ORIGINAL RESEARCH

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Electrocardiographic Predictors of Coronary Heart Disease and Sudden Cardiac Deaths in Men and Women Free From Cardiovascular Disease in the Atherosclerosis Risk in Communities Study

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***Background*—**We evaluated predictors of coronary heart disease (CHD) death and sudden cardiac death (SCD) in the Atherosclerosis Risk in Communities (ARIC) study.

***Methods and Results*—**The study population included 13 621 men and women 45 to 65 years of age free from manifest cardiovascular disease at entry. Hazard ratios from Cox regression with 95% confidence intervals were computed for 18 dichotomized repolarization-related ECG variables. The average follow-up was 14 years. Independent predictors of CHD death in men were TaVR- and rate-adjusted QTend (QT_{ea}), with a 2-fold increased risk for both, and spatial angles between mean QRS and T vectors and between Tpeak (T_p) and normal R reference vectors [$\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$, respectively], with a >1.5-fold increased risk for both. In women, independent predictors of the risk of CHD death were $\theta(R_m|T_m)$, with a 2-fold increased risk for $\theta(R_m|T_m)$, and $\theta(T_p|T_{ref})$, with a 1.7-fold increased risk. Independent predictors of SCD in men were $\theta(T_p|T_{ref})$ and QT_{ea}, with a 2-fold increased risk, and $\theta(T_{init}|T_{term})$, with a 1.6-fold increased risk. In women, $\theta(T_{init}|T_{term})$ was an independent predictor of SCD, with a >3-fold increased risk, and $\theta(R_m|T_m)$ and TV1 were >2-fold for both.

***Conclusions*—**$\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$, reflecting different aspects of ventricular repolarization, were independent predictors of CHD death and SCD, and TaVR and TV1 were also independent predictors. The risk levels for independent predictors for both CHD death and SCD were stronger in women than in men, and QT_{ea} was a significant predictor in men but not in women. **(*J Am Heart Assoc.* 2013;2:e000061 doi: 10.1161/JAHA.113.000061)**

Key Words: electrocardiography • ischemic heart disease • prognosis • repolarization • sudden death

Evaluation of the risk of adverse cardiac effects for QT prolongation has been the focal point of numerous clinical and epidemiological studies.[1] However, QT is known to have notable limitations,[2–4] and professional organizations and governmental regulatory agencies have recognized the need for more sensitive predictors of adverse cardiac events than QT.[5–7] There is limited information about the utility of repolarization subintervals and associated repolarization-related ECG variables for prediction of adverse cardiac events. However, several investigations have found increased mortality risk in various clinical and general populations for the spatial angle between the mean QRS and T vectors [$\theta(R_mT_m)$].[8–12]

The objective of our study was to evaluate the risk of coronary heart disease (CHD) death and sudden cardiac death (SCD) in cardiovascular disease (CVD)–free men and women for a comprehensive set of repolarization-related ECG parameters.

Methods

Study Population

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 CHD. Risk factors were

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measured and outcomes evaluated in a population-based probability sample of adults 45 to 65 years of age at the 1987 to 1989 baseline examination; follow-up of the cohort is ongoing. Study population and definitions of prevalent diseases at baseline and outcomes have been described previously.[13–15] Deaths were classified into definite or possible CHD death, non-CHD death, and unclassified death.

SCD was defined as definite or possible CHD death that occurred within 1 hour after the onset of acute symptoms. CHD at baseline was classified by angina pectoris using the questionnaire of Rose et al[16] or myocardial infarct (MI), defined by a self-reported episode requiring hospitalization for >1 week, MI diagnosed by a physician, major Q waves at the baseline ECG (Minnesota Code 1.1),[17] or previous coronary artery bypass graft or coronary angioplasty. Prevalent (baseline) heart failure (HF) was determined on the basis of evidence of use of HF-related medications and classified according to Gothenburg criteria.[18] Baseline cerebrovascular disease was defined as self-reported stroke or transient ischemic attack that was verified by a study physician's review of the reported symptoms.

After exclusion of ECGs of participants with bundle branch blocks, artificial pacemakers, Wolf-Parkinson-White pattern, and technical errors in ECG recording detected in visual inspection of all the study ECGs using computer graphics terminals, source data for the present investigation were available from 15 005 ARIC participants. Participants with CVD at baseline (n=1384) were excluded from the present study (CHD, hospitalized HF, or cerebrovascular disease classified by criteria as noted above), leaving a CVD-free subgroup of 5937 men and 7684 women for the present study. The outcome data for CHD and SCD were available from a mean follow-up period of 14 years.

Electrocardiographic Procedures and Quality Control

Standardized procedures were used for recording the 12-lead ECGs with MAC Personal Computer (Marquette Electronics, Milwaukee, WI) in each clinical center. ECGs were processed in a central ECG laboratory initially using the Dalhousie Novacode ECG program.[19] All ECGs were later reprocessed with the GE Marquette 12-SL program (GE Marquette, Milwaukee, WI). The quasi-orthogonal XYZ leads were derived from the 8 linearly independent component-leads of the 12-lead ECG signals using Kors' transformation,[20] and these leads were used as the source data to derive ECG parameters for the repolarization model.

QTpeak (QT_p), QTend (QT_e), and QTonset (QT_o) intervals were first rate-adjusted as power functions of the RR interval derived in CVD-free men and women by regressing lnQT on lnRR. The exponent for RR was 0.33 for QT_e for men and women and ranged from 0.36 to 0.40 for QT_p and QT_o. It was noticed that as long as proper functional form was used for rate adjustment, the exact value of the exponent for the RR interval had little influence on the R-square values. Additional analyses were performed to compare the above exponential rate adjustment formulas with simpler linear functions of the RR interval in the CVD-free groups of men and women (Table 1). The results revealed that the differences in the accuracy of rate adjustment in terms of the R-square values were quite small. Recognizing that using different rate adjustment functions for QT_e and QT_p is an added complexity, a simpler QT_p rate adjustment as the difference (QT_{ea}–T_pT_e interval) was derived as shown in the middle section of Table 1. This became possible because the T_pT_e interval in the CVD-free groups was practically independent from heart rate (R-square, 0.120 for men and 0.045 for women).

