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Electrocardiographic Predictors of Incident Heart Failure in Men and Women Free From Manifest Cardiovascular Disease (from the Atherosclerosis Risk in Communities [ARIC] Study)

Pentti M. Rautaharju, MD, PhD^{a,*}, Zhu-Ming Zhang, MD^a, Wesley K. Haisty Jr, MD^b, Ronald J. Prineas, MB, BS, PhD^a, Anna M. Kucharska-Newton, PhD, MPH^c, Wayne D. Rosamond, PhD^c, and Elsayed Z. Soliman, MD, MSc, MS^{a,b}

Pentti M. Rautaharju: pentti.rautaharju@gmail.com

^aDivision of Public Health Sciences, Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston Salem, North Carolina

^bSection on Cardiology, Department of Medicine, Wake Forest School of Medicine, Winston Salem, North Carolina

^cDepartment of Epidemiology and Community Health, University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, North Carolina

Abstract

The risk of incident hospitalized heart failure (HF) was evaluated for 23 electrocardiographic (ECG) variables in men and women free from cardiovascular disease. The hazard ratios with 95% confidence intervals were determined from Cox regression analysis for 13,428 participants 45 to 65 years old in the Atherosclerosis Risk in Communities (ARIC) study. New-onset HF during a 14-year follow-up period occurred in 695 men (11.9%) and 721 women (9.5%). Several ECG variables were significant predictors of incident HF when evaluated as single ECG variables. Predominant among them were spatial angles, reflecting deviations of the direction of the repolarization sequence from the normal reference direction. After controlling for collinearity among the ECG variables, the spatial angle between T peak and normal T reference vectors, $(T_p|T_{ref})$, was a significant independent predictor in men (HF risk increased 31%) and women (HF risk increased 46%). Other independent predictors in men included epicardial repolarization time (62% increased risk) and T wave peak to T wave end (T_pT_e) interval, reflecting global dispersion of repolarization (27% increased risk). The independent predictors in women, in addition to $(T_p|T_{ref})$, were $(R|STT)$ the spatial angle between the mean QRS and STT vectors (54% increased risk) and QRS nondipolar voltage (46% increased risk). In conclusion, wide $(T_p|T_{ref})$, wide $(R|STT)$, and increased QRS nondipolar voltage in women and wide $(T_p|T_{ref})$, increased epicardial repolarization time, prolonged T_pT_e interval and T wave complexity in men were independent predictors of incident HF, and the presence of these abnormal findings could warrant additional diagnostic evaluation for possible preventive action for HF.

Evaluation of the risk of adverse cardiac effects for QT prolongation has been the focal point of many clinical trials, particularly in the evaluation of arrhythmic events such as torsades de pointes as adverse effects of cardioactive agents.¹ Of particular concern has been that 70% of torsades de pointes events occur in women.² However, QT is known to have notable

limitations.^{2–5} Earlier investigations have found several other electrocardiographic (ECG) variables to be valuable supplements to QT in the prediction of new-onset heart failure (HF), including a wide spatial angle between the mean QRS and T vectors [$\angle(R|STT)$], QRS nondipolar voltage, ST depression in V_1 and increased T wave V_1 amplitude.^{6,7} The main objective of the present study was to evaluate the risk of incident hospitalized HF for a comprehensive set of repolarization-related ECG parameters derived by a recently developed repolarization model^{8–10} and to evaluate gender differences in the predictors of HF.

Methods

The Atherosclerosis Risk in Communities (ARIC) study was designed as a prospective investigation of the cause and natural history of atherosclerosis, its clinical manifestations, and the community burden of coronary heart disease. The risk factors were measured and the outcomes evaluated in this population-based probability sample of adults aged 45 to 65 years at the 1987 to 1989 baseline examination; follow-up of the cohort is ongoing. The study population and definition of prevalent diseases at baseline and the outcomes have been previously described.^{11–14}

The clinical outcomes were evaluated at the follow-up examinations through December 31, 2006. Deaths were classified as definite or possible coronary heart disease death, noncoronary heart disease death, and unclassified death. Coronary heart disease at baseline was classified as angina pectoris identified using the questionnaire from Rose et al.¹⁵ Myocardial infarction was defined by a self-reported episode requiring hospitalization for >1 week, myocardial infarct diagnosed by a physician, major Q waves at the baseline electrocardiogram (Minnesota Code 1.1),¹⁶ or previous coronary artery bypass grafting or coronary angioplasty. HF events were defined as a hospitalization discharge diagnosis code (“International Classification of Disease, Ninth Revision, Clinical Modification,” code 428). Prevalent (baseline) HF was determined on the basis of evidence of the use of HF-related medications and classified according to the Gothenburg criteria.¹⁷ Baseline cerebrovascular disease was defined as self-reported stroke or transient ischemic attack verified by a study physician's review of the reported symptoms.

