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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