Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 19, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.09.004

EXPEDITED PUBLICATION

Prognostic Value of T-Wave Alternans in Patients With Heart Failure Due to Nonischemic Cardiomyopathy

Results of the ALPHA Study

Jorge A. Salerno-Uriarte, MD,* Gaetano M. De Ferrari, MD,† Catherine Klersy, MD,‡ Roberto F. E. Pedretti, MD,§ Massimo Tritto, MD,‖ Luciano Sallusti, BS,¶ Luigi Libero, MD,# Giacinto Pettinati, MD,** Giulio Molon, MD,†† Antonio Curnis, MD,‡‡ Eraldo Occhetta, MD,§§ Fabrizio Morandi, MD,* Paolo Ferrero, MD,# Francesco Accardi, BS,¶ for the ALPHA Study Group Investigators

Varese, Pavia, Tradate, Castellanza, Milano, Torino, Casarano, Negrar, Brescia, and Novara, Italy

Objectives The aim of this study was to assess the prognostic value of T-wave alternans (TWA) in New York Heart Association (NYHA) functional class II/III patients with nonischemic cardiomyopathy and left ventricular ejection fraction (LVEF) ≤40%.

Background There is a strong need to identify reliable risk stratifiers among heart failure candidates for implantable cardioverter-defibrillator (ICD) prophylaxis. T-wave alternans may identify low-risk subjects among post-myocardial infarction patients with depressed LVEF, but its predictive role in nonischemic cardiomyopathy is unclear.

Methods Four hundred forty-six patients were enrolled and followed up for 18 to 24 months. The primary end point was the combination of cardiac death + life-threatening arrhythmias; secondary end points were total mortality and the combination of arrhythmic death + life-threatening arrhythmias.

Results Patients with abnormal TWA (65%) compared with normal TWA (35%) tests were older (60 ± 13 years vs. 57 ± 12 years), were more frequently in NYHA functional class III (22% vs. 19%), and had a modestly lower LVEF (29 ± 7% vs. 31 ± 7%). Primary end point rates in patients with abnormal and normal TWA tests were 6.5% (95% confidence interval [CI] 4.5% to 9.4%) and 1.6% (95% CI 0.6% to 4.4%), respectively. Unadjusted and adjusted hazard ratios were 4.0 (95% CI 1.4% to 11.4%; p = 0.002) and 3.2 (95% CI 1.1% to 9.2%; p = 0.013), respectively. Hazard ratios for total mortality and for arrhythmic death + life-threatening arrhythmias were 4.6 (p = 0.002) and 5.5 (p = 0.004), respectively; 18-month negative predictive values for the 3 end points ranged between 97.3% and 98.6%.

Conclusions Among NYHA functional class II/III nonischemic cardiomyopathy patients, an abnormal TWA test is associated with a 4-fold higher risk of cardiac death and life-threatening arrhythmias. Patients with normal TWA tests have a very good prognosis and are likely to benefit little from ICD therapy. (J Am Coll Cardiol 2007;50:000–000)

Patients with heart failure still have a high mortality rate, with sudden cardiac death being 1 of the leading causes of death (1). Primary prophylaxis with implantable

See page xxxx

From the *Dipartimento di Scienze Cardiovascolari, Università degli Studi dell'Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy; †Dipartimento di Cardiologia; and ‡Servizio di Biometria ed Epidemiologia Clinica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; §Divisione di Cardiologia, IRCCS Fondazione Salvatore Maugeri, Istituto Scientifico, Tradate, Italy; ‖Laboratorio di Elettrofisiologia, Dipartimento di Cardiologia, Istituto Clinico Mater Domini, Castellanza, Italy; ¶Dipartimento Clinico, Guidant Italia (Boston Scientific Corporation), Milano, Italy; #Divisione Universitaria di Cardiologia, Università degli Studi di Torino, Azienda Ospedaliera San Giovanni Battista, Torino, Italy; **Divisione di Cardiologia, Presidio Ospedaliero F. Ferrari, Casarano, Italy; ††Divisione di Cardiologia, Ospedale Sacro Cuore, Negrar, Italy; ‡‡Unità Operativa di Cardiologia, Università degli Studi di Brescia, Spedali Civili, Brescia, Italy; and the §§1° Divisione di Cardiologia, Università degli Studi del Piemonte Orientale, Ospedale Maggiore, Novara, Italy. See the Online Appendix for a complete list of the ALPHA Study Group Investigators. Luciano Sallusti and Francesco Accardi are employees of Guidant Italy (Boston Scientific Corporation). This study was sponsored by Guidant Italy (Boston Scientific Corporation). The main data were presented at the Late-Breaking Clinical Trial Session I of the American College of Cardiology 56th Scientific Session, March 25, 2007, New Orleans, Louisiana.

Manuscript received May 15, 2007; revised manuscript received August 9, 2007, accepted September 7, 2007.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI = confidence interval
CRT = cardiac resynchronization therapy
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
NPV = negative predictive value
NYHA = New York Heart Association
PPV = positive predictive value
TWA = T-wave alternans
VF = ventricular fibrillation
VT = ventricular tachycardia

cardioverter-defibrillators (ICDs) in patients with heart failure and left ventricular ejection fraction (LVEF) <35% has significantly improved survival (2). However, the absolute benefit is relatively small (7.2% over 5 years). Because of the psychologic and economic burden as well as the potential for side effects, controversies exist concerning an approach of widespread primary prophylaxis with ICDs (3). Therefore, there is a need for better risk stratifiers (4), as also recognized by the Centers for Medicare and Medicaid Services (CMS) (5). A marker with a high negative predictive value (NPV) would be particularly useful to identify patients who are unlikely to benefit from ICD prophylaxis despite the presence of heart failure and left ventricular dysfunction.

