Repolarization Heterogeneity Measured With T-Wave Area Dispersion in Standard 12-Lead ECG Predicts Sudden Cardiac Death in General Population

BACKGROUND: We developed a novel electrocardiographic marker, T-wave area dispersion (TW-Ad), which measures repolarization heterogeneity by assessing interlead T-wave areas during a single cardiac cycle and tested whether it can identify patients at risk for sudden cardiac death (SCD) in the general population.

METHODS AND RESULTS: TW-Ad was measured from standard digital 12-lead ECG in 5618 adults (46% men; age, 50.9±12.5 years) participating in the Health 2000 Study—an epidemiological survey representative of the Finnish adult population. Independent replication was performed in 3831 participants of the KORA S4 Study (Cooperative Health Research in the Region of Augsburg; 49% men; age, 48.7±13.7 years; mean follow-up, 8.8±1.1 years). During follow-up (7.7±1.4 years), 72 SCDs occurred in the Health 2000 Survey. Lower TW-Ad was univariately associated with SCD (0.32±0.36 versus 0.60±0.19; $P<0.001$); it had an area under the receiver operating characteristic curve of 0.809. TW-Ad (≤0.46) conferred a hazard ratio of 10.8 (95% confidence interval, 6.8–17.4; $P<0.001$) for SCD; it remained independently predictive of SCD after multivariable adjustment for clinical risk markers (hazard ratio, 4.6; 95% confidence interval, 2.7–7.4; $P<0.001$). Replication analyses performed in the KORA S4 Study confirmed an increased risk for cardiac death (unadjusted hazard ratio, 5.5; 95% confidence interval, 3.2–9.5; $P<0.001$; multivariable adjusted hazard ratio, 1.9; 95% confidence interval, 1.1–3.5; $P<0.05$).

CONCLUSION: Low TW-Ad, reflecting increased heterogeneity of repolarization, in standard 12-lead resting ECGs is a powerful and independent predictor of SCD in the adult general population.

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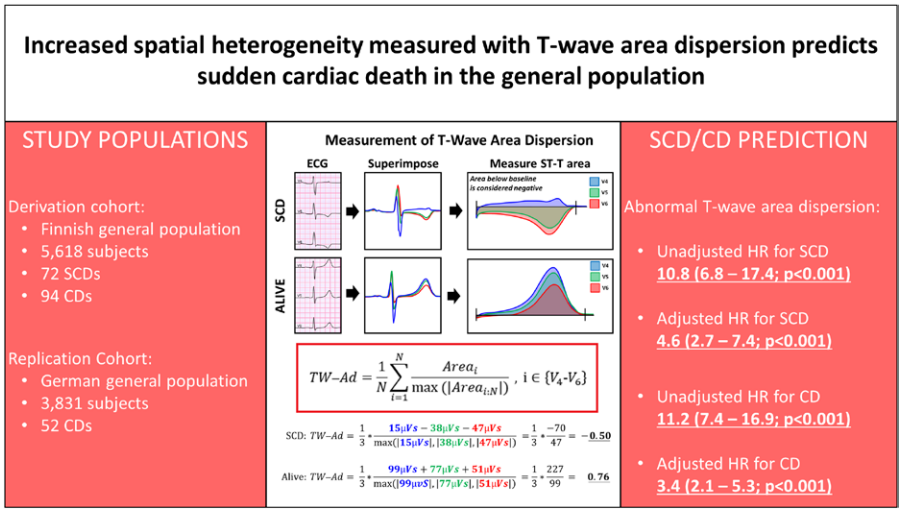

Identifying patients at elevated risk for sudden cardiac death (SCD) remains a clinical dilemma, especially in the general population, where the majority of SCDs occur.[1] Wide-spread use of standard 12-lead ECG offers a low-cost and easily accessible platform for noninvasive identification of patients at risk for SCD.

WHAT IS KNOWN?

- Sudden cardiac death (SCD) is the most common and often the first manifestation of coronary heart disease. It is estimated to cause ≈40% to 50% of the annual cardiovascular deaths, claiming ≈1 to 2 per 1000 lives each year in the developed countries.
- There is a great need for means to identify subjects at risk for SCD, especially in the general population, where the majority of SCDs occur. Recently, the noninvasive identification of high-risk patients has focused on the analysis of ventricular repolarization from ECG, as repolarization abnormalities have been shown to predispose to the onset of life-threatening ventricular arrhythmias and SCD.

WHAT THE STUDY ADDS?

- We have developed a novel ECG risk marker that builds on T-wave area measurements and spatial T-wave heterogeneity, namely T-wave area dispersion, which can be measured automatically and accurately from standard 12-lead ECG and is predictive of impending SCD.
- In our study, abnormal T-wave area dispersion was the strongest ECG-based risk marker and was associated with 4.6-fold adjusted risk for SCD.
- T-wave area dispersion has the potential to be used as a means of initial screening for SCD risk in the general population.

Nearing et al[2] proposed a method of measuring T-wave heterogeneity based on the Newton second central moment technique. This method quantifies the dispersion of T-wave morphology between left precordial leads during a single cardiac cycle. Increased T-wave heterogeneity measured with this method has been shown to be predictive of impending ventricular arrhythmias[3] and SCD.[4] However, in patients with flat or inverted T waves across the studied leads, measurement of interlead dispersion of repolarization can lead to low heterogeneity values, despite the altered repolarization sequence indicated by the abnormal T waves. Considering the prognostic value of minor ST-T segment abnormalities,[5,6] T-wave inversions,[7–9] and T-wave amplitude[10,11] in recent studies, integrating T-wave area or amplitude measures into interlead dispersion measurements could improve the noninvasive identification of patients at risk for SCD. Therefore, in this study, we sought to combine measurement of interlead heterogeneity with T-wave area's ability to track subtle changes in the ST-T segment and aimed to develop an improved assessment of repolarization heterogeneity for SCD risk stratification.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The participants in our derivation cohort were drawn from the Health 2000 Survey, which is a cross-sectional, general population-based epidemiological survey conducted in Finland between 2000 and 2001. The study enrolled a sample of 8028 Finnish adults aged ≥30 and <80 years and was representative of the entire Finnish adult population at the time. Baseline interviews and health examinations were performed on 6354 subjects. Detailed descriptions of the survey protocol and disease definitions used in the current study

have been published elsewhere.[12,13] The study was approved by the Institutional Ethics Committee of the Helsinki and Uusimaa Hospital District, and it was performed according to the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Subjects with preexcitation syndrome (ECG manifestation), complete bundle branch block, nonsinus rhythm, low-quality ECG, and use of QT-prolonging medication or digoxin were excluded from the analysis. A drug was considered to potentially prolong the QT interval if it was listed as a drug with risk of Torsades de Pointes at www.qtdrugs.org. After exclusions, a total of 5618 eligible participants remained in the cohort.

