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### Permalink

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### Journal

Journal of the American Heart Association, 3(4)

### ISSN

2047-9980



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### Publication Date

2014-08-15

### DOI

10.1161/jaha.114.001005

Peer reviewed



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ORIGINAL RESEARCH

# Electrocardiographic Repolarization-Related Variables as Predictors of Coronary Heart Disease Death in the Women's Health Initiative Study

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***Background***—We evaluated 25 repolarization-related ECG variables for the risk of coronary heart disease (CHD) death in 52 994 postmenopausal women from the Women's Health Initiative study.

***Methods and Results***—Hazard ratios from Cox regression were computed for subgroups of women with and without cardiovascular disease (CVD). During the average follow-up of 16.9 years, 941 CHD deaths occurred. Based on electrophysiological considerations, 2 sets of ECG variables with low correlations were considered as candidates for independent predictors of CHD death: Set 1, $\Theta(T_p|T_{ref})$, the spatial angle between T peak ($T_p$) and normal T reference ($T_{ref}$) vectors; $\Theta(T_{init}|T_{term})$, the angle between the initial and terminal T vectors; STJ depression in V6 and rate-adjusted $QT_p$ interval ($QT_{pa}$); and Set 2, TaVR and TV1 amplitudes, heart rate, and QRS duration. Strong independent predictors with over 2-fold increased risk for CHD death in women with and without CVD were $\Theta(T_p|T_{ref})$ >42° from Set 1 and TaVR amplitude >−100 μV from Set 2. The risk for these CHD death predictors remained significant after multivariable adjustment for demographic/clinical factors. Other significant predictors for CHD death in fully adjusted risk models were $\Theta(T_{init}|T_{term})$ >30°, TV1 >175 μV, and QRS duration >100 ms.

***Conclusions***—$\Theta(T_p|T_{ref})$ angle and TaVR amplitude are associated with CHD mortality in postmenopausal women. The use of these measures to identify high-risk women for further diagnostic evaluation or more intense preventive intervention warrants further study.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000611. **(*J Am Heart Assoc*. 2014;3: e001005 doi: 10.1161/JAHA.114.001005)**

**Key Words:** coronary heart disease • electrocardiography • mortality • repolarization • risk factors

Electrocardiographic depolarization- and repolarization-related abnormalities as predictors of coronary heart disease (CHD) mortality and morbidity have been a subject of many electrocardiographic investigations. From repolarization-related abnormalities, QT prolongation has been a common topic in studies on general populations and in clinical study groups, particularly with cardiovascular disease (CVD).[1] Some newer reports from general populations have documented increased risk for CHD death for widened spatial angle between mean QRS and ST-T vectors ($\Theta(QRS|STT)$).[2,3] ST- and T-wave findings in women with CVD are generally considered as secondary abnormalities of little importance in clinical ECG interpretation, although some studies have associated them with CHD mortality risk,[4–7] including the risk of sudden cardiac death (SCD). From depolarization-related ECG abnormalities, QRS duration increase even within its upper normal range has been found to be an independent predictor of CHD death, including SCD.[4,8,9]

A recently developed repolarization model introduced several novel repolarization-related variables from various repolarization time (RT) subintervals such as QT peak ($QT_p$) interval, epicardial repolarization time ($RT_{epi}$), left ventricular crossmural RT gradient ($XMRT_{grad}$) and, in addition to

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Received April 7, 2014; accepted June 20, 2014.

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Θ(QRS|STT), several other spatial angles representing deviation of the repolarization sequence from normal direction during various RT subintervals.[3,10–12] The primary objective of the present study was to evaluate the risk of CHD death for these novel ECG risk predictors in postmenopausal women from the Women's Health Initiative (WHI) study.

## Methods

### Study Population

The WHI is a 40-center, national study of risk factors and the prevention of common causes of mortality, morbidity, and impaired quality of life in women. Postmenopausal women aged 50 to 79 years from various ethnic groups were recruited from 1994 to 1998. Details of the study design, protocol sampling procedures, and selection and exclusion criteria have been published previously.[13] The present study group consisted of 68 133 women, a subgroup of the clinical trial component of WHI, which had digital ECGs and comprehensive documentation of outcome events available. Participants with missing or incomplete ECG data (n=966) were excluded; ECGs with inadequate quality or technical errors by visual inspection (n=614), bundle branch blocks (n=1739), electronic pacemakers or WPW pattern (n=109), and 47 ECGs with heart rate >100/min and 3 ECGs with incomplete data were also excluded. From the remaining group of 64 661 participants, 12 569 were found to have had a CVD event while 52 092 were CVD-free at baseline. The sequential steps in selection of the study group for risk analyses are shown in the block diagram in Figure 1.

