

# Onset Heart Rate of Microvolt-Level T-Wave Alternans Provides Clinical and Prognostic Value in Nonischemic Dilated Cardiomyopathy

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<b>OBJECTIVES</b>	This study was designed to determine the prognostic value of onset heart rate (OHR) in T-wave alternans (TWA) in patients with nonischemic dilated cardiomyopathy (DCM).
<b>BACKGROUND</b>	One of the current major issues in DCM is to prevent sudden cardiac death (SCD). However, the value of the OHR of TWA as a prognostic indicator in DCM remains to be elucidated.
<b>METHODS</b>	We prospectively investigated 104 patients with DCM undergoing TWA testing. The end point of this study was defined as SCD, documented sustained ventricular tachycardia/ventricular fibrillation. Relations between clinical parameters and subsequent outcome were evaluated.
<b>RESULTS</b>	Forty-six patients presenting with TWA were assigned to one of the following two subgroups according to OHR for TWA of $\leq 100$ beats/min: group A ( $n = 24$ ) with OHR $\leq 100$ beats/min and group B ( $n = 22$ ) with $100 < \text{OHR} \leq 110$ beats/min. T-wave alternans was negative in 37 patients (group C) and indeterminate in 21 patients. The follow-up result comprised 83 patients with determined TWA. During a follow-up duration of $21 \pm 14$ months, there was a total of 12 arrhythmic events, nine of which included three SCDs in group A, two in group B and one in group C. The forward stepwise multivariate Cox hazard analysis revealed that TWA with an OHR $\leq 100$ beats/min and left ventricular ejection fraction were independent predictors of these arrhythmic events ( $p = 0.0001$ and $p = 0.0152$ , respectively).
<b>CONCLUSIONS</b>	The OHR of TWA is of additional prognostic value in DCM. (J Am Coll Cardiol 2002; 39:295–300) © 2002 by the American College of Cardiology

Nonischemic dilated cardiomyopathy (DCM) is a syndrome characterized by left or biventricular dilatation and systolic contractile dysfunction, with an incidence of five to eight cases per 100,000 population per year (1,2). Approximately 50% of patients with recently diagnosed DCM die within the first year (3), and the distribution between sudden and non-sudden (heart failure [HF]) deaths is approximately equal (4). Significant improvements in medical therapy, such as the development of angiotensin-converting enzyme inhibitors (5), beta-adrenergic blocking agents (6) and amiodarone (7) have been shown to improve the prognosis of patients with congestive HF. However, sudden cardiac death (SCD) is often the first clinically recognized manifestation of heart disease (8). Various approaches for predicting the risk of SCD, such as electrophysiologic testing (9,10), signal-averaged electrocardiogram (SAECG) (10–12), baroreceptor sensitivity (13) and heart rate (HR) variability (14,15) have been used to identify a high-risk subgroup. However, the positive predictive value of any of these measures of risk, used in combination with each other or with other clinical findings (10–12), has proven insufficient to predict SCD and, accordingly, to warrant implantable cardioverter defibrillator (ICD) therapy. Recently, the spectral method for detecting microvolt-level T-wave alter-

nans (TWA) was developed. Using this technique, the presence of subtle alternation in TWA was found to be strongly associated with inducibility of sustained ventricular tachycardia/ventricular fibrillation (SVT/VF) and has, therefore, been proposed as a powerful non-invasive tool for identifying high-risk patients with ischemic heart disease (16–21).

T-wave alternans is a threshold phenomenon, which inversely correlated with the ventricular fibrillation threshold in animal studies (19). Recent studies indicated that there is a specific HR threshold beyond which TWA continues to increase with increasing HRs (22,23). The concurrence of TWA and a sufficiently low HR is reportedly associated with increased cardiac risk under pathological conditions (24,25). However, the prognostic value of the onset heart rate (OHR) of TWA in patients with DCM remains to be elucidated. Therefore, the goal of this study was to clarify whether the OHR of TWA is of prognostic value in patients with DCM.