For replication purposes, we investigated the KORA S4 Study (Cooperative Health Research in the Region of Augsburg)—a cross-sectional, community-based survey conducted in Germany in the years 1999 to 2001.[14] The ethics committee of the Bavarian Medical Association approved the study, which adhered to all principles outlined in the Declaration of Helsinki. All participants provided written informed consent. The cohort enrolled 4261 participants. Following the same exclusions as in the Health 2000 Survey, a total of 3831 individuals were available for analysis. For better comparability between the derivation and replication cohorts, follow-up was administratively censored after a maximum of 9 years.

Electrocardiography

Digital standard 12-lead ECGs were recorded using the Marquette MAC 5000 ECG (GE Marquette Medical Systems, Milwaukee, WI) in the Health 2000 Survey and the Hörmann Bioset 9000 (Hörmann Medizintechnik, Zwönitz, Germany) in KORA S4. Representative median beats for each of the 12 leads were produced from the 10-second digital ECG strip. Custom-made software written in Matlab (MathWorks, Inc, Natick, MA) was used in the analysis of these ECG recordings. The software detects QRS boundaries[15] and T-wave offset (based on the least-squares fit),[16] as well as baseline level (TP interval) from each median beat. The T-wave area dispersion (TW-Ad) is then calculated as the average of normalized T-wave areas, where the normalization is accomplished by dividing the T-wave area of each lead with the maximum absolute area within the selected leads (Figure 1; Equation). Therefore, TW-Ad receives values between −1 and 1, where 1 indicates identical positive T-wave areas across the examined leads and −1, identical negative T-wave areas across the examined leads (Figure 1). Additionally, TW-Ad was calculated from leads I, II, and V_4 through V_6 because T waves in these leads are normally upright, and inversions in them have been shown to convey prognostic value.[7,8] Other lead combinations were excluded because T waves in other leads are normally either negative (aVR), variable (III, aVL, aVF, and V_1), or susceptible to persistent juvenile T-wave inversions (V_1 through V_3). Calculation of TW-Ad was performed using the following formula,

$$TW-Ad=\frac{1}{N}\sum_{i=1}^{N}\frac{Area_i}{\max\left(\left|Area_{i:N}\right|\right)},\ i\in\{V_4\text{-}V_6\}$$

where N refers to the number of leads (i) and area, to the corresponding T-wave area between the QRS offset and T-wave offset. Leads I and II can be added when calculating TW-Ad for the extended model, that is, $i\in\{I,II,V_4\text{-}V_6\}$.

In the Health 2000 Survey, measurements were first made fully automatically, after which these measurements were reproduced manually by an analyst blinded to the participants' outcome to allow comparisons between automated and manual measurements. In Kora S4, all measurements were made manually blinded to the outcome. In the manual measurements, the same custom-made software was used with user interface enabled, which allowed the user to verify and adjust the automatically detected waveform onsets and offsets, as well as the baseline levels on screen. These visually verified indices were used in the analysis of all ECG markers, including QT interval and R- and T-wave heterogeneity.[2] The QRS duration and QT interval were based on manual measurements from leads V_4 through V_6 (maximum value). Heart rate-corrected QT interval was produced with the Bazett formula, and left ventricular hypertrophy (LVH) was considered to be present if either Sokolow–Lyon (>3.5 mV) or Cornell voltage (>2.0 mV [women] and >2.8 mV [men]) was fulfilled. ST-segment amplitude was measured at 80 ms after the J point, and the minimum value (in any lead) was taken to represent each case.

Follow-Up and Adjudication of SCD

In the Health 2000 Survey, follow-up started at the study baseline and continued until January 1, 2009. Primary end point was SCD, and secondary end points were cardiac death and death from any cause. The mortality data were determined by examining death certificates from Statistics Finland. Because Finland maintains extensive administrative registers, every death in the country is recorded. The quality and validity of these registries has been shown to be high.[17]

The protocol used in the present study has been described previously in detail.[18] In brief, adjudication of the cause of death was based on the national registers on drug reimbursement, hospital admission and discharge, and causes of deaths. Registers were analyzed independently by 2 physicians who classified deaths as probable SCD, possible SCD, unlikely SCD, and unknown cause of death. In cases of disagreement, the final decision was made by consensus of 4 physicians, including 2 independent physicians. In the present study, probable and possible SCDs were pooled in the analyses, and all other deaths were considered as censored observations. Autopsies were performed in 67% of the SCDs.

In KORA S4, causes of death were ascertained based on diagnosis codes according to the ninth revision of the *International Classification of Diseases*, obtained from the death certificates of the local health authorities. We adjudicated cardiac death in case of *International Classification of Diseases, Ninth Revision* codes 390 to 429 and 798.

Statistics

Comparisons between participants with and without events were made with nonparametric *U* test for unequally distributed data and with *t* test for normally distributed data. Categorical variables were compared with Fisher exact test. All continuous risk variables were dichotomized