The study group of 13,428 men and women was derived from a source file of 14,126 ARIC participants, excluding those with bundle branch block or Wolf-Parkinson-White patterns (QRS duration ≥ 120 ms), participants with cardiovascular disease at entry classified as coronary heart disease, stroke, or HF according to the criteria listed, and 193 participants with missing clinical data or ECG parameters from various ECG programs and special algorithms derived for the study. The mean follow-up period was 14 years.

Standardized procedures were used to record the 12-lead electrocardiograms using a MAC personal computer (Marquette Electronics, Milwaukee, Wisconsin) at each clinical center. The electrocardiograms were processed in a central ECG laboratory, initially using the Dalhousie ECG program.^{17,18} All electrocardiograms in the initial digital ECG file of 15,571 records were inspected visually. In addition, the ECG quality was graded using a computer algorithm. A total of 116 electrocardiograms was rejected because of poor quality or lead reversals, and electrocardiograms with a QRS duration of ≥ 120 ms were excluded. Occasional outliers in interval measurements by computer were corrected using an interactive computer graphics display system. All electrocardiograms were reprocessed using the GE Marquette 12-SL program (GE Marquette), and the global time points from that program were used to compute the derived ECG parameters used in the present study. However, the time point of the T wave end from the Dalhousie program was found to match

more closely the visually verified T wave end, and the QT interval from Dalhousie program was used in the present study.

The schematic in Figure 1 illustrates the key variables of the repolarization model, defined in more explicit terms in Table 1. Because of the special importance of the QT peak interval (QT_p) and QT end interval (QT_e) for the parameters used in the repolarization model, special algorithms were used to detect the outlier measurements of QT_p and QT_e . Gender-specific predicted values were first computed for QT_e as a linear function of the RR interval derived in cardiovascular disease-free men and women. QT_e values above the 99th or below the 1st percentile limit of the distribution of the difference of each interval from the predicted value were replaced by the predicted value. The rate-adjusted QT_e was computed using the formula also listed in Table 1. The rate-adjusted QT_p was then derived as the difference of the rate-adjusted QT_e -T wave peak (T_p)-T wave end interval. In 2% of the T_p -T wave end measurements, the values were >128 ms and were <50 ms in another 2%. Outlier measurements >128 ms were constrained to 128 ms and those <50 ms to 50 ms. Similarly, the rate-adjusted QT onset was computed using the rate-adjusted QT_p (QT_{pa}) and T wave onset to T_p as the difference between the 2 (Table 1).

Repolarization measurements were made using temporal reference points derived from the “global” T wave, the spatial T vector magnitude curve obtained from a transformation matrix used to derive the XYZ leads from the 8 linearly independent component leads of the 12-lead ECG signals.¹⁹ The QRS nondipolar voltage, QRS duration, and a set of 21 repolarization-related ECG variables from the repolarization model were chosen for evaluation because of their role in the generation of abnormal repolarization waveforms or because of previous data of their value as risk predictors.^{6–10} The QRS duration was included as the second depolarization-related parameter with the QRS nondipolar voltage, because even moderate QRS prolongation has been known to induce secondary repolarization abnormalities.

