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ORIGINAL RESEARCH

Lack of Prognostic Value of T-Wave Alternans for Implantable Cardioverter-Defibrillator Benefit in Primary Prevention

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BACKGROUND: New methods to identify patients who benefit from a primary prophylactic implantable cardioverter-defibrillator (ICD) are needed. T-wave alternans (TWA) has been shown to associate with arrhythmogenesis of the heart and sudden cardiac death. We hypothesized that TWA might be associated with benefit from ICD implantation in primary prevention.

METHODS AND RESULTS: In the EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators) study, we prospectively enrolled 2327 candidates for primary prophylactic ICD. A 24-hour Holter monitor reading was taken from all recruited patients at enrollment. TWA was assessed from Holter monitoring using the modified moving average method. Study outcomes were all-cause death, appropriate shock, and survival benefit. TWA was assessed both as a contiguous variable and as a dichotomized variable with cutoff points <47 μV and <60 μV. The final cohort included 1734 valid T-wave alternans samples, 1211 patients with ICD, and 523 control patients with conservative treatment, with a mean follow-up time of 2.3 years. TWA ≥60 μV was a predicter for a higher all-cause death in patients with an ICD on the basis of a univariate Cox regression model (hazard ratio, 1.484 [95% CI, 1.024–2.151]; *P*=0.0374; concordance statistic, 0.51). In multivariable models, TWA was not prognostic of death or appropriate shocks in patients with an ICD. In addition, TWA was not prognostic of death in control patients. In a propensity score–adjusted Cox regression model, TWA was not a predictor of ICD benefit.

CONCLUSIONS: T-wave alternans is poorly prognostic in patients with a primary prophylactic ICD. Although it may be prognostic of life-threatening arrhythmias and sudden cardiac death in several patient populations, it does not seem to be useful in assessing benefit from ICD therapy in primary prevention among patients with an ejection fraction of ≤35%.

Key Words: appropriate shock ■ heart failure ■ implantable cardioverter-defibrillator ■ death ■ T-wave alternans

The implantable cardioverter-defibrillator (ICD) is a cornerstone of treatment for primary prevention of patients at risk of sudden cardiac death. The landmark studies guiding current indications were published at the beginning of the millennium.[1–3] The recent prospective EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators) cohort showed a 27% lower mortality rate in patients with an ICD when compared with the control group.[4] Current European Society of Cardiology guidelines recommend primary prophylactic ICD implantation in patients with ischemic cardiomyopathy with a left ventricular ejection fraction of ≤35%. Implantation should

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CLINICAL PERSPECTIVE

What Is New?

- T-wave alternans (TWA) has been shown to associate with arrhythmogenesis of the heart and sudden cardiac death; however, studies of patients with TWA and a primary prophylactic implantable cardioverter-defibrillator (ICD) have been conflicting.
- We investigated the role of TWA in a prospective EU-CERT-ICD (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators) study cohort of patients with a primary prophylactic ICD and a control group, and TWA did not predict benefit from implantation of a primary prophylactic ICD.

What Are the Clinical Implications?

- Based on our results, TWA cannot be used to select patients for primary prophylactic ICD therapy with reduced left ventricular ejection fraction among a contemporary patient population.
- Other methods beyond TWA are needed to identify patients with or without true benefit from primary prophylactic ICD implantation among patients with a left ventricular ejection fraction ≤35%.

Nonstandard Abbreviations and Acronyms

ABCD	Alternans Before Cardioverter Defibrillator
EU-CERT-ICD	European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators
EUTrigTreat	Arrhythmia Risk Stratification and Genetic Trial
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial II
MASTER	Microvolt TWA Testing for Risk Stratification of Post–Myocardial Infarction Patients
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
TWA	T-wave alternans

be considered in patients with nonischemic cardiomyopathy.[5] The American Heart Association guidelines are mainly comparable with those in Europe, except patients with nonischemic pathogenesis are recommended to receive primary prophylactic ICD (class I recommendation). In addition, American Heart Association guidelines include additional class I indications for patients with a left ventricular ejection fraction (LVEF) ≤30% in New York Heart Association class I and those with LVEF <40% with inducible sustained ventricular tachycardia or ventricular fibrillation at electrophysiological study due to prior myocardial infarction.[6]