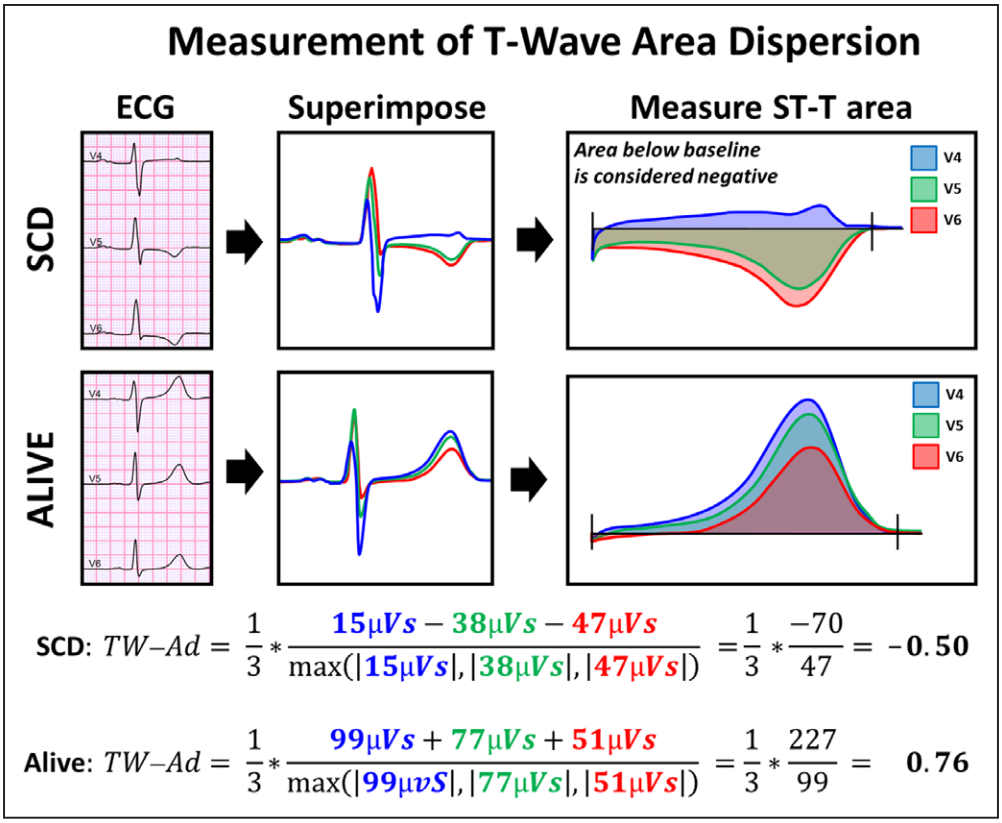

Figure 1. Measurement of T-wave area dispersion (TW-Ad).
First, the selected leads are superimposed, and the area under the T-wave is calculated between the J point and the T offset in each lead. Area below baseline is considered negative. Subsequently, the areas are normalized with the maximum absolute area within the selected leads, and TW-Ad is calculated as the average of the normalized values as shown in the equation. Values close to 1 indicate similar morphology across the studied leads, and values close to 0 indicate increased dispersion in T-wave area, whereas –1 indicates identical but inverted T waves across the leads. ALIVE indicates a participant who survived the follow-up; and SCD, sudden cardiac death.

according to their optimal cut points obtained from the receiver operating characteristic curves for risk analysis in the Health 2000 Survey. Replication analysis in KORA S4 used cut points derived from the Health 2000 Survey. Univariate and multivariate hazard ratios (HRs) were estimated with Cox proportional hazards model. Adjusted HRs were calculated with a stepwise backward model where the ECG-based risk markers were entered into the final step of the model one at a time. To allow comparisons between heterogeneity variables, unadjusted and adjusted HRs were calculated per increments of 1 SD. The proportional hazard assumption was verified for each risk marker by plotting Schoenfeld residuals against survival time transformed into natural logarithms. The improvement in model discrimination and risk reclassification was assessed by C statistics, integrated discrimination improvement, and the net reclassification improvement (NRI).[19,20] In addition, Cox models with penalized splines were used to assess and plot the relationship between the risk for SCD and TW-Ad. Analyses were performed using SPSS (version 24; IBM SPSS Statistics, Armonk, NY) and R Statistics (3.3.0; The R Foundation for Statistical Computing, Vienna, Austria). All tests were 2 sided, and $P<0.05$ was considered statistically significant.

RESULTS

During the follow-up (7.7±1.4 years), a total of 72 (1.3%) SCDs occurred in the Health 2000 Survey; average SCD incidence rate was 0.17% per year. Of these SCDs, 52 (72%) were probable and 20 (28%) were possible SCDs. In the subsequent analyses, probable and possible SCDs were pooled. Clinical characteristics are presented in Table 1.

TW-Ad and SCD

TW-Ad measured from leads I, II, and V_4 through V_6 performed marginally better than measurements from leads V_4 through V_6 (Tables 2 and 3). Therefore, in the following, TW-Ad refers to measurements done in the former-mentioned leads. Low value of TW-Ad was associated with SCD during the follow-up of this study (Figures 2 and 3). Decrease of 1 SD in TW-Ad was associated with a 3.4-fold increase in the risk for SCD (95% confidence interval [CI], 2.7–4.3; $P<0.001$). With optimized cutoff, TW-Ad ≤0.46 was associated with a

Table 1. Characteristics of the Study Populations

	Health 2000 Survey			KORA S4		
	Non-SCD (n=5546)	SCD (n=72)		Noncardiac Death (n=3779)	Cardiac Death (n=52)	
Variable	Mean±SD	Mean±SD	*P* Value	Mean±SD	Mean±SD	*P* Value
Age, y	50.8±12.5	62.9±10.6	<0.001	48.5±13.7	64.7±8.5	<0.001
Body mass index, kg/m^2	26.9±4.7	27.1±4.2	0.663	27.1±4.7	29.9±5.1	<0.001
Systolic blood pressure, mm Hg	133.0±20.2	145.9±25.0	<0.001	127.9±19.3	140.9±21.8	<0.001
Total cholesterol/HDL ratio	4.8±1.7	5.6±1.8	<0.001	4.3±1.5	4.9±1.7	0.002
Heart rate, bpm	63.1±10.6	67.5±14.0	0.008	65.4±10.6	73.0±13.9	<0.001
QRS duration, ms	93.0±9.2	96.0±12.2	0.038	91.9±9.4	95.7±12.4	0.030
QT interval, ms	399.2±31.9	397.1±42.4	0.677	407.3±27.2	403.6±32.2	0.202
QTc interval, ms	405.9±24.2	415.2±24.0	<0.001	421.9±20.3	438.0±22.5	<0.001
TW-Ad (I, II, V_4 through V_6)	0.60±0.19	0.32±0.36	<0.001	0.59±0.21	0.38±0.40	<0.001
TW-Ad (V_4 through V_6)	0.71±0.23	0.42±0.46	<0.001	0.70±0.25	0.46±0.51	<0.001
T-wave area in aVR, μVs	−23.4±12.5	−10.7±13.8	<0.001	−0.62±4.2	−0.91±4.8	<0.001
T-wave area in V_1, μVs	10.0±16.9	27.0±24.5	<0.001	0.38±3.7	1.82±9.7	<0.001
R-wave heterogeneity, μV	374±187	481±269	<0.001	262±126	299±131	0.024
T-wave heterogeneity, μV	92±64	140±94	<0.001	87±57	74±50	0.066
	n (%)	n (%)	*P* value	n (%)	n (%)	*P* value
Men	2588 (46%)	58 (81%)	<0.001	1826 (48%)	37 (71%)	0.001
Smoking	1252 (23%)	35 (49%)	<0.001	1002 (27%)	14 (27%)	1.00
LVH (ECG)	787 (14%)	18 (25%)	0.016	270 (7%)	8 (0.2%)	0.051
Hypertension	2465 (44%)	57 (79%)	<0.001	1342 (36%)	33 (63%)	<0.001
Diabetes mellitus	280 (5%)	7 (10%)	0.096	125 (3%)	10 (19%)	<0.001
Coronary artery disease	275 (4%)	19 (26%)	<0.001	NA	NA	
Previous myocardial infarction	99 (2%)	11 (15%)	<0.001	58 (2%)	8 (15%)	<0.001

bpm indicates beats per minute; HDL, high-density lipoprotein; KORA S4, Cooperative Health Research in the Region of Augsburg; LVH, left ventricular hypertrophy; NA, not available; QTc, corrected QT interval; SCD, sudden cardiac death; and TW-Ad, T-wave area dispersion.