The conceptual model used to derive the repolarization parameters for the present study has been previously reported.^{8–10} The algorithms used to derive the epicardial repolarization time (RT_{epi}) and other the key parameters of the repolarization model are described explicitly in Table 1. The RT_{epi} was obtained from the QT_{pa} , modified by the cosine of the T wave peak deviation angle [$(T_p|T_{ref})$] from the normal reference direction of repolarization (T_{ref}) in men and women free from cardiovascular disease. Thus, RT_{epi} was assigned the value equal to QT_{pa} when the T_p vector deviation angle was 0 (reverse repolarization sequence) and the value equal to QT_{pa} plus left ventricular cross-mural RT gradient if the T_p vector deviation angle was 180° (concordant repolarization sequence). The left ventricular cross-mural RT gradient will be equal to the $T_p T_{xd}$ interval, where T_{xd} is the time point of the minimum slope (inflexion point) at the T wave downstroke. $(T_p|T_{ref})$ is a measure of the deviation of the repolarization sequence from the normal direction of repolarization. In addition to $(T_p|T_{ref})$ and $(R|STT)$, several other spatial angles between the T vectors from various repolarization subintervals and other interval and amplitude variables were used in various phases of the study. Their definitions are listed in the footnotes of the corresponding tabular data. Left ventricular hypertrophy was defined by the Cornell voltage.²⁰

Descriptive statistics were used to determine the mean values, SDs, and upper and lower 20th percentiles (quintiles) for continuous variables and numbers and percentages for categorical variables. Cox proportional hazards regression analysis was used to compute hazard ratios (HR) and 95% confidence intervals (CIs) for the risk of HF. The ECG predictors were first evaluated as continuous variables and then stratified into quintiles. Quintiles 2 to 4 were first used as the reference group to evaluate the risk for the lowest and

highest quintile to observe breakpoints at the high or low end of the distributions. The HRs were evaluated for increased values of the ECG parameters (quintile 5) as the test group, with quintiles 1 to 4 as the reference group. Finally, quintile 1, corresponding to decreased values, was used as the test group for T wave in lead aVL and T_p in lead V, with the remaining 4 quintiles as the reference group.

Gender interactions with HF risk for each ECG variable was evaluated, and the HRs for variables with a significant gender interaction ($p < 0.05$) were listed separately for men and women; otherwise, both gender groups were combined. The HF risk data were summarized first by listing the unadjusted HRs and 95% CIs and then for multivariate-adjusted models with an adjustment for demographic (age, race, gender, education) and clinical (smoking status, diabetes, hypertension, family history of coronary heart disease or stroke, body mass index, systolic blood pressure, total cholesterol to high-density lipoprotein cholesterol ratio, glucose, creatinine, uric acid) factors. In addition to the single ECG variable models, the independent ECG predictors for incident HF were identified. When evaluating the collinearity among the ECG variables, it was observed that rate-adjusted QT_e and rate-adjusted QT onset correlated highly with QT_{pa} , which is functionally closely related to RT_{epi} . From these 4 variables, it was decided to retain RT_{epi} because of its central role in the repolarization model. The remaining set of ECG variables with low correlations ($r < 0.5$) was chosen to evaluate the independent ECG predictors of incident HF. These variables were entered simultaneously into Cox regression model, first without additional adjustment and then after adjustment for demographic and clinical factors. Statistical analyses were performed using Statistical Analysis Systems, version 9.1.3 (SAS Institute, Cary, North Carolina) and Microsoft Excel 2007 version 5.0 (Microsoft, Redmond, Washington).

Results

The age range of the study population was 45 to 65 years (mean age 54; Table 2). The study population was predominantly white (73%). Some notable gender differences of clinical interest were present in the ECG parameters. The rate-adjusted QT_e was 10 ms shorter and the rate-adjusted QT_p 18 ms shorter in the men than in the women. The $(R|STT)$ was 10° wider in the men than in the women. Notable among the other gender differences were the lower T onset vector magnitude and T_p vector magnitude in women than in men and greater T wave onset/ T_p vector magnitude ratio in the men than in the women.

New-onset HF occurred in 695 men (11.9%) and 721 women (9.5%). Summary results for the ECG predictors of incident HF are presented in Table 3 for multivariate-adjusted single ECG variable models such that the risk of incident HF was evaluated separately for each of the 23 ECG variables. A significant gender interaction with incident HF was found for 13 ECG variables, which have been listed separately for men and women in Table 3. For most of these 13 variables, the HRs were slightly stronger for the men than the women, and for 4 of the variables, the HR was significant for men only. The highest increased risk of incident HF in men, 1.76-fold, was observed for the spatial angle $(T_{init}|T_{term})$ and 1.71-fold increased risk for T-wave aVR amplitude. Of the remaining 10 ECG variables with no significant gender interaction, the HRs were significant for 5, with the highest level of increased risk of incident HF for 2 of the spatial angles, 1.63-fold for $(R|STT)$ and 1.59-fold for $(T_p|T_{ref})$.

