Average T-wave alternans activity in ambulatory ECG records predicts sudden cardiac death in patients with chronic heart failure

Short title: Average T-wave alternans and sudden cardiac death

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Acknowledgment: This work was supported by CIBER de Bioingeniería, Biomateriales y Nanomedicina through Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional, and by Projects TEC2010-21703-C03-02 of Ministerio de Ciencia e Innovación (MICINN), and GTC T-30 from DGA (Spain).

Conflict of interest: none

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Abstract

Background
T-wave alternans (TWA) is a well documented noninvasive ECG method useful for identifying patients at risk for sudden cardiac death (SCD).

Objective
The purpose of this study was to evaluate if the long-term average TWA activity on Holter monitoring provides prognostic information in patients with chronic heart failure (CHF).

Methods
Twenty-four-hour Holter ECGs from 650 ambulatory patients with mild to moderate CHF were analyzed in the study. Average TWA activity was measured using a fully-automated multilead technique, and two indices were proposed to quantify TWA: an index quantifying the average TWA activity in the whole recording (AAI), which was used to define a positive/negative TWA test, and an index quantifying the average TWA activity at heart rates between 80 and 90 bpm (AAI90).

Results
Patients were divided into TWA positive (TWA+) and TWA negative (TWA–) groups by setting a cut point for AAI of 3.7 µV, corresponding to the 75th percentile of the distribution of AAI in the population. After a median follow-up of 48 months, survival rate was significantly higher in group TWA– for cardiac death (CD) and SCD (p = 0.017 and p = 0.001 respectively). Multivariate Cox proportional hazards analysis revealed that both TWA+ and AAI90 were associated with SCD with hazard rates of 2.29 (p = 0.004) and 1.07 per µV (p = 0.046) respectively.

Conclusion
The average TWA activity automatically measured from Holter ECGs predicts SCD in patients with CHF.
Keywords

T-wave alternans; Multilead analysis; Holter ECG; Chronic heart failure; Sudden cardiac death

Abbreviations

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
bpm = beats per minute
CD = cardiac death
CI = confidence interval
CHF = chronic heart failure
HR = heart rate
ICD = implantable cardioverter defibrillator
LV = left ventricle
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
SCD = sudden cardiac death
TWA = T-wave alternans
Introduction

Sudden cardiac death (SCD) remains an important cause of mortality in patients with mild-to-moderate heart failure (NYHA class II and III). Although previous studies have shown the benefit of ICD implantation in this type of population (1), the cost effectiveness of the therapy is low, as only a minority of patients with implanted ICD benefitted from this therapy during the follow-up period (2). Therefore, finding effective techniques for risk stratification remains a clinical problem.

T-wave alternans (TWA) is a beat-to-beat alternation in the morphology of the ST segment and the T wave, and reflects temporal and spatial heterogeneity of repolarization (3). The utility of TWA testing during ambulatory monitoring has been subject to intense investigation in recent years (4) (5). In ambulatory recordings, the maximum amplitude of TWA has been semi-automatically quantified using the Modified Moving Average (MMA) method (4), and then compared to a cut point to decide if such TWA level should be considered normal or abnormal. This binary TWA index is a strong predictor of arrhythmic events and cardiac mortality in different populations (5). In the last years, quantitative analysis of TWA amplitude as a continuous variable has also been shown to indicate an increasing cardiac risk (6) (7).

In this work, we present a fully-automated method to analyze TWA in ambulatory records, and demonstrate that the average TWA activity in a 24-hour period is an independent predictor of SCD and cardiac death (CD) in patients with chronic heart failure (CHF). Following the approaches of existing studies (6) (7) (8), we propose two risk indices: a binary index that defines a positive/negative TWA test, and a quantitative continuous index that reflects an increasing degree of cardiac risk.
Methods

Study population

Consecutive patients with symptomatic CHF corresponding to NYHA classes II and III were enrolled in the MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective, multicenter study designed to assess risk predictors for cardiovascular mortality in ambulatory patients with CHF (9). The study protocol was approved by institutional investigation committees and all patients signed informed consent. The Holter recordings of 650 patients with sinus rhythm were available for the present study.

The collection of clinical data for this population was reported in previous studies (9) (10). The clinical characteristics of studied patients as well as medication are listed in Table 1. No medications were withdrawn during Holter monitoring.