10.8-fold increase in the risk for SCD (95% CI, 6.8–17.4; *P*<0.001). After multivariable adjustment, TW-Ad remained an independent predictor of SCD. Adjusted HR for decrement of 1 SD in TW-Ad was 2.0 (95% CI, 1.6–2.6; *P*<0.001), whereas TW-Ad ≤0.46 resulted in a 4.6-fold (CI, 2.7–7.4; *P*<0.001) increase in risk for SCD. Similarly, TW-Ad in leads V_4 through V_6, T-wave heterogeneity, and T-wave area in aVR and V_1, and ECG signs of LVH, heart rate, and ST-segment depression remained independent predictors of SCD (Tables 2 and 3).

After the exclusion of cases with previously diagnosed myocardial infarction, TW-Ad remained as an independent predictor of SCD (Table I in the Data Supplement) with 4.3-fold adjusted risk (95% CI, 2.6–7.4; *P*<0.001). However, T-wave heterogeneity, ECG signs of LVH, and ST-segment depression became statistically insignificant after the exclusion of cases with prior myocardial infarction.

When all ECG-derived markers were entered simultaneously into a stepwise backward model, TW-Ad, heart rate, and T-wave area in leads aVR and V_1 remained in the final step of the model. As these variables were then entered simultaneously into the clinical model, TW-Ad, T-wave area in lead V_1, and heart rate remained independently predictive of SCD (Table 4).

Associations With Cardiac and All-Cause Mortality

A total of 307 (5.6%) deaths occurred during the follow-up, including 94 (1.7%) cardiac deaths. TW-Ad was associated with 3.4-fold adjusted risk (95% CI, 1.1–3.5; *P*<0.001) for cardiac and with 1.7-fold (95% CI, 1.3–2.2; *P*<0.001) for all-cause mortality in the Health 2000 Survey (Table 4). Similarly, T-wave heterogeneity and heart rate remained independent predictors of both cardiac and all-cause mortality.

Replication Analysis in KORA S4

In KORA S4, a total of 184 (4.8%) deaths occurred during the follow-up (8.8±1.1 years), of which 52 (1.4%) were cardiac deaths. Of 3831 participants, 1968 (51.4%) were women. The cohort's mean age was

Table 2. Unadjusted and Adjusted HRs and Their 95% Confidence Intervals for Sudden Cardiac Death in the Health 2000 Survey for Increment/Decrement of 1 SD

Per Increment/Decrement of 1 SD	Decrement/ Increment	SD	Unadjusted HR	Age- and Sex-Adjusted HR	Multivariable Adjusted HR
TW-Ad (I, II, V_4 through V_6), unitless	Decrement	0.20	3.4 (2.7–4.3)*	2.4 (1.9–3.1)*	2.0 (1.6–2.6)*
TW-Ad (V_4 through V_6), unitless	Decrement	0.24	3.1 (2.5–4.0)*	2.3 (1.8–3.0)*	2.0 (1.5–2.6)*
T-wave area in aVR, µVs	Increment	13 µVs	2.5 (2.1–2.9)*	1.9 (1.6–2.3)*	1.7 (1.3–2.1)*
T-wave area in V_1, µVs	Increment	17 µVs	2.0 (1.7–2.3)*	1.5 (1.3–1.8)*	1.4 (1.2–1.7)*
T-wave heterogeneity, µV	Increment	65 µV	1.9 (1.5–2.4)*	1.4 (1.1–1.8)‡	1.4 (1.1–1.7)‡
R-wave heterogeneity, µV	Increment	189 µV	1.5 (1.3–1.7)*	1.2 (1.0–1.4)†	1.2 (1.0–1.4)†
QTc, ms	Increment	24 ms	1.5 (1.2–1.9)*	1.4 (1.2–1.8)*	1.4 (1.1–1.8)†
QRS duration, ms	Increment	9 ms	1.4 (1.1–1.7)‡	1.1 (0.9–1.4)^{NS}	1.1 (0.9–1.3)^{NS}
ST depression, mV	Decrement	0.040 mV	2.0 (1.6–2.4)*	1.6 (1.3–2.0)*	1.5 (1.2–1.9)*
Heart rate, bpm	increment	11	1.4 (1.2–1.8)*	1.4 (1.2–1.8)*	1.4 (1.2–1.7)*

QTc cutoff for men, 440 ms and for women, 460 ms. Multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/HDL ratio, arterial hypertension, current smoking, diabetes mellitus, coronary artery disease, and previous myocardial infarction. bpm indicates beats per minute; HDL, high-density lipoprotein; HR, hazard ratio; NS, not significant; QTc, corrected QT interval; and TW-Ad, T-wave area dispersion.

*P<0.001, †P<0.05, ‡P<0.01.

48.7±13.7 years. Cohort characteristics are presented in Table 1.

Corresponding to the results in the Health 2000 Survey, we focused our replication analysis on TW-Ad assessed in leads I, II, and V_4 through V_6 in association with cardiac death. We found an HR of 2.2 (95% CI, 1.6–2.8; P<0.001) for cardiac death per 1-SD decrease of TW-Ad. This association was attenuated following multivariable adjustment. Applying the cutoff of TW-AD ≤0.46, the ECG marker conferred a 5.5-fold increased risk for cardiac death (95% CI, 3.2–9.5; P<0.001)—a relation that remained significant after multivariable adjustment: 1.9 (95% CI, 1.1–3.5; P=0.025). Further details, including the replication of other ECG parameters, are presented in Table 5 and Figure 3 (right).

Improvement in Model Discrimination and Reclassification of Patients

Table 6 shows the improvement in model discrimination and risk reclassification with the inclusions of ECG-based risk markers in the prediction of SCD. When TW-Ad was inserted into the clinical model, the C index rose from 0.865 to 0.891. Similarly, integrated discrimination improvement and NRI indicated better model discrimination and reclassification with the inclusion of TW-Ad into the model. Categorical NRI analysis showed that a combined net percentage of 25.4% of non-SCD and SCD cases (–2.4% versus 27.8%, respectively) was correctly reclassified between risk categories (<6% | 6%–20% | >20%). This was a result from 24 (33.3%) SCD cases being reclassified to a higher and 4 (–5.6%) to a lower risk category. Similarly, 179 (–3.2%) non-SCD cases were reclassified to a higher risk and 49 (0.9%) to a lower risk category. Continuous NRI showed that a combined net percentage of 94.2% of non-SCD and SCD cases (74.8% and 19.4%, respectively) had their individual risk adjusted in the correct direction after the inclusion of TW-Ad into the model; 43 (59.7%) SCD cases were reclassified toward higher and 29 (40.3%) toward lower risks. Similarly, 699 (12.6%) of non-SCD cases were reclassified toward higher and 4847 (87.4%) toward lower risks.