## METHODS

**Patient population.** We prospectively investigated 104 patients with DCM who were referred to the Kobe University School of Medicine Hospital and Himeji Cardiovascular Center between February 1997 and April 2000. All patients underwent both non-invasive and invasive evaluation, including TWA during ergometer exercise stress

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**Abbreviations and Acronyms**

DCM	= nonischemic dilated cardiomyopathy
ICD	= implantable cardioverter defibrillator
LVDd	= left ventricular end-diastolic diameter
LVEF	= left ventricular ejection fraction
NSVT	= nonsustained ventricular tachycardia
OHR	= onset heart rate
SAECG	= signal-averaged electrocardiogram
SCD	= sudden cardiac death
SVT/VF	= sustained ventricular tachycardia/ventricular fibrillation
TWA	= T-wave alternans

testing. All patients were in sinus rhythm. None of the patients had been treated with beta-blockers, angiotensin-converting enzyme inhibitors or beta-agonists before entry to this study. Nonischemic dilated cardiomyopathy was clinically diagnosed according to the criteria recommended by the World Health Organization and the National Heart, Lung and Blood Institute (1). The protocol of the study was explained to all patients, and informed consent was obtained from each patient.

**Measurement of TWA.** T-wave alternans was measured at rest and during controlled bicycle exercise testing using a CH 2000 system (Cambridge Heart, Inc., Bedford, Massachusetts) as previously described (26). The alternans analysis was performed blind to all clinical data. T-wave alternans was prospectively defined as positive when it was sustained with an alternans voltage of  $1.9 \mu\text{V}$  during exercise with an OHR  $\leq 110$  beats/min or below 70% of maximum predicted HR or  $1.0 \mu\text{V}$  at rest for a period of at least 1 min, provided that the alternans ratio was  $\geq 3$ . T-wave alternans was prospectively defined as negative if artifact-free criteria were met while the HR was maintained at a level of  $\geq 105$  beats/min. Otherwise, TWA was defined as indeterminate (19–21,26,27). The OHR for TWA was determined during the period when HR was stable and constant. To define the high-risk subgroup, TWA-positive patients were categorized according to the following value based on previous reports (22,28). The predetermined cut-off point of OHR for TWA of  $\leq 100$  beats/min represented the division between the two groups; group A consisted of the patients with OHR  $\leq 100$  beats/min and group B with  $100 < \text{OHR} \leq 110$ . T-wave alternans negative patients were defined as group C.

**Measurement of conventional risk markers.** Left ventricular end-diastolic diameter (LVDd) and the left ventricular ejection fraction (LVEF) were calculated by M-mode and two-dimensional echocardiography. The predetermined cut-off point of an LVEF  $\leq 35\%$  was used to define the high-risk group (29). Patients underwent 24 h of ambulatory monitoring during normal daily activities. Nonsustained ventricular tachycardia (NSVT) was defined as present if at least one episode of  $\geq 3$  consecutive premature beats at a rate of  $\geq 100$  beats/min was documented. The patients underwent SAECG recording. Orthogonal bipolar

**Table 1.** Patient Characteristics

Patients (n)	104
Age (yrs)	$52 \pm 15$
Gender: men	84
NYHA	$1.68 \pm 0.72$
NSVT (%)	33 (32%)
Medications at discharge (%)	
Digitalis	26 (25%)
Diuretics	49 (47%)
ACE inhibitor	73 (70%)
Beta-blocker	53 (51%)

ACE = angiotensin-converting enzyme; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association class.

X, Y and Z leads were recorded until a noise level of  $0.4 \mu\text{V}$  was reached using the standard techniques (Fukuda Denshi FDX-6521, Tokyo, Japan). The criteria for abnormality of the SAECG were defined as previously described (26).

**Follow-up.** Patients were prospectively followed. Survival status was obtained by telephone contact with the patients, their relatives or referring physician and from the review of hospital records. For patients who died in the hospital or at home, the cause of death was obtained from medical records, families and the local physician who had signed the death certificate. Patients were followed from the day of TWA testing until they suffered a cardiac event or until the most recent follow-up appointment. Sustained ventricular tachycardia was defined as a documented episode of tachycardia of ventricular origin at a rate of  $>100$  beats/min and lasting for  $>30$  s or resulting in hemodynamic collapse. Sudden cardiac death was defined as death from unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within 1 h of the onset of symptoms. The end point in this study was defined as SCD or documented SVT/VF. T-wave alternans determinate patients were analyzed in the follow-up result. The relationship between clinical parameters and subsequent clinical outcome was evaluated.

