Cardiovascular history	
Prior MI	422 (75%)
Prior CABG	325 (57%)
Prior PCI	263 (47%)
LV dysfunction due to CAD	369 (65%)
Angina	120 (21%)
Risk factors	
Diabetes	174 (31%)
Hyperlipidemia	430 (75%)
Hypertension	358 (63%)
Family history of CAD	209 (37%)
Family history of SCD	22 (4%)
Cardiovascular symptoms	
Chronic angina	77 (14%)
Dyspnea at rest	34 (6%)
Dyspnea with exertion	272 (48%)
Palpitations	101 (18%)
None	156 (27%)
Medical therapy	
ACE inhibitor or ARB	501 (89%)
Beta-blocker	488 (86%)
Statin	457 (81%)
Diuretic	345 (61%)
Digoxin	190 (34%)
Calcium-channel blocker	61 (10%)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SCD = sudden cardiac death.

a sensitivity and specificity of 62% and 62% at 1 year and 54% and 63% at 2 years, respectively.

The pre-specified analysis comparing "positive/negative MTWA tests" (i.e., excluding indeterminate tests) with EPS also achieved noninferiority (95% upper confidence limit for Δ was 4.8% and 6.7% for the PPV and 2.8% and 5.7% for the NPV at 1 and 2 years, respectively). Similarly, a pre-specified analysis comparing "abnormal/normal MTWA" with EPS also achieved noninferiority (95% upper confidence limit for Δ was 5.2% and 9.1% for the PPV and 2.8% and 5.9% for the NPV at 1 and 2 years, respectively). Importantly, neither of these definitions depends on EPS to determine "positivity" of the MTWA strategy.

Pre-specified secondary analyses were performed to determine interactions between MTWA and EPS in predicting events. As shown in Figure 3, many (55%) patients had discordant test results. Importantly, the event rate in patients with 2 normal tests was approximately 3-fold lower than in patients with 1 abnormal test and approximately 6-fold lower than patients with 2 abnormal tests, suggesting that the 2 tests were complementary in predicting outcomes (Fig. 3). Because 33% of patients with both normal EPS and a normal MTWA test did not receive an ICD, it is possible that the absence of ICDs could have reduced detection of events in this subgroup of patients. Therefore, data were reanalyzed after excluding patients without ICDs. The 1-year event rate remained low (3.2%) in the MTWA-normal/EPS-negative group, reaffirming that the predictive value of risk stratification was not substantially affected by variations in ICD use between groups.

The Kaplan-Meier event rates predicted by EPS and MTWA are shown in Figure 4. Time-dependent hazard ratios (HRs) (where HRs were estimated separately for below or above the stated time cutoff) are plotted with their confidence intervals as insets. Statistically significant HRs ($p < 0.05$) are indicated by asterisks. The EPS was a significant predictor of events starting at 9 months and for the remainder of the follow-up period (Fig. 4A), with HRs consistently in the 2 to 3 range. In contrast, MTWA, whether with the MTWA-directed or MTWA-normal/abnormal definitions (Figs. 4B and 4C), was predictive of clinical outcomes earlier (at 6 months) than EPS but not later in the follow-up period (i.e., no longer predictive by 12 to 15 months).

Table 2 Actuarial Event Rates by Group Assignment

Group Assignment	Subjects	Subjects With ICD Inserted	12-Month Event Rate (Number of Events)	24-Month Event Rate (Number of Events)
A: MTWA+/EPS−	166	153	6.5% (10)	12.0% (17)
B: MTWA−/EPS+	66	66	7.8% (5)	15.3% (9)
C: MTWA+/EPS+	94	94	11.1% (10)	15.7% (13)
D: MTWA−/EPS−	99	68	2.3% (2)	10.1% (7)
E: MTWA (Ind)/EPS+	62	62	14.8% (7)	22.9% (13)
F: MTWA (Ind)/EPS−	79	52	4.6% (3)	11.0% (6)
Total	566	495	7.5% (39)	14.0% (65)

EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; Ind = indeterminate; MTWA = microvolt T-wave alternans.