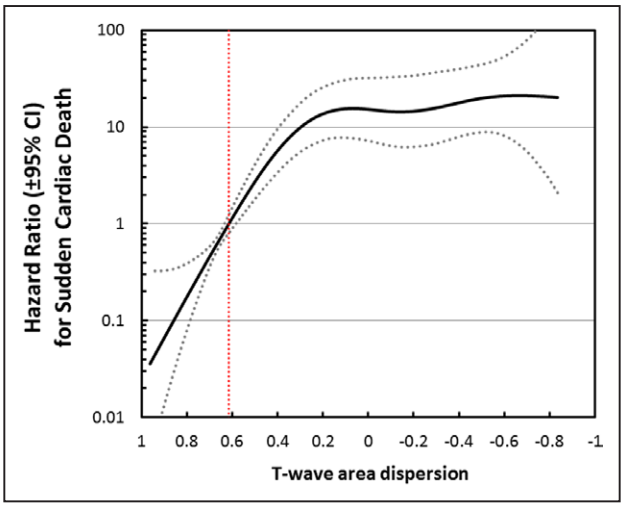

Figure 2. Continuous association between the unadjusted risk for sudden cardiac death (SCD; log-scale) and values of T-wave area dispersion (TW-Ad) in leads I, II, and V_4 through V_6.
The risk for SCD increases with decreasing TW-Ad values. Highest risk is observed with negative TW-Ad values, which indicate significant ST-segment or T-wave negativity in at least 1 of the examined leads. Reference level is set at 0.62. CI indicates confidence interval.

Table 3. Unadjusted and Adjusted HRs and Their 95% Confidence Intervals for SCD in the Health 2000 Survey for Dichotomized Risk Markers

For Optimal/Established Cutoff Points	Cutoff	SCDs (No. at Risk)	Unadjusted HR	Age- and Sex-Adjusted HR	Multivariable Adjusted HR
TW-Ad (I, II, V_4 through V_6), unitless	≤0.46	43 (742)	10.8 (6.8–17.4)*	6.1 (3.7–9.9)*	4.6 (2.7–7.4)*
TW-Ad (V_4 through V_6), unitless	≤0.61	42 (804)	9.3 (5.8–14.8)*	4.6 (2.8–7.5)*	4.0 (2.4–6.6)*
T-wave area in aVR, µVs	≥–13.9	42 (1195)	5.6 (3.5–8.9)*	4.0 (2.5–6.6)*	2.8 (1.7–4.7)*
T-wave area in V_1, µVs	≥18.7	44 (1469)	4.6 (2.8–7.3)*	2.7 (1.6–4.4)*	2.4 (1.4–3.9)*
T-wave heterogeneity, µV	≥102	44 (1924)	2.8 (1.8–4.5)*	1.8 (1.1–3.0)†	1.8 (1.1–2.9)†
R-wave heterogeneity, µV	≥357	48 (2394)	2.5 (1.5–4.1)*	1.6 (0.9–2.6)^{NS}	1.5 (0.8–2.4)^{NS}
QTc, ms	≥440/460	8 (204)	3.5 (1.7–7.4)*	1.7 (0.8–3.6)^{NS}	1.8 (0.8–3.7)^{NS}
QRS duration, ms	≥110	7 (241)	2.5 (1.1–5.4)†	2.1 (1.0–4.4)†	1.2 (0.5–2.6)^{NS}
ST depression, mV	≤–0.1	3 (32)	9.1 (2.9–29.0)*	4.3 (1.4–13.8)†	4.8 (1.5–15.8)†
Heart rate, bpm	≥65	41 (2043)	2.3 (1.5–3.7)*	2.7 (1.7–4.3)*	2.4 (1.5–3.8)*
ECG signs of LVH	…	18 (805)	2.1 (1.2–3.5)‡	1.6 (0.9–2.8)^{NS}	1.8 (1.1–3.1)†

QTc cutoff for men, 440 ms and for women, 460 ms. Multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/HDL ratio, arterial hypertension, current smoking, diabetes mellitus, coronary artery disease, and previous myocardial infarction. bpm indicates beats per minute; HDL, high-density lipoprotein; HR, hazard ratio; LVH, left ventricular hypertrophy; NS, not significant; QTc, corrected QT interval; SCD, sudden cardiac death; and TW-Ad, T-wave area dispersion.

*P<0.001, †P<0.05, ‡P<0.01.

In addition, inclusion of T-wave heterogeneity, heart rate, and T-wave area in leads aVR and V_1 improved model performance. However, ECG-based LVH did not yield improvement in model discrimination (C index or integrated discrimination improvement), despite the statistically significant improvement in continuous NRI, indicating that the risk reclassification did not exceed the thresholds for reclassification between risk categories for this marker. Similarly, inclusion of ST-segment depression did not improve model discrimination or reclassification of patients.

Associations With Other Risk Markers

Decreased TW-Ad was associated with male sex, smoking, coronary artery disease, prior myocardial infarction, diabetes mellitus, arterial hypertension, and ECG signs of LVH. Statistically significant correlations were observed between TW-Ad and age (r=–0.220; P<0.001), systolic blood pressure (r=–0.204; P<0.001), and ST-segment amplitude (r=0.221; P<0.001). Significant correlations with other ECG markers were observed as well: T-wave area in aVR (r=–0.385; P<0.001) and V_1 (r=–0.466; P<0.001), R- (r=–0.332; P<0.001) and T-wave heterogeneity (r=–0.619; P<0.001). No significant correlations were observed between TW-Ad and heart rate, QRS duration, QT, or corrected QT intervals.

Manual Versus Automated Measurements

The mean absolute error between the automatically and manually measured TW-Ad values was 1.2% (95% CI, 0.8–1.7) in the Health 2000 Survey. In linear regression analysis, the fitted line between the values of automated and manual measurements produced an R square value of 0.981. The areas under the curve for SCD discrimination in manual and automated measurements of TW-Ad differed only marginally (0.809 versus 0.808, respectively). Similarly, for TW-Ad measured from left precordial leads (V_4 through V_6), areas under the curve for manual and automated measurements were 0.792 and 0.791, respectively.