Independent ECG predictors for incident HF were identified after considering collinearity among the ECG variables, as described in the "Methods" section. The correlation matrix in Table 4 lists the ECG variables with low correlation ($r < 0.5$) chosen to evaluate independent predictors of incident HF. The risk of incident HF for these 8 variables was evaluated by entering them simultaneously into the multiple ECG variable models, and each variable was

thus adjusted to the other ECG variables without any additional adjustment. Four ECG variables for men and three for women were significant independent predictors of incident HF (Table 5). $(T_p|T_{ref})$ was a significant independent predictor in men (HF risk increased 31%) and in women (HF risk increased 46%). The other independent predictors were the epicardial RT (62% increased risk) and T_p -T wave end interval (27% increased risk) in men and the QRS nondipolar voltage (46% increased risk) in women.

Discussion

The most salient results from the present investigation can be summarized as follows. First, most of the ECG variables evaluated were predictors of hospitalized HF as significant as single ECG variables with adjustment for demographic and clinical variable. Second, after controlling for collinearity among the ECG variables, the significant independent predictors of hospitalized incident HF in women were $(R|STT)$, with 54% increased risk, $(T_p|T_{ref})$, with 46% increased risk, and QRS nondipolar voltage with 46% increased risk. Third, in men, the significant independent predictors were $(T_p|T_{ref})$, with 31% increased risk, RT_{epi} , with 62% increased risk, T_p -T wave end interval, with 27% increased risk, and T wave complexity, with 32% increased risk.

It should be noted that this set of independent predictors of incident HF is not unique, because many ECG variables were highly correlated. In particular, if QT_p or QT_e had been chosen for evaluation of independent predictors, instead of RT_{epi} , the HRs would have been close to those observed for RT_{epi} . Similarly, some STT variables such as the T- wave aVR amplitude and ST onset amplitude in V_6 would likely be significant predictors of incident HF if chosen for evaluation instead of $(T_p|T_{ref})$ or $(R|STT)$ because of the high level of correlation between them.

Concerning the validity of the repolarization model, electrophysiologic evidence,^{21–23} and electrocardiographic potential theory applied to the generation of T waves support the concept that with normal direction of the repolarization sequence, RT_{epi} coincides with the time point of T_p . The timing of the endocardial RT was less clear. The repolarization model assumes that the inflexion point at global T wave downstroke occurs when the largest number of left ventricular myocytes leaves phase 3 of their action potential within the same increment of RT. It is conceivable that this occurs when most endocardial myocytes have reached the end of phase 3 of their repolarization. The repolarization model uses the T_pT_{xd} interval (where T_{xd} is the time point of the minimum slope [inflexion point] at the T wave downstroke) and RT_{epi} to derive a tentative estimate for a representative value for endocardial RT.

$(T_p|T_{ref})$ is a measure of deviation of the direction of the repolarization sequence from normal reference direction during initial repolarization phases dominated by regional cross-mural repolarization of the left ventricular lateral wall. Figure 2 shows a progressive decrease in T wave V_5 amplitude with $(T_p|T_{ref})$ widening from its median value of 17° to 42° at the 95th percentile of the $(T_p|T_{ref})$ distribution. The T wave at lead V_5 becomes flat and slightly negative at $(T_p|T_{ref})$, widening to 65°, the 98% normal limit. Although not shown, a parallel change occurs in T wave of lead aVR, which becomes progressively less negative and turns positive at abnormal widening of $(T_p|T_{ref})$. The trends in the men were closely similar to those in the women. $(T_p|T_{ref})$ and other spatial angles reflecting deviation of the repolarization sequence from normal reference direction might have utility in the evaluation of regional contributions to the prolongation of the overall QT interval and global RT, particularly in various abnormal clinical conditions and as an abnormal response to cardioactive agents.

Coronary heart disease, valvular heart disease, and hypertensive heart disease are clinically known to be the primary determinants of HF. In our study population, the prevalence of ECG left ventricular hypertrophy was low (1.5% in men and 3.9% in women), just as was the prevalence of Q wave myocardial infarction (3.0% in men and 1.4% in women). Thus, in these cardiovascular disease-free men and women, the ECG predictors of incident HF might be early manifestations of otherwise undetected coronary heart disease or hypertensive heart disease.