**Statistical analysis.** Values are expressed as means  $\pm$  SD for continuous variables and percentages for categorical variables. Patient groups were compared by the unpaired *t* test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Event-free curves were generated using the Kaplan-Meier method, and groups were compared by the log-rank test. Univariate predictors of arrhythmic events were evaluated using the Cox proportional hazards model. Significant factors by univariate Cox regression analysis were reassessed by forward stepwise selection manner with values for inclusion and elimination set at  $p = 0.20$ , respectively. A statistical probability of  $<0.05$  was considered significant.

**RESULTS**

**Study group.** The study group consisted of 104 patients with DCM: 84 men and 20 women with a mean age of  $52 \pm 15$  years. The clinical characteristics of these patients are shown in Table 1. Upon TWA testing, 70 patients (84%) were minimally symptomatic (New York Heart

**Table 2.** Clinical Characteristics and Results of Risk Stratification Tests for Both Groups

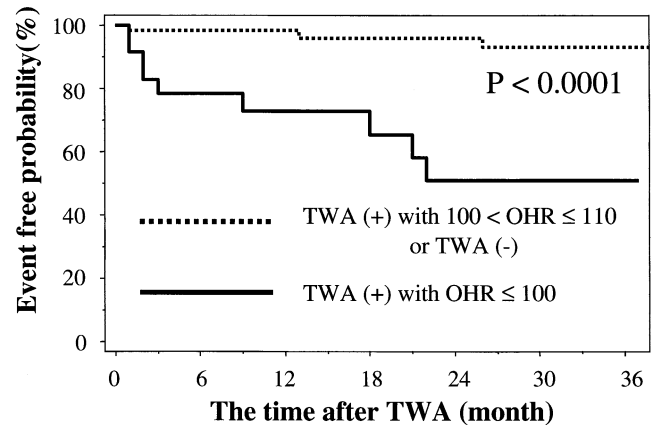
Variables	Group A	Group B	p Value
Patients	24	22	
Age	50 ± 17	52 ± 14	NS
HR (beats/min)	77 ± 9	81 ± 9	NS
BP (mm Hg)			
Systole	117 ± 22	123 ± 18	NS
Diastole	70 ± 11	75 ± 11	NS
NYHA I/II/III/IV	10/8/6/0	10/7/5/0	NS
Follow-up month	16 ± 14	19 ± 14	NS
Medication			
Digitalis	6	5	NS
Diuretics	12	9	NS
ACE	18	15	NS
Beta-blocker	11	10	NS
LVDd (mm)	66 ± 10	63 ± 9	NS
LVEF (%)	36 ± 12	38 ± 14	NS
NSVT ≥ 3 (%)	58	68	NS
SAECG (%)	38	18	NS

BP = blood pressure; HR = heart rate; LVDd = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SAECG = signal-averaged electrocardiogram. Other abbreviations as in Table 1.

Association functional class I or II), and 13 (16%) had moderate symptoms (New York Heart Association functional class III); 33 patients (32%) had a previous history of NSVT before TWA testing. Twenty-one patients were excluded from further study because of poor electrocardiogram recordings with noise (n = 4), frequent ectopic beats (n = 10) or a failure to achieve a HR of 105 beats/min (n = 7). Therefore, the follow-up result involved 83 patients.

**Arrhythmic events during follow-up.** In an average follow-up of 21 ± 14 months, arrhythmic events were observed in 12 (14%) of 83 patients. Sudden death occurred in three patients (4%), one with witnessed cardiac arrest; two sudden deaths were unwitnessed. Nine patients (11%) survived an episode of SVT/VF, which was documented by monitoring electrocardiograms.

**Results of TWA measurement.** Forty-six patients (44%) were TWA positive, and 37 (36%) were TWA negative. T-wave alternans was indeterminate in 21 patients (20%). T-wave alternans positive patients were classified into the following two subgroups according to OHR: group A included 24 patients (23%), and group B had 22 patients (21%). In both groups, clinical characteristics and the result of risk stratification tests were comparable (Table 2). There was no difference between group A and group B in terms of target HR. The OHR of TWA was not significantly correlated with the LVEF (r = 0.025; p = 0.87). There were nine cardiac events (three SCD, six SVT/VF) in group A and two (two SVT/VF) in group B. Only a patient in group C experienced SVT during the follow-up period. Kaplan-Meier analysis showed that the determination of OHR in combination with TWA could identify the high-risk subgroup among 83 DCM patients with TWA determinate results (log-rank test; p < 0.0001) (Fig. 1). Clinical parameters did not differ significantly between group B and group C, except



**Figure 1.** The arrhythmia-free survival in 83 patients with determined T-wave alternans (TWA) results. The event-free probability of patients with the onset heart rate (OHR) ≤100 beats/min was significantly lower than that of patients without OHR ≤100 beats/min.

for the high incidence of NSVT in group B. The statistical accuracy of TWA for arrhythmic events was shown in Table 3.