Among patients with prior myocardial infarction and LVEF ≤30%, T-wave alternans (TWA) may identify patients who are likely and not likely to benefit from ICD therapy (6). There are limited and conflicting data regarding the prognostic value of TWA in patients with heart failure due to nonischemic cardiomyopathy (7–13), a setting in which the search for reliable risk stratifiers has been particularly frustrating (14,15).

Accordingly, we designed and conducted a multicenter, prospective, longitudinal, observational study to assess the capability of TWA to predict cardiac death and life-threatening arrhythmias among consecutive patients with New York Heart Association (NYHA) functional class II and III heart failure due to nonischemic cardiomyopathy and LVEF ≤40%.

Methods

Patient selection. Every patient seen at the heart failure clinics of the 9 participating Italian hospitals during the period of enrollment was screened for eligibility for the study. The design of the study has been previously published (16). The study was approved by the ethical committees of each participating center. Overall, 3,513 patients were screened and constitute the ALPHA (T-Wave Alternans in Patients With Heart Failure) registry, a source of potentially useful epidemiologic data (17). Among these patients, main noneligibility criteria (more than 1 could be present) were: other etiology, mainly ischemic, of the cardiomyopathy (n = 1,608); presence of atrial fibrillation or flutter at the time of screening (n = 778); LVEF >40% (n = 719); NYHA functional class I or IV (n = 545); age <18 or >80 years (n = 134); the presence of an implanted pacemaker or ICD (n = 373); and a history of cardiac arrest, sustained ventricular tachycardia, or syncope, or a clear-cut indication for ICD implantation (mostly class I indications following the guidelines active at the time of patient enrollment, such as secondary prevention) (n = 65). Logistical reasons prevented enrollment 42 patients, and 46 refused written informed consent to the study. Compared with enrolled patients, eligible but not enrolled patients (n = 88) had the same age (59.2 ± 12.7 years), LVEF (29.3 ± 6.3%), prevalence of NYHA functional class III (20%), and QRS interval duration (123.7 ± 30.5 ms).

Overall, 446 patients (349 male, 97 female) entered the study. Three hundred twenty-six patients had idiopathic dilated cardiomyopathy, 72 had a hypertensive etiology, 9 had a valvular etiology, and 39 had other etiologies. Coronary angiography was highly recommended to establish the diagnosis of nonischemic cardiomyopathy, with the exception of young patients with familiar/genetic cardiomyopathy, and was available for almost every patient. The first patient was enrolled in June 2001, the last in July 2004. Each patient's medical history was recorded on enrollment; physical examination, echocardiographic evaluation, 24-h Holter monitoring, assessment of quality of life by means of the Minnesota Living With Heart Failure questionnaire, and cardiopulmonary exercise test with measurement of peak O_2 uptake were carried out in addition to TWA testing.

TWA testing. Patients performed the TWA exercise test while taking their regular medications, including beta-blockers. The exercise was performed on a bicycle in 83% of cases and on a treadmill in 17% of cases.

Careful skin preparation and high-resolution electrodes were used to minimize noise. Electrocardiographic leads were placed at the standard 12-lead positions and in an orthogonal X, Y, and Z configuration. Measurements were made with a CH2000 or Heartwave system (Cambridge Heart, Bedford, Massachusetts) and used a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude (18). The TWA test was automatically interpreted within the CH2000 or Heartwave system by the Alternans Report Classifier (version D10 used in all centers; Cambridge Heart) and classified according to previously described criteria (19). This classification was done locally in each center. An expert in TWA classification was present during the first 5 tests in each center and was available thereafter as external support to facilitate the learning curve and to ensure uniformity throughout the different centers. The expert was always blinded to patient characteristics. The original protocol designed in the year 2000 planned to compare positive and negative TWA tests. However, studies published during the enrollment phase of the present trial revealed that positive and indeterminate TWA tests have similar event rates, suggesting that they should be grouped together as abnormal tests and be

compared with normal (negative) TWA tests (19–21). Therefore, before the study was closed, the steering committee decided to make all comparisons between patients with abnormal and patients with normal TWA tests, an approach that has been adopted in all recent studies (22,23).

Follow-up. Patients were evaluated every 6 months up to 18 months, as planned in the protocol of the study. Follow-up could be extended to 24 months according to investigator willingness and was censored at the first event recorded.

End points. All end points were adjudicated by an events committee that was unaware of the TWA test results. Deaths were classified according to the Hinkle-Thaler (24) system, as modified in the MUSTT (Multicenter Unsustained Tachycardia Trial) study (25).

The prognostic role of TWA was assessed for the combined primary end point of cardiac death and life-threatening ventricular arrhythmias (ventricular fibrillation, resuscitated cardiac arrest, and sustained ventricular tachycardia either symptomatic or revealed by a subsequently implanted device).

The prognostic role of TWA was also assessed for the following secondary end points: 1) total mortality; 2) a combined end point of arrhythmic death and life-threatening arrhythmias; and 3) hospitalization rate.

Statistical analysis. Data were described as mean and standard deviation for continuous variables and as count and percentage for categoric variables. Median follow-up and its 25th to 75th percentile (interquartile) range was calculated with the inverse Kaplan-Meier method (26). Baseline characteristics (Table 1) were compared between TWA groups by means of general linear models.