Table 1. Rate-Adjustment Formulas for QTend, QTpeak, and QTonset by Linear (Top Section) and Power (Bottom Section) Functions of the RR Interval by Sex

	Adjustment Formulas	R-Square
Linear functions		
QT_e*		
Men	$QT_{ea}=QT_e+127\times(1-RR)$	0.571
Women	$QT_{ea}=QT_e+136\times(1-RR)$	0.529
QT_p*		
Men	$QT_{pa}=QT_p+116\times(1-RR)$	0.496
Women	$QT_{pa}=QT_p+130\times(1-RR)$	0.477
QT_o*		
Men	$QT_{oa}=QT_o+84\times(1-RR)$	0.451
Women	$QT_{oa}=QT_o+100\times(1-RR)$	0.422
QT_p		
Men and women	$QT_{pa}=QT_{ea}-T_pT_e$†	
Exponential functions		
QT_e		
Men	$QT_{ea}=QT_e+416\times(1-RR^{1/3})$	0.571
Women	$QT_{ea}=QT_e+435\times(1-RR^{1/3})$	0.529
QT_p		
Men	$QT_{pa}=QT_p+295\times(1-RR^{0.40})$	0.498
Women	$QT_{pa}=QT_p+303\times(1-RR^{0.40})$	0.436
QT_o		
Men	$QT_{oa}=QT_o+206\times(1-RR^{0.40})$	0.452
Women	$QT_{oa}=QT_o+238\times(1-RR^{0.40})$	0.425

RR interval is in seconds, other intervals in milliseconds.
*QT_{ea}, QT_{pa}, and QT_{oa} refer to rate-adjusted QTend (QT_e), QTpeak (QT_p), and QTonset (QT_o), respectively.
†An alternative QT_{pa} formula as (QT_{ea}–T_pT_e interval) with linear QT_{ea} of men and women on top of the table.

Definitions of Repolarization Parameters

A set of 18 repolarization-related ECG variables was chosen for evaluation based on previous data of the variables' value as risk predictors or because of their functional role in the generation of normal and abnormal repolarization waveforms. QRS duration was included among these repolarization-related parameters because even moderate QRS prolongation has been shown to induce secondary repolarization abnormalities associated with adverse cardiac events.

The conceptual model used to derive the repolarization parameters for the present study has been described in previous publications.[21,22] Temporal landmarks and measurement points for key intervals and amplitudes in the repolarization model are shown in the sketch of the ST-T vector magnitude curve in Figure 1. The time of T onset (T_o) corresponding to the rate-adjusted QTonset interval (QT_{oa}) in reference to QRS onset was obtained by extrapolating the line from the point of maximum slope at T-wave upstroke (T_{xc}) to the intersection with the horizontal line drawn from the minimum ST after the J-point. Time of the minimum slope at T-wave downstroke (T_{xd}) defines the end point of the T_pT_{xd} interval, which is conceived in the repolarization model to represent initial left ventricular repolarization time (RT) dispersion. RT peak (RT_p) is computed as a function of the rate-adjusted QTpeak interval (QT_{pa}). Briefly, $RT_p=QT_{pa}-\{[\text{Cos}\ \theta(T_p|T_{ref})-1]\times[T_pT_{xd}]\}/2$, where $\theta(T_p|T_{ref})$ is the spatial angle between T_p vector and T_{ref} is the reference mean T vector direction in normal repolarization (sex- and race-specific components of the unit vectors of T_{ref} are listed in the footnote of Table 3). T_p–T_{xd}, in turn, is the interval from T_p to T_{xd}, where T_{xd} is the inflexion point (the minimum slope) at global T-wave downstroke. Left ventricular (LV) RT at point T_{xd} (RT_{xd}) is obtained with an algorithm similar to that for RT_p, whereby $RT_{xd}=QT_{pa}+\{[\text{Cos}\ \theta(T_p|T_{ref})+1]\times[T_pT_{xd}]\}/2$. The key role of RT_p and RT_{xd} for deriving ECG estimates for RT_{epi} and RT_{endo} is considered in detail in the Discussion section in the subsection "Validity of the Repolarization Model."

In addition to $\theta(T_p|T_{ref})$, a number of other spatial angles reflecting deviations of the direction of repolarization from the reference normal direction during various repolarization subintervals and other repolarization-related interval and amplitude variables were used in various phases of the study. Their definitions are listed in the footnotes of the corresponding tables.

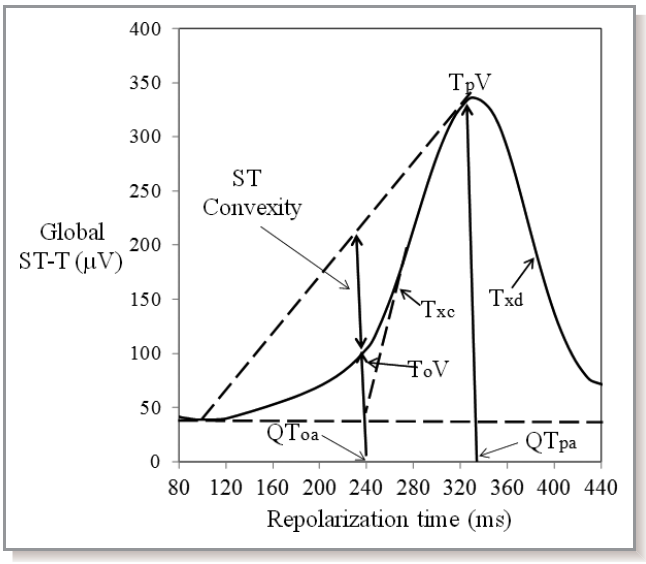

Figure 1. ST-T vector magnitude curve with temporal landmarks and measurement points for key intervals and amplitudes in the repolarization model. The peak of the global T wave (T_p) coincides with the rate-adjusted QTpeak (QT_{pa}). The time point of Tonset (T_o) corresponding to the rate-adjusted QTonset interval (QT_{oa}) is obtained by extrapolating the line from the time of maximum slope at T-wave upstroke (T_{xc}) to the intersection with the horizontal line drawn from the minimum ST after the J-point. The time of the minimum slope at the T-wave downstroke (T_{xd}) defines the end point of the T_pT_{xd} interval conceived in the repolarization model to represent initial left ventricular repolarization time (RT) dispersion. Double arrow signifies ST segment convexity as the difference of the ST segment from the gradient line from the ST onset to T_p.