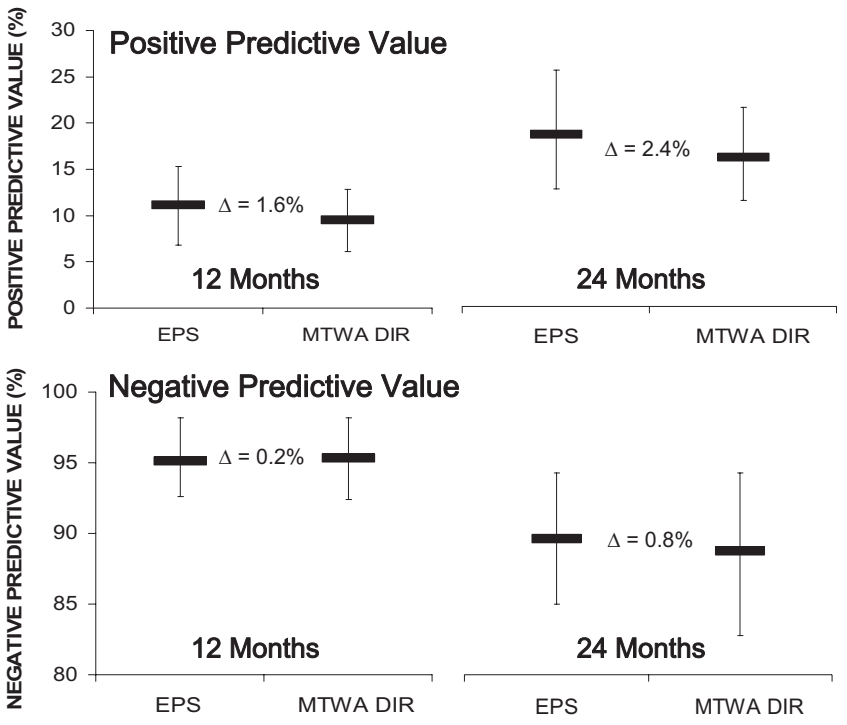

Figure 2 **Comparison Between PPV and NPV**

Comparison between positive predictive value (PPV) **(top panels)** and negative predictive value (NPV) **(bottom panels)** of EPS and MTWA-directed ICD insertion (MTWA DIR) at 12 months and 24 months of follow-up (mean **[solid bar]** and 95% confidence intervals **[error bars]** are shown; Δ = mean difference between EPS and MTWA DIR). The 95% upper confidence limit for the difference in PPV was 4.2% at 1 year and 5.8% at 2 years and, for the NPV, 2.1% at 1 year and 4.3% at 2 years. Abbreviations as in Figure 1.

Discussion

The ABCD trial provides a unique opportunity for comparing risk stratification strategies in a relevant and large cohort of patients. We found that ICD insertion directed by noninvasive MTWA testing is comparable to one guided by EPS in predicting the risk of ventricular tachyarrhythmias or SCD in patients with coronary artery disease, LVEF ≤0.40, and NSVT. In addition, by using the tests in a complementary fashion, the efficiency of SCD prevention is increased further.

Initial recommendations for ICD insertion for primary prevention of SCD included NSVT and inducibility at EPS (1,2). Such a strategy identifies a high-risk group of patients, but it is costly, invasive, and hence impractical for broad-based screening. Although EPS is no longer generally used for this purpose, excellent data show that the cost-effectiveness of primary prevention of SCD and reduction in total mortality are doubled if risk stratification is used to guide ICD insertion (9,19). Therefore, despite the evolution in practice standards, the results of the ABCD trial remain highly relevant to contemporary issues regarding optimal selection of patients for primary prevention of SCD. In fact, the comparable predictive accuracy of noninvasive MTWA testing carries significant clinical importance, because this test can obviously be applied more broadly in clinical practice than EPS.

In support of the primary hypothesis of the ABCD trial, the PPV and NPV of an MTWA-directed strategy compared with EPS were essentially identical. The NPV of the MTWA-directed strategy was 95% at 1 year (Fig. 2), similar to prior MTWA trials (13,20). This is most important, because the clinically relevant question today is who should not receive an ICD (i.e., who is at low enough risk where the risk of ICD insertion might outweigh its benefit). The PPV of MTWA observed in the ABCD trial was somewhat lower than expected compared with previous trials (12,13). One explanation is that beta-blocker therapy was withheld before MTWA testing, possibly converting some normal MTWA tests to abnormal (21) in patients who did not experience events.

The event rates observed in ABCD were low and demonstrate that, even in a population that for the most part satisfies current indications for ICD insertion, the absolute risk of a ventricular tachyarrhythmic event is low. On the basis of the MADIT 1 (Multicenter Automatic Defibrillator Trial) and MUSTT (Multicenter Unsustained Tachycardia Trial) annualized ICD shock rates (30% and 37%, respectively), we estimated that the overall event rate in the ABCD trial would be approximately 25% at 1 year.

