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

Pentti M. Rautaharju, MD, PhD; Zhu-Ming Zhang, MD; James Warren, MSc; Richard E. Gregg, MSEE; Wesley K. Haisty, Jr, MD; Anna M. Kucharska-Newton, PhD; Wayne D. Rosamond, PhD; Elsayed Z. Soliman, MD, MSc, MS

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 (QTea), with a 2-fold increased risk for both, and spatial angles between mean QRS and T vectors and between Tpeak (Tp) and normal R reference vectors [θ(Rm | Tm) and θ(Tp | Tref), respectively], with a >1.5-fold increased risk for both. In women, independent predictors of the risk of CHD death were θ(Rm | Tm), with a 2-fold increased risk for θ(Rm | Tm), and θ(Tp | Tref), with a 1.7-fold increased risk. Independent predictors of SCD in men were θ(Tp | Tref) and QTend, with a 2-fold increased risk, and θ(Tinit | Tterm), with a 1.6-fold increased risk. In women, θ(Tinit | Tterm) was an independent predictor of SCD, with a >3-fold increased risk, and θ(Rm | Tm) and TV1 were >2-fold for both.

Conclusions—θ(Rm | Tm) and θ(Tp | Tref), 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 QTend 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. However, QT is known to have notable limitations, and professional organizations and governmental regulatory agencies have recognized the need for more sensitive predictors of adverse cardiac events than QT. 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 [θ(Rm | Tm)].

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...
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 al16 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 (QTp), QTend (QTe), and QTonset (QT0) 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 QTe for men and women and ranged from 0.36 to 0.40 for QTp and QT0. 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 QTp and QTe is an added complexity, a simpler QTp rate adjustment as the difference (QTpa−TpTe interval) was derived as shown in the middle section of Table 1. This became possible because the TpTe 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**

|                   | Linear functions | R-Square |
|-------------------|------------------|----------|
| QT e *            |                   |          |
| Men               | QTe = QT e 127 × (1−RR) | 0.571 |
| Women             | QTe = QT e 136 × (1−RR) | 0.529 |
| QT p *            |                   |          |
| Men               | QTp = QT p 116 × (1−RR) | 0.496 |
| Women             | QTp = QT p 130 × (1−RR) | 0.477 |
| QT o *            |                   |          |
| Men               | QT o = QT o 84 × (1−RR) | 0.451 |
| Women             | QT o = QT o 100 × (1−RR) | 0.422 |
| QT p              |                   |          |
| Men               | QT pa = QT p 416 × (1−RR 1/3) | 0.571 |
| Women             | QT pa = QT p 435 × (1−RR 1/3) | 0.529 |
| QT o              |                   |          |
| Men               | QT pa = QT o 295 × (1−RR 0.40) | 0.498 |
| Women             | QT pa = QT o 303 × (1−RR 0.40) | 0.436 |

**Table 2 from page 2**

RR interval is in seconds, other intervals in milliseconds.

* QTsa, QTpa, and QTsa refer to rate-adjusted QTend (QTsa), QTpeak (QTpa), and QTonset (QTsa), respectively.

† An alternative QTsa formula as (QTsa−TpTe interval) with linear QTsa 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. 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 (To) corresponding to the rate-adjusted QTonset interval (QToa) in reference to QRS onset was obtained by extrapolating the line from the point of maximum slope at T-wave upstroke (Txc) 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 (Txd) defines the end point of the TpTxd interval, which is conceived in the repolarization model to represent initial left ventricular repolarization time (RT) dispersion. RT peak (RTp) is computed as a function of the rate-adjusted QTpeak interval (QTpa). Briefly, \( RTp = QTpa - (\cos \theta(Tp|Tref) - 1) \times (TpTxd) / 2 \), where \( \theta(Tp|Tref) \) is the spatial angle between Tp vector and Tref is the reference mean T vector direction in normal repolarization (sex- and race-specific components of the unit vectors of Tref are listed in the footnote of Table 3). Tp–Txd, in turn, is the interval from Tp to Txd, where Txd is the inflexion point (the minimum slope) at global T-wave downstroke. Left ventricular (LV) RT at point Txd (RTxd) is obtained with an algorithm similar to that for RTp, whereby \( RTxd = QTpa + (\cos \theta(Tp|Tref) + 1) \times (TpTxd) / 2 \). The key role of RTp and RTxd for deriving ECG estimates for RTepi and RTepf is considered in detail in the Discussion section in the subsection “Validity of the Repolarization Model.”