For each TWA group, we computed the rates of events per 100 person-years, together with their 95% confidence intervals (CIs) and the Kaplan-Meier cumulative event-free survival. We used the log-rank test to compare groups and fitted a Cox model to estimate hazard ratios (HRs) and 95% CIs for the prognostic role of TWA. We computed the unadjusted HR and the HR adjusted for age, gender, NYHA functional class, and LVEF in a multivariable analysis. The proportional hazards assumption was tested by means of Schoenfeld residuals (27). The assumption was satisfied in all cases ($p > 0.05$). To account for all of the baseline characteristics differing between TWA groups with a p value of 0.10 or less (age; gender; NYHA functional class; LVEF; left ventricular end-systolic volume; use of beta-blockers, angiotensin-converting enzyme [ACE] inhibitors aldosterone antagonists, or digoxin; QRS duration >120 ms; presence of left bundle branch block; and quality of life), data reduction was performed by means of factor analysis (using the principal components method), and the first 3 factors were included in the model together with TWA. We calculated the NPV and positive predictive value (PPV) of the TWA test for the prediction of events at 12 and 18 months. We compared rates of hospitalization by means of a Poisson model for counts and computed the incidence rate ratios and 95% CI to quantify the association. All tests were 2 sided. A p value of <0.05 was used for statistical significance. Stata 9 (StataCorp, College Station, Texas) was used for computation.

Results

Baseline characteristics. Among the 446 patients enrolled, 154 (34.6%) had negative, 200 (44.8%) positive, and 92 (20.6%) indeterminate TWA tests. Causes of indeterminate tests included frequent ventricular arrhythmia (13%), noise (5%), and inadequate heart rate levels (5%). In case of a heart rate level lower than needed in the first test, the suggestion was made to perform a second TWA test to reduce the number of indeterminate tests. Baseline characteristics of the overall population and of the 154 normal and 292 abnormal (positive + indeterminate) TWA patients are summarized in Table 1. Patients with abnormal TWA tests were 2.5 years older, had a worse quality of life, and were more frequently in NYHA functional class III. They also showed larger left chamber sizes and lower LVEF. However, the cardiopulmonary test, available in 70% of the cohort, yielded comparable results in the 2 groups for both maximal exercise O_2 consumption and Weber classification. Concerning pharmacologic therapy, digitalis and ACE inhibitors were administered more frequently in the abnormal TWA test group.

Events during follow-up. Follow-up was completed in 100% of the patients. The main events occurring during the median follow-up of 19 months (interquartile range 18 to 20 months) are listed in Table 2.

Table 3 shows the rates of the end points occurring in the overall population and the HRs associated with an abnormal TWA test, as well as the NPV and PPV of the test. The primary end point (cardiac death + life-threatening arrhythmia) was reached in 29 of 292 patients (9.9%) from the abnormal and 4 of 154 patients (2.6%) from the normal TWA test group (Fig. 1). In the Cox model, the unadjusted HR for the primary end point was 4.01 (95% CI 1.41 to 11.41; $p = 0.002$). In a multivariable analysis, the HR adjusted for age, gender, NYHA functional class, and LVEF was 3.21 (95% CI 1.12 to 9.22; $p = 0.013$) and the HR adjusted for digoxin, ACE inhibitor, aldosterone antagonist, and beta-blocker treatment was 4.23 (95% CI 1.46 to 12.21; $p = 0.0018$). In the data reduction model that accounted for: age; gender; NYHA functional class; LVEF; left ventricular end-systolic volume; use of beta-blockers, ACE inhibitors, aldosterone antagonists, or digoxin; QRS duration >120 ms; presence of left bundle branch block; and quality of life, the HR for TWA was 3.98 (95% CI 1.20 to 13.27; $p = 0.008$).

The NPV of a normal TWA test at 12 and 18 months exceeded 97% (Table 3). A significantly increased risk was also found when comparing patients with a positive versus patients with a negative TWA test, with an HR of 3.16 (95% CI 1.06 to 9.45; $p = 0.023$).