Follow-up and end-points

Patients were followed up every 6 months for a median of 48 months, with total mortality as a primary end point, and CD and SCD as secondary end points. Information about end points was obtained from medical records, patients’ physicians, and family members. Cardiac death was defined as death from cardiac causes, but excluding such vascular causes as pulmonary embolism, aortic aneurysm dissection/aneurysm, or stroke. Sudden cardiac death was defined as: a) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac was obvious, b) an unwitnessed death (<24 hours) in the absence of preexisting progressive circulatory failure or other causes of death, or c) death during attempted resuscitation. End points were reviewed and classified by the MUSIC Study Endpoint Committee. Table 2 summarizes the number of deaths in the study population during the median 48-month period.
Measurement of TWA

Twenty-four-hour ambulatory ECG recordings (XYZ orthogonal leads, 200 Hz sampling rate) were performed using SpiderView recorders (ELA Medical, Sorin Group, Paris, France). Heart beats were detected and labeled with the Aristotle ECG analysis software (11). Baseline wander was cancelled using a cubic-splines technique (12). Automatic TWA analysis was performed on every ECG recording in three steps: 1) selection of signal segments that were suitable for automatic analysis, 2) estimation of the TWA amplitude in those segments, and 3) computation of indices reflecting the general TWA activity through the record.

Selection of segments: ECGs were analyzed in segments of 128 beats with a 50% overlap between adjacent segments. Each segment was included in automatic TWA analysis if 1) the difference between the maximum and the minimum instantaneous HR during the segment was ≤ 20 beats per minute (bpm), and 2) at least 80% of the beats fulfilled the following conditions: a) it was labeled as normal sinus beat, b) the difference between the RR interval of that beat and the previous RR interval was ≤ 150 ms, and c) the difference between the baseline voltage measured at the PQ segment in that beat and the one measured in the preceding beat was ≤ 300 µV.

Estimation of TWA amplitude: If an ECG segment (denoted as the kth segment) was suitable for analysis, a measurement of the TWA amplitude in that segment (denoted as $V_k$) was computed with a multilead scheme that combines a technique called periodic component analysis ($\pi$CA) with the Laplacian Likelihood Ratio (LLR) method for TWA analysis (13).

First, the ECG segment was low-pass filtered at 15 Hz to eliminate noise that could affect the estimation of TWA amplitudes. Figure 1a shows an example of an ECG signal with TWA after baseline cancellation and low-pass filtering.
Then, the three leads of the ECG segment were linearly combined to obtain a new lead in which the visibility of TWA over noise was maximized (Figure 1b). This combination can be expressed as:

\[
\text{combined lead} = a \cdot \text{lead } X + b \cdot \text{lead } Y + c \cdot \text{lead } Z
\]

where coefficients \( a, b \) and \( c \in \mathbb{R} \) were specifically computed for each segment with the \( \pi \)CA technique, and depended on how the periodic components of the signal were distributed among the ECG leads. Using \( \pi \)CA for TWA analysis reveals TWA episodes embedded in noise that can be undetectable if leads are analyzed separately (14).

Finally, TWA amplitude was measured in the new combined lead as follows. In each beat, an interval of 350 ms after the end of the QRS was selected (ST-T complex, marked with dashed lines in Figure 1b). The median difference between ST-T complexes of even and odd beats was computed with the LLR method (13), obtaining an estimation of the median TWA waveform in the segment (Figure 1c). The amplitude of TWA in the segment \( (V_k) \) was finally measured as the absolute value of the mean of the estimated TWA waveform (Figure 1c).

**Computation of TWA indices:** two sets of indices were computed. The first set reflected the average amplitude of TWA and the second set quantified the maximum TWA amplitude in the segments under study.

The first set consisted of the Average Alternans Index (AAI) and the heart-rate-restricted Average Alternans Indices (AAI\(_h\)). AAI was computed as the average of all \( V_k \) in the ECG, and reflected the average TWA activity during the 24-hour period. Note that, for instance, a 24-hour ECG that presented TWA only during 5% of the time with an amplitude of 60 \( \mu V \) would have an AAI = 3 \( \mu V \), which means that the AAI cannot be interpreted as a direct measurement of the TWA amplitude at any single point. Restricted Average Alternans Indices (AAI\(_h\)) were computed as the average of only those \( V_k \) measured in segments with average HR ranging
from X-10 to X bpm, with \( X = \{70, 80, 90, 100, 110\} \). For instance, AAI_{70} would reflect the average TWA activity at HR between 80 and 90 bpm in the 24 hours.