In addition to \( \theta(Tp|Tref) \), 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.

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 TpV, 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. 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. QTpa, the rate-adjusted QTpeak, was 18 ms shorter and QToa, the rate-adjusted QTonset, 21 ms shorter in men than in women. The sex difference in global rate-adjusted QT (QTea) 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/m²   | 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 QTea and the rate-adjusted TPt 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 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 QTea 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 increased 1.7-fold for \( \theta(T_p|T_{ref}) \).

Independent predictors of SCD in men were \( \theta(T_p|T_{ref}) \) and QTea, 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
notable sex difference was that QT<sub>ea</sub> 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 <i>θ</i>[R<sub>m</sub>|T<sub>m</sub>], the spatial angle between the mean QRS and T vectors, and <i>θ</i>[T<sub>p</sub>|T<sub>ref</sub>], the spatial angle between Tpeak and the normal T reference vector. <i>θ</i>[R<sub>m</sub>|T<sub>m</sub>] is a measure of the overall deviation angle between depolarization and repolarization sequences, and <i>θ</i>[T<sub>p</sub>|T<sub>ref</sub>] 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. <i>θ</i>[R<sub>m</sub>|T<sub>m</sub>] 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 <i>θ</i>[T<sub>p</sub>|T<sub>ref</sub>] was a strong

\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Mean (SD)} & \text{P Value*} & \text{Test Group Threshold} \\
\hline
\text{Men} & \text{Women} & \text{Men} & \text{Women} & \text{Men} & \text{Women} \\
\hline
\text{Heart rate/min} & 65 (10.2) & 67 (10.0) & <0.001 & >73 & >73 \\
\text{QRS duration, ms} & 95 (9.1) & 87 (8.3) & <0.001 & 102 & 96 \\
\text{RNDPV,† μV} & 54 (22.6) & 43 (17.4) & <0.001 & 69 & 56 \\
\text{QT<sub>ea</sub>,‡ ms} & 413 (16.4) & 423 (17.5) & <0.001 & 426 & 437 \\
\text{QT<sub>oa</sub>,‡ ms} & 216 (18.3) & 237 (15.6) & <0.001 & 199 & 222 \\
\text{QT<sub>oa</sub>,‡ ms} & 311 (18.1) & 329 (19.8) & <0.001 & 268 & 207 \\
\text{RT<sub>epi</sub>,§ ms} & 316 (17.8) & 332 (18.8) & <0.001 & 329 & 347 \\
\text{RT<sub>endo</sub>,§ ms} & 348 (19.6) & 366 (20.1) & <0.001 & 364 & 381 \\
\text{T<sub>p</sub>T<sub>ea</sub>,k ms} & 36 (14.7) & 38 (15.3) & <0.001 & 48 & 50 \\
\text{h(T<sub>p</sub>T<sub>ea</sub>)},§§ ms} & 100 (13.9) & 95 (15.7) & <0.001 & 110 & 106 \\
\text{h(R<sub>m</sub>|T<sub>m</sub>),**, (°) } & 58 (26.8) & 4 (24.4) & <0.001 & 71 & 56 \\
\text{h(T<sub>p</sub>|T<sub>ref</sub>),†† (°) } & 21 (15.7) & 21 (19.0) & 0.0151 & 24 & 23 \\
\text{h(T<sub>init</sub>|T<sub>term</sub>),‡‡ (°) } & 0.34 (0.16) & 0.36 (0.18) & <0.001 & 0.47 & 0.51 \\
\text{T complexity§§} & 0.34 (0.16) & 0.36 (0.18) & <0.001 & 0.47 & 0.51 \\
\text{TaVR, lV/C0} & 219 (96.9) & 201 (86.7) & <0.001 & 146 & 131 \\
\text{TaVL, lV} & 94 (95.6) & 75 (80.3) & <0.001 & 24 & 0 \\
\text{TV1, lV} & –133 (146.0) & –12 (119.6) & <0.001 & 244 & 122 \\
\text{ST<sub>V</sub>, †† μV} & 54 (27.9) & 36 (19.7) & <0.001 & 75 & 53 \\
\text{TpV, μV} & 148 (56.7) & 104 (41.0) & <0.001 & 194 & 138 \\
\text{TpV, μV} & 418 (157) & 336 (132) & <0.001 & 268 & 207 \\
\text{VT<sub>p</sub>/VT<sub>p</sub>,** μV} & 0.39 (0.09) & 0.36 (0.11) & <0.001 & 0.45 & 0.42 \\
\hline
\end{array}
\]