Table 1 Baseline Characteristics According to TWA Testing

Characteristic	Overall Population (n = 446)	Abnormal TWA Test (n = 292)	Normal TWA Test (n = 154)	p Value
General				
Age (yrs)	59.0 (12.5)	59.9 (12.7)	57.4 (12.1)	0.042
Gender (male)	349 (78.2%)	229 (78.4%)	120 (77.9%)	0.904
HF duration (yrs)	4.0 (4.3)	4.2 (4.5)	3.5 (3.8)	0.375
NYHA functional class III	75 (16.2%)	57 (19.2%)	18 (11.7%)	0.045
Hb (g/dl)	14.0 (1.5)	14.0 (1.5)	14.0 (1.6)	0.871
Plt (10^3/l)	216.1 (55.8)	216.6 (56.3)	215.2 (55.0)	0.805
Na (mEq/l)	139.9 (3.4)	139.8 (3.75)	140.0 (2.7)	0.453
K (mEq/l)	4.2 (0.4)	4.24 (0.46)	4.25 (0.44)	0.779
Creatinine (mg/dl)	1.03 (0.33)	1.02 (0.34)	1.04 (0.30)	0.581
BMI (kg/m^2)	26.7 (4.5)	26.6 (4.6)	27.0 (4.5)	0.404
SBP (mm Hg)	124.5 (16.8)	124.1 (16.7)	125.2 (16.9)	0.503
DBP (mm Hg)	76.0 (12.8)	77.4 (8.7)	78.4 (9.1)	0.299
Minnesota QOL score	20.9 (16.1)	22.9 (17.1)	17.0 (13.1)	<0.001
History of				
Stroke	10 (2.3%)	9 (3.1%)	1 (0.6%)	0.176
Peripheral artery disease	11 (2.6%)	5 (1.9%)	6 (4.0%)	0.210
Hypertension	168 (38.4%)	102 (35.8%)	66 (43.1%)	0.149
Diabetes	57 (13.0%)	39 (13.6%)	18 (11.8%)	0.657
Electrocardiogram				
Heart rate (beats/min)	74.1 (13.9)	74.4 (14.6)	73.7 (12.5)	0.576
IVCD				0.036
No	248 (55.6%)	154 (52.7%)	94 (61.0%)	
LBBB	190 (42.6%)	130 (44.5%)	60 (39.0%)	
RBBB	8 (1.8%)	8 (2.7%)	0 (0%)	
QRS (ms)	124.9 (33.4)	126.8 (33.3)	121.2 (33.6)	0.090
Echocardiographic findings				
LVEDD (mm)	66.7 (8.1)	67.9 (8.0)	64.6 (7.9)	<0.001
LVESD (mm)	55.1 (9.6)	56.8 (9.2)	51.9 (9.6)	<0.001
LA (mm)	44.4 (7.1)	45.5 (7.1)	42.4 (6.9)	<0.001
LVEDV (ml)	208.7 (79.0)	217.7 (79.3)	193.1 (76.2)	0.004
LVESV (ml)	149.2 (66.9)	157.6 (66.4)	134.3 (65.5)	0.001
LVEF (%)	29.5 (7.1)	28.6 (6.9)	31.3 (7.29)	<0.001
Cardiopulmonary test (n = 311)				
Peak VO_2 (ml/kg/min)	16.8 (5.8)	16.7 (5.7)	17.1 (5.9)	0.519
Weber				0.253
1	87 (27.9%)	60 (29.0)	27 (26.0%)	
2	96 (30.9%)	57 (27.5%)	39 (37.5%)	
3	101 (32.5%)	73 (35.3%)	28 (26.9%)	
4	27 (8.7%)	17 (8.2%)	10 (9.6%)	
Treatment				
ACE inhibitors	381 (85.4%)	258 (88.4%)	123 (79.9%)	0.023
Beta-blockers	357 (80.0%)	232 (79.4%)	125 (81.2%)	0.710
Digitalis	168 (37.7%)	123 (42.1%)	45 (29.2%)	0.008
Diuretics	394 (88.3%)	263 (90.1)	131 (85.1%)	0.123
Aldosterone antagonists	159 (36.7%)	103 (35.3%)	56 (36.4%)	0.836
Antiarrhythmics	88 (19.7%)	56 (19.2%)	32 (20.8%)	0.708

Values in parentheses are standard deviations for continuous variables or percentages for discrete variables.

ACE = angiotensin-converting enzyme; BMI = body mass index; DBP = diastolic blood pressure; Hb = hemoglobin; HF = heart failure; IVCD = intraventricular conduction delay; LA = left atrium; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; Plt = platelets; QOL = Living With Heart Failure quality of life questionnaire; RBBB = right bundle branch block; SBP = systolic blood pressure; TWA = T-wave alternans; VO_2 = oxygen uptake.

At the time of screening, patients were evaluated for eligibility for a biventricular device. The indication for a biventricular device was given independently, in most cases before the TWA test, and was based on the presence of advanced NYHA functional class and wide QRS. Overall, 31 patients were considered to be candidates for cardiac

Table 2 Events During Follow-Up

Event	Overall Population (n = 446)	Normal TWA Test (n = 154)	Abnormal TWA Test (n = 292)
Total mortality	28 (6.3%)	3 (1.9%)	25 (8.6%)
Cardiac death	18 (4.0%)	2 (1.3%)	16 (5.5%)
Sudden death	7 (1.6%)	0	7 (2.4%)
Symptomatic sustained VT or VF	11 (2.5%)	2 (1.3%)	9 (3.1%)
Documented VF	4 (0.9%)	0	4 (1.4%)
Sustained VT revealed by device	4 (0.9%)	0	4 (1.4%)
Hospitalization	85 (19.1%)	24 (15.6%)	61 (20.9%)

TWA = T-wave alternans; VF = ventricular fibrillation; VT = ventricular tachycardia.

resynchronization therapy (CRT): 17 were implanted with a CRT-pacing device (15 of 17 in NYHA functional class III, average QRS duration 182 ± 24 ms, 16 with abnormal and 1 with a normal TWA test) and 14 were implanted with a CRT-defibrillator device (11 of 14 in NYHA functional class III, average QRS duration 166 ± 19 ms, 12 with abnormal and 2 with normal TWA tests). In the late part of the study, following the most recent evidence of ICD benefit among NYHA functional class II and III patients (28), 21 additional patients were implanted with an ICD (16 with abnormal and 5 with normal TWA tests).

The imbalance in the proportion of patients with an implanted device in the abnormal TWA test group may have led to a slight overestimation of the rate of events in this group. Accordingly, we performed a sensitivity analysis of the primary end point by dropping the 4 events identified through the device (all in the abnormal TWA test group). The event rate in this group decreased from 6.5 to 5.7 (95% CI 3.8 to 8.4), and the corresponding HR with respect to patients with normal TWA tests decreased from 4.00 to 3.44 (95% CI 1.20 to 9.90; p = 0.008), still denoting a significant excess risk in the abnormal TWA test group. An analysis was also performed dropping all patients with an implanted biventricular device; the HR associated with an abnormal TWA test was found to be 3.43 (95% CI 1.19 to 9.92; p = 0.009). Finally, an analysis was performed excluding the 5 cases of indeterminate TWA tests because of noise; the HR associated with an abnormal TWA test was found to be 3.93 (95% CI 1.38 to 11.21; p = 0.010).