Statistical Methods

One baseline ECG per participant was used for all analyses. Mean values and standard deviations were determined for continuous variables and frequencies and percents for categorical variables. Cox proportional hazards regression was used to assess associations of ECG variables with the risk of CHD death and SCD using both univariable and multivariable risk models. Predictor ECG parameters were first evaluated as continuous variables and then dichotomized using quintiles to define test and reference groups. The thresholds for test groups are listed in Table 3. Hazard ratios (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. However, quintile 1 corresponding to decreased values was used as the test group for TaVL and T_pV, with the remaining 4 quintiles as the reference group. ECG predictors were first evaluated as unadjusted single variables and subsequently in multivariable-adjusted models with adjustment for age, sex, center, race, education, smoking status, diabetes, hypertension, family history of CHD/stroke, BMI, SBP, ratio of total cholesterol/high-density lipoprotein, glucose, creatinine, and uric acid. An association was considered significant when $P<0.05$ and no adjustment for multiplicity of comparisons had been considered. Finally, to identify independent ECG risk predictors, those ECG variables that were significant predictors in single variable models were entered simultaneously into the Cox

regression model, and each was adjusted to other ECG variables.

Participants who had no events during the follow-up period were censored in the analysis at their date of last contact. A participant who died from CHD with the death not SCD was censored at the date of the CHD non-SCD death. No attempt was made to evaluate possible competing risks. All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Study Group Characteristics

Demographic and clinical characteristics of the study population listed in Table 2 have been described in more detail in previous publications.[21,23] The age range of the study population was 45 to 65 years, with mean age of 54 years (SD, 5.7 years). The study population was predominantly white (73%). The prevalence of hypertension was ≈30% in men and women.

ECG variables including all repolarization-related parameters evaluated are listed in Table 3. Most of the differences between men and women were statistically significant. QT_{pa}, the rate-adjusted QTpeak, was 18 ms shorter and QT_{oa}, the rate-adjusted QTonset, 21 ms shorter in men than in women. The sex difference in global rate-adjusted QT (QT_{ea}) was smaller, 10 ms. $\theta(R_m|T_m)$, the spatial angle between the mean QRS and T vectors, was 12° wider in men than in women. Among other notable differences in ECG parameters, T_oV, Tonset vector magnitude, was ≈30% lower in women than in men, and a similar difference was observed in T_pV, the spatial magnitude of the Tpeak vector.

Table 2. Key Demographic/Clinical Characteristics of Study Population by Sex (Mean [SD] or Number [%])

	Men	Women	*P* Value
Age, y	54.2 (5.8)	53.6 (5.7)	<0.001
Body mass index, kg/m^2	27 (4.1)	28 (6.0)	0.012
White, n (%)	4563 (76.9)	5450 (70.9)	<0.001
Current smokers, n (%)	1623 (27.4)	1877 (24.5)	<0.001
Systolic blood pressure, mm Hg	122 (17.5)	120 (19.2)	<0.001
Hypertensives, n (%)	1837 (31.1)	2442 (31.9)	0.288
Diabetes mellitus, n (%)	621 (10.5)	785 (10.3)	0.681
MI by MC criteria, %	3.0	1.4	<0.001
LVH by Cornell voltage, %	1.5	3.9	<0.001

MI indicates myocardial infarction; MC, Minnesota Code; LVH, left ventricular hypertrophy.

CHD Death Predictors

Summary results are presented Table 4 for ECG variables evaluated in Cox regression as unadjusted single predictors and as multivariable adjusted single ECG predictors. From the set of 18 ECG variables, 12 in men and 13 in women were significant predictors of CHD death in unadjusted single ECG variable models. The set of significant unadjusted single predictors was the same in men and in women except that QRS duration was a significant predictor in women but not in men. Angular variables and T-wave amplitudes were the strongest single predictors of CHD mortality risk. Seven of the predictors in men and 5 in women remained significant after adjustment for demographic and clinical risk factors.

Sudden Cardiac Death Predictors

As for CHD death, many repolarization-related variables (11 in men and 11 in women) were significant predictors of SCD when evaluated as unadjusted single ECG-variables (Table 5). Significant predictors were in general the same parameters in both sexes except that QT_{ea} and the rate-adjusted T_pT_e interval ($[T_pT_e]_a$) were significant predictors in men but not in women. HRs were particularly high for some of the ECG predictors in women: in 9 of them, HR was >2-fold and in 7 of them >3-fold. Five predictors in both men and women remained significant in the fully adjusted multivariable model.

Independent Predictors of CHD Death and SCD

Angular variables were commonly chosen as independent predictors of CHD death and SCD (Table 6). In addition, QT_{ea} was a significant independent predictor of CHD death and SCD in men, TV1 an independent predictor of CHD death and SCD in women, and TaVR an independent predictor of CHD death in men. Risk levels in women for both CHD death and SCD were stronger than in men. In terms of the magnitude of increased risk of CHD death for these ECG predictors, in men TaVR and QT_{ea} were the strongest predictors, with a 2-fold increased risk for both variables. Also significant independent predictors were $\theta(R_m|T_m)$ and $\theta(T_{init}|T_{term})$ with an >1.5-fold increased risk (although the *P* values were marginally significant). In women, the risk of CHD death was increased 2-fold for $\theta(R_m|T_m)$ and increasd 1.7-fold for $\theta(T_p|T_{ref})$.

Independent predictors of SCD in men were $\theta(T_p|T_{ref})$ and QT_{ea}, with a 2-fold increased risk, and $\theta(T_{init}|T_{term})$, with a 1.6-fold increased risk. In women the strongest independent predictor of SCD was $\theta(T_p|T_{ref})$ (HR, 3.55; CI, 1.85 to 6.81; *P*<0.001). In addition, the risk of SCD for $\theta(R_m|T_m)$ and TV1 was increased >2-fold for both.

In terms of sex differences, the risk levels in women for both CHD death and SCD were stronger than in men. Another

Table 3. Means (SDs) for Electrocardiographic Variables by Sex and Threshold Values for Test Quintiles Used for Risk Evaluation Models in Tables 3 through 7