HRs were evaluated for quintile 5 (quintile 1 for QT<sub>oa</sub>, TaVL, and TP) 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<sub>ea</sub>, QT<sub>oa</sub>, and QT<sub>oa</sub> refer to rate-adjusted QT<sub>end</sub> (QT<sub>e</sub>), QTpeak (QT<sub>p</sub>), and QTonset (QT<sub>o</sub>) intervals, respectively, using linear formulas listed in Table 1.

§RT<sub>epi</sub> and RT<sub>endo</sub> denote subepicardial and subendocardial repolarization times (see Methods section).

¶TpT<sub>x</sub>d interval representing dispersion of the initial left ventricular repolarization.

kGlobal repolarization time dispersion (interval from QT<sub>ea</sub> to QT<sub>ref</sub>).**

††Global repolarization time dispersion (interval from QT<sub>oa</sub> to QT<sub>ref</sub>).††

‡‡Global repolarization time dispersion (interval from QT<sub>oa</sub> to QT<sub>ref</sub>).‡‡

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

Symbol “V” in ST<sub>V</sub>, TV<sub>V</sub>, and TPV refers to spatial magnitudes of ST<sub>V</sub>, T<sub>V</sub>, and Tp vectors, respectively.

||ToV/TpV is the ratio of the To and Tp spatial vector magnitudes.
Table 4. Hazard Ratios With 95% Confidence Intervals for ECG Predictors of Coronary Heart Disease Death in Men and Women

|                | Men                              | P Value | Women                              | P Value |
|----------------|----------------------------------|---------|------------------------------------|---------|
|                | Univariable*                      |         | Multivariable*                      |         |
| QRS duration, ms | 1.26 (0.93 to 1.72)               | 0.143   | 1.33 (0.97 to 1.82)                | 0.081   |
| RNDPV          | 1.30 (0.95 to 1.78)               | 0.099   | 1.21 (0.85 to 1.71)                | 0.297   |
| QT mean, ms    | 1.88*** (1.42 to 2.50)            | <0.001  | 1.49 (1.11 to 2.00)                | 0.084   |
| TpTxd, ms      | 1.11 (0.81 to 1.52)               | 0.508   | 0.94 (0.68 to 1.30)                | 0.720   |
| o(TpT3a)       | 1.35 (0.99 to 1.82)               | 0.051   | 1.14 (0.83 to 1.57)                | 0.416   |
| RTcomplex      | 1.77 (1.33 to 2.34)               | <0.001  | 1.46 (1.08 to 1.97)                | 0.014   |
| (Rm|Tm),°         | 2.12 (1.61 to 2.79)               | <0.001  | 1.46 (1.09 to 1.95)                | 0.012   |
| (Tinit|Tterm),°      | 2.46 (1.88 to 3.23)               | <0.001  | 1.85 (1.39 to 2.46)                | <0.001  |
| (Tp|Tref),°        | 2.12 (1.61 to 2.79)               | <0.001  | 1.58 (1.18 to 2.21)                | 0.002   |
| T complexity   | 1.07 (0.78 to 1.47)               | 0.661   | 0.63 (0.69 to 1.32)                | 0.783   |
| TV1 amplitude, μV | 2.56 (1.96 to 3.34)               | <0.001  | 1.66 (1.25 to 2.22)                | <0.001  |
| TV1 amplitude, μV | 1.57 (1.17 to 2.11)               | 0.003   | 1.22 (0.89 to 1.66)                | 0.224   |
| STV1,°         | 1.38 (1.01 to 1.89)               | 0.045   | 1.13 (0.79 to 1.60)                | 0.502   |
| TVo, μV        | 1.25 (0.91 to 1.73)               | 0.171   | 1.22 (0.85 to 1.76)                | 0.273   |
| TVp, μV        | 0.82 (0.57 to 1.17)               | 0.271   | 1.02 (0.85 to 1.56)                | 0.747   |
| TVp/Tv/T101°   | 1.79 (1.34 to 2.40)               | 0.096   | 1.11 (0.69 to 1.50)                | 0.936   |