In an earlier ARIC study with 9 years of follow-up, the QRS nondipolar voltage was an independent ECG predictor of risk of new-onset HF only in women, just as it was in the present ARIC study with 14 years of follow-up. In postmenopausal women in the Women's Health Initiative study, the independent predictors of incident HF were wide (R|STT), ST-segment depression in V₁, increased T wave V₁ amplitude, QT prolongation, and increased heart rate variability.⁷ QRS nondipolar voltage was the only significant depolarization-related predictor in women in that study. Previous studies have postulated microvascular disease and fragmentation of ventricular conduction as a possible mechanism for QRS nondipolar voltage as a predictor of incident HF. However, in the Women's Ischemia Syndrome Study (WISE), a wide QRS/T angle, QRS duration, and prolonged QT interval were independent predictors of incident fatal and nonfatal coronary heart disease events, but the QRS nondipolar voltage was not.²⁴ The question of the mechanism for increased risk of incident HF for QRS nondipolar voltage in women remains open.

Incident HF events in the study group were identified by hospitalization and evidence of HF as the discharge diagnosis, without, however, performing centralized adjudication. The study population consisted of men and women free of clinically manifest cardiovascular disease; however, no clinical data with evaluation of cardiac function were available for the present study.

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Figure 1.

A schematic illustrating key repolarization model's variables defined explicitly in Table 1. In normal repolarization sequence, RT_p represents the RT_{epi} . The T_pT_e interval is a measure of global temporal RT gradient or global RT dispersion, and the T_pT_{xd} interval is the local left ventricular free wall cross-mural RT gradient ($XMRT_{grad}$). A line extrapolated backward to the intersection of the horizontal line from the end of QRS identified time point of T_o . T_e = T wave end; T_o = T wave onset; T_{xc} = inflexion point (maximum slope) at T wave upstroke; T_{xd} = inflexion point (minimum slope) at T wave downstroke. STT vector magnitude curve is shown at 40 sample points along RT from QRS end to T_e . Arrows at RT_p , RT_{xd} , and RT_{end} indicate RT at point of T_p , T_{xd} , and T_e , respectively.

Figure 2.

TV₅ waveforms in women free of cardiovascular disease with widening of the spatial angle between T_p and normal T reference vectors, (T_p/T_{ref}) . A progressive decrease occurred in TV₅ amplitude with (T_p/T_{ref}) widening from the median 17° to 42° at the 95th percentile. TV₅ becomes flat and slightly negative at (T_p/T_{ref}) , widening to 65°, the 98% normal limit. As a parallel change (not shown), aVR amplitudes became progressively less negative and turned positive at abnormal widening of (T_p/T_{ref}) . The trends in men were closely similar to those in women.

Table 1
Definitions of electrocardiographic variables used in the repolarization model

Acronym	Description	Excel Algorithm
Pred. QT _e	Predicted QT end interval (ms)	Pred. QT _e = 183 × RR + 224 in men Pred. QT _e = 188 × RR + 228 in women
QT _{ea} [*]	Rate-adjusted QT _e interval (ms)	QT _{ea} = QT _e + 183 × (1 – RR) for men QT _{ea} = QT _e + 186 × (1 – RR) for women
QT _{pa}	Rate-adjusted QT peak interval (ms)	QT _{pa} = QT _{ea} – T _p T _e , where T _p T _e is the interval from T wave peak to T wave end
QT _{oa}	Rate-adjusted QT onset interval (ms)	QT _{oa} = QT _{pa} – T _o T _p , where T _o T _p is the interval from T wave onset to T wave peak
(T _p T _{ref})	T _p vector deviation angle from normal reference direction (°)	(T _p T _{ref}) = 57.3 × arccosine (T _{ref} x × T _p x + T _{ref} y × T _p y + T _{ref} z × T _p z)/(T _{ref} V × T _p V) [†]
T _p T _{xd}	Left ventricular cross-mural repolarization time gradient (ms)	T _p T _{xd} = interval from T _p to T _{xd} , where T _{xd} is the inflection point at global T wave downstroke
RT _{epi}	Epicardial repolarization time (ms)	RT _{epi} = QT _{pa} – (Cos (T _p T _{ref}) – 1) × T _p T _{xd} /2
RT _{xd}	Left ventricular repolarization time at time point T _{xd} (ms)	RT _{xd} = QT _{pa} + (Cos (T _{init} T _{ref}) + 1) × T _p T _{xd} /2

* R-square 0.81 for men, 0.77 for women in regression of QT_e on RR interval.