The second set consisted of the Maximum Alternans Index (MAI) and the restricted Maximum Alternans Indices (MAI_{x}). MAI was computed as the maximum of all \( V_k \) in the ECG. Restricted Maximum Alternans Indices (MAI_{x}) were computed as the maximum of the \( V_k \) measured in segments with average HR ranging from X-10 to X bpm, with \( X = \{70, 80, 90, 100, 110\} \). For instance, MAI_{90} would represent the maximum TWA amplitude at HR between 80 and 90 bpm in the 24 hours.

Statistical Analysis

Data are presented as mean \( \pm \) standard deviation for continuous variables, and number and percentage for categorical variables. Two-tailed Mann-Whitney and Fisher’s exact tests were used for univariate comparison of quantitative and categorical data respectively. Survival probability was estimated using Kaplan-Meier methods with comparison of cumulative events using log-rank tests. The prognostic value of TWA indices in predicting the end points was determined with univariate and multivariate Cox proportional hazards analyses. Cox regression models were built considering a significance \( \leq 0.05 \) as the criterion for entry into a model. Correlation between quantitative TWA indices and HR was evaluated with Spearman’s correlation coefficient. A \( p \)-value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (version 15.0; SPSS Inc. Chicago, IL).

Results

The mean value of AAI in the study population was 3.3 \( \pm \) 2.1 \( \mu \)V, and the 25th, 50th and 75th percentiles were 2.4, 2.9 and 3.7 \( \mu \)V respectively (Figure 2). The AAI 75th percentile varied less than 1 \( \mu \)V for different subgroups such as NYHA class II vs. class III patients (3.64 vs. 3.76 \( \mu \)V respectively), and patients with vs. without SCD (4.38 vs. 3.61 \( \mu \)V respectively). A weak
negative correlation was found between AAI and the average HR in the Holter recording ($\rho = -0.083$, $p$-value = 0.035).

The mean values of $\text{AAI}_X$ were $\text{AAI}_{70} = 2.8 \pm 1.9$ $\mu$V, $\text{AAI}_{80} = 3.3 \pm 2.3$ $\mu$V, $\text{AAI}_{90} = 3.9 \pm 2.4$ $\mu$V, $\text{AAI}_{100} = 5.0 \pm 3.1$ $\mu$V and $\text{AAI}_{110} = 6.1 \pm 5.5$ $\mu$V. The mean values of $\text{AAI}_X$ increased with local HR, and there were significant differences between indices from all adjacent HR intervals (Figure 2). Not all ECGs presented a HR span from 60 to 110 bpm; also, all segments within a certain HR range were discarded for TWA analysis in some recordings (according to the inclusion rules described in the Methods section). Therefore, not every $\text{AAI}_X$ could be computed for every patient. The percentages of indeterminate values for the entire population are included in Figure 2. The correlation between $\text{AAI}_{90}$ and the average HR in the Holter recording was $\rho = -0.474$ ($p$-value < 0.001).

Patients were divided into TWA positive (TWA+) and negative (TWA−) groups by setting a cut point for AAI of 3.7 $\mu$V, corresponding to the 75th percentile of the distribution of AAI in the population. Of the 650 studied patients, 493 (75.8%) were included in the TWA− group ($\text{AAI} \leq 3.7$ $\mu$V) and 157 (24.2%) in the TWA+ group ($\text{AAI} > 3.7$ $\mu$V).

Upon comparison of clinical variables between TWA+ and TWA− groups (Table 1), a significant difference was found for wide QRS (QRS > 120 ms). Patients with wide QRS were more likely than patients with narrow QRS (QRS $\leq 120$ ms) to have a TWA+ outcome (29.9% vs. 19.4%, $p=0.002$). However, AAI was not significantly different in wide vs. narrow QRS patients: $3.44 \pm 1.45$ vs. $3.16 \pm 2.44$ $\mu$V ($p=0.085$).