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 TVaL and TVaV, 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 QTpa,Tamp,aVL and TpV) as the test group, with the remaining 4 quintiles as the reference group.

RTp is computed as a function of QTpa, which is the key parameter in the algorithms for RTp and RTxd. RTp is conceived by the repolarization model to represent the RT of LV myocytes, which repolarize at the time of Tp during the initial fast phase of LV lateral wall repolarization. It is noted from the algorithms for deriving RTp as a function of QTpa that the RTp is modified by the cosine of (Tp|Tref). These relationships imply that RTp=QTpa if and only if (Tp|Tref)=0° and that QTpa is assigned to RTxd if (Tp|Tref)=180°; if (Tp|Tref)=90°, RTp and RTxd are both equal to QTpa. 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 Tp timing always coincides with QTep. Potential theory supports the assertion that at the time of RTp the majority of LV lateral wall myocytes are in phase 3 of their action potential and that

Validity of the Repolarization Model

As noted in the Methods section, RTp is computed as a function of the QTpa, which is the key parameter in the algorithms for RTp and RTxd. RTp is conceived by the repolarization model to represent the RT of LV myocytes, which repolarize at the time of Tp during the initial fast phase of LV lateral wall repolarization. It is noted from the algorithms for deriving RTp as a function of QTpa that the RTp is modified by the cosine of (Tp|Tref). These relationships imply that RTp=QTpa if and only if (Tp|Tref)=0° and that QTpa is assigned to RTxd if (Tp|Tref)=180°; if (Tp|Tref)=90°, RTp and RTxd are both equal to QTpa. 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 Tp timing always coincides with QTep. Potential theory supports the assertion that at the time of RTp 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, k/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              | 2.29 (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 |
| Tp_Tx, 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 |
| d(Tp, Tref)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_ea, 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 |
| d(R_ea, Tref)_h, °     | 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 4.43) | 0.003 |
| d(Tp, Tref)_h, °       | 2.91 (1.93 to 4.38) | <0.001 | 2.22 (1.43 to 3.43) | <0.001 | 5.90 (3.30 to 10.47) | <0.001 | 2.59 (1.39 to 4.82) | 0.003 |
| d(Tinit|Tterm)_h, °          | 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 |
| ToVR, 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_ea, V, 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 |
| Tp, 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 |
| TpV, 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 |
| TpV, μV                | 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) | 0.181 |

HRs were evaluated for quintile 5 (quintile 1 for QT_ea, TpV, and Tp) 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.

1RNDPV, ORS nondipolar voltage from singular value decomposition (square root of pooled variance of components 4 to 8).

2QT_ea, rate-adjusted QRe where QT_ea=QT_ea+127 (1–RR) for men and QT_ea=QT_ea+136 (1–RR) for women.

3Tinit|Tterm, ms interval representing dispersion of the initial left ventricular repolarization.

4Tinit|Tref, global repolarization time dispersion (interval from QT_ea to QT_ea).

5RTref denotes subepicardial repolarization time (see Methods section).