Patients receiving primary prophylaxis ICD are not a homogeneous group. Several patient groups, such as elderly patients, female patients, patients with New York Heart Association class III, and patients with nonischemic cardiomyopathy have been shown to have a limited benefit from the device.[7–10] The majority of implanted ICDs never deliver life-saving therapy. Regardless of the fact that the appropriate shock rate has decreased over the past 2 decades, the complication rate remains high.[11] When considering all-cause death, appropriate shock rates, side effects, and competing risks of nonarrhythmic death, the benefit–risk ratio of primary prophylactic ICD treatment seems to have declined and is becoming less favorable.[12–17] It is crucial to identify patient groups who truly benefit or who do not benefit from ICD therapy, to reduce the number of unnecessary implantations. There must be an appropriate balance between the risk of arrhythmic death and the risks and costs related to the implantation.

T-wave alternans (TWA) distinguishes heterogeneity and fluctuation of beat-to beat ST-segment and T-wave amplitudes. TWA analysis requires high-quality Holter monitoring and sinus rhythm, while it cannot be analyzed from recordings with atrial fibrillation or a significant number of ventricular beats. A high level of TWA coincides with vulnerability to lethal ventricular arrhythmias. Several studies have shown that TWA is a predictor for sudden cardiac death and all-cause death in patients with cardiac disease.[18] In addition, TWA has been shown to be a predictor for sudden cardiac death in the general population.[19] TWA might reflect arrhythmia substrates better than LVEF, and it seems to be a promising tool to assess benefit from primary prophylactic ICD implantation. However, studies of patients with TWA and an ICD have been conflicting, and definite evidence to support the use of TWA testing in clinical practice is missing.[20] We sought to investigate the role of TWA in a prospective EU-CERT-ICD study cohort of patients with a primary prophylactic ICD and a control group. We hypothesized that TWA might help to assess the survival benefit among patients with a primary prophylactic ICD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The present study is a part of the EU-CERT-ICD study. EU-CERT-ICD is a nonrandomized, controlled, prospective multicenter study (ClinicalTrials.gov identifier: NCT02064192), funded by the European Community's Seventh Framework Programme. The study protocol and the prospective study objectives have been published previously in detail.[4,21] Analysis of TWA was based on the original research plan within the EU-CERT-ICD framework.

The study was approved by local ethics committees at all participating centers. All patients provided written informed consent before inclusion. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles.

Study Population and Outcomes

Details of the study population and study outcomes have been published previously.[21,22] In brief, EU-CERT-ICD includes 2 groups of patients: patients who underwent first primary prophylactic ICD implantation and a control group of patients receiving optimal medical treatment. All patients were candidates for primary prophylactic ICD treatment according to the current guidelines due to ischemic or nonischemic cardiomyopathy. All patients with nonischemic cardiomyopathy in our cohort had dilated cardiomyopathy. Patients with atrial fibrillation were excluded from the TWA analysis. The control group was required to fulfill the same inclusion and exclusion criteria and the control patients also received optimal conservative therapy.

In the ICD group, ICDs were implanted according to local practice at individual centers. ICD programming was consistent between participating centers, and modern therapy zone limits were used. ICD programming could be individualized by the physician on clinical grounds.

Both patient groups were followed up regularly. Episodes of shock or antitachycardia pacing were stored as electrograms for adjudication, and programming changes were recorded. Documented clinical variables included demographics, risk factors, and medical history.

The primary outcome of the study reported here was all-cause death. The co-primary outcomes were time to first appropriate shock and ICD benefit. All-cause death and first appropriate shock were reviewed by the external committee, which provided blind adjudication. ICD shocks were adjudicated after review of device electrograms and classified as appropriate or inappropriate. A minimum follow-up time of 1 year was used in the present investigation.

T-Wave Alternans Assessment

A 24-hour Holter-ECG monitor reading was taken from all recruited patients at enrollment. Holter data were digitally stored at the University of Göttingen (Göttingen, Germany). Data preprocessing was done at the Technical University of Munich (Munich, Germany).

TWA analyses were performed blinded to outcomes at the University of Oulu (Oulu, Finland). The peak TWA value was analyzed using modified moving average method with Cardioday software (Getemed, Teltow, Germany). All automated analyses were confirmed visually by a researcher (T.K.). TWA was assessed both as a continuous variable and with cutoff points <47 μV and <60 μV.