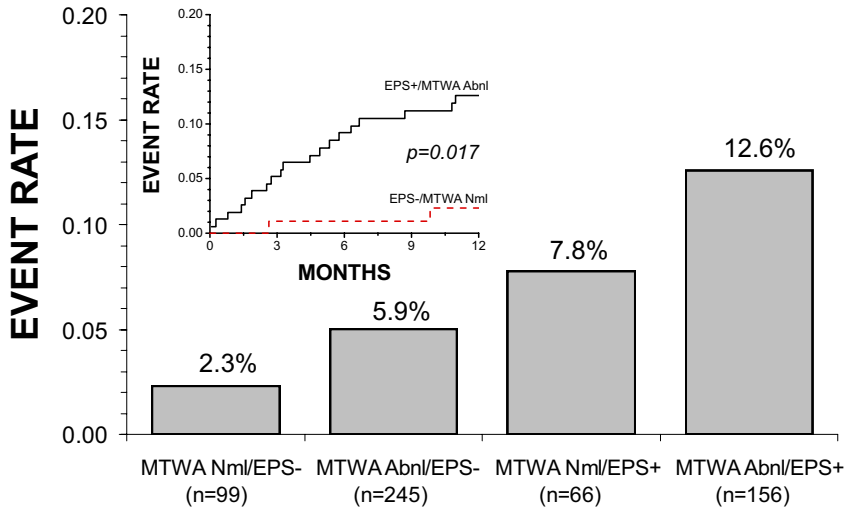

Figure 3 **Combined Effect of MTWA and EPS Risk Stratification on 1-Year Actuarial Event Rates**

Patients having both normal MTWA tests and negative EPS (MTWA Nml/EPS−) exhibited lowest event rate, whereas patients having both positive EPS and abnormal MTWA tests (MTWA Abnl/EPS+) exhibited the highest event rate. Patients with discordant risk stratification testing (either MTWA Abnl/EPS− or MTWA Nml/EPS+) exhibited intermediate event rates, indicating a synergistic progression of risk with combined risk stratification. The **inset** compares Kaplan-Meier event rates between the groups with 2 negative versus 2 positive risk stratification tests. Abnl = abnormal; Nml = normal; other abbreviations as in Figure 1.

The actual overall event rate for the end point of ICD discharges or SCD was only 7.5% and 14% at 1 and 2 years, respectively. The low event rate reduced the power of the study to prove the primary hypothesis, because it could have masked the detection of differences in PPV and NPV between EPS and MTWA. This is an important limitation of the ABCD trial and other trials designed to show noninferiority. Unfortunately, the requirements for demonstrating noninferiority of new diagnostic tests, especially in overlapping groups of patients, are challenging and the focus of considerable debate in the published statistical literature.

Although not a primary end point of the ABCD trial, appropriate ICD discharges or total mortality were still lower than expected (11% and 19%, respectively) but comparable to those of recently published studies on MTWA. More recently, the MADIT II (4) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (5) studies