Table 4. Independent Prognostic Value of Dichotomized ECG Risk Markers in the Health 2000 Survey After Entering All ECG-Based Variables Into a Stepwise Backward Cox Regression Model (Hazard Ratios and Their CIs at Last Regression Step) With Sudden Cardiac Death as the Outcome

	Hazard Ratios (95% CI) for SCD	
ECG Parameter	Unadjusted	Multivariable Adjusted
TW-Ad (I, II, V_4 through V_6)	5.4 (2.9–10.0)*	2.8 (1.5–5.2)*
T-wave area in aVR	1.7 (0.9–3.1)^{NS}	1.1 (0.6–2.0)^{NS}
T-wave area in V_1	2.9 (1.8–4.9)*	1.7 (1.0–2.9)†
Heart rate	2.1 (1.3–3.4)‡	2.3 (1.4–3.9)*

All ECG variables were entered into a stepwise backward model. ECG variables included QRS duration, QTc interval, ST depression, T-wave area dispersion (TW-Ad, both leadsets), T-wave area in leads aVR and V_1, R- and T-wave heterogeneity, heart rate, and ECG signs of left ventricular hypertrophy. Variables that remained in the final step (values shown above) were then entered into the clinical model simultaneously. Clinical model included age, sex, arterial hypertension, current smoking, and coronary artery disease. CI indicates confidence interval; NS, not significant; QTc, corrected QT interval; SCD, sudden cardiac death; and TW-Ad, T-wave area dispersion.

*P<0.001, †P<0.05, ‡P<0.01.

Table 5. Unadjusted and Adjusted HRs and Their 95% Confidence Intervals for Cardiac Mortality and All-Cause Mortality for Dichotomized ECG-Based Risk Markers

	Health 2000		KORA	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Cardiac death				
TW-Ad (I, II, V_4 through V_6)	11.2 (7.4–16.9)*	3.4 (2.1–5.3)*	5.5 (3.2–9.5)*	1.9 (1.1–3.5)†
TW-Ad (V_4 through V_6)	8.5 (5.6–12.7)*	2.7 (1.7–4.2)*	5.3 (3.1–9.2)*	2.0 (1.2–3.6)†
T-wave heterogeneity	3.0 (2.0–4.5)*	2.1 (1.3–3.2)‡	0.8 (0.5–1.5)^{NS}	1.2 (0.7–2.3)^{NS}
R-wave heterogeneity	2.6 (1.7–3.8)*	1.3 (0.8–2.0)^{NS}	1.3 (0.7–2.5)^{NS}	0.9 (0.4–1.7)^{NS}
QTc	2.6 (1.3–5.4)‡	1.1 (0.5–2.3)^{NS}	5.5 (3.0–10.1)*	2.2 (1.1–4.4)†
QRS duration	3.0 (1.6–5.7)*	1.2 (0.7–2.4)^{NS}	5.1 (1.2–21.0)†	2.9 (0.7–12.1)^{NS}
ECG signs of LVH	2.2 (1.4–3.5)*	1.8 (1.1–2.8)†	2.4 (1.1–5.0)†	1.3 (0.6–2.8)^{NS}
Heart rate	1.9 (1.3–2.9)*	2.1 (1.4–3.2)*	2.7 (1.5–5.0)‡	2.1 (1.1–3.9)†
All-cause mortality				
TW-Ad (I, II, V_4 through V_6)	4.7 (3.7–5.9)*	1.7 (1.3–2.2)*	3.4 (2.5–4.6)*	1.4 (1.0–1.9)^{NS}
TW-Ad (V_4 through V_6)	4.2 (3.3–5.2)*	1.6 (1.3–2.1)*	3.2 (2.4–4.4)*	1.4 (1.0–1.9)†
T-wave heterogeneity	1.9 (1.5–2.4)*	1.6 (1.2–2.0)‡	0.9 (0.6–1.2)^{NS}	1.2 (0.8–1.3)^{NS}
R-wave heterogeneity	1.9 (1.5–2.4)*	1.2 (0.9–1.5)^{NS}	1.4 (1.0–2.0)^{NS}	0.9 (0.7–1.3)^{NS}
QTc	2.7 (1.8–4.1)*	1.4 (0.9–2.1)^{NS}	3.7 (2.6–5.3)^{NS}	1.8 (1.2–2.7)‡
QRS duration	1.7 (1.1–2.6)†	0.9 (0.6–1.4)^{NS}	2.8 (1.1–7.6)†	2.2 (0.8–6.0)^{NS}
ECG signs of LVH	1.6 (1.2–2.1)*	1.2 (0.9–1.6)^{NS}	2.1 (1.4–3.2)*	1.2 (0.8–1.8)^{NS}
Heart rate	1.6 (1.3–2.0)*	1.6 (1.2–2.0)*	1.8 (1.4–2.5)*	1.5 (1.1–2.0)†

A total of 94 and 52 cardiac deaths were observed in the Health 2000 Survey and in the KORA S4, respectively. QTc cutoff for men, 440 ms and for women, 460 ms. Multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/HDL ratio, arterial hypertension, current smoking, diabetes mellitus, coronary artery disease (not available in the KORA), and previous myocardial infarction. HDL indicates high-density lipoprotein; HR, hazard ratio; KORA S4, Cooperative Health Research in the Region of Augsburg; LVH, left ventricular hypertrophy; NS, not significant; QTc, corrected QT interval; and TW-Ad, T-wave area dispersion.

*P<0.001, †P<0.05, ‡P<0.01.

DISCUSSION

In the present study, we describe a new method for SCD risk stratification, which combines the measurement of T-wave area and interlead dispersion of repolarization, namely TW-Ad. Based on the results of this study, including independent replication, decreased TW-Ad is a strong and independent predictor of SCD in the adult general population, conveying predictive information beyond that of conventional risk markers and other ECG-based risk markers. This new parameter, TW-Ad, can be measured within a single cardiac cycle in a fully automated manner, instantaneously, and with excellent accuracy compared with manual measurements.

The concept of TW-Ad builds on interlead dispersion of repolarization and T-wave area, both of which have

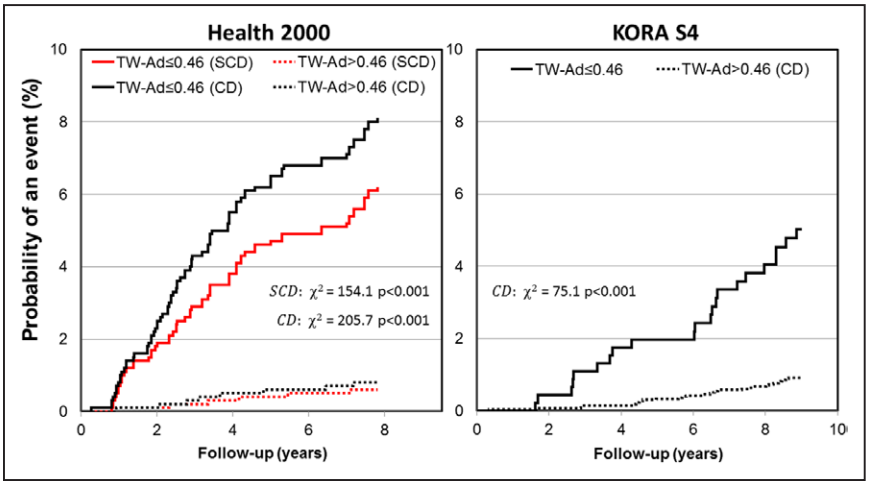

Figure 3. Cumulative incidences of sudden cardiac death (SCD) and cardiac death (CD) for Health 2000 Survey (left) and cumulative CD for KORA S4 (Cooperative Health Research in the Region of Augsburg; right) are plotted for T-wave area dispersion (TW-Ad) in leads I, II, and V_4 through V_6 ≤0.46 (solid lines) vs >0.46 (dotted lines).