Statistical Analysis

Continuous variables are presented as means and SDs, categorical variables as absolute and relative frequencies. A Cox regression model was used to analyze the time-dependent probability of all-cause death. The time to first appropriate shock was analyzed using a Fine and Gray competing risk model accounting for death, heart transplantation, and implantation of a ventricular assist device as events competing to appropriate shocks. Results on survival models are reported using hazard ratio (HR) with 95% CI along with the concordance statistic. A P value <0.05 was considered statistically significant.

We accounted for the nonrandomized nature of this study and the potential differences in patient characteristics between the treatment groups by adjusting the analyses for baseline characteristics. These baseline characteristics were already identified for the analyses of Bauer et al[23] and Zabel et al[4] by stepwise selection with P<0.1 for entry and stay. All multivariable analyses were additionally stratified by region (Hungary, Bulgaria, Croatia, Poland, Slovakia, and the Czech Republic in Eastern Europe; Germany, Belgium, Netherlands, and Switzerland in Western/Central Europe; Denmark, Sweden, and Finland in Northern Europe (ie, Scandinavia); and Spain and Greece in Southern Europe). The assessment of TWA as a predictor for death was performed for both treatment groups, while for the first appropriate shock the assessment was performed in the ICD treatment group only. We calculated the concordance statistic for evaluating the discriminative performance of the Cox model.[24]

We further examined the interaction between TWA and ICD benefit within Cox proportional hazards models, employing the same stratification method by propensity score quintiles as described by Bauer et al[23] to adjust for baseline characteristic differences. The propensity score models the likelihood of receiving ICD versus control. Additional details on the development of the propensity score are available in Bauer et al[23] and Zabel et al.[4] To evaluate the interaction between TWA and ICD, the Cox regression included the ICD effect as the factor and TWA as a covariate, along with

their interaction term. The binary TWA variable, defined by thresholds (<47 μV and <60 μV), was included as a factor into the Cox regression models. Additionally, the models considered the interaction between this binary TWA variable and ICD benefit. To demonstrate the robustness of the results, a matched analysis of patients (2 patients with an ICD for each control patient, 2:1 matching) was performed.

RESULTS

Baseline Characteristics

In total, 44 centers across 15 EU countries enrolled 2327 patients with ischemic cardiomyopathy or dilated cardiomyopathy between May 12, 2014, and September 7, 2018. The recruitment included 1553 patients with ICD implantation and 774 control patients. The final population of our study consisted of 1734 patients (19.2% women), 1211 patients (69.8%) with ICD and 523 control patients (30.2%); the flowchart is shown in Figure 1. At the time of the implantation, mean age was 61.4±11.8 years (Table 1). During a mean follow-up time of 2.3 years to death or censoring, 240 deaths (13.8%) occurred. Of patients with an ICD, 73 (6.0%) received their first appropriate shock during mean follow-up time (2.6±1.0 years) to appropriate shock, death, or censoring (Table 2).

Mean TWA in our cohort was 46.4 μV. In the ICD group and control group, mean TWA was 45.3 μV and 48.9 μV, respectively. Almost half of the patients had TWA ≥47 μV (42.9%), while TWA ≥60 μV was found in 15.9% (Table 1).

Compared with the control group, there were some differences in baseline characteristics in the ICD group. However, groups were mostly well matched and comparable (Table 1). The differences between groups were considered in the statistical analysis.

TWA as a Predictor for the Outcomes

When observing TWA as a predictor of all-cause death, TWA ≥60 μV is associated with higher all-cause death in patients with an ICD in a univariate Cox regression model (HR, 1.484 [95% CI, 1.024–2.151]; *P*=0.0374; concordance statistic, 0.51). However, when the model was adjusted, TWA was not associated with death in both ICD recipients and control patients. For appropriate shocks in patients with an ICD, TWA yielded no predictive value. The concordance statistic for appropriate shocks in patients with an ICD based on an adjusted Cox regression model is displayed in Table 3. In a propensity score–adjusted Cox regression model, TWA was not associated with an ICD benefit. As a subgroup analysis, we analyzed ICD benefit in relation to TWA among ischemic and nonischemic subgroups. No statistically significant difference for the probability of ICD benefit was found in patients with either ischemic or nonischemiccardiomyopathy. For the sensitivity analysis of the propensity score–based models investigating the interaction of TWA and ICD, see Table 4. Figures 2 and 3 show Kaplan–Meier curves of all-cause death in patients with ICD and control patients with TWA <47 μV and TWA ≥47 μV and with TWA <60 μV and TWA ≥60 μV, respectively. Figure 4 shows the cumulative incidence of appropriate shock in patients with ICD with TWA <47 μV and TWA ≥47 μV and with TWA <60 μV and TWA ≥60 μV, respectively. Negative predictive value for survival and TWA <47 μV was 0.888, while negative predictive value for survival and TWA <60 μV was 0.881 on the basis of all patients.