Survival rate was significantly higher in group TWA− for primary and secondary end points (Table 2). Univariate Cox analysis revealed that a TWA+ outcome was associated with all-cause mortality, CD, and SCD (Table 3). No association was found between a TWA+ outcome and non-cardiac mortality. Multivariate Cox proportional hazards model were constructed by adjusting for (1) age, gender, NYHA class, LVEF < 35, and diabetes, and (2) use of beta-blockers,
amiodarone and ACE or ARB inhibitors in addition to covariables in model (1). For model (1), a TWA+ outcome was the variable most significantly associated to SCD risk, with a hazard ratio of 2.38 (95% CI: 1.37-4.14, p=0.002), similar to LVEF < 35% (hazard ratio 2.55, 95% CI: 1.35-4.80, p=0.004). For model (2), a TWA+ outcome was the covariable with the second highest hazard ratio (2.29) after LVEF < 35% (hazard ratio 2.65, 95% CI: 1.39-5.03, p=0.003). Figure 3 shows the event-free curves for CD and SCD. In patients with maximum HR < 90 bpm (N=6), a TWA+ outcome was more predictive of SCD than in the whole population, with a univariate hazard ratio of 6.06 (95% CI: 1.10 – 33.25, p=0.038).

Univariate Cox analysis was performed for all AAIx, and only AAI90 was found to be associated with SCD. Multivariate analysis confirmed this association (Table 3). AAI90 was not associated to all-cause mortality or non-cardiac mortality.

The mean value of MAI in the study population was 31.4 ± 25.3 µV, and the percentiles 25th, 50th and 75th were 17.9, 24.7 and 38.0 µV respectively (Figure 2). No association to CD or SCD risk was found for MAI as a continuous variable or as a categorical variable after dichotomization with the 75th percentile. The mean values of MAIx were MAI70 = 16.1 ± 13.1 µV, MAI80 = 17.2 ± 10.6 µV, MAI90 = 17.5 ± 12.1 µV, MAI100 = 19.7 ± 12.1 µV and MAI110 = 20.6 ± 22.6 µV. MAIx were not significantly associated to CD or SCD risk according to Cox univariate and multivariate analyses.

**Discussion**

This study demonstrates that the quantification of the average TWA activity over long periods is a strong, independent predictor of SCD in patients with CHF. Two indices quantifying the TWA activity in a 24-hour period, AAI and AAI90, independently predicted CD and SCD, but did not predict non-cardiac mortality. These findings support the hypothesis that elevated TWA activity reflects abnormal cardiac function predisposing to cardiac death.
The results of recent studies involving different types of TWA analysis in similar populations have led to divergent conclusions. In the SCD-Heft study (15), TWA measured using the Spectral Method during submaximal treadmill exercise did not predict arrhythmic events or mortality in patients with symptomatic heart failure and LV systolic dysfunction. On the other hand, results in the EPHESUS study (16) (involving post-myocardial infarction patients with LV dysfunction) and in (17) (involving patients with LV dysfunction) showed that maximal TWA measured in ambulatory records using the MMA technique with posterior visual inspection predicted SCD and CD respectively. In our study, the average TWA activity in 24 hours (AAI) was the covariable most strongly associated to the risk of SCD.

In our population, only a weak correlation was found between AAI and the patient’s HR, which indicates that AAI is not merely a surrogate measure of the patient’s HR, but also reflects the influence of HR-independent factors in TWA. Therefore, AAI may provide a measure of the extent of cardiac vulnerability, because a higher influence of HR-independent factors in TWA amplitude reflects a higher degree of cardiac electrical instability (18).

This finding does not contradict the well described fact that, for a particular patient, instantaneous TWA amplitudes rise with HR (as reflected by AAI indices in Figure 2). This effect can be observed, for example, in the AAI of the first patient enrolled in the study with SCD and the first patient who survived the follow-up period: for the SCD patient, AAI70=1.68 µV, AAI90=3.16 µV, AAI90=4.68 µV, and AAI100=5.01 µV; for the survivor, AAI70=1.12 µV, AAI90=1.57 µV, AAI90=1.83 µV, and AAI100=2.38 µV. In a patient with high cardiac risk, we would expect a lower onset HR (the HR at which TWA can be elicited) than in a low risk patient (19). Therefore, in a high risk patient, TWA would appear more often during the 24-h period, and with higher magnitude for a given HR, so the resulting 24-h average index (AAI) would be higher than in a low risk patient. If we then assume that the average HR might be lower in a high risk patient, we would obtain a negative correlation between AAI and average HR. This
would also explain the negative correlation between AAI<sub>90</sub> and HR. In the example, the SCD patient had an average HR of 76 bpm and an AAI=3.80 µV, whereas the survivor had an average HR of 93 bpm and an AAI=2.22 µV.