Protocols for human studies were reviewed and approved by Institutional Review Boards of each participating center, and informed consent was obtained from each participant.

### ECG Methods

Standard 12-lead ECGs were recorded in all women in the supine position using MAC PC electrocardiographs (GE Marquette, Inc, Milwaukee, WI). ECG technicians in all participating centers were trained to use carefully standardized procedures for ECG acquisition including locating the chest electrodes in precise positions using a special chest electrode locator.[14] All electrocardiograms received at a Central ECG Laboratory (EPICARE Center, University of Alberta; Edmonton, Alberta, Canada and later at Wake Forest University, Winston-Salem, NC) were inspected visually to detect technical errors, missing leads, and inadequate quality, and such records were rejected from ECG data files. The ECGs were processed by 2001 version of the Marquette 12SL program (GE Marquette, Inc, Milwaukee, WI).

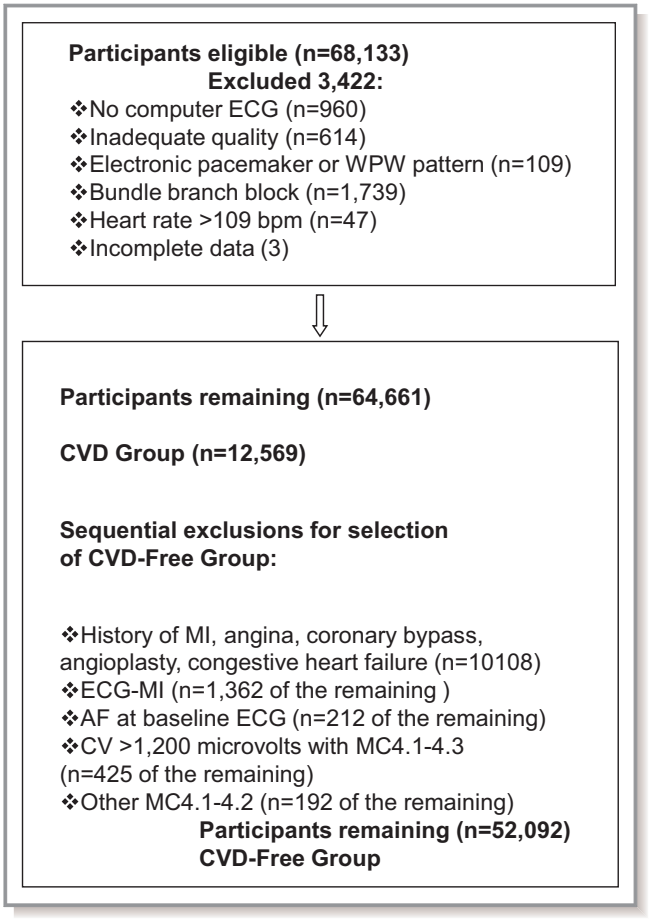


**Figure 1.** A block diagram for exclusions and sequential selections of the study group. AF indicates atrial brillation; CV, Cornell Voltage; CVD, cardiovascular disease; MI, myocardial infarction; WPW, Wolf-Parkinson-White pattern.

### Repolarization Parameters from the Repolarization Model

The orthogonal Frank XYZ leads were obtained from the 8 independent components (leads I, II, V1 to V6) using a transformation matrix from the 116-lead body surface map library of Horáček containing recordings for 892 adults aged 16 to 85 years.[15] Repolarization measurements were made utilizing temporal reference points derived from the spatial T-vector magnitude curve derived from the XYZ leads (the "global" T wave), including QT end ($QT_e$), QTpeak ($QT_p$), and QTonset ($QT_o$) intervals. $QT_e$, $QT_p$, and $QT_o$ intervals were rate adjusted ($QT_{ea}$, $QT_{pa}$ and $QT_{oa}$, respectively) as linear functions of the RR interval with the following formulas derived in the CVD-free group: $QT_{ea}=QT_e+184\times(1-RR)$, $QT_{pa}=QT_p+135\times(1-RR)$ and $QT_{oa}=QT_o+113\times(1-RR)$. Heart rate, QRS duration, QRS nondipolar voltage from singular value decomposition and a set of 22 repolarization-related ECG variables from our repolarization model were chosen for evaluation because of their functional role in generation of normal and abnormal repolarization

waveforms or because of their previously shown value as risk predictors.[2,3,10–12] QRS duration was included as the second depolarization-related parameter in addition to QRS nondipolar voltage from singular value decomposition because even moderate QRS prolongation is known to induce secondary repolarization abnormalities, which may be associated with adverse cardiac events over and above those induced by QRS prolongation alone.