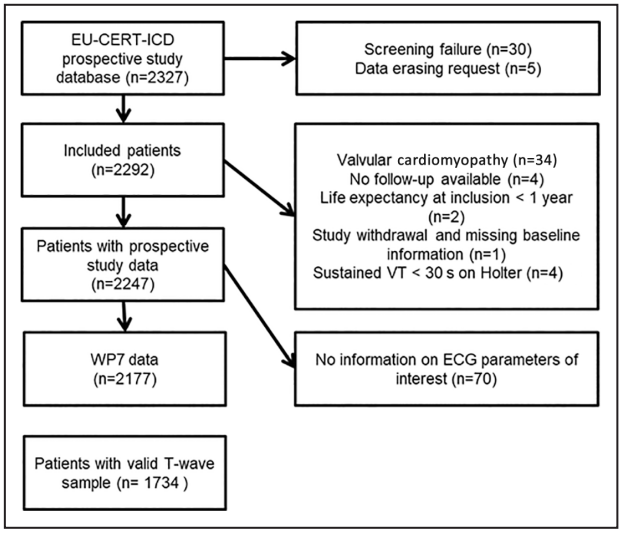

Figure 1. Flowchart of study data.
EU-CERT-ICD indicates European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators; and VT, ventricular tachycardia.

DISCUSSION

The findings of our study suggest that TWA does not predict benefit from implantation of primary prophylactic ICD. We have analyzed TWA from 24-hour Holter monitoring in a large, prospective EU-CERT-ICD cohort of both patients with an ICD and a control group with conservative treatment. None of the TWA variables reached statistical significance in multivariable analyses toward study outcomes. Based on these results, TWA cannot be used to select patients for primary prophylactic ICD therapy with reduced LVEF.

When Hohnloser et al analyzed TWA from a pooled cohort of 129 MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II)–type patients without ICD, they found that abnormal TWA is a predictor for sudden cardiac death or cardiac arrest.[25] In line with Hohnloser et al, Bloomfield et al reported that normal

Table 1. Baseline Characteristics

	ICD group (n=1211)		Control group (n=523)		Total (n=1734)			
	N	%	N	%	N	%	SMD	*P* value
Female sex	233	(19.2)	93	(17.8)	326	(18.8)		0.518
Age, y	61.0	11.7	62.4	12.0	61.4	11.8	0.12	0.019
BMI, kg/m^2	27.7	5.1	27.8	4.9	27.7	5.1	0.02	0.732
Creatinine, mg/dL	1.1	0.6	1.2	0.6	1.2	0.6	0.11	0.032
Diastolic blood pressure, mmHg	73.9	11.1	74.5	10.8	74.1	10.9	0.06	0.296
Hemoglobin, g/dL	13.8	1.9	13.9	1.7	13.8	1.8	0.03	0.528
Sodium, mmol/L	139.1	3.2	139.4	3.2	139.2	3.2	0.08	0.111
LVEF, %	27.6	5.5	29.3	5.4	28.1	5.5	0.30	<0.001
QTc, ms	438.0	36.7	430.7	51.5	435.8	41.8	0.16	0.222
QRS, ms	106.1	17.1	103.9	17.9	105.4	17.4	0.13	0.015
Diabetes	364	(30.1)	156	(29.8)	520	(30.0)	0.01	0.969
COPD	137	(11.3)	47	(9.0)	184	(10.8)	0.08	0.174
Leading cardiac disease								0.001
Ischemic cardiomyopathy	846	(69.9)	320	(61.2)	1166	(67.2)	0.18	
Dilated cardiomyopathy	365	(30.1)	203	(38.8)	568	(32.8)	0.09	
NYHA class								0.109
I or II	771	(63.7)	311	(59.5)	1082	(62.4)		
III or IV	440	(36.3)	212	(40.5)	652	(37.6)		
Tobacco use	795	(63.7)	268	(51.2)	1063	(61.3)	0.30	<0.001
Amiodarone	91	(7.5)	73	(14.0)	164	(9.5)	0.21	<0.001
AT1 antagonist	228	(18.8)	127	(24.3)	355	(20.5)	0.13	0.012
β Blocker	1152	(95.1)	488	(93.3)	1640	(94.6)	0.08	0.155
Loop diuretic	844	(69.7)	383	(73.2)	1227	(70.8)	0.08	0.153
TWA, μV	45.3	15.1	48.9	15.3	46.4	15.2	0.23	<0.001
TWA ≥47 μV	519	(42.9)	277	(53.0)	796	(45.9)	0.20	<0.001
TWA ≥60 μV	193	(15.9)	118	(22.6)	311	(17.9)	0.17	0.001