**Results of other non-invasive risk stratification tests.** The mean LVEF was 41 ± 13%, and LVDd was 62 ± 9 mm. During 24-h Holter monitoring, at least one episode of NSVT was recorded in 36 patients (43%). The SAECG was positive in 20 patients (24%). The event-free survival for 83 patients with determinate TWA results was examined according to LVEF, displayed in Figure 2 (log-rank test: p = 0.0087). The statistical accuracy of LVEF, SAECG, LVDd and NSVT for arrhythmic events is shown in Table 3.

**Predictors of arrhythmic events.** Univariate predictors of arrhythmic events are shown in Table 4. Neither age, gender, systolic blood pressure, diastolic blood pressure, New York Heart Association (NYHA) functional class nor SAECG was found to be statistically significant. To improve the predictive accuracy for arrhythmic events, we performed univariate analyses on the combination of TWA and OHR and on that of TWA and LVEF. The statistical accuracy of TWA-positive patients with OHR ≤100 beats/min and TWA-positive patients with LVEF ≤35% for arrhythmic events is shown in Table 3. T-wave alternans with OHR ≤100 beats/min was the best variable model of the prediction for arrhythmic events. In addition, the Cox hazard model analysis was used to examine the capability of identifying a high-risk subgroup within DCM. The forward stepwise Cox multivariate analysis indicated that TWA with OHR ≤100 beats/min and LVEF were independent predictors for identifying high-risk patients with DCM (Table 5).

## DISCUSSION

This is the first clinical study to elucidate the prognostic value of the OHR of TWA in patients with DCM. Our present study shows that in patients with DCM of low-to-moderate symptom status, the presence of TWA identified the arrhythmogenic substrate and was associated with a higher probability of major arrhythmic events. In these

**Table 3.** TWA, LVEF, SAECG, LVDd, NSVT and the Combination of TWA and the OHR or LVEF as Predictor of Event-Free Survival

	Se	Sp	PPV	NPV	PA	RR (95% CI)
TWA(+)	91.7	50.7	23.9	97.3	56.6	8.8 (1.2-65.4)
LVEF $\leq$ 35%	66.7	66.2	25.0	92.2	66.3	3.2 (1.0-9.7)
SAECG	41.7	78.9	25.0	88.9	73.5	2.3 (0.8-6.3)
LVDd $>$ 64 mm	66.7	66.2	25.0	92.2	66.3	3.2 (1.0-9.7)
NSVT $\geq$ 3	66.7	60.6	22.2	91.5	61.4	2.6 (0.9-8.0)
TWA(+) LVEF $\leq$ 35%	58.3	77.5	30.4	91.7	74.5	3.7 (1.3-10.4)
TWA(+) OHR $\leq$ 100 beats/min	75.0	78.9	37.5	94.9	78.3	7.4 (2.2-24.9)

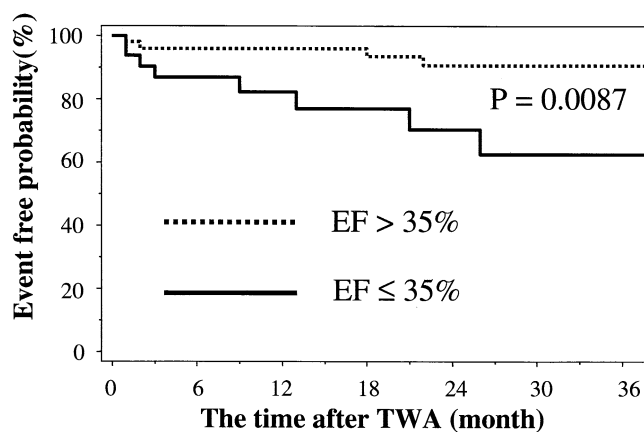
CI = confidence intervals; NPV = negative predictive value; OHR = onset heart rate; PA = predictive accuracy; PPV = positive predictive value; RR = relative risk; Se = sensitivity; SP = specificity; TWA = T-wave alternans. Other abbreviations as in Tables 1 and 2.

patients, the OHR of TWA added prognostic power to TWA when compared with LVEF or other risk stratification tests and clearly identified those patients with a potential high risk of SCD.