The conceptual model used to derive RT subintervals and other model parameters for the present study has been described in detail in previous publications.[2,3,10–12] A simplified summary description of the main model variables in nonstatistical terms is contained in Table 6. In more basic terms, RT of the subepicardial myocyte layers ($RT_{epi}$), 1 of the main repolarization model parameters, is considered to represent RT of left ventricular (LV) myocytes at the time of global T-wave peak ($T_p$) when the majority of LV lateral wall myocytes are at some point of phase 3 of their action potential. $RT_{epi}$ is computed as a function of $QT_{pa}$ whereby $RT_{epi}=QT_{pa}-(1-\text{Cos}\Theta(T_p|T_{ref})\times(T_pT_{xd}))/2$, where $\Theta(T_p|T_{ref})$ is the spatial angle between the $T_p$ vector and $T_{ref}$ is the reference normal $T_p$ vector with xyz components (0.75, 0.57, −0.33). $T_pT_{xd}$, in turn, is the interval from $T_p$ to $T_{xd}$, where $T_{xd}$ is the inflexion point (the steepest negative slope) at global T wave downstroke. Thus, $RT_{epi}$ is obtained from $QT_{pa}$ by modifying it by the degree of deviation of direction of the initial repolarization from the direction of normal repolarization. RT at time point $T_{xd}$ ($RT_{xd}$) is obtained with an algorithm similar to that for $RT_{epi}$, whereby $RT_{xd}=QT_{pa}-(1+\text{Cos}\Theta(T_p|T_{ref})\times(T_pT_{xd}))/2$. In addition to $\Theta(T_p|T_{ref})$ noted above, a number of other spatial angles between various QRS and T vectors and other interval and amplitude variables were used in various phases of the study.

## Ascertainment of Outcome Events

After baseline, deaths and hospitalization events were ascertained in each clinical center by annual follow-up calls, review of vital records, and community surveillance of hospitalized and fatal events. Detailed definitions for criteria for CHD death classification have been published previously.[16] Briefly, CHD deaths included death with no known non-CHD death and either a history of chest pain within 72 hours before death or a history of chronic ischemic heart disease in the absence of valvular heart disease. The average follow-up was 15.9 years (up to 17 years).

## Statistical Methods

Frequency distributions of ECG variables from the repolarization model were first inspected to rule out anomalies and outliers. $QT_e$ distributions were skewed, but otherwise, no anomalies that would notably interfere with analyses were observed. ECG predictors were first evaluated individually in unadjusted single ECG variable models and subsequently in multivariable-adjusted models adjusted for age, race, smoking status, diabetes, hypertension, family history of CHD and stroke, body mass index, hypercholesterolemia, and study component/arm groups (hormone therapy/dietary modification/calcium, and vitamin D).

In the search for independent predictors for CHD death, 1 primary concern was the collinearity of variables with high correlations. A previous investigation in participants free from cardiovascular disease from the Atherosclerosis Research in Communities Study found $\Theta(T_p|T_{ref})$ and aVR amplitude as independent predictors of CHD death and SCD.[3] These 2 correlated variables ($r$=0.56) were used as primary explanatory variables, and a search was performed separately for each to identify other variables with low correlations ($r$<0.4). This procedure produced 2 sets of predictors as candidates for independent predictors for CHD death: Set 1, $\Theta(T_p|T_{ref})$ and spatial angle between the initial and terminal T vectors $\Theta(T_{init}|T_{term})$, respectively), STJ depression in V6, rate-adjusted $QT_p$ interval ($QT_{pa}$); and Set 2, TaVR and TV1 amplitudes, heart rate, and QRS duration. An association was considered significant when the $P$-value (2-sided) was <0.05.