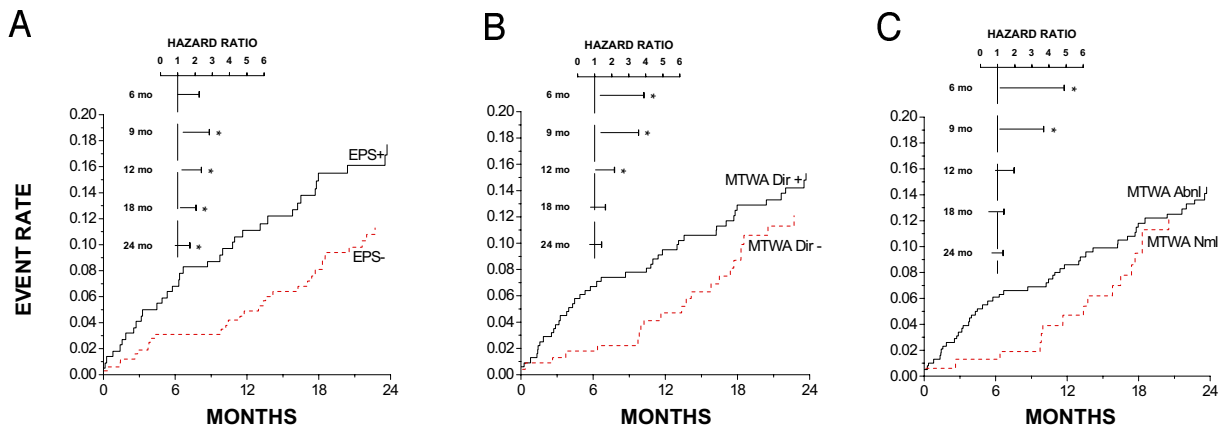

Figure 4 **Kaplan-Meier Plots and Time-Dependent Hazard Ratios**

Kaplan-Meier plots and time-dependent hazard ratios for EPS **(A)**, MTWA-directed insertion **(B)**, and MTWA normal versus abnormal **(C)**. Statistically significant hazard ratios (estimated for below or above the stated cutoff time) are depicted by **asterisks**. Event rates were as follows: n = 25 for <6 months; n = 14 for 6 to 12 months; n = 16 for 12 to 18 months; n = 10 for >18 months. Note that EPS is a significant marker of events from 9 months onward, whereas MTWA is predictive earlier (6 months) but loses significance at 15 **(B)** or 12 **(C)** months of follow-up.

demonstrated annualized appropriate ICD therapy rates of 12% and 7.3%, respectively. The event rates of the ABCD trial are in close agreement with the SCD-HeFT study, because in both trials ATP was programmed off per protocol, as opposed to MADIT II, where 40% of all ICD discharges were related to ATP.

A majority of patients (55%) manifested discordant MTWA and EPS results, suggesting that the 2 tests might assess different components of the arrhythmogenic substrate. Interestingly, the 2 tests were complementary in predicting risk (Fig. 3), because subjects testing negative for both markers were at considerably lower risk than those testing positive by 1 marker or by both markers. It is noteworthy that the 1-year event rate of patients with negative MTWA and negative EPS was only 2.3% and remained low (3.2%) even after excluding from analysis the 33% of these patients who did not receive ICDs. These data suggest that multiple risk markers used in combination might improve our ability to identify high- and low-risk patients and improve the therapeutic efficiency of SCD prevention.

An aim of the ABCD trial was to determine whether strategies incorporating MTWA, alone or in combination with EPS—in addition to low LVEF—would enable physicians to better identify patients at the highest and lowest risk of SCD. Although the definitive answer to this question awaits randomized clinical trials, a strength of the ABCD trial is that all patients underwent screening with both MTWA and EPS. This provided a unique opportunity to compare the effectiveness of these markers in identifying candidates for primary prevention of SCD. Table 3 shows the outcomes derived from the 1-year event rate, had several potential clinical strategies been applied to the ABCD trial population. Unique insights into the risk and benefit of each potential strategy are provided. In agreement with previous ICD trials, the ABCD trial demonstrated that a strategy of inserting ICDs on the basis of a low LVEF alone results in the vast majority (93%) of ICD recipients not receiving therapy after 1 year (Table 3, "LVEF alone" strategy). This is relevant to current clinical practice, because 86% of ABCD patients had an LVEF ≤0.35 and therefore qualify for ICD insertion on the basis of current indications.

By contrast, risk-stratifying all ABCD patients by EPS alone (Table 3, "EPS alone" strategy) would have resulted in 344 patients not receiving an ICD (60% with a normal EPS). After 1 year of follow-up, such a strategy would have improved therapeutic efficiency (9 ICDs inserted to save 1 life compared with 15 with "LVEF alone" strategy), but 15 potentially untreated patients would have experienced a primary end point event. A strategy based on an "abnormal" MTWA alone (i.e., inserting ICDs in patients with a positive or indeterminate MTWA test) would have resulted in 165 patients not receiving an ICD (29% with a normal MTWA test). This strategy would also improve therapeutic efficiency compared with the "LVEF alone" strategy (13 vs. 15 ICDs inserted to save 1 life), whereas only 7 potentially untreated patients would have experienced a primary end point event at 1 year (Table 3, "MTWA normal/abnormal" strategy). Because of the complementary prognostic value of EPS and MTWA (Fig. 3), combining the 2 tests can further enhance risk stratification. For example, if one applied the "MTWA-directed" strategy to guide ICD insertion (Table 3, "MTWA-directed" strategy), 244 patients (43%) would forego ICD insertion, and 10 potentially untreated patients would experience a primary end point event at 1 year. With such a strategy, only 25% of patients would undergo an EPS (those with an indeterminate MTWA test) and 11 ICDs would be inserted to save 1 life. Finally, if one wanted to adopt the most conservative and safest strategy of foregoing ICD insertion only if both MTWA and EPS were normal, one could insert ICDs in all MTWA-abnormal patients and go on to an EPS in the 29% of patients with a normal MTWA to guide ICD insertion (Table 3, "EPS/MTWA combined" strategy). With such a strategy, one would forego ICD insertion in only 99 patients (17%) and insert 13 ICDs to save 1 life, whereas only 2 untreated patients would experience an event.