**Additional prognostic value of OHR in DCM.** Non-ischemic dilated cardiomyopathy is a common cause of congestive HF and represents another important substrate for ventricular arrhythmia developing into SVT/VF (3). Significant progress in medical treatment has reduced the mortality and morbidity of congestive HF (5-7), with nearly half of all deaths in DCM occurring suddenly due to SVT/VF (4). Unfortunately, the majority of SCDs occurs among low-risk patients, including those with NYHA functional class I or II. The ICD has been reported to be a beneficial therapy for the secondary prevention of SCD (30). However, such an effective strategy has limited population impact because the current indications for ICD therapy in patients with DCM include surviving an episode of cardiac arrest and having syncopal ventricular tachycardia or non-suppressible hemodynamically compromising ventricular arrhythmia (31). Whether patients with asymptomatic NSVT and severe left ventricular dysfunction should receive an ICD remains unclear as yet. Various non-invasive tools for determining risk have been reported by numerous studies, but the positive accuracy of these conventional tests (9-15) is not yet sufficiently powerful to warrant ICD.

Therefore, the need for a simple and accurate non-invasive method to stratify large sections of the population at potential risk from SCD is well recognized, as it would enable primary prevention. Recently, TWA was proposed as an effective non-invasive diagnostic tool that identifies high-risk patients with ischemic heart disease. However, simply assessing the presence of TWA alone in order to identify which patients with heart disease are at potential risk from SCD, presumably in relation to SVT/VF, carries its own risk in light of low specificity, low positive predictive value and low predictive accuracy (32) (Table 3).

At first we compared TWA with the SAECG, LVDd, NSVT, and LVEF of non-invasive risk tests. Grimm et al. (33) reported that SAECG was not useful for risk stratification in light of its low sensitivity (50%) and low positive predictive value (22%) for serious arrhythmic events during follow-up. Furthermore, they also reported that the measurements of NSVT and LVDd had univariate statistical significance, which is consistent with the results of this study (34). Hoffman et al. (29) reported that 84% of patients with idiopathic dilated cardiomyopathy with an LVEF  $<$ 35% died at a mean 39 months, compared with 46% of patients with an LVEF  $>$ 35%. Moreover, the preliminary data of the Marburg Cardiomyopathy study suggests a higher rate of TWA among patients with idiopathic dilated cardiomyopathy and an LVEF  $<$ 30% when compared with those with an LVEF of  $\geq$ 30% (35). Similar to their study, our data indicates that among the non-invasive tests, TWA and LVEF were also significant univariate predictors for arrhythmic events in patients with DCM. In addition, TWA yielded high sensitivity (92%) but relatively low specificity (51%), positive predictive value (24%) and predictive accuracy (57%), although when combined with the OHR of TWA, the OHR  $\leq$ 100 beats/min dramatically increased the specificity, positive predictive value and predictive accuracy to 79%, 38% and 78%, respectively. On the other hand, by combining TWA and LVEF, the specificity and predictive accuracy improved from 51% to 77% and from 57% to 75%, respectively, although positive predictive value changed only slightly (Table 3). The model of the combination of TWA and OHR was superior to that of TWA and LVEF for predicting arrhythmic events. Multivariate Cox regression analysis showed the greatest benefit



**Figure 2.** The arrhythmia-free survival in 83 patients with determined T-wave alternans (TWA) results according to left ventricular ejection fraction (EF).

**Table 4.** Univariate Predictors of Arrhythmic Events in Dilated Cardiomyopathy Patients With Determinate TWA Results

Prediction of Arrhythmic Events				
Variables	Parameter Estimate	Hazard Ratio	95% CI	p Value
NSVT	1.2220	3.39	1.01 to 11.39	0.0479
LVDd	0.0571	1.06	1.00 to 1.12	0.0368
TWA	2.4765	11.90	1.53 to 92.59	0.0180
LVEF	-0.0681	0.93	0.89 to 0.98	0.0108
TWA(+) LVEF ≤ 35%	1.6161	5.03	1.58 to 16.01	0.0062
TWA(+) OHR ≤ 100 beats/min	2.2759	9.79	2.62 to 36.21	0.0007

Abbreviations as in Tables 1 to 3.

in adding OHR to TWA for predicting arrhythmic events when compared with LVEF (Table 5). The OHR in TWA was the most powerful tool to stratify the high-risk subgroup among patients with DCM, and it provided additional prognostic value in risk stratification.