The values are depicted as mean (SD) or counts (percentages). BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QTc, QT interval corrected by Framingham's formula; SMD, standard mean difference; and TWA, T-wave alternans.

TWA associated with a lower all-cause mortality rate in patients without an ICD who met MADIT-II criteria for ICD implantation.[26] After these studies, it was speculated that TWA could be considered as a tool to select patients for primary prophylactic ICD implantation. When comparing these studies with ours, patients did not receive an ICD as they did in the present study. Without an ICD, it cannot be precisely stated that the device would prevent sudden cardiac death or reduce the total mortality rate. In addition, Hohnloser et al used sudden cardiac death or cardiac arrest as primary end point, while our study outcomes were all-cause death, appropriate shock, and ICD benefit. Due to competing risks of death, all-cause death indicates true benefit from the device.

However, in the MASTER (Microvolt TWA Testing for Risk Stratification of Post-Myocardial Infarction

Table 2. Study Outcomes

	ICD group (n=1211)		Control group (n=523)		Total (n=1734)	
	N	%	N	%	N	%
FU until death or censoring	2.7	1.0	1.7	1.2	2.4	1.1
FU until first appropriate shock, death, or censoring	2.6	1.0	1.7	1.2	2.3	1.2
Death	163	(13.5)	77	(14.7)	240	(13.8)
First appropriate shock	73	(6.0)	…		…	

The values are depicted as mean (SD) or counts (percentages). FU indicates follow-up time (y); and ICD, implantable cardioverter-defibrillator.

Table 3. Adjusted Cox Regression Model Stratified by Region on Death in Patients With ICD and Controls, and Multiple Fine and Gray Competing Risk Model on First Appropriate Shock in ICD Patients Stratified By Region

Death, patients with ICD	HR	95% CI		*P* value	Concordance statistic
TWA, μV	1.00	0.99	1.01	0.64	0.72
TWA ≥60 μV	1.31	0.88	1.95	0.18	0.73
TWA ≥47 μV	1.02	0.73	1.41	0.93	0.72
Death, control patients					
TWA, μV	1.00	0.98	1.01	0.83	0.78
TWA ≥60 μV	1.03	0.58	1.82	0.92	0.78
TWA ≥47 μV	0.94	0.58	1.58	0.82	0.78
Appropriate shock, patients with ICD					
TWA, μV	1.01	1.00	1.03	0.05	NA
TWA ≥60 μV	0.87	0.44	1.72	0.69	NA
TWA ≥47 μV	1.29	0.81	2.07	0.28	NA

HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; and TWA, T-wave alternans.

Patients) trial, 575 MADIT-II–indicated patients underwent TWA testing followed by ICD implantation. As a result, the risk of ventricular tachyarrhythmia events did not differ according to TWA classification. In this study, the total mortality rate was significantly higher in patients who were nonnegative for TWA.[27] These findings are well in line with our study. In our cohort, the total mortality rate did not differ between TWA groups either. This may be explained by other advanced treatment of patients. Patients in the MASTER trial were gathered between 2003 and 2007, while patients in EU-CERT-ICD prospective cohort were recruited between 2014 and 2018. Both pharmaceutical and interventional therapies of acute coronary syndrome and heart failure have evolved, which may explain why TWA could not separate patients at higher risk for all-cause death in our patient population.