Results of the secondary end points are consistent with those of the primary end point and show a significant increase in risk in the abnormal TWA test group for both event-free survival curves (Fig. 2). Negative predictive values between 99.3% and 98% were found at 12 and 18 months, for both total mortality and arrhythmic death + life-threatening arrhythmias. On the other hand, the rate of hospitalization tended to be higher in the abnormal TWA test group, but the difference did not reach statistical significance.

Positive predictive values were relatively low (6.5% and 9.0% for the primary end point at 12 and 18 months) (Table 3), slightly increasing to 7.9 and 10.9 at 12 and 18 months, respectively, among patients with LVEF ≤35%.

No significant interaction was found between TWA prediction and either QRS duration or LVEF. Specifically, the predictive role of the TWA test was only marginally influenced by the presence of QRS enlargement. The NPV

Table 3 Role of TWA Tests (Abnormal vs. Normal) on the End Points

End Point	No. of Events		Rate* (95% CI)		HR (95% CI)	p Value	NPV† (95% CI)		PPV‡ (95% CI)	
	Abnormal TWA Test	Normal TWA Test	Abnormal TWA Test	Normal TWA Test			12 months	18 months	12 months	18 months
Primary end point										
Cardiac death + life-threatening arrhythmia	29	4	6.5 (4.5–9.4)	1.6 (0.6–4.4)	4.01 (1.41–11.41)	0.002	98.7% (95.4–99.8)	97.3% (93.3–99.3)	6.5 (4.0–10.0)	9.0 (5.9–13.0)
Secondary end points										
Total mortality	25	3	5.7 (3.8–8.4)	1.2 (0.4–3.8)	4.60 (1.39–15.25)	0.002	99.3% (96.4–100)	98.0% (94.2–99.6)	4.2 (2.2–7.3)	7.7 (4.1–11.5)
Arrhythmic death + life-threatening arrhythmia	20	2	4.5 (2.9–7.0)	0.8 (0.2–3.3)	5.53 (1.29–23.65)	0.004	99.3% (96.4–100)	98.6% (95.2–99.8)	4.9 (2.7–8.1)	7.0 (4.3–10.7)
Hospitalization	61	24	13.8 (10.6–17.8)	9.9 (6.3–14.7)	IRR 1.39 (0.86–2.32)	0.165				

*Rate is expressed as events per 100 person-years (number of events/sum of follow-up times in years/100 persons). †Negative predictive value of a normal TWA test (and 95% CI) with respect to the prediction of events at 12 and 18 months. ‡Positive predictive value of an abnormal TWA test (and 95% CI) with respect to the prediction of events at 12 and 18 months.
CI = confidence interval; HR = hazard ratio; NPV = negative predictive value; PPV = positive predictive value; TWA = T-wave alternans.

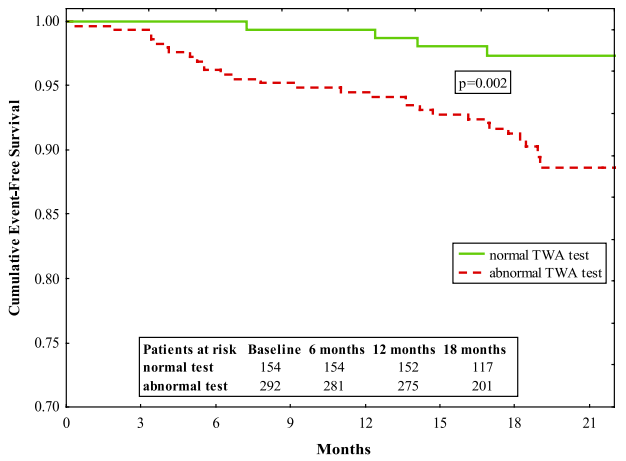

Figure 1 **Freedom From Cardiac Death + Life-Threatening Arrhythmias**

Primary end point: Kaplan-Meier cumulative event-free survival according to T-wave alternans (TWA) test. Patients at risk at selected time points are reported.

for a normal TWA test relative to the primary end point of the study at 12 months was 99% among patients with a QRS duration ≤120 ms and 98.3% among patients with a QRS duration >120 ms. Conversely, the PPV for the same end point was 5.6 and 7.7 among patients with QRS durations ≤120 and >120 ms, respectively.

Because recent guidelines advocate ICD implantation for heart failure patients with LVEF ≤35%, we assessed the predictive role of TWA in this subgroup of patients (n = 339). Within this group of patients, the event rates of the primary end point were 8.1 (95% CI 5.6 to 11.6) per 100 person-years among patients with abnormal TWA tests and 1.9 (95% CI 0.6 to 5.9) per 100 person-years among patients with normal TWA tests. The unadjusted and adjusted HRs associated with an abnormal TWA test were, respectively, 4.28 (95% CI 1.30 to 14.05; p = 0.004) and 3.91 (95% CI 1.18 to 12.90, p = 0.025), and the NPVs at 12 montsh and 18 months were, respectively, 99.0% (95% CI 94.4 to 100) and 96.8% (95% CI 91.0 to 99.3).