**Potential pathological mechanism linking the OHR of TWA and SCD in DCM.** T-wave alternans is an electrocardiogram phenomenon consisting of beat-to-beat changes in T-wave amplitude and duration of ventricular repolarization and is associated with vulnerability to ventricular tachyarrhythmias (16-21). In addition, the reported clinical factors that modulate TWA are ischemia, HR and sympathetic activation. Among these factors, TWA has also been reported to be critically dependent on HR and to have a threshold effect as the HR is elevated (22,23). Pastore *et al.* (25) demonstrated that membrane repolarization alternates with the opposite phase between the neighboring cells (*i.e.*, discordant alternans) above a critical HR threshold, which creates large spatial dispersion of repolarization, developing into reentrant ventricular fibrillation. Furthermore, recent studies indicated that TWA is frequently observed at relatively low HRs under pathological conditions including a long QT syndrome (24,25). In fact, in this study, those patients having sustained alternans occurring with the OHR ≤100 beats/min had a high incidence of severe ventricular tachycardia. In addition, our results demonstrated that the determination of OHR concomitantly with the presence of TWA made the specificity, positive predictive value and predictive accuracy improve dramatically in predicting arrhythmic events in DCM. Thus, the OHR of TWA appears to be a useful tool in identifying the presence of arrhythmogenic substrate, the probability of an arrhythmia-initiating event and vulnerability of substrate to initiating events. It has not been sufficiently evaluated why lower HR

thresholds for alternans increase cardiac risk, especially arrhythmic risk under pathological circumstances, but its potential mechanism may be mainly due to an underlying disturbance in cardiac repolarization that is dependent on HR, in that impaired functions of several ion channels involving the potassium channel, sodium channel or sodium channel electrogenically interacting with the calcium channel probably reduce the HR threshold required to elicit TWA (24,25,36).

**Implications of this study.** In the prognostic non-invasive clinical procedures of risk stratification in DCM, the detection of TWA plays a fundamental role in identifying those patients at a potential high risk of SCD. T-wave alternans testing was the best risk stratification method for predicting arrhythmic events in DCM, consistent with previous studies (16-21,23,24,26,35,37,38). Furthermore, in this study, the OHR of TWA provided new information on the risk stratification of patients with DCM. Given the available data, we speculate that the OHR provoking TWA in this prognostic stratification of patients with DCM is strictly linked to electrical instability, arrhythmogenic substrate and the underlying disturbance in cardiac repolarization. Our study suggests that the OHR of TWA should be taken into consideration when stratifying the high-risk subgroup in DCM. Therefore, the determination of the OHR in TWA must be the primary preventative approach for the indication of ICD implantation in patients with DCM. By further electrophysiological investigations, the role of OHR as an inducer of TWA in the pathogenesis of DCM will provide an important insight into the mechanism of SCD.

**Study limitations.** Several limitations should be acknowledged in this study. One limitation was the low number of arrhythmic events, which may determine instability of the results by multivariate analysis. Second, within the sample population, the cut-off point of OHR for TWA was defined as ≤100 beats/min, which worked well in differentiating the high-risk subgroup from the low-to-moderate-risk patients with DCM. Third, many of the patients with DCM had atrial fibrillation, frequent ectopic beats or were pacemaker-dependent. Therefore, we had to exclude them because it was not possible to analyze their electrocardiograms. However, such patients, in light of the clinical course, are considered to be high-risk, and they are less likely to suffer SCD due to SVT/VF.

**Table 5.** Multivariate Predictors of Arrhythmic Events in Dilated Cardiomyopathy Patients With Determinate TWA Results

Variables	Parameter Estimate	Hazard Ratio	95% CI	p Value
LVEF	-0.06523	0.94	0.89 to 0.99	0.0152
TWA(+) OHR ≤ 100 beats/min	2.18983	8.93	2.38 to 33.52	0.0001

Abbreviations as in Tables 1 to 4.

**Conclusions.** T-wave alternans is a powerful risk stratifier for patients potentially at risk from SCD. The OHR of TWA has additional prognostic value in patients with DCM. Therefore, it appears likely that it will be the most useful clinical predictor of subsequent arrhythmic events in low-to-moderate-risk patients with DCM.

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