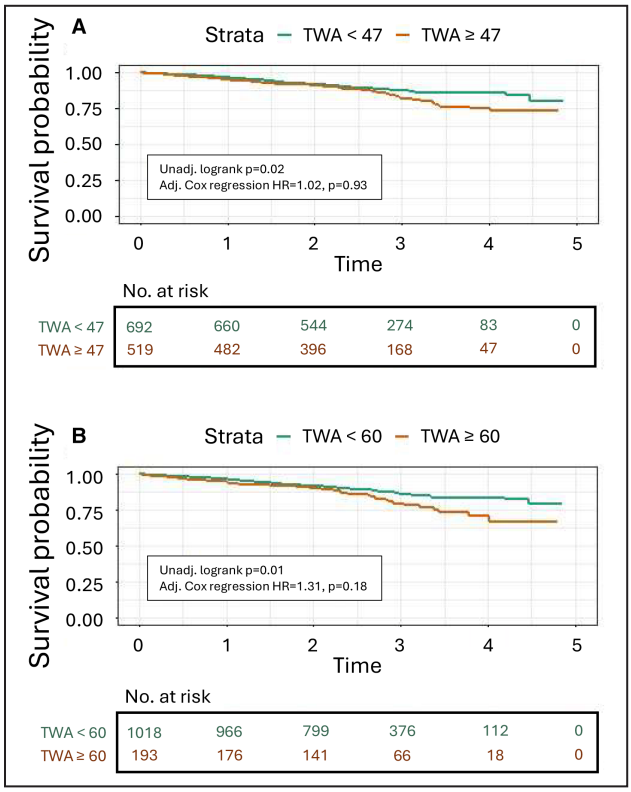

Figure 2. Kaplan–Meier curve of all-cause death in patients with an ICD with TWA<47 μV and TWA≥47 μV (A) and with TWA<60 μV and TWA≥60 μV (B).
TWA is not associated with death among patients with a primary prophylactic ICD. HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; and TWA, T-wave alternans.

TWA was also investigated in a substudy of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),

Table 4. Propensity Score–Adjusted Cox Regression Results for T-Wave Alternans on ICD Benefit: All Patients, Ischemic Patients, and NonIschemic Patients; Stratified by Propensity Score Quintiles: All Patients, Ischemic Patients, and Non-Ischemic Patients

Interaction with ICD effect	HR interaction	95% CI		*P* value	Concordance statistics
All patients					
TWA, μV	1.00	0.98	1.02	0.98	0.57
TWA <60 μV	0.85	0.43	1.67	0.64	0.56
TWA <47 μV	1.05	0.60	1.85	0.87	0.56
Ischemic patients					
TWA, μV	1.01	0.99	1.03	0.27	0.60
TWA <60 μV	1.23	0.56	2.71	0.61	0.57
TWA <47 μV	1.23	0.62	2.44	0.55	0.57
Nonischemic patients					
TWA, μV	0.98	0.95	1.01	0.20	0.57
TWA <60 μV	0.45	0.12	1.65	0.23	0.56
TWA <47 μV	0.82	0.29	2.32	0.70	0.56

HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; and TWA, T-wave alternans.