The preceding discussion is based on the assumption that ICDs are always effective in preventing SCD and that ICD insertion has no associated risk. However, 7 of the 10 SCD events occurred in patients "protected" by an ICD, suggesting that not all SCD is preventable. The acceptable threshold to determine which patients should be treated as opposed to those who need treatment is ultimately a societal

Table 3 Comparison of the Performance of Various Potential Risk Stratification Strategies Derived From the Pre-Specified 1-Year Primary End Point Event Rate (n = 39) of the ABCD Population (n = 566)

	Patients Undergoing Risk Stratification (%)		Potential Number of Patients With ICDs		Potential Number of Patients Without ICDs	
Risk Stratification Strategy	MTWA	EPS	Event+	Event−	Event+	Event−
EPS alone	0%	100%	24	198	15	329
MTWA-directed	100%	25%	29	293	10	234
MTWA normal/abnormal alone	100%	0%	32	369	7	158
EPS and MTWA combined	100%	29%	37	430	2	97
LVEF alone	None	None	39	527	None	None

"MTWA-Directed": all patients would undergo an MTWA test and go on to EPS only if MTWA was indeterminate; "EPS and MTWA combined": all patients would undergo MTWA test and go on to EPS only if the MTWA was normal (see text for discussion).

Abbreviations as in Tables 1 and 2.

decision. In the end, the clinician must consider which strategy is most appropriate for each individual patient, depending on comorbidities, potential risk of ICD insertion itself, willingness of the patient to undergo insertion, and the risk of SCD weighed against the competing risk of nonsudden or noncardiac death.

Our results also show that the predictive values of EPS and MTWA were time-dependent. As shown in Figure 4, the Kaplan-Meier event rates converge and the HRs decrease over time (particularly after 1 year) for MTWA and, to a lesser degree, for EPS. In fact, the NPV of MTWA at 2 years is significantly reduced. Because arrhythmic risk changes over time due to changes in the arrhythmogenic substrate, it is not surprising that the predictive accuracy of a risk marker would diminish over time. Although unique and interesting, the time-varying prediction of outcomes needs to be interpreted with caution. The trial was not powered to assess end points beyond 1 year, because only 362 of 566 patients (64%) reached the 2-year follow-up point. Moreover, the apparent loss of predictive value of MTWA beyond 1 year was not observed in other trials (12), which relied on mortality rather than on ICD-related end points, raising concerns that the use of surrogate end points rather than the MTWA's ability to track relevant end points might explain the lack of correlation over longer time periods. Nonetheless, these data suggest that sequential profiling of arrhythmic risk over time might be appropriate and, specifically, that MTWA testing and/or other risk stratifiers might need to be repeated at regular intervals.

Limitations of the trial. The ABCD trial patients were selected on the basis of LVEF <0.40, raising the possibility that these patients might have been at somewhat lower risk than those currently selected for ICD insertion on the basis of LVEF ≤0.35 (4,5). Moreover, because heart rate must be elevated gradually to measure MTWA, exclusion of patients with atrial fibrillation, chronotropic incompetence, and intolerance to exercise could have further reduced the event rate in our population. However, the LVEF selection criteria probably did not substantially lower risk, because only 77 patients had LVEF >0.35, and other factors such as the requirement for NSVT might actually have increased the population's risk. The comparable event rates measured in the ABCD trial and in earlier primary prevention trials suggest that the ABCD trial patients possessed a similar risk profile as the patients in those trials.

The ABCD trial used a combined end point of "ICD discharge or SCD," which might have overestimated the actual SCD rate by 2-fold (22) compared with studies using total mortality as an end point. Because most patients (87%) received ICDs (i.e., a very sensitive detector of events) programmed in a consistent fashion, one can argue that by overestimating the number of SCD events, the ABCD trial underestimated the potential NPV that could be achieved by MTWA testing. This highlights an important limitation of surrogate end points derived from ICDs. These arguments serve to emphasize the importance of future randomized risk stratification trials using mortality end points.

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Key Words: coronary disease ■ electrophysiological study ■ sudden death ■ T-wave alternans.

APPENDIX

For participants in the ABCD trial, please see the online version of this article.