Consistent with our previous risk data in studies with different end points,[11,12] it was observed that CHD risk in general started to increase after the 80th percentile of the ECG variable distribution. Therefore, hazard ratios were constructed to evaluate the risk for CHD death with quintile 5 as the test group with quintiles 1 to 4 as the reference group. However, for ST J point and T-wave amplitudes in aVL and V6, the risk of CVD death was observed to increase at values below the 20th percentile of the distribution and quintile 1 was used as the test group for these variables, with quintiles 2 to 5 as the reference group. Risk for CHD death was first evaluated using group-specific cut points for the test group at 80th or 20th percentile. The quintiles were chosen for evaluation with the expectation that significant predictors for CHD death in test quintiles would be strong predictors with higher cut points. Finally, cut points were set at values representing upper or lower fifth percentiles of the CVD-free group, and these dichotomized cut points were used also for the CVD group.

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

# Results

## Characteristics of the Study Population

The subgroup of women considered CVD-free after exclusion of women with clinical or ECG evidence of any CVD was relatively healthy (Table 1). Still, 31% were hypertensive or on antihypertensive medication. All women with ECG-LVH

**Table 1.** Demographic/Clinical Characteristics* of the Study Group by CVD Status at Baseline

| Characteristics | CVD-Free (n=52 092) | CVD (n=12 569) |
|---|---|---|
| Age, y | 62; 6.9 | 65; 7.0 |
| Weight, kg | 76; 16.5 | 78; 17.2 |
| Body mass index, kg/m$^2$ | 28.8; 5.8 | 29.6; 6.1 |
| Systolic blood pressure, mm Hg | 127; 17.0 | 131; 18.2 |
| Diastolic blood pressure, mm Hg | 76; 9.0 | 76; 9.4 |
| Smoking | | |
| Never | 51.3 | 49.9 |
| Past | 40.7 | 41.9 |
| Current | 7.9 | 8.2 |
| Hypertension | 30.1 | 49.6 |
| Diabetes | 5.2 | 10.5 |
| History of AF by self-report | 0.1 | 19.5 |
| ECG-AF at baseline | — | 1.7 |
| Ectopic ventricular complexes | 3.4 | 5.2 |
| ECG-LVH & major STT† | — | 2.8 |
| Major ST depression‡ | — | 8.6 |
| Left atrial enlargement‖ | 4.3 | 7.5 |
| ECG-MI by MC‖ | — | 13.0 |

$P<0.001$ for all except $P=0.002$ for diastolic blood pressure and 0.011 for smoking. From Student $t$ test for differences between the means or from $z$ test for proportions. AF indicates atrial fibrillation; CVD, cardiovascular disease; MI, myocardial infarction.
*Mean and SD or %.
†ECG-LVH=left ventricular hypertrophy by Cornell Voltage (RaVL+SV3) ≥2200 μV and ST depression by Minnesota Code (MC) 4.1 to 4.3.
‡MC 4.1 or 4.2.
‖MC 9.6.

(RaVL+SV3 >2200 μV with ST depression including the so-called LV strain pattern (ECG-LVH with down sloping ST and negative T wave) had been transferred to the CVD group. Five percent of the CVD-free women had diabetes, and 0.1% had atrial fibrillation by self-report. As expected, most differences between CVD and CVD-free groups were statistically significant. Nearly one half of the women with CVD were hypertensive, 11% had diabetes, 20% had atrial fibrillation by self-report and 1.7% had atrial fibrillation in the baseline ECG. Approximately one half of women in both groups had never smoked and about 8% were current smokers.

## Single ECG Variables as Predictors of CHD Death

More than one half of the 25 ECG variables evaluated were significant predictors of CHD death in unadjusted single ECG variable risk models (not shown) and remained significant predictors in multivariable adjusted (Table 2). Four ECG variables in CVD-free women had an over 1.50-fold increased risk for CHD death. The strongest predictor in CVD-free women was $T_oV/T_pV$ (hazard ratios 1.93 [1.42 to 2.63], $P<0.001$), the ratio of the spatial magnitudes of T vectors at T wave onset and T wave peak. Increased value of this variable reflects reduced convexity of ST magnitude curve which in turn is thought to reflect triangularization of phase 3 of LV lateral wall action potentials. Many ECG variables in women with CVD were strong predictors of CHD death, including $T_oV/T_pV$ and STJ-point and T wave amplitudes in several ECG leads. Twelve of the ECG variables had an over 1.5-fold increased risk for CHD death, and for 2 of them, $\Theta(T_p|T_{ref})$ and STJV6, there was an over 2-fold increased risk.