Discussion

The present study aimed to assess the capability of TWA to predict cardiac death and life-threatening arrhythmias among patients with NYHA functional class II and III heart failure due to nonischemic cardiomyopathy and LVEF ≤40%. The presence of an abnormal TWA test was associated with an increased risk of death and arrhythmic events, and the test allowed identification of a large group of patients who have an excellent prognosis and are unlikely to benefit from ICD prophylaxis despite the presence of heart failure and left ventricular dysfunction.

There is a great need to stratify patients at risk for sudden cardiac death, especially among patients with nonischemic cardiomyopathy (3–5). The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guideline for management of patients with ventricular arrhythmias and prevention of sudden cardiac death (4) suggests for the first time that the use of TWA is reasonable for risk stratification of patients who are at risk for developing life-threatening ventricular arrhythmias. The recommendation is classified as class IIa, indicating the presence of not completely conclusive data and some conflicting evidence.

The favorable evidence derives mostly from patients with ischemic cardiomyopathy (6,23,29). However, the mechanisms of arrhythmias in patients with nonischemic heart failure (30,31) are quite different from those present in patients with a previous myocardial infarction. Evaluation of the arrhythmogenic substrate, by means of electrophysiologic testing and signal-averaged electrocardiogram, ap-

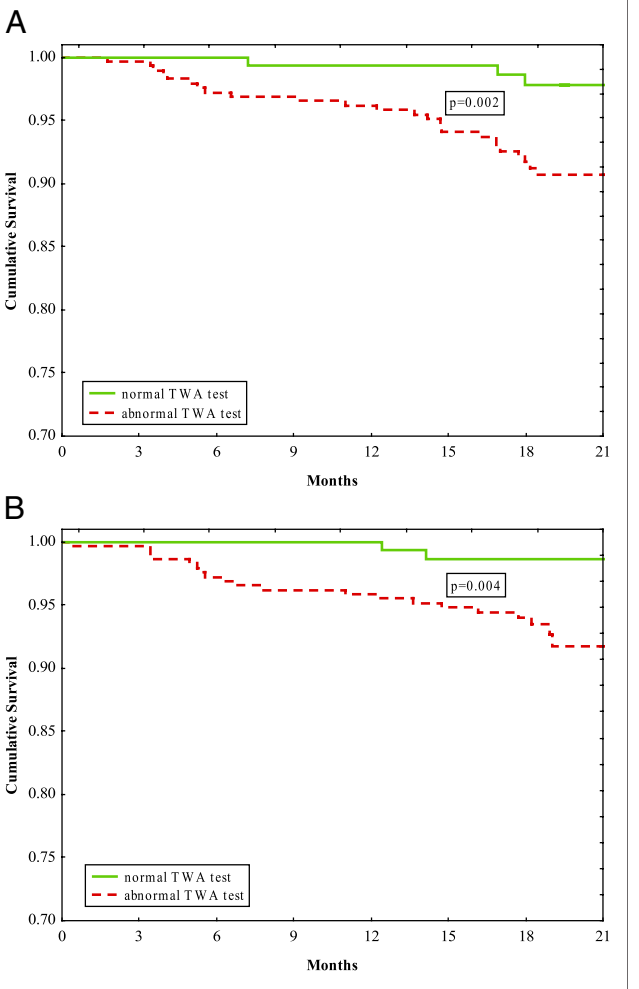

Figure 2 **Freedom From Total Mortality and Arrhythmic Death + Life-Threatening Arrhythmias**

Secondary end points: **(A)** Kaplan-Meier cumulative survival (total mortality) and **(B)** Kaplan-Meier event-free survival (arrhythmic death + life-threatening arrhythmias) according to T-wave alternans (TWA) test.

pears to provide prognostic information in patients with a previous myocardial infarction (25,28–34) but not in patients with nonischemic cardiomyopathy (5,35).

Data on a predictive role of TWA in patients with nonischemic cardiomyopathy are relatively limited and present conflicting evidence. Klingenheben et al. (7) studied 107 patients with heart failure (40 nonischemic) and LVEF <45%. Arrhythmic end points occurred in 11 of 52 patients with positive, 2 of 22 patients with indeterminate, and 0 of 33 patients with negative TWA tests ($p < 0.005$). Kitamura et al. (9) studied 104 patients and Hohnloser et al. (10) 137 patients with nonischemic cardiomyopathy. In both reports, data showed a significant predictive power of TWA for arrhythmic events. Nevertheless, some limitations were present in both reports; in the first study, no LVEF cutoff was selected and patients were not treated at baseline with beta-blockers or ACE inhibitors, and in the second, 37 of 137 patients (27%) were already implanted with an ICD, mostly because of previous cardiac arrest or documented ventricular tachycardia.

Grimm et al. (11) studied 263 patients with nonischemic cardiomyopathy, a mean age of 48 years, and LVEF of 30%, and mostly in NYHA functional classes II and III. Fifty percent of the patients were on beta-blockers at the time of entry, but the drug was withheld before the TWA test in almost all of the patients. During the 52-month follow-up, arrhythmic events occurred in 18 of 137 patients (13%) with positive, 13 of 54 patients (24%) with indeterminate, and 7 of 72 patients (10%) with negative TWA tests. On multivariate analysis, only LVEF was a predictor of arrhythmic events and TWA was not. Potential limitations of the study are the beta-blocker withdrawal before the test, their nonuniform use during the follow-up period, and the loss of a considerable number of patients to cardiac transplantation. Also, positive and indeterminate TWA tests were analyzed separately, rather than together as suggested by the most recent studies (19–23).

Finally, the recent study by Bloomfield et al. (22) included 282 nonischemic patients. The patients had an LVEF <40%, and almost two-thirds were in NYHA functional classes II and III. Over a 16-month follow-up, 8.6% of the patients with abnormal TWA tests died compared with 0% of patients with normal TWA tests.