Table 6. Comparisons of Models With and Without ECG Markers for Prediction of Sudden Cardiac Death in the Health 2000 Survey

	C Index	Categorical NRI (%)	Continuous NRI (%)	IDI
Original clinical model	0.865 (0.825 to 0.905)	…	…	…
+TW-Ad (I, II, V_4 through V_6)	0.891 (0.853 to 0.929)	25.4 (12.5 to 38.3)*	94.2 (71.5 to 117.0)*	0.0210 (0.0065 to 0.0356)‡
+TW-Ad (V_4 through V_6)	0.887 (0.850 to 0.924)	25.3 (11.9 to 38.8)*	88.0 (65.2 to 110.9)*	0.0172 (0.0024 to 0.0319)‡
+T-wave area in aVR	0.879 (0.840 to 0.917)	16.8 (7.9 to 25.7)*	75.1 (52.2 to 98.0)*	0.0088 (–0.0013 to 0.0189)^{NS}
+T-wave area in V_1	0.878 (0.840 to 0.916)	13.5 (5.5 to 21.5)*	70.8 (48.2 to 93.5)*	0.0099 (–0.0015 to 0.0153)^{NS}
+Heart rate	0.872 (0.834 to 0.909)	14.3 (6.0 to 22.6)*	41.7 (18.7 to 64.7)*	0.0106 (0.0019 to 0.0193)†
+T-wave heterogeneity (V_4 through V_6)	0.870 (0.830 to 0.910)	7.7 (1.3 to 14.1)†	50.4 (27.8 to 73.1)*	0.0030 (–0.0027 to 0.0087)^{NS}
+ECG-based LVH	0.870 (0.830 to 0.909)	2.4 (–1.4 to 6.2)^{NS}	21.6 (1.5 to 41.7)†	0.0018 (–0.0022 to 0.0059)^{NS}
+ST-segment depression	0.864 (0.824 to 0.904)	3.9 (–0.7 to 8.6)^{NS}	18.2 (–3.7 to 40.1)^{NS}	0.0049 (–0.0030 to 0.0128)^{NS}

Values presented in brackets are 95% confidence intervals for the values. Categorical NRI: low risk, <6%; intermediate risk, 6% to 20%; high risk, >20%. IDI indicates integrated discrimination improvement; LVH, left ventricular hypertrophy; NRI, net reclassification improvement; NS, not significant; and TW-Ad, T-wave area dispersion.

*P<0.001, †P<0.05, ‡P<0.01.

been shown to track repolarization heterogeneity.[2,21] In prior studies, spatial dispersion of repolarization, measured with T-wave heterogeneity, has been shown to be predictive of impending ventricular arrhythmias[3] and SCD.[4] The arrhythmogenic nature of T-wave heterogeneity has been demonstrated in several experimental studies.[2,22,23] The prognostic value of T-wave area has not been explored before our study, but in experimental studies on isolated canine and rabbit hearts, it has been shown to have significant correlations with dispersion of action potential durations and dispersion of recovery times,[24,25] suggesting it could act as a noninvasive predictor of arrhythmia vulnerability. In body surface mapping, ST-T integral has been proven capable in the detection of myocardial ischemia[26] and old infarction,[27] both of which contribute to arrhythmia mechanisms.[28] Furthermore, T-wave area is able to track even minor ST-segment and T-wave abnormalities, which in previous studies have been shown to carry long-term prognostic information on cardiovascular mortality in apparently healthy populations.[5,6] Recent studies in general population-based samples have also documented the prognostic value of T-wave inversions[7–9] and T-wave amplitude,[6,10,11] which are also reflected in T-wave area measurements. Moreover, it has been suggested that more pronounced T-wave inversions could be related to more severe coronary heart disease[29] and thus a higher risk for SCD.

In the present study, TW-Ad was the strongest predictor of SCD—a relation that was further substantiated by replication in a large, independent cohort. When TW-Ad and other ECG-based markers were entered simultaneously into the multivariable risk model, TW-Ad was the strongest independent predictor for SCD. In part, this finding supports our hypothesis that measurement of interlead heterogeneity can be enhanced with the measurement of T-wave area, which emphasizes the polarity of the ST-T segment. Furthermore, it shows that the predictive value of T-wave heterogeneity and T-wave area measures overlap with that of TW-Ad. This is partly explained by the common phenomenon they describe, namely altered repolarization, but also the way they are mathematically composed. Altered repolarization sequences in leads I, II, and V_4 through V_6, which contribute to TW-Ad measurement, are reflected as reciprocal changes in T-wave area in leads aVR and V_1. Similarly, the spatial dispersion of repolarization, measured with T-wave heterogeneity, estimates the splay around a constructed mean repolarization waveform and the left precordial leads, whereas TW-Ad calculates the mean normalized T-wave area. High, normalized T-wave area translates into low variability across the leads and thus lowered T-wave heterogeneity values because the variation around the mean is low. The high inverse correlation between TW-Ad and T-wave heterogeneity (r=–0.619) also indicates that TW-Ad is closely related to spatial dispersion. Similarly, TW-Ad was strongly associated with T-wave area in leads aVR (r=–0.385) and V_1 (r=–0.466); their correlation being the highest among the T-wave areas recorded in any of the 12 leads (data not shown here).

In a previous study, Porthan et al[30] studied the T-wave peak to T-wave end interval, which is considered to reflect transmural dispersion of repolarization. They discovered that although T-wave peak to T-wave end interval had no prognostic value, several morphological features were associated with SCD. The best ECG marker in their study was T-wave morphology dispersion,[31] which reflects spatial dispersion of repolarization. Similar to TW-Ad, T-wave morphology dispersion quantifies the variation of T-wave morphology between individual leads (leads I, II, and V_2 through V_6). Both of these studies underline the importance of spatial heterogeneity of cardiac repolarization in the assessment of SCD risk. When comparing the age- and sex-adjusted HRs of continuous T-wave morphology dispersion values reported by Porthan et al[30] and TW-Ad values within this article (1.6 [1.3–2.0] versus 2.4 [1.9–3.1], respectively), it seems TW-Ad performs slightly better in SCD risk assessment, which, in part, might be because of the selection of leads.

In this study, increased T-wave area in either aVR or V_1 alone was independently predictive of SCD, which is in line with the previous studies reporting increased risk of coronary heart disease and cardiovascular mortality with increased amplitude in T-wave in these leads.[6,9–11] Interestingly, these simple ECG measures were able to compete with computationally more complex repolarization measures in the prediction of SCD death.