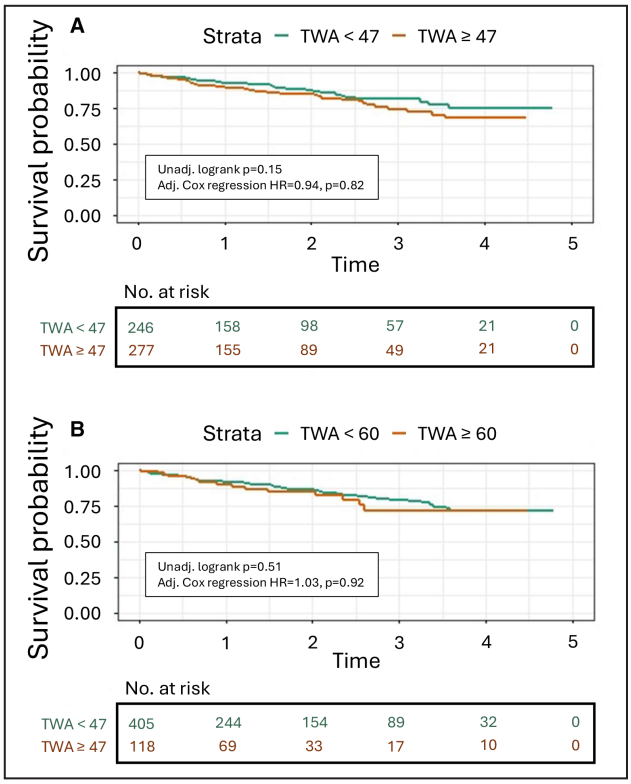

Figure 3. Kaplan–Meier curve of all-cause death in control patients with TWA<47 μV and TWA≥47 μV (A) and with TWA<60 μV and TWA≥60 μV (B).
TWA is not associated with death among patients with primary prophylactic ICD indication with conservative treatment. HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; and TWA, T-wave alternans.

one of the landmark studies of primary prophylactic ICD benefit. Among 490 patients with an ICD, TWA status was not prognostic of arrhythmic events or the total mortality rate.[28] While MADIT-II enrolled only patients with ischemic pathogenesis, the SCD-HeFT cohort included both patients with ischemic cardiomyopathy and patients with nonischemic cardiomyopathy. Thus, both the cohorts and the results of this substudy are well comparable with our study, although the patient population in our study is significantly larger and represents a current European sample of primary prophylactic ICD recipients.

The prospective ABCD (Alternans Before Cardioverter Defibrillator) trial tested whether TWA could guide primary prophylactic ICD therapy in patients with ischemic cardiomyopathy, LVEF ≤40%, and nonsustained ventricular tachycardia. The main objective of the trial was to compare TWA testing with electrophysiological study. TWA was found to be noninferior to electrophysiological study, and event rates of appropriate ICD discharge or sudden death were >2-fold higher among patients with abnormal TWA at the 1-year end point, compared with normal TWA. However, TWA was not a significant predictor of study outcomes at 2 years.[29] In our results, mean follow-up time is 2.3 years, and study outcomes differ from the ABCD trial. It is worth questioning if a 1-year follow-up period is long enough to assess the benefit from a device implantation.

The EUTrigTreat (Arrhythmia Risk Stratification and Genetic Trial) clinical study prospectively recruited 635 patients with an ICD from 4 European centers with ischemic and nonischemic cardiomyopathies and arrhythmogenic heart disease from January 2010 through April 2014. The study aimed at investigating the evolution of noninvasive risk stratification tests and the additional clinical value of repeating risk stratification. In 268 patients, at least 2 measurements of TWA were available. In adjusted analysis, there was no significant interaction between TWA status and survival. A single baseline TWA status was not associated with appropriate shocks, but patients with consistent nonnegative TWA tests had a higher risk of appropriate shocks.[22] When compared with our study, this clinical study included patients with both primary and secondary