We believe the present data contribute significantly to this area of study. First, the study represents the largest population studied so far. Second, unlike all previous studies, only patients in NYHA functional classes II and III were enrolled, mirroring class I candidates for ICD implantation proposed by the recent guideline (4). Finally, consecutive patients were prospectively enrolled, thus minimizing the risk of selection bias present in previous studies.

We found that patients with abnormal TWA tests had a 3- to 6-fold higher likelihood of all-cause mortality and arrhythmic end points. This also occurred after adjusting for baseline confounding variables as well as omitting from the analysis the arrhythmic end points revealed by the implanted device to control for this potential bias.

More importantly, patients with normal TWA tests had an extremely good outcome, with a 1.2 annual mortality rate and a 0.8 annual rate of arrhythmic death + life-threatening arrhythmia. After 18 months' follow-up, the rate of cardiac death + life-threatening arrhythmias, total mortality, or arrhythmic death + life-threatening arrhythmias ranged from 2.7% to 1.4%. Accordingly, the NPVs ranged from 97.3% to 98.6%.

Given the potential complications and adverse effects related to ICDs (36–39), as well as the costs of ICD therapy, the present data suggest that a normal TWA test is useful in identifying individuals who are unlikely to benefit from ICD implantation.

The PPV of the test was relatively low, as expected (9% for the primary end point over 18 months); it increased modestly when combined with other variables (10.3% among patients with QRS >120 ms and 10.9% among patients with LVEF ≤35%).

Study limitations. As in all studies evaluating TWA, we could not include patients with atrial fibrillation. However, these patients are known to be at higher risk compared with patients in sinus rhythm (31), and the NPV of any prognostic test would be weaker.

Less than one-half of the deaths observed during the study were sudden arrhythmic, and the overall event rate was relatively low. For instance, the 1-year all-cause mortality rate we observed (4.2%) was lower than that (6.2%) found in the conventional treatment arm of the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial (40). Three main differences in the patient population are likely to underlie this apparent discrepancy. First, the upper cutoff value for LVEF was 35% for the DEFINITE trial and 40% for the present trial, and the average LVEFs were 21.4% and 29.5%, respectively. Second, the presence of ambient arrhythmias was required for enrollment in the DEFINITE trial. Third, 24.5% of patients in the DEFINITE trial had atrial fibrillation, a condition associated with a worse prognosis, as mentioned in the preceding text (31). Conversely, Bloomfield et al. (22), similarly to the present study, excluded patients with atrial fibrillation and patients with LVEF >40%. They reported a 2-year combined event rate of all-cause mortality + nonfatal sustained ventricular arrhythmias in the nonischemic population of 8.9% (compared with 10.2% in the present study).

Therefore, the event rate of the present study is not lower than that reported by the most recent studies when the different patient populations are taken into account. Also, because we enrolled consecutive unselected patients, at variance with clinical trials, we believe the conclusions reached in the present study can be reliably transferred to clinical practice. It is important to point out that higher event rates would lead to lower NPVs. For instance, in case of a 47% greater 1-year mortality, as observed in the

DEFINITE study, the corresponding NPV would decrease from 99.3% to 99.0%, which is still a rather high value. Similarly, the NPV among the subgroup of patients with LVEF ≤35% was also found to be high.

Finally, the predictive value was only assessed over the 18-month minimum follow-up period. Future studies will need to evaluate whether TWA testing should be repeated to allow dynamic risk assessment.

Conclusions

The present study assessed the prognostic capability of TWA among patients with NYHA functional class II and III heart failure due to nonischemic cardiomyopathy and LVEF ≤40%. An abnormal TWA test was associated with a 4-fold higher risk of cardiac death + life-threatening ventricular arrhythmias over an 18-month follow-up.

Clinical implications. The most important clinical implications derive from the finding that patients with a normal TWA test appear to have a very good prognosis, as shown by the high NPV of the test. Although additional confirmatory studies are needed before advocating a change in the current treatment guidelines, the results of the present study suggest that TWA may be effectively used to identify a subgroup of patients who are likely to have little benefit from ICD therapy despite heart failure and left ventricular dysfunction.

Reprint requests and correspondence: Prof. Jorge A. Salerno-Uriarte, Department of Cardiological Science, Ospedale di Circolo e Fondazione Macchi, Universitá dell'Insubria, Viale Borri 57, 21100 Varese, Italy. E-mail: jorge.salerno@ospedale.varese.it