[†]In (T_p|T_{ref}) algorithm, T_{ref}x, T_{ref}y, T_{ref}z, T_px, T_py, and T_pz are the x, y, and z components of T_{ref} and T_p vectors; T_{ref} V is the vector magnitude of T_{ref} Vector (=1); and T_pV is the vector magnitude of T_p vector; T_{ref} is the normal T reference vector in men and women free of cardiovascular disease with unit Vector xyz components (0.66, 0.48, –0.67). Spatial direction of repolarization is diametrically opposite to T_{ref} vector.

Table 2
Characteristics of study population for key demographic, clinical, and electrocardiographic (ECG) variables stratified by gender

Variable	Men (n = 5,842)	Women (n = 7,596)
Demographic/clinical		
Age (yrs)	54.2 ± 5.8	53.6 ± 5.7 *
Body mass index (kg/m ²)	27 ± 4.1	28 ± 6.0
White	4,563 (77%)	5,450 (71%) *
Current smokers	1,623 (27%)	1,877 (25%) *
Systolic blood pressure (mm Hg)	122 ± 17.5	120 ± 19.2 *
Hypertension	1,837 (31%)	2,442 (32%)
Diabetes mellitus	621 (11%)	785 (10%)
Q wave myocardial infarction by Minnesota Code criteria	179 (3.0%)	107 (1.4%) *
LVH by Cornell Voltage	91 (1.5%)	297 (3.9%) *
LVH and strain	9 (0.2%)	34 (0.4%)
ECG parameters		
Heart rate	65 ± 10.2	67 ± 10.0 *
PR interval (ms)	166 ± 25.5	161 ± 25.4 *
QRS duration (ms)	95 ± 9.1	87 ± 8.3 *
RNDPV (μV)	54 ± 22.6	43 ± 17.4 *
QT _{ea} (ms)	408 ± 12.9	415 ± 14.1 *
QT _{pa} (ms)	316 ± 18.7	334 ± 18.2 *
QT _{oa} (ms)	226 ± 18.9	244 ± 19.3 *
RT _{epi} (ms)	318 ± 19.3	336 ± 18.7 *
RT _{endo} (ms)	351 ± 18.6	367 ± 18.2 *
T _p T _{xd} (ms)	37 ± 10.2	35 ± 11.4 *
T _p T _e (ms)	91 ± 14.9	81 ± 14.98 *
(R STT) (°)	58 ± 26.8	48 ± 24.5 *
(R _p T _p) (°)	51 ± 30.5	39 ± 19.4 *
(T _p T _{ref}) (°)	21 ± 16.3	26 ± 18.4 *
(T _{init} T _{term}) (°)	18 ± 11.5	16 ± 11.0 *
T wave complexity	0.34 ± 0.16	0.36 ± 0.18 *
TaVR (μV)	-219 ± 96.9	-201 ± 86.9 *
TaVL (μV)	94 ± 95.5	75 ± 80.3 *
TV ₁ (μV)	-133 ± 145.6	-12 ± 119.8 *
ST _o V (μV)	54 ± 27.9	36 ± 19.8 *
T _o V (μV)	148 ± 56.7	104 ± 41.1 *

Variable	Men (n = 5,842)	Women (n = 7,596)
T_pV (μV)	390 ± 141.3	$315 \pm 122.5^*$
VT_o/VT_p (μV)	0.39 ± 0.09	$0.36 \pm 0.11^*$

(R|STT) and (R_p|T_p) = spatial angle (°) between mean QRS and STT and between R_p and T_p vectors, respectively; (T_{init}|T_{term}) = spatial angle between the initial T vectors from quintiles 1–3 and the terminal T vectors from quintiles 4 and 5; (T_p|T_{ref}) = spatial angle between T_p vector and T reference (T_{ref}) vector; LVH = left ventricular hypertrophy; MI = myocardial infarction; QT_{oa}, QT_{ea}, and QT_{pa} = QT onset and QT end intervals, respectively, rate-adjusted with formulas listed in Table 1; RNDPV = QRS non-dipolar voltage from singular value decomposition (square root of pooled variance of components 4 to 8); RT_{epi} and RT_{endo} = epicardial and endocardial repolarization time, respectively (see “Methods” section); T_oV/T_pV = ratio of T_o and T_p spatial vector magnitudes; T_pT_e = interval from QT_p to end of global T wave, representing global repolarization time gradient; T_pT_{xd} = interval from T_p to T_{xd} (T_pT_{xd} represents left ventricular cross-mural repolarization time gradient); T wave complexity = ratio of the second to the first principal component from singular value decomposition of the T wave; T_{xd} = inflection point at T wave downstroke; V in ST_oV, T_oV, and T_pV = spatial magnitudes of ST_o, T_o, and T_p vectors.