The prognostic value of quantitative TWA measurements is increasingly being studied (6) (7) (8). In this study, an index of quantitative TWA (AAI<sub>90</sub>) independently predicted SCD. Higher magnitudes of TWA are known to predict a greater risk of serious outcomes when measured at moderate heart rates (3). For TWA to predict cardiovascular events, maximum HR limits ranging from 100 to 125 bpm are usually considered (18). In this study, the average TWA activity was associated to SCD when measured at lower rates, between 80 and 90 bpm (AAI<sub>90</sub>). A possible explanation for this difference is that heart failure lowers the HR threshold to elicit TWA (20). This finding was consistent with results by Tanno et al. (21), who demonstrated that higher TWA at HR ≤ 90 bpm were associated to an increasing incidence of cardiac events.

Unsupervised maximum TWA amplitudes, (MAI and MAI<sub>X</sub>) did not predict cardiac risk. Although the values obtained for MAI were comparable to maximum TWA amplitudes reported in the literature (between 30 and 60 µV), no significant association was found between MAI and risk of SCD or CD. This was not unexpected, since measuring local TWA amplitudes without testing for its significance, either visually or automatically, can lead to inaccurate results due to noise and artifacts (22). In recent studies with ambulatory ECGs (16) (17) (23) (24), the maximum TWA amplitude in a record was measured with the MMA method, and then was visually verified.

We found that quantifying the average TWA activity (AAI) instead of the maximum amplitude (MAI) eliminates the necessity of visually discarding erroneous measurements, and allows the prediction of CD and SCD in the study population. Long-term averaging of cardiac measurements has been applied to quantify subtle phenomena such as heart rate turbulence (25), deceleration capacity (26) or baroreflex sensitivity (27). In this study we applied long-term
averaging to produce a reliable and noise insensitive characterization of TWA in ambulatory recordings. To our best knowledge, the method presented here is the first one that allows a multilead, fully-automated computation of TWA markers of cardiac risk in ambulatory ECGs.

Several limitations of this work need to be acknowledged. First, only patients with sinus rhythm were included in the study. Also, although results indicate that the average TWA activity over a 24-hour period provides important prognostic information in patients with CHF, it would be premature to extend our observations to other groups. The use of a 75th percentile cut point for TWA measures is a common starting point when a technique is first tested on a population (28) (29), but additional prospective evaluation is still required, particularly on the applicability of the cut point derived in this study.

Conclusion

Fully-automated analysis of TWA in ambulatory ECGs can be a robust tool for risk stratification. The average TWA activity over a 24-hour period provides important prognostic information in patients with CHF. Two novel indices, AAI and AAI_{90}, are proposed to quantify the average TWA activity, and are found to be strong independent predictors of SCD.

References


### Table 1: Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Overall Population (n = 650)</th>
<th>TWA – (n = 493)</th>
<th>TWA + (n = 157)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 12</td>
<td>63 ± 11</td>
<td>64 ± 13</td>
<td>0.091</td>
</tr>
<tr>
<td>Gender (men)</td>
<td>462 (71.1%)</td>
<td>350 (71.0%)</td>
<td>112 (71.3%)</td>
<td>0.999</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>117 (18.0%)</td>
<td>87 (17.6%)</td>
<td>30 (19.1%)</td>
<td>0.721</td>
</tr>
<tr>
<td>LVEF ≤ 35</td>
<td>356 (54.8%)</td>
<td>262 (53.1%)</td>
<td>94 (59.9%)</td>
<td>0.142</td>
</tr>
<tr>
<td>QRS &gt; 120 ms</td>
<td>294 (45.2%)</td>
<td>206 (41.8%)</td>
<td>88 (56.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>245 (37.7%)</td>
<td>190 (38.5%)</td>
<td>55 (35.0%)</td>
<td>0.451</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>454 (69.8%)</td>
<td>350 (71.0%)</td>
<td>104 (66.2%)</td>
<td>0.273</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>59 (9.1%)</td>
<td>43 (8.7%)</td>
<td>16 (10.2%)</td>
<td>0.632</td>
</tr>
<tr>
<td></td>
<td>Overall Population</td>
<td>TWA – (n = 493)</td>
<td>TWA + (n = 157)</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>ARB or ACE inhibitors</td>
<td>573 (88.2%)</td>
<td>441 (89.4%)</td>
<td>132 (84.1%)</td>
<td>0.088</td>
</tr>
<tr>
<td>Average heart rate (bpm)</td>
<td>75 ± 12</td>
<td>76 ± 12</td>
<td>75 ± 12</td>
<td>0.581</td>
</tr>
<tr>
<td>Maximum heart rate (bpm)</td>
<td>122 ± 26</td>
<td>123 ± 27</td>
<td>119 ± 25</td>
<td>0.100</td>
</tr>
<tr>
<td>Heart rate range (bpm)</td>
<td>65 ± 28</td>
<td>63 ± 27</td>
<td>66 ± 28</td>
<td>0.204</td>
</tr>
</tbody>
</table>