	Mean (SD)			Test Group Threshold	
	Men	Women	*P* Value*	Men	Women
Heart rate/min	65 (10.2)	67 (10.0)	<0.001	>73	>75
QRS duration, ms	95 (9.1)	87 (8.3)	<0.001	102	96
RNDPV,† μV	54 (22.6)	43 (17.4)	<0.001	69	56
QT_{ea},‡ ms	413 (16.4)	423 (17.5)	<0.001	426	437
QT_{oa},‡ ms	216 (18.3)	237 (15.6)	<0.001	199	222
QT_{pa},‡ ms	311 (18.1)	329 (19.8)	<0.001	268	207
RT_{epi},§ ms	316 (17.8)	332 (18.8)	<0.001	329	347
RT_{endo},§ ms	348 (19.6)	366 (20.1)	<0.001	364	381
T_pT_{xd},¶ ms	36 (14.7)	38 (15.3)	<0.001	48	50
$\theta(T_pT_{ea})a$,‖ ms	100 (13.9)	95 (15.7)	<0.001	110	106
$\theta(R_m\|T_m)$,** (°)	58 (26.8)	4 (24.4)	<0.001	71	56
$\theta(T_p\|R_{ref})$,†† (°)	21 (15.7)	21 (19.0)	0.0151	28	30
$\theta(T_{init}\|T_{term})$,‡‡ (°)	18 (11.6)	16 (11.1)	<0.001	24	23
T complexity§§	0.34 (0.16)	0.36 (0.18)	<0.001	0.47	0.51
TaVR, μV	−219 (96.9)	−201 (86.7)	<0.001	−146	−131
TaVL, μV	94 (95.6)	75 (80.3)	<0.001	24	0
TV1, μV	−133 (146.0)	−12 (119.6)	<0.001	244	122
ST_oV,¶¶ μV	54 (27.9)	36 (19.7)	<0.001	75	53
T_oV, μV	148 (56.7)	104 (41.0)	<0.001	194	138
T_pV, μV	418 (157)	336 (132)	<0.001	268	207
VT_o/VT_p,‖‖ μV	0.39 (0.09)	0.36 (0.11)	<0.001	0.45	0.42

HRs were evaluated for quintile 5 (quintile 1 for QT_{oa}, TaVL, and T_pV) as the test group, with the remaining 4 quintiles as the reference group. SD indicates standard deviation; HR, hazard ratio; CI, confidence interval.

**P* values for *z* test for ratios and for *t* test for sex differences.

†RNDPV=QRS nondipolar voltage from singular value decomposition (square root of pooled variance of components 4 to 8).

‡QT_{ea}, QT_{pa}, and QT_{oa} refer to rate-adjusted QTend (QT_e), QTpeak (QT_p), and QTonset (QT_o) intervals, respectively, using linear formulas listed in Table 1.

§RT_{epi} and RT_{endo} denote subepicardial and subendocardial repolarization times (see Methods section).

¶T_pT_{xd}=T_pT_{xd} interval representing dispersion of the initial left ventricular repolarization.

‖$\theta(T_pT_{ea})a$, global repolarization time dispersion (interval from QT_{pa} to QT_{ea}).

**$\theta(R_m|T_m)$, spatial angle between the mean QRS and T vectors.

††$\theta(T_p|T_{ref})$, spatial angle between T_p vector and the T reference (T_{ref}) vector.

‡‡$\theta(T_{init}|T_{term})$, spatial angle between initial and terminal T vectors.

§§T-wave complexity, ratio of the second to the first principal component from singular value decomposition of the T wave.

¶¶Symbol "V" in ST_oV, T_oV, and T_pV refers to spatial magnitudes of ST_o, T_o, and Tp vectors, respectively.

‖‖T_oV/T_pV is the ratio of the T_o and T_p spatial vector magnitudes.

notable sex difference was that QT_{ea} was a significant independent predictor of CHD death and SCD in men but not in women.

Discussion

A majority of the 18 ECG parameters were significant CHD death and SCD predictors when evaluated as unadjusted single ECG variables, and many remained significant in multivariable-adjusted models. Notable among these predictors were $\theta(R_m|T_m)$, the spatial angle between the mean QRS and T vectors, and $\theta(T_p|T_{ref})$, the spatial angle between Tpeak and the normal T reference vector. $\theta(R_m|T_m)$ is a measure of the overall deviation angle between depolarization and repolarization sequences, and $\theta(T_p|T_{ref})$ is a measure of deviation of the direction of the repolarization sequence from the normal reference direction during regional cross-mural repolarization of the left ventricular lateral wall. $\theta(R_m|T_m)$ was also an independent predictor for CHD death in men, with a 62% increased risk, and in women, with a 2-fold increased risk, and $\theta(T_p|T_{ref})$ was a strong

Table 4. Hazard Ratios With 95% Confidence Intervals for ECG Predictors of Coronary Heart Disease Death in Men and Women

	Men				Women			
	Univariable*	*P* Value	Multivariable*	*P* Value	Univariable	*P* Value	Multivariable	*P* Value
QRS duration, ms	1.26 (0.93 to 1.72)	0.143	1.33 (0.97 to 1.82)	0.081	1.57 (1.09 to 2.25)	0.015	1.19 (0.81 to 1.76)	0.372
RNDPV[†]	1.30 (0.95 to 1.78)	0.099	1.21 (0.85 to 1.71)	0.297	1.24 (0.83 to 1.86)	0.230	1.03 (0.66 to 1.60)	0.372
QT_{ea},[‡] ms	1.88*** (1.42 to 2.50)	<0.001	1.49 (1.11 to 2.00)	0.084	1.74 (1.21 to 2.50)	0.003	1.25 (0.85 to 1.85)	0.365
T_pT_{xd},[§] ms	1.11 (0.81 to 1.52)	0.508	0.94 (0.68 to 1.30)	0.720	0.86 (0.56 to 1.33)	0.499	0.65 (0.40 to 1.06)	0.084
$\theta(T_pT_e)a$,[¶] ms	1.35 (0.99 to 1.82)	0.051	1.14 (0.83 to 1.57)	0.416	1.41 (0.96 to 2.06)	0.080	0.92 (0.60 to 1.41)	0.695
RT_{epi},[‖] ms	1.77 (1.33 to 2.34)	<0.001	1.46 (1.08 to 1.97)	0.014	1.90 (1.32 to 2.73)	<0.001	1.33 (0.90 to 1.98)	0.153
$\theta(R_m\|T_m)$,** (°)	2.12 (1.61 to 2.79)	<0.001	1.46 (1.09 to 1.95)	0.012	3.85 (2.75 to 5.40)	<0.001	2.32 (1.59 to 3.39)	<0.001
$\theta(T_p\|T_{ref})$,[††] (°)	2.46 (1.88 to 3.23)	<0.001	1.85 (1.39 to 2.46)	<0.001	3.31 (2.35 to 4.64)	<0.001	1.61 (1.09 to 2.36)	0.016
$\theta(T_{init}\|T_{term})$,[‡‡] (°)	2.12 (1.61 to 2.79)	<0.001	1.58 (1.18 to 2.11)	0.002	2.92 (2.07 to 4.11)	<0.001	1.81 (1.23 to 2.66)	0.003
T complexity[§§]	1.07 (0.78 to 1.47)	0.661	0.63 (0.69 to 1.32)	0.783	1.23 (0.83 to 1.81)	0.302	1.01 (0.67 to 1.53)	0.970
TaVR amplitude, μV	2.56 (1.96 to 3.34)	<0.001	1.66 (1.25 to 2.22)	<0.001	2.94 (2.09 to 4.13)	<0.001	1.54 (1.05 to 2.25)	0.027
TV1 amplitude, μV	1.57 (1.17 to 2.11)	0.003	1.22 (0.89 to 1.66)	0.224	3.18 (2.26 to 4.46)	<0.001	1.89 (1.29 to 2.76)	0.001
ST_oV,[¶¶] μV	1.38 (1.01 to 1.89)	0.045	1.13 (0.79 to 1.60)	0.502	1.87 (1.29 to 2.71)		1.04 (0.67 to 1.62)	0.851
TVo, μV	1.25 (0.91 to 1.73)	0.171	1.22 (0.85 to 1.76)	0.273	1.14 (0.76 to 1.74)	0.525	0.82 (0.51 to 1.33)	0.425
T_pV, μV	0.82 (0.57 to 1.17)	0.271	1.02 (0.85 to 1.56)		0.74 (0.46 to 1.19)	0.212	0.66 (0.59 to 1.65)	0.967
T_oV/T_pV[‖‖]	1.79 (1.34 to 2.40)		1.11 (0.69 to 1.50)	0.936	2.10 (1.47 to 3.00)	<0.001	0.98 (0.64 to 1.50)	0.919