* $p < 0.001$.

† $p < 0.05$, z-test for proportions and *t* test for gender differences.

Table 3
Hazard ratios (HRs) with 95% confidence intervals (CIs) for electrocardiographic (ECG) predictors of incident heart failure (HF) from multivariate-adjusted risk model in men and women

ECG Variable	Multivariate-Adjusted Single ECG Variable Model*		
	Men	Women	p Value (Gender Interaction)
RNDPV (μV)	1.34 (1.09–1.64)	1.50 (1.26–1.78)	<0.001
QT _{oa} (ms)	1.57 (1.33–1.86)	1.32 (1.16–1.51)	0.018
QT _{pa} (ms)	1.55 (1.31–1.83)	1.35 (1.19–1.54)	0.0027
T _p T _e (ms)	1.40 (1.17–1.67)	1.09 (0.95–1.25)	0.037
RT _{epi} (ms)	1.65 (1.39–1.94)	1.38 (1.21–1.57)	0.006
RT _{endo} (ms)	1.30 (1.09–1.55)	1.39 (1.22–1.57)	0.016
(T _p T _{ref}) (°)	1.65 (1.40–1.95)	1.07 (0.90–1.28)	<0.001
(T _{init} T _{term}) (°)	1.76 (1.49–2.07)	1.32 (1.12–1.57)	0.024
T wave complexity	1.57 (1.33–1.86)	1.31 (1.16–1.48)	<0.001
ST _o Amp. aVR (μV)	1.45 (1.23–1.71)	1.27 (1.12–1.44)	0.024
T Amp. aVR (μV)	1.71 (1.45–2.01)	1.51 (1.34–1.70)	0.037
T _o V (μV)	1.31 (1.10–1.55)	1.05 (0.92–1.20)	<0.001
T _p V (μV)	1.31 (1.10–1.55)	1.21 (0.07–1.37)	0.040
Men and Women			
Heart rate (beats/min)	1.50 (1.33–1.69)	0.508	
QRS duration (ms)	1.12 (0.98–1.28)	0.810	
T _p T _e interval (ms)	1.09 (0.95–1.25)	0.845	
QT _{ea} (ms)	1.29 (1.14–1.46)	0.134	
T _p T _{xd} (ms)	1.05 (0.93–1.19)	0.845	
(R STT) (°)	1.63 (1.45–1.83)	0.558	
(R _p T _p)	1.59 (1.41–1.79)	0.130	
(T _{term} T _{ref}) (°)	1.24 (1.09–1.40)	—	
ST _o Amp. V ₆ (μV)	1.34 (1.19–1.52)	0.062	
ST _o Amp. aVL (μV)	1.19 (1.04–1.37)	0.851	
T Amp. aVL (μV)	1.32 (1.17–1.49)	0.120	
T Amp. V ₁ (μV)	1.24 (1.09–1.41)	0.068	
T _o V/T _p V	1.26 (1.10–1.44)	0.445	
ST _o V (μV)	1.01 (0.88–1.16)	0.177	

HRs evaluated for quintile 5 (quintile 1 for QT_{oa} and T_pV) as the test group, with the remaining 4 quintiles as the reference group.

HRs for ECG variables with significant gender interaction for HF risk are listed separately for men and women, otherwise the gender groups were combined.