Data are presented as absolute frequencies and percentages, and as mean ± standard deviation.

**Table 2: Events during follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Overall Population</th>
<th>TWA –</th>
<th>TWA +</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>146 (22.5%)</td>
<td>99 (20.1%)</td>
<td>47 (30.0%)</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>CD</td>
<td>119 (18.3%)</td>
<td>81 (16.4%)</td>
<td>38 (24.2%)</td>
<td><strong>0.033</strong></td>
</tr>
<tr>
<td>SCD</td>
<td>52 (8.0%)</td>
<td>30 (6.1%)</td>
<td>22 (14.0%)</td>
<td><strong>0.003</strong></td>
</tr>
</tbody>
</table>

Data expressed as absolute frequencies and percentages.
### Table 3. Association of TWA indices with mortality

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate&lt;sup&gt;(1)&lt;/sup&gt;</th>
<th>Multivariate&lt;sup&gt;(2)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AAI &gt; 3.7 μV</td>
<td>1.62 (1.15 – 2.29)</td>
<td>0.006</td>
<td>1.54 (1.09 – 2.19)</td>
</tr>
<tr>
<td>AAI&lt;sub&gt;90&lt;/sub&gt;</td>
<td>1.04 (0.99 – 1.10)</td>
<td>0.150</td>
<td>1.05 (0.98 – 1.11)</td>
</tr>
<tr>
<td><strong>CD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAI &gt; 3.7 μV</td>
<td>1.60 (1.09 – 2.35)</td>
<td>0.017</td>
<td>1.54 (1.04 – 2.26)</td>
</tr>
<tr>
<td>AAI&lt;sub&gt;90&lt;/sub&gt;</td>
<td>1.05 (1.00 – 1.11)</td>
<td>0.051</td>
<td>1.06 (1.00 – 1.13)</td>
</tr>
<tr>
<td><strong>SCD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAI &gt; 3.7 μV</td>
<td>2.48 (1.43 – 4.30)</td>
<td>0.001</td>
<td>2.38 (1.37 – 4.14)</td>
</tr>
<tr>
<td>AAI&lt;sub&gt;90&lt;/sub&gt;</td>
<td>1.07 (1.01 – 1.15)</td>
<td>0.041</td>
<td>1.07 (1.00 – 1.15)</td>
</tr>
</tbody>
</table>

<sup>(1)</sup> Adjusted model includes age, gender, NYHA class, LVEF < 35, and diabetes.

<sup>(2)</sup> Adjusted model includes covariables in (1) plus use of betablockers, amiodarone, and ARB or ACE inhibitors.
Figure 1: Example of TWA amplitude estimation. (a) ECG segment selected for automatic analysis after low-pass filtering and baseline cancellation. (b) Combined lead, computed with periodic component analysis. (c) Median TWA waveform in the segment, estimated with the Laplacian likelihood ratio method, and absolute TWA amplitude in the segment $V_k = 18.5 \mu V$. 
Figure 2: Top: boxplot of the average alternans indices computed in the 24 hours (AAI), and in intervals with HR in the range of X-10 to X bpm (AAIx). Bottom: boxplot of the maximum alternans indices computed in the 24 hours (MAI), and in intervals with HR in the range of X-10 to X bpm (MAIx). The number (percentage) of records in which indices could be computed is indicated above the boxes. Significant differences between the medians of adjacent AAIx and MAIx boxes are indicated by * (p < 0.05) and ** (p < 0.001).
Figure 3: Event-free curves for CD (top) and SCD (bottom)