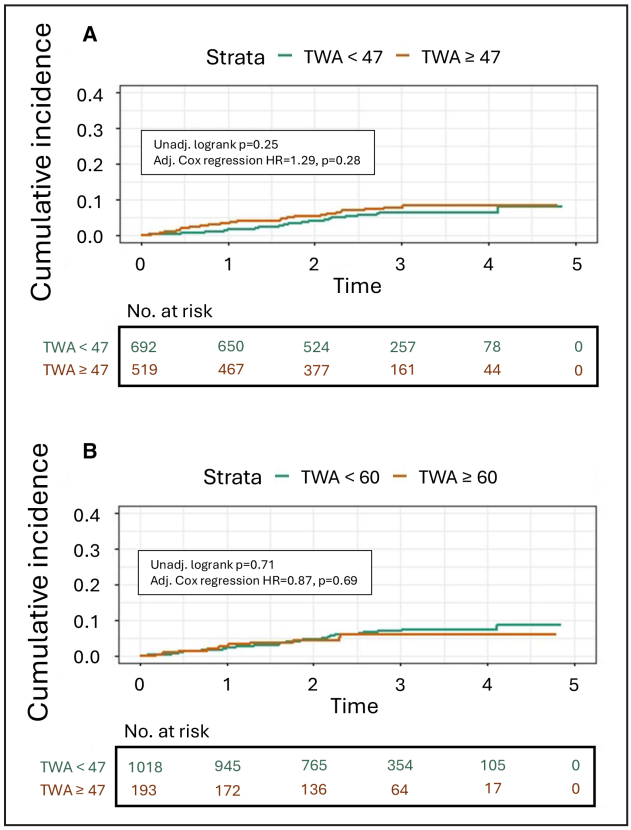

Figure 4. Cumulative incidence of appropriate shock in patients with an ICD with TWA<47 μV and TWA≥47 μV (A) and with TWA<60 μV and TWA≥60 μV (B).
TWA is not associated with appropriate shocks among patients with a primary prophylactic ICD. HR indicates hazard ratio; ICD, implantable cardioverter-defibrillator; and TWA, T-wave alternans.

ICDs. However, the results show that risk stratification of ventricular arrhythmias may be improved by repeating TWA analysis.

In this study, we used the modified moving average method, in which no special electrodes or target heart rate are required. Some prior studies have used the spectral method. A relatively large proportion of tests in the spectral method are classified as "indeterminate."[20] Some differences between these studies and our results may be explained by that, but the methods are analytically comparable. We used TWA cutoff points <47 μV and <60 μV, which are commonly used cutoff points in the modified moving average method to define abnormal and severely abnormal TWA.[18]

Despite justified expectations, it seems that TWA was not associated with benefit from primary prophylactic ICD implantation. While TWA cannot be assessed among patients with atrial fibrillation or a significant number of ventricular beats, it further decreases the clinical relevance of this method. Other methods, for example, magnetic resonance imaging and novel risk scores, should be researched for risk stratification in ICD candidates.[30,31] Some of the positive findings in prior studies may be explained by the fact that the relation between possible risk stratifier and outcome is not fully comparable between patients with and without an ICD. In addition, implanting an ICD does not always reduce the risk of sudden cardiac death or all-cause death. For example, high-risk patients with diabetes seem not to benefit from ICD implantation, possibly due to competing risks of death and other mechanisms of cardiac arrest than shockable rhythm.[32] In general, patients eligible for primary prophylactic ICD implantation have an abnormal cardiac substrate with the associated neurohormonal changes that accompany heart failure with reduced ejection fraction, and risk assessment is not fully comparable with the general population. TWA may still have a role as a risk marker among patients with normal LVEF.

Throughout the article, we use the term *predict* in line with its common clinical usage, implying risk estimation. However, this clinical interpretation does not convey the same meaning as in a statistical context, where predict refers exclusively to an association, not to causality.

Study Limitations

The main limitation of this study is its nonrandomized nature. Randomization as a study design was rejected after strict ethical assessment during EU-CERT-ICD design. The main difference between study groups was the difference in the pathogenesis of cardiac disease. However, to our knowledge, this is a unique prospective cohort of patients with a primary prophylactic ICD and a control group assessing the role of TWA. Sophisticated statistical methods were used to compensate minor baseline differences seen between groups. In addition, annual appropriate shock rate in the present study was relatively low (2.3%/year). This may be explained by both ICD programming and medical treatment. We used modern programming, and we think that this could reduce the number of shocks that are appropriate but not lifesaving. Antitachycardia pacing may also have a role in low appropriate shock rate. In addition, modern heart failure medications reached very high percentages in both groups. Low number of appropriate shock events may underestimate the difference between study groups and the prognostic significance of the variable under research. Moreover, we analyzed TWA only once, at the enrollment. Repeating analyses might enhance the quality of TWA assessment, but it would be more difficult to be implemented to clinical practice. However, none of the study outcomes reached statistical significance, showing that TWA is not predictive for true benefit from the device. In this study, we used only the modified moving average method, and the data for the spectral method were not available. The spectral method might lead to different results. However, when summarizing our results and the findings of prior studies, it can be concluded that other methods beyond TWA are needed to identify patients with or without true benefit from implantation among patients with LVEF ≤35%.

CONCLUSIONS

TWA is poorly prognostic in patients with a primary prophylactic ICD. Although it may be associated with life-threatening arrhythmias and sudden cardiac death in several patient populations, it is not useful in assessing benefit from an ICD in primary prevention among a contemporary patient population with LVEF ≤35%.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Appendix S1

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