6Tinit|Tref, spatial angle between mean ORS and T vectors.

7Tinit|Tref, spatial angle between the initial T vectors from quintiles 1 to 3 and the terminal T vectors from quintiles 4 to 5.

8T wave complexity, ratio of the second to the first principal component from singular value decomposition of the T wave.

*Symbol “V” in ST_ea, V, Tp, and TpV refers to spatial magnitudes of the ST_ea, Tp, and Tp vectors, respectively.

RTp timing coincides with the timing of the global Tp. It thus seems a rational proposition to maintain the labels RT_epi and RTxkd as derived by modifying RTp by d(Tp, Tref). 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 Tp and RTp, LV lateral wall subepicardial myocytes in the region where repolarization starts earliest have already reached phase 3 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 electro-physiological data relating the timing of QTp with QT_epi in normal repolarization.23–26 Parameter Tp 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 Tp_Txkd interval is diametrically opposite to the direction of the Tp vector, and Tp_Txkd is the magnitude of the temporal RT gradient vector representing RT dispersion during the Tp_Txkd 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,24–25 there is consistent evidence that the spatial LV repolarization sequence remains throughout repolarization closely in the direction of inferior-left-anterior to superior-right-posterior, approximately in the direction of the lead vector of aVR but with a
Mechanisms of Generation of Repolarization Abnormalities as Independent Predictors of CHD Death and SCD

Anterior-right rotation of the Tp vector is a predominant determinant of widened \( \theta(R_m|T_m) \) and \( \theta(T_p|T_{ref}) \) angles.10,21 Tp 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 repolarization10 that in turn has been postulated to be associated with increased dyssynchrony of ventricular repolarization as another possible risk mechanism.26

QTee 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<sub>ea</sub> is a measure of the global RT, QT<sub>pe</sub> and RT<sub>epi</sub> are measures of regional RT. The present investigation revealed an 18-ms sex difference in QT<sub>pe</sub> (Figure 2), indicating that the sex difference in RT<sub>p</sub> remains more pronounced in middle-aged men and women than the 10-ms sex difference in QT<sub>ea</sub> as listed in Table 3. It is not known whether prolonged regional repolarization time (RT<sub>p</sub>) might play some role in explaining the higher vulnerability of women than men to the proarrhythmic effects of cardioactive drugs.  

**Comparison With Previous Studies**

Two recent publications in general population samples of men and women<sup>30,31</sup> and 1 in men<sup>32</sup> found QRS duration to be a significant predictor of CHD death and 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<sup>8–12</sup> and abnormal T-wave axis.<sup>33,34</sup> 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<sup>35</sup> and in a large clinical male population.<sup>36</sup>

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**

If[|RM|TM] and If[Tp|Tel], 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<sub>ea</sub> 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.

**Acknowledgments**

The authors thank the staff and participants of the ARIC study for their important contributions.

**Sources of Funding**

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

**Disclosures**

Mr Gregg is an employee of the Advanced Algorithms Research Center of Philips Health Care.

**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. Huijbers HV, Castellanos A, Myerburg RJ. SCD due to cardiac arrhythmias. *N Engl J Med*. 2001;345:1473–1482.
5. Hohnloser SH, Klingenhheben T, Singh BN. Amiodarone-associated proarrhythmic effects. *Circulation*. 1994;90:529–535.
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 MD, 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, Levitin EB, Newman JD, Rautaharju PM, Davidson KW, Muntner P. Relations between QRS Tangle, 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;129:678–702.

14. White AD, Folsom AR, Chambless LE, Sharrett 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, Macnlin PJ, Stock S, Helppi RK, Rautaharju PM. The Dalhousie Program. A comprehensive analysis program for rest and exercise electrocardiograms. In: Zywietz 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 Bemmelen JJ. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1091–1092.

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. Ophoff 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, Junntila 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, Reimer 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, Makikallio TH, Rautaharju P, Kivim€aki M, 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 Bemmelen JJ, Groebee 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, Gott dieiner J, Furbeg 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. Aanttila 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.