HR was evaluated for increased values of the ECG parameters (quintile 5) as the test group, with quintiles 1 to 4 as the reference group. However, quintile 1 corresponding to decreased values was used as the test group for TaVL and T_pV, with the remaining 4 quintiles as the reference group. HR indicates hazard ratio; CI, confidence interval; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Univariable refers to unadjusted single ECG variable model and multivariable to single ECG variable multivariable-adjusted risk model adjusted for age, race, education level, smoking status, alcohol status, asthma, cancer, diabetes, hypertension, family history of CHD and stroke, body mass index, systolic and diastolic blood pressure, HDL, LDL, triglycerides, white blood count, glucose, creatinine, and uric acid. HRs were evaluated for quintile 5 (quintile 1 for QT_{oa},T_{amp}.aVL and T_pV) as the test group, with the remaining 4 quintiles as the reference group.

[†]RNDPV, QRS nondipolar voltage from singular value decomposition (square root of pooled variance of components 4 to 8).

[‡]QT_{ea}, rate-adjusted QRe where $QT_{ea}=QT_e+127$ (1−RR) for men and $QT_{ea}=QT_e+136$ (1−RR) for women.

[§]$T_pT_{xd}=T_pT_{xd}$ interval representing dispersion of the initial left ventricular repolarization.

[¶]$\theta(T_pT_e)a$, global repolarization time dispersion (interval from QT_{pa} to QT_{ea}).

[‖]RT_{epi} denotes subepicardial repolarization time (see Methods section).

[**]$\theta(R_m|T_m)$, spatial angle between mean QRS and T vectors.

[††]$\theta(T_p|T_{ref})$, spatial angle between T_p vector and the T reference (T_{ref}) vector.

[‡‡]$\theta(T_{init}|T_{term})$, spatial angle between the initial T vectors from quintiles 1 to 3 and the terminal T vectors from quintiles 4 to 5.

[§§]T-wave complexity, ratio of the second to the first principal component from singular value decomposition of the T wave.

[¶¶]Symbol "V" in ST_oV, T_oV, and T_pV refers to the spatial magnitudes of the ST_o, T_o, and Tp vectors, respectively.

[‖‖]T_oV/T_pV is the ratio of the T_o and T_p spatial vector magnitudes.

independent predictor for SCD, with a nearly 2-fold increased risk in men and a >3-fold increased risk in women. It is worth noting that increased CHD death and SCD risk were observed in 20% of men and women (the upper quintile), with a relatively moderate widening (23° to 30°) of $\theta(T_p|T_{ref})$ and $\theta(T_{init}|T_{term})$. QT prolongation was an independent predictor for CHD death and SCD in men but not in women.

Validity of the Repolarization Model

As noted in the Methods section, RT_p is computed as a function of the QT_{pa}, which is the key parameter in the algorithms for RT_p and RT_{xd}. RT_p is conceived by the repolarization model to represent the RT of LV myocytes, which repolarize at the time of T_p during the initial fast phase of LV lateral wall repolarization. It is noted from the algorithms for deriving RT_p as a function of QT_{pa} that the RT_p is modified by the cosine of $\theta(T_p|T_{ref})$. These relationships imply that $RT_p=QT_{pa}$ if and only if $\theta(T_p|T_{ref})=0°$ and that QT_{pa} is assigned to RT_{xd} if $\theta(T_p|T_{ref})=180°$; if $\theta(T_p|T_{ref})$ is 90°, RT_p and RT_{xd} are both equal to QT_{pa}. These functional relationships in the repolarization model are based on consideration of potential theory as applied to the generation of T wave, and they differ from the notions from some electrophysiological reports on animal models using wedge preparations that T_p timing always coincides with QT_{epi}.[23–26] Potential theory supports the assertion that at the time of RT_p the majority of LV lateral wall myocytes are in phase 3 of their action potential and that

Table 5. Hazard Ratios With 95% Confidence Intervals for Sudden Cardiac Death in Men and Women