(R|STT) = spatial angle between the mean QRS and STT vectors; (R_p|T_p) = spatial angle between peak QRS and T vectors (R_p and T_p, respectively); (T_{init}|T_{term}) = spatial angle between initial and terminal T vectors from T wave quintiles 1–3 and 4 and 5, respectively; (T_p|T_{ref}) = spatial angle between T_p vector and T reference (T_{ref}) vector; (T_{term}|T_{ref}) = spatial angle between mean terminal T vector from T wave

quintiles 4 and 5 and T_{ref} vector; QT_{Oa} and QT_{Pa} and QT_{Ea} = rate-adjusted QT onset, QT peak, and QT end intervals (formulas listed in Table 1); $RNDPV$ = QRS nondipolar voltage from singular value decomposition (square root of pooled variance of components 4–8); RT_{epi} and RT_{endo} = epicardial and endocardial repolarization time, respectively (see Figure 1 and “Methods” section); $STo\ Amp.$ = ST onset amplitude at end of QRS (the J-point); T_OV/T_PV = ratio of T_O and T_P vector magnitudes; TpT_e = interval from the peak to the end of the global T wave, considered as global RT gradient; TpT_{Xd} = interval from T_P to inflection point at T wave downstroke (T_{Xd}) considered as cross-mural repolarization time gradient (XMRTgrad); T wave complexity = ratio of second to first principal component from singular value decomposition of T wave; V in ST_OV , T_OV , and T_PV = vector magnitude of ST_O , T_O , and T_P vectors, respectively.

* Adjusted for age, race, education level, smoking status, alcohol status, asthma, cancer, diabetes, hypertension, family history of coronary heart disease and stroke, body mass index, systolic and diastolic blood pressure, high-density lipoprotein, low-density lipoprotein, triglycerides, white blood cells, glucose, creatinine, and uric acid.

[†] Statistically significant.

Table 4
Correlations among electrocardiographic (ECG) variables selected for evaluation of independent electrocardiographic (ECG) predictors of heart failure (HF)

	(R STT)	(T _p T _{ref})	RT _{epi}	RNDPV	T _p T _e	T _o V/T _p V	T Wave Complexity	QRS Duration (ms)
(R STT) (°)	1							
(T _p T _{ref}) (°)	0.346	1						
RT _{epi} (ms)	-0.07	0.29	1					
RNDPV (μV)	0.05	0.07	-0.11	1				
T _p T _e (ms)	0.18	0.07	-0.34	0.18	1			
T _o V/T _p V	0.36	0.02	0.23	0.23	0.21	1		
T wave complexity	0.20	0.09	0.09	0.02	0.01	0.28	1	
QRS duration (ms)	0.24	0.03	-0.06	0.28	0.04	0.14	0.04	1

Abbreviations as in Table 3.

Table 5
Hazard ratios (HRs) and 95% confidence intervals (CIs) for independent predictors* of incident heart failure (HF) by gender and cardiovascular disease status at baseline

CVD-Free Men		CVD-Free Women	
ECG Predictors With Test Group Threshold	HR (95% CI)	ECG Predictors With Test Group Threshold	HR (95% CI)
$RT_{\text{epi}} > 329 \text{ ms}$	1.62 (1.34–1.97) [†]	$RNDPV > 54 \mu\text{V}$	1.46 (1.24–1.73) [†]
$T_p T_e > 110 \text{ ms}$	1.27 (1.06–1.54) [‡]	$(R STT) > 64^\circ$	1.54 (1.29–1.85) [†]
$(T_{\text{pl}} T_{\text{ref}}) > 28^\circ$	1.31 (1.07–1.61) [§]	$(T_{\text{pl}} T_{\text{ref}}) > 28^\circ$	1.46 (1.21–1.76) [†]
T complexity	1.32 (1.10–1.58) [§]		

($R|STT$) = spatial angle between the mean QRS and STT vectors; ($T_{\text{pl}}|T_{\text{ref}}$) = spatial angle between T peak vector and reference T vector (T_{ref}) with x, y, z components (0.686, 0.528, −0.501) (direction of repolarization is diametrically opposite to Tref vector); CVD = cardiovascular disease; RNDPV = non-dipolar QRS voltage; RT_{epi} = epicardial repolarization time; $T_p T_e$ = T peak-T end interval (global RT_{grad}); T wave complexity = ratio of second to first principal component of T wave from singular value decomposition.

* Independent predictors were obtained by entering the predictors significant on univariate single ECG parameter models simultaneously into Cox regression model and adjusting each variable to other significant ECG predictors. HRs were evaluated for quintile 5. with quintiles 1–4 as the reference group.

[†] $p < 0.001$.

[‡] $p < 0.05$.

[§] $p < 0.01$ for HR.