REFERENCES

1. Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation 1998;98:2334–51.
2. Bardy GH, Lee KL, Mark DB, et al., Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
3. Buxton AE, Moss AJ. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter defibrillator? Circulation 2005;111:2537–49.
4. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). Circulation 2006;114:1088–132.
5. Centers for Medicare and Medicaid Services. Decision memo for implantable defibrillators (CAG-00157R3). Available at: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=148. Accessed November 16, 2006.
6. Bloomfield DM, Steinman RC, Namerow PB, et al. 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. Circulation 2004;110:1885–9.
7. Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. Lancet 2000;356:651–2.
8. Sarzi Braga S, Vaninetti R, Laporta A, Picozzi A, Pedretti RFE. T-wave alternans is a predictor of death in patients with congestive heart failure. Int J Cardiol 2004;93:31–8.
9. Kitamura H, Ohnishi Y, Okajima K, et al. Onset heart rate of microvolt-level T-wave alternans provides clinical and prognostic value in nonischemic dilated cardiomyopathy. J Am Coll Cardiol 2002;39:295–300.
10. Hohnloser SH, Klingenheben T, Bloomfield D, Dabbous O, Cohen RJ. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. J Am Coll Cardiol 2003;41:2220–4.
11. Grimm W, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy. Results of the Marburg Cardiomyopathy Study. Circulation 2003;108:2883–91.
12. Baravelli M, Salerno-Uriarte D, Guzzetti D, et al. Predictive significance for sudden death of microvolt-level T wave alternans in New York Heart Association class II congestive heart failure patients: a prospective study. Int J Cardiol 2005;105:53–7.
13. Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 2006;47:269–81.
14. Strickberger SA, Hummel JD, Bartlett TG, et al., AMIOVIRT Investigators. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia. J Am Coll Cardiol 2003;41:1707–12.
15. Grimm W, Glaveris C, Hoffmann J, et al. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: design and first results of the Marburg Cardiomyopathy Study. Pacing Clin Electrophysiol 1998;21:2551–6.
16. Salerno-Uriarte JA, Pedretti RFE, Tritto M, De Ferrari GM, Klersy C, Sallusti L. The ALPHA study (T-Wave Alternans in Patients With Heart Failure): rationale, design and end-points. Ital Heart J 2004;5:587–92.
17. De Ferrari GM, Klersy C, Ferrero P, et al., ALPHA Study Group. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. Eur J Heart Fail 2007;9:502–9.
18. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330:235–41.
19. Bloomfield DM, Hohnloser SH, Cohen RJ. Interpretation and classification of microvolt T wave alternans tests. J Cardiovasc Electrophysiol 2002;13:502–12.
20. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. Lancet 2003;362:125–6.
21. Kaufman ES, Bloomfield DM, Steinman RC, et al. "Indeterminate" microvolt T-wave alternans tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;48:1399–404.
22. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;47:456–63.
23. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. J Am Coll Cardiol 2006;47:1820–7.
24. Hinkle LE Jr., Thaler HT. Clinical classification of cardiac deaths. Circulation 1982;65:457–64.
25. Buxton AE, Lee KL, DiCarlo L, et al., Multicenter Unsustained Tachycardia Trial Investigators. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937–45.
26. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Contr Clin Trials 1996;17:343–6.
27. Schoenfeld D. Partial residuals for the proportional hazard regression model. Biometrika 1982;69:239–41.
28. Bardy GH, Lee KL, Mark DB, et al., Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT) Investigators. Amiodarone or an implant-

able cardioverter-defibrillator for congestive heart failure. New Engl J Med 2005;352:225–37.
29. Gehi AK, Stein RH, Metz LD, Gomes JA. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events. A meta-analysis. J Am Coll Cardiol 2005;46:75–82.
30. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004;95:754–763.
31. De Ferrari GM, Tavazzi L. The role of arrhythmias in the progression of heart failure. Eur J Heart Fail 1999;1:35–40.
32. Gomes JA, Winters SL, Ip J. Post myocardial infarction stratification and the signal-averaged electrocardiogram. Prog Cardiovasc Dis 1993; 35:263–70.
33. Pedretti R, Etro MD, Laporta A, Sarzi Braga S, Carù B. Prediction of late arrhythmic events after acute myocardial infarction from combined use of noninvasive prognostic variables and inducibility of sustained monomorphic ventricular tachicardia. Am J Cardiol 1993;71:1131–41.
34. De Ferrari GM, Rordorf R, Frattini F, Petracci B, De Filippo P, Landolina M. Predictive value of programmed ventricular stimulation in patients with ischemic cardiomyopathy: implications for the selection of candidates for an implantable defibrillator. Europace 2007. In press.
35. Turitto G, Ahuja RK, Caref EB, el-Sherif N. Risk stratification for arrhythmic events in patients with nonischemic dilated cardiomyopathy and nonsustained ventricular tachycardia: role of programmed ventricular stimulation and the signal-averaged electrocardiogram. J Am Coll Cardiol 1994;24:1523–8.
36. Rosenqvist M, Beyer T, Block M, den Dulk K, Minten J, Lindemans F, European 7219 Jewel ICD Investigators. Adverse events with transvenous implantable cardioverter-defibrillators: a prospective multicenter study. Circulation 1998;98:663–70.
37. Kron J, Herre J, Renfroe EG, et al., AVID Investigators. Lead- and device-related complications in the Antiarrhythmics Versus Implantable Defibrillators trial. Am Heart J 2001;141:92–8.
38. Schron EB, Exner DV, Yao Q, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation 2002;105:589–94.
39. Irvine J, Dorian P, Baker B, et al. Quality of life in the Canadian Implantable Defibrillator Study (CIDS). Am Heart J 2002;144: 282–9.
40. Kadish A, Dyer A, Daubert JP, et al., Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

APPENDIX

For a complete list of investigators, please see the online version of this article.

Prognostic Value of T-Wave Alternans in Patients With Heart Failure Due to Nonischemic Cardiomyopathy: Results of the ALPHA Study

Jorge A. Salerno-Uriarte, Gaetano M. De Ferrari, Catherine Klersy, Roberto F.E. Pedretti, Massimo Tritto, Luciano Sallusti, Luigi Libero, Giacinto Pettinati, Giulio Molon, Antonio Curnis, Eraldo Occhetta, Fabrizio Morandi, Paolo Ferrero, Francesco Accardi, for the ALPHA Study Group Investigators

J. Am. Coll. Cardiol. published online Oct 12, 2007;
doi:10.1016/j.jacc.2007.09.004