	Men				Women			
	Univariable*	*P* Value	Multivariable*	*P* Value	Univariable	*P* Value	Multivariable	*P* Value
QRS duration, ms	1.15 (0.71 to 1.87)	0.564	1.11 (0.66 to 1.84)	0.701	1.53 (0.83 to 2.82)	0.173	1.08 (0.57 to 2.05)	0.804
RNDPV,† μV	1.18 (0.73 to 1.90)	0.503	1.09 (0.64 to 1.84)	0.759	1.25 (0.64 to 2.46)	0.511	0.84 (0.41 to 1.69)	0.617
QT_{ea},‡ ms	2.28 (1.50 to 3.48)	<0.001	1.94 (1.25 to 3.01)	0.003	1.63 (0.87 to 3.03)	0.126	1.18 (0.63 to 2.23)	0.605
T_pT_{xd},§ ms	1.24 (0.78 to 2.00)	0.354	1.11 (0.69 to 1.80)	0.663	1.79 (0.97 to 3.30)	0.061	1.34 (0.71 to 2.51)	0.366
$\theta(T_pT_e)a$,¶ ms	1.63 (1.05 to 2.55)	0.031	1.44 (0.91 to 2.29)	0.120	1.69 (0.91 to 3.15)	0.010	0.90 (0.47 to 1.73)	0.748
RT_{epi},‖ ms	1.82 (1.17 to 2.83)	0.008	1.42 (0.89 to 2.26)	0.145	2.09 (1.15 to 3.82)	0.016	1.55 (0.83 to 2.90)	0.165
$\theta(R_m\|T_m)$,** (°)	2.29 (1.51 to 3.48)	<0.001	1.54 (0.99 to 2.41)	0.058	4.91 (2.78 to 8.67)	<0.001	2.36 (1.27 to 4.39)	0.003
$\theta(T_p\|Tr_{ef})$,†† (°)	2.91 (1.93 to 4.38)	<0.001	2.22 (1.43 to 3.43)	<0.001	5.90 (3.32 to 10.47)	<0.001	2.59 (1.39 to 4.82)	0.003
$\theta(T_{init}\|T_{term})$,‡‡ (°)	2.34*** (1.54 to 3.56)	<0.001	1.68 (1.07 to 2.62)	0.023	3.35 (1.89 to 5.93)	<0.001	1.47 (0.79 to 2.72)	0.226
T complexity§§	1.20 (0.75 to 1.93)	0.451	0.66 (0.60 to 1.62)	0.958	1.88 (1.03 to 3.44)	0.039	1.31 (0.71 to 2.43)	0.388
TaVR, μV	2.52 (1.67 to 3.82)	<0.001	1.64 (1.04 to 2.58)	0.032	3.94 (2.24 to 6.95)	<0.001	1.79 (0.97 to 3.29)	0.063
ST_oV,¶¶ μV	1.53 (0.97 to 2.40)	0.067	1.31 (0.78 to 2.19)		1.60 (0.85 to 3.02)	0.149	0.66 (0.34 to 1.32)	0.242
T_oV, μV	1.18 (0.73 to 1.90)	0.500	1.16 (0.68 to 1.98)	0.592	1.02 (0.51 to 2.06	0.948	1.27 (0.62 to 2.62)	0.509
T_pV, μV	1.17 (0.73 to 1.89)	0.512	1.41 (0.84 to 2.37)	0.192	1.80 (0.98 to 3.32)	0.223	0.78 (0.33 to 1.89)	0.585
T_oV/T_pV	1.62 (1.04 to 2.53)	0.034	1.18 (0.71 to 1.98)	0.5338	2.69 (1.51 to 4.79)	<0.001	0.93 (0.50 to 1.74)	0.818

HRs were evaluated for quintile 5 (quintile 1 for QT_{oa}, T_{amp}.aVL, and T_pV) as the test group, with the remaining 4 quintiles as the reference group. HR indicates hazard ratio; CI, confidence interval; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Univariable refers to unadjusted single ECG variable model and multivariable to single ECG variable multivariable-adjusted risk model adjusted for age, race, education level, smoking status, alcohol status, asthma, cancer, diabetes, hypertension, family history of CHD and stroke, body mass index, systolic and diastolic blood pressure, HDL, LDL, triglycerides, white blood count, glucose, creatinine, and uric acid.

†RNDPV, QRS nondipolar voltage from singular value decomposition (square root of pooled variance of components 4 to 8).

‡QT_{ea}, rate-adjusted QRe where $QT_{ea}=QT_e+127\ (1-RR)$ for men and $QT_{ea}=QT_e+136\ (1-RR)$ for women.

§T_pT_{xd},T_pT_{xd} interval representing dispersion of the initial left ventricular repolarization.

¶$\theta(T_pT_e)a$, global repolarization time dispersion (interval from QT_{pa} to QT_{ea}).

‖RT_{epi} denotes subepicardial repolarization time (see Methods section).

**$\theta(R_m|T_m)$, spatial angle between mean QRS and T vectors.

††$\theta(T_p|T_{ref})$, spatial angle between T_p vector and the T reference (T_{ref}) vector with sex- and race-specific unit vectors as follows: white men, 0.619; 0.483, −0.619; black men, 0.574; 0.390, −0.720; white women, 0.721; 0.583, −0.370; black women, 0.776; 0.504, −0.379).

‡‡$\theta(T_{init}|T_{term})$, spatial angle between the initial T vectors from quintiles 1 to 3 and the terminal T vectors from quintiles 4 to 5.

§§T wave complexity, ratio of the second to the first principal component from singular value decomposition of the T wave.

¶¶Symbol "V" in ST_oV, T_oV, and T_pV refers to spatial magnitudes of the ST_o, T_o, and T_p vectors, respectively.

RT_p timing coincides with the timing of the global T_p. It thus seems a rational proposition to maintain the labels RT_{epi} and RT_{xd} as derived by modifying RT_p by $\theta(T_p|T_{ref})$. In a strict sense, the label RT_{epi} refers to the RT of subepicardial myocyte layers and should be considered as a representative value of LV epicardial RT and not RT at any specific epicardial location.

Potential theory is also compatible with the notion that at the time of T_p and RT_p, LV lateral wall subepicardial myocytes in the region where repolarization starts earliest have already reached phase 4 of their action potential, no longer contribute to the generation of the T wave, and T amplitude starts to decline. This occurrence is the likely explanation for electrophysiological data relating the timing of QT_p with QT_{epi} in normal repolarization.[23–26] Parameter T_{xd} in the repolarization model is the inflexion point (the minimum slope) at the global T-wave downstroke, considered by the repolarization model to occur when the largest number of LV myocytes leaves phase 3 of their action potential within the same increment of RT. With the normal direction of the RT sequence, this conceivably occurs when the majority of subendocardial myocytes reach their resting potential. Spatial direction of repolarization during the T_pT_{xd} interval is diametrically opposite to the direction of the T_p vector, and T_pT_{xd} is the magnitude of the temporal RT gradient vector representing RT dispersion during the T_pT_{xd} interval dominated by the LV lateral wall repolarization. Contrary to the notions from electrophysiological studies suggesting that LV lateral wall repolarization is perpendicular to the epicardial surface,[23–25] there is consistent evidence that the spatial LV repolarization sequence remains throughout repolarization closely in the direction from inferior-left-anterior to superior-right-posterior, approximately in the direction of the lead vector of aVR but with a

Table 6. Hazard Ratios (95% Confidence Limits) for Independent Predictors* of Coronary Heart Disease and Sudden Cardiac Deaths by Sex