Compared with the results in the Health 2000 Survey forming the derivation cohort, in our replication cohort KORA S4, the strength of association of TW-Ad with the outcome seems somewhat attenuated. Whereas this outcome was adjudicated SCD in the Health 2000 Survey, in KORA S4, we had to rely on adjudicated cardiac death. Along the line that TW-Ad is a marker of fatal arrhythmias leading to SCD, we interpret the weaker association in the replication cohort as an effect of the less-specific outcome definition. Yet, it lends support to the generalizability of our findings.

Limitations

Despite the promising results of our study, some methodological points deserve mention. First, left ventricular ejection fraction, which is currently one of the most important clinical parameters used in the prediction of SCD, was not measured in this study. However, we assume it to be preserved in the vast majority of the study participants given the population-based background of both the derivation and replication cohorts. Second, because the analyses were performed on a short ECG recording, fluctuations in patients' autonomic tone could have affected the measurement. It remains to be determined whether long-term monitoring of TW-Ad from ambulatory or exercise ECG could provide more accurate information on the propensity for SCD than a simple resting ECG. Because of the long-term follow-up in both health surveys, changes in health habits or medications could not be taken into account. Lastly, we were not able to have SCD follow-up data from the KORA population, only all-cause and cardiac mortality were available. Therefore, the results should still be confirmed in other independent samples.

Conclusions

The results of our study indicate that decreased values of TW-Ad reflecting increased repolarization heterogeneity are associated with increased risk for SCD and cardiac death, respectively, in the general population and convey predictive information beyond that of conventional risk markers, as well as other ECG-based risk markers. Future research should assess the predictive power of this index in other populations and other modalities of ECG measurement.

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DISCLOSURES

None.

AFFILIATIONS

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FOOTNOTES

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Repolarization Heterogeneity Measured With T-Wave Area Dispersion in Standard 12-Lead ECG Predicts Sudden Cardiac Death in General Population

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Unadjusted and adjusted hazard ratios (HR) and their 95% confidence intervals for sudden cardiac death for increment/decrement of 1 standard deviation (top) and for dichotomized risk markers (bottom) in subjects without myocardial infarction (N = 5,508) in the Health 2000 Survey.

Per increment/decrement of 1 SD	Decrement/increment	SD	Unadjusted HR	Age- and sex-adjusted HR	Multivariable adjusted HR
TW-Ad (I, II, V_4-V_6), unitless	Decrement	0.20	3.2 (2.5-4.2)‡	2.6 (2.0-3.5)‡	2.3 (1.7-3.0)‡
TW-Ad (V_4-V_6), unitless	Decrement	0.24	3.0 (2.3-3.9)‡	2.5 (1.9-3.4)‡	2.3 (1.7-3.0)‡
T-wave area in aVR, µVs	Increment	13µVs	2.4 (2.0-2.9)‡	2.0 (1.7-2.5)‡	1.9 (1.5-2.4)‡
T-wave area in V_1, µVs	Increment	17 µVs	2.0 (1.7-2.3)‡	1.5 (1.3-1.8)‡	1.5 (1.2-1.8)‡
T-wave heterogeneity, µV	Increment	65 µV	1.8 (1.4-2.3)‡	1.4 (1.1-1.8)*	1.3 (1.0-1.8)*
R-wave heterogeneity, µV	Increment	189 µV	1.2 (0.9-1.5)^{NS}	1.2 (1.0-1.5)*	1.2 (1.0-1.4)^{NS}
QTc, ms	Increment	24 ms	1.4 (1.1-1.8)†	1.6 (1.2-2.0)†	1.5 (1.2-1.9)†
QRS duration, ms	Increment	9 ms	1.0 (0.8-1.3) ^{NS}	0.8 (0.6-1.1)^{NS}	0.8 (0.7-1.1)^{NS}
ST depression, mV	Decrement	0.040 mV	1.8 (1.5-2.3)	1.7 (1.3-2.1)‡	1.6 (1.3-2.1)‡
Heart rate, bpm	Increment	11 bpm	1.6 (1.3-2.0)‡	1.6 (1.3-1.9)‡	1.4 (1.1-1.7)†
For optimal/established cutoff points	**Cutoff**	**SCDs (number at risk)**	**Unadjusted HR**	**Age- and sex-adjusted HR**	**Multivariable adjusted HR**
TW-Ad (I, II, V_4-V_6), unitless	≤0.46	33 (672)	9.2 (5.6-15.3)‡	5.6 (3.3-9.4)‡	4.3 (2.6-7.4)‡
TW-Ad (V_4-V_6), unitless	≤0.61	32 (769)	7.4 (4.5-12.1)‡	4.7 (2.8-7.8)‡	3.9 (2.3-6.5)‡
T-wave area in aVR, µVs	≥-13.9	33 (1,122)	4.9 (2.9-8.1)‡	3.8 (2.2-6.4)‡	2.8 (1.6-4.8)‡
T-wave area in V_1, µVs	≥ 18.7	34 (1,405)	3.8 (2.3-6.2)‡	2.3 (1.3-3.9)†	2.2 (1.3-3.6)†
T-wave heterogeneity, µV	≥102	31 (1,857)	2.1 (1.2-3.4)†	1.4 (0.8-2.3)^{NS}	1.3 (0.8-2.2)^{NS}
R-wave heterogeneity, µV	≥357	41 (2,536)	2.5 (1.4-4.2)†	1.5 (0.9-2.6)^{NS}	1.4 (0.8-2.3)^{NS}
QTc, ms	≥440/460	7 (194)	3.7 (1.7-8.3)‡	2.4 (1.1-5.2)*	1.9 (0.9-4.2)^{NS}
QRS duration, ms	≥110	2 (217)	0.8 (0.2-3.4)*	0.5 (0.1-2.1)^{NS}	0.4 (0.1-1.8)^{NS}
ST depression, mV	≤-0.1mV	1 (26)	3.8 (0.5-27.7)^{NS}	2.2 (0.3-15.6)^{NS}	2.7 (0.4-20.2)^{NS}
Heart rate, bpm	≥65	37 (2,015)	2.7 (1.6-4.5)‡	3.0 (1.8-5.0)‡	2.4 (1.4-4.0)†
ECG signs of LVH	-	15 (783)	2.0 (1.1-3.6)*	1.6 (0.9-2.8)^{NS}	1.7 (0.9-3.1)^{NS}

*P<0.05, †P<0.01, ‡P<0.001.HR, hazard ratio; LVH, left ventricular hypertrophy; TW-Ad, T-wave area dispersion; SD, standard deviation. QTc cutoff for men 440ms and for women 460ms. Multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/HDL ratio, arterial hypertension, current smoking, diabetes, coronary artery disease, previous myocardial infarction.