Men			Women		
	HR (95% CI)	*P* Value		HR (95% CI)	*P* Value
Coronary heart disease death					
$\theta(R_m\|T_m)$,† (°)	1.62 (1.03, 2.55)	0.037	$\theta(R_m\|T_m)$, (°)	2.04 (1.36, 3.07)	<0.001
$\theta(T_{init}\|T_{term})$,‡ (°)	1.50‖ (1.00, 2.25)	0.049	$\theta(T_p\|T_{ref})$,¶ (°)	1.70 (1.11, 2.61)	0.015
TaVR, μV	2.05 (1.20, 3.49)	0.009	TV1, μV	2.03 (1.40, 2.96)	<0.001
QT_{ea},§ ms	2.05 (1.20, 3.49)	0.004			
Sudden cardiac death					
$\theta(T_p\|T_{ref})$, (°)	1.91 (1.14, 3.20)	0.013	$\theta(T_p\|T_{ref})$,§ (°)	3.55 (1.85, 6.81)	<0.001
$\theta(T_{init}\|T_{term})$, (°)	1.61 (1.01, 2.56)	0.044	$\theta(R_m\|T_m)$, (°)	2.28 (1.17, 4.45)	0.016
QT_{ea}, ms	1.98 (1.29, 3.03)	0.002	TV1, μV	2.26 (1.20, 4.25)	0.012

*Independent predictors were obtained by entering the predictors that were significant in multivariable adjusted models in Tables 4 and 5 simultaneously into the Cox regression model and adjusting each variable to other significant predictors.
†$\theta(R_m|T_m)$, spatial angle between mean QRS and T vectors.
‡$\theta(T_{init}|T_{term})$, spatial angle between the initial T vectors from quintiles 1 to 3 and the terminal T vectors from quintiles 4 to 5.
§QT_{ea}, rate-adjusted QT_e where $QT_{ea}=QT_e+127\ (1-RR)$ for men and $QT_{ea}=QT_e+136\ (1-RR)$ for women.
¶$\theta(T_p|T_{ref})$, spatial angle between T_p and T_{ref} vectors.

posterior component.[21,22] This implies that LV lateral wall repolarization is cross-mural, oblique rather than perpendicular to the epicardial surface.[10,21,22,27]

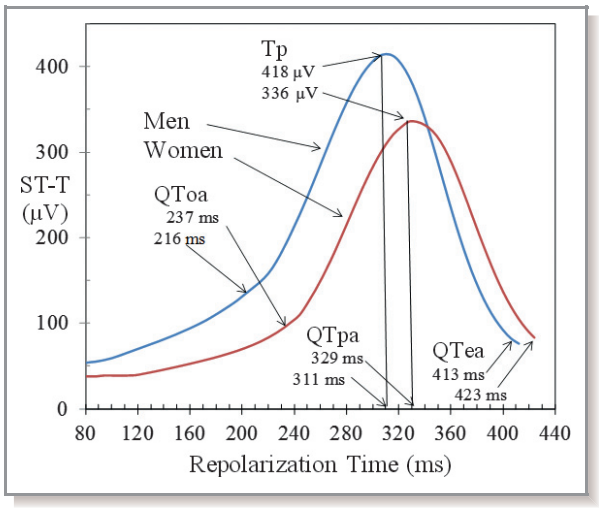

Figure 2. Mean global ST-T waveforms in men and women free from cardiovascular disease highlighting sex differences in rate-adjusted QTpeak (QT_{pa}), QTend (QT_{ea}), and QTonset (QT_{oa}) intervals and Tpeak (T_p) amplitudes. The ST-T curve was generated by sampling the ST-T vector magnitude function between the end of QRS and the end of the T wave (T_e) at 60 equally spaced sample points, subsequently aligning the Tpeak (T_p) time with the mean QT_{pa} and rescaling the temporal RT axis back to the original to match T_pT_e and T_oT_p intervals with the mean QT_{pa} and T_{oa}–T_{pa} intervals of men and women. Compared with that in women, repolarization in men starts earlier, the ST segment has a steeper upslope, and T_p is shifted to the left, corresponding to an earlier end of epicardial repolarization as reflected by an 18-ms shorter QT_{pa} in men. CVD indicates cardiovascular disease.

Mechanisms of Generation of Repolarization Abnormalities as Independent Predictors of CHD Death and SCD

Anterior-right rotation of the T_p vector is a predominant determinant of widened $\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$ angles.[10,21] T_p vector rotation closer to the aVR lead axis results in decreased (less negative) TaVR amplitude that ultimately becomes positive with a more pronounced widening of $\theta(T_p|T_{ref})$. Altered direction of the repolarization sequence may reflect subepicardial action potential duration shortening such as takes place in anterior subepicardial myocardial ischemia.[21] Thus, the increased $\theta(T_p|T_{ref})$ observed in the present study as a common predictor for CHD death and SCD may possibly be an early marker of evolving subclinical CHD in men and women free from manifest CVD. $\theta(T_p|T_{ref})$ widening also reflects a gradual change from the normal predominantly reverse sequence of the cross-mural left ventricular wall repolarization to a concordant repolarization with respect to depolarization and increasing dyssynchrony of repolarization[10] that in turn has been postulated to be associated with increased dyssynchrony of ventricular repolarization as another possible risk mechanism.[26]

QT_{ea} was not an independent predictor for either end point in women, but in men it was a significant independent predictor, with a 48% increased risk for CHD death and a 98% increased risk for SCD. Sex difference in QT is actually not a result of QT prolongation in women, as commonly claimed, but arises from pronounced QT shortening in adolescent boys.[28] QT gradually prolongs with age in adult men, and the sex difference becomes small or vanishes after middle age.

Although QT_{ea} is a measure of the global RT, QT_{pa} and RT_{epi} are measures of regional RT. The present investigation revealed an 18-ms sex difference in QT_{pa} (Figure 2), indicating that the sex difference in RT_p remains more pronounced in middle-aged men and women than the 10-ms sex difference in QT_{ea} as listed in Table 3. It is not known whether prolonged regional repolarization time (RT_p) might play some role in explaining the higher vulnerability of women than men to the proarrhythmic effects of cardioactive drugs.[29]

Comparison With Previous Studies

Two recent publications in general population samples of men and women[30,31] and 1 in men[32] found QRS duration to be predictive of SCD. In our study population of CVD-free men and women, QRS duration was a significant predictor only in the unadjusted single ECG variable risk model in women for CHD death.

Several publications have documented an increased mortality risk for a wide mean QRS|T angle[8–12] and abnormal T-wave axis.[33,34] Various angular measures of altered repolarization sequence were the most common predictors for CHD death and SCD in our study. Increased T-wave amplitude in aVR was reported to be a significant predictor of cardiac mortality in the general population of men and women[35] and in a large clinical male population.[36]

The previous investigations cited above have evaluated ECG predictors of CHD death and SCD as single variables or as a limited group of variables. The present investigation is the first large-scale population study with simultaneous evaluation of a comprehensive set of repolarization-related parameters.

Limitations of This Investigation

Although the multivariable models employed were adjusted for a variety of demographic and clinical factors, competing risk analysis was not performed. The primary objective of the study was to identify in CVD-free men and women a subset of ECG parameters for future risk evaluation studies as potentially more sensitive predictors of CHD death and SCD than the QT interval.

Clinical Significance and Avenues for Future Research

$\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$, reflecting different aspects of ventricular repolarization, were found to be independent predictors of CHD death and SCD, and TaVR and TV1, readily available in standard ECG reports, were also independent predictors. Among notable sex differences, the risk levels for independent predictors for both CHD death and SCD were stronger in women than in men, and QT_{ea} was a significant predictor in men but not in women. These ECG variables identified as independent predictors of CHD death and SCD are the primary candidates that warrant consideration in risk evaluation studies. However, all the repolarization-related parameters that were significant when evaluated as single variables need attention in the evaluation of possible markers of toxic drug effects using well-validated annotated data files from drug trials.

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Disclosures

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References

1. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22:660–670.
2. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013–1022.
3. Shah R, Hondeghem LM. Refining detection of drug-induced proarrhythmia: QT interval and TRIaD. *Heart Rhythm*. 2005;2:758–772.
4. Huikuri HV, Castellanos A, Myerburg RJ. SCD due to cardiac arrhythmias. *N Engl J Med*. 2001;345:1473–1482.
5. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. *Ann Intern Med*. 1994;121:529–535.
6. Stockbridge N, Brown BD. Annotated ECG waveform data at FDA. *J Electrocardiol*. 2004;37(suppl):63–64.
7. International conference on Harmonization: guidance for industry E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. *Fed Regist*. 2005;70:61134.
8. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. *Circulation*. 2006; 113:473–480.
9. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM; ARIC Research Group. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). *Am J Cardiol*. 2007; 100:844–849.
10. Rautaharju PM, Zhou SH, Gregg RE, Startt-Selvester RH. Heart rate, gender differences, and presence versus absence of diagnostic ST elevation as determinants of spatial QRS|T angle widening in acute coronary syndrome. *Am J Cardiol*. 2011;107:744–750.
11. Lown MT, Munyombwe T, Harrison W, West RM, Phil D, Hall AS, Gale CP. Association of frontal QRS-T angle–age risk score on admission electrocardiogram with mortality in patients admitted with an acute coronary syndrome.

Evaluation of methods and management of acute coronary events (EMMACE) investigators. *Am J Cardiol*. 2012;109:307–313.

12. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, Muntner P. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). *Am J Cardiol*. 2012;109:981–987.
13. The ARIC Investigators. The atherosclerosis in communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129:687–702.
14. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol*. 1996;49:223–233.
15. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR. Electrocardiographic findings in a healthy biracial population. The ARIC Study. *Am J Cardiol*. 1998;81:453–459.
16. Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*. Geneva, Switzerland: World Health Organization; 1982.
17. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. *Circulation*. 1960;21:1160–1175.
18. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016–1022.
19. Wolf HK, MacInnis PJ, Stock S, Helppi RK, Rautaharju PM. The Dalhousie Program. A comprehensive analysis program for rest and exercise electrocardiograms. In: Zywiets C, Schneider B, eds. *Computer Application on ECG and VCG Analysis*. Amsterdam-London: North Holland Publishing Co; 1973:231–240.
20. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J*. 1990;11:1083–1092.
21. Rautaharju PM, Zhou SH, Gregg RE, Startt-Selvester RH. Electrocardiographic estimates of action potential durations and transmural repolarization time gradients in healthy subjects and in acute coronary syndrome patients—profound differences by sex and by presence vs absence of diagnostic ST elevation. *J Electrocardiol*. 2011;44:309–319.
22. Rautaharju PM, Zhou SH, Gregg RE, Startt-Selvester RH. Electrocardiographic estimates of regional action potential durations and repolarization time subintervals reveal ischemia-induced abnormalities in acute coronary syndrome not evident from global QT. *J Electrocardiol*. 2011;44:718–724.
23. Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburges J, Nesterenko VV, Burashnikov A, Di Diego J, Saffitz J, Thomas GP. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol*. 1999;10:1124–1152.
24. Yan GX, Shimizu W, Antzelevitch C. The characteristics and distribution of M cells in arterially-perfused canine left ventricular wedge preparations. *Circulation*. 1998;98:1921–1927.
25. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation*. 1998;98:1928–1936.
26. Zhu TG, Patel C, Martin S, Quan X, Wu Y, Burke JF, Chernick M, Kowey PR, Yan GX. Ventricular transmural repolarization sequence: its relationship with ventricular relaxation and role in ventricular diastolic function. *Eur Heart J*. 2009;30:372–380.
27. Opthoff T, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart? *Circulation*. 2009;2:89–96.
28. Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, Davignon A. Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol*. 1992;8:690–695.
29. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA*. 1993;270:2590–2597.
30. Aro AL, Anttonen O, Tikkanen JT, Junttila MJ, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population. *Circ Arrhythm Electrophysiol*. 2011;4:704–710.
31. Teodorescu C, Reinier K, Uy-Evanado A, Navarro J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged QRS duration on the resting ECG is associated with SCD risk in coronary disease, independent of prolonged ventricular repolarization. *Heart Rhythm*. 2011;8:1562–1567.
32. Kurl S, Mäkikallio TH, Rautaharju P, Kiviniemi V, Laukkanen JA. Duration of QRS complex in resting electrocardiogram is a predictor of sudden cardiac death in men. 987. *Circulation*. 2012;125:2588–2594.
33. Kors JA, de Bruyne MC, Hoes AW, van Herpen G, Hofman A, van Bemmel JH, Groebbee DE. T axis as an independent indicator of risk of cardiac events in elderly people. *Lancet*. 1998;352:601–605.
34. Rautaharju PM, Clark-Nelson J, Kronmal RA, Zhang ZM, Robbins J, Gottdiener J, Furberg C, Manolio T, Fried L. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease. The CHS Study. *Am J Cardiol*. 2001;88:118–123.
35. Anttila I, Nikus K, Nieminen T, Jula A, Salomaa V, Reunanen A, Nieminen MS, Lehtimäki T, Virtanen V, Kähönen M. Relation of positive T wave in lead aVR to risk of cardiovascular mortality. *Am J Cardiol*. 2011;108:1735–1740.
36. Tan SY, Engel G, Myers J, Sandhi M, Froelicher VF. The prognostic value of T wave amplitude in lead aVR in men. *Ann Noninvasive Electrocardiol*. 2008;13:113–119.