## Independent ECG Predictors of CHD Death

It was observed that many of the repolarization variables including several of T wave and STJ-point amplitudes were correlated with $\Theta(T_p|T_{ref})$ ($r>0.4$) (Table 3). A smaller subset of variables with lower correlation with $\Theta(T_p|T_{ref})$ ($r<0.4$) were chosen initially to search for independent predictors for CHD death. Two sets of predictors were identified as independent predictors of CHD death (Table 4). Set 1, spatial angles between T peak ($T_p$) and normal T reference ($T_{ref}$) vectors and between the initial and terminal T vectors ($\Theta(T_p|T_{ref})$ and $\Theta(T_{init}|T_{term})$, respectively), STJ depression in V6; and Set 2, TaVR and TV1 amplitudes and QRS duration. The strongest independent predictors in women with and without CVD were $\Theta(T_p|T_{ref})$ >42° in Set 1 and TaVR amplitude less negative than −100 μV in Set 2 with an over 2-fold increased risk for both, and also heart rate >84 had an over 2-fold increased risk among Set 2 variables in CVD-free women. For the other independent predictors of CHD death in Set 1, risk increase ranged from 30% for ST J-point amplitude in V6 to 87% for heart rate and in Set 2 from 56% for TV1 amplitude to 64% for QRS duration. These independent predictors of CHD death in multivariable Model 1 remained significant with additional multivariate adjustment for demographic and clinical factors in Model 2. It is noteworthy that Set 2 ECG variables TaVR and heart rate were as strong predictors for the risk of CHD death as the computationally more complex best Set 1 variable $\Theta(T_p|T_{ref})$.

## Clinical Diseases and Related ECG Findings as Predictors of CHD Death

Hazard ratios are listed in Table 5 for selected clinical classification categories and related ECG findings of interest. Atrial fibrillation by self-report was the strongest predictor in the remaining classification categories in CVD-free women, with an over 4-fold increased risk for CHD death in multivariable-adjusted model. However, the prevalence of this condition was low in CVD-free women (0.1%, Table 1).

**Table 2.** Single ECG Variable Multivariable-Adjusted Hazard Ratios With 95% CI for CHD Death in Women by CVD Status at Baseline

| | CVD-Free Group | | | | CVD Group | | | |
|---|---|---|---|---|---|---|---|---|
| ECG Variables | Test Quintile | Limit* | HR (95% CI)† | *P* Value‡ | Test Quintile | Limit* | HR (95% CI)† | *P* Value |
| Heart rate | Q5 | >74 | 1.51 (1.28 to 1.79) | <0.001 | Q5 | >74 | 1.37 (1.12 to 1.68) | 0.0022 |
| QRS duration, ms | Q5 | >92 | 1.19 (0.99 to 1.43) | 0.0679 | Q5 | >94 | 1.39 (1.13 to 1.70) | 0.0022 |
| $QT_{ea}$, ms§ | Q5 | >425 | 1.25 (1.07 to 1.49) | 0.0077 | Q5 | >428 | 1.23 (1.00 to 1.51) | 0.0468 |
| $QT_{pa}$, ms§ | Q5 | >354 | 1.48 (1.25 to 1.74) | <0.001 | Q5 | >358 | 1.28 (1.04 to 1.58) | 0.0181 |
| $QT_{oa}$, ms§ | Q5 | >268 | 1.46 (1.24 to 1.72) | <0.001 | Q5 | >273 | 1.30 (1.06 to 1.59) | 0.0116 |
| $T_pT_{xd}$, ms‖ | Q5 | >40 | 1.05 (0.87 to 1.26) | 0.6373 | Q5 | >42 | 1.22 (0.99 to 1.50) | 0.0618 |
| (TpTe)a, ms¶ | Q5 | >90 | 0.89 (0.74 to 1.08) | 0.2351 | Q5 | >92 | 1.03 (0.83 to 1.29) | 0.7786 |
| $RT_{epi}$, ms# | Q5 | >350 | 1.43 (1.21 to 1.70) | <0.001 | Q5 | >352 | 0.97 (0.77 to 1.22) | 0.8126 |
| $RT_{endo}$, ms** | Q5 | >383 | 1.36 (1.15 to 1.61) | 0.0003 | Q5 | >387 | 1.14 (0.92 to 1.41) | 0.2416 |
| RNDPV, μV†† | Q5 | >52 | 1.09 (0.90 to 1.32) | 0.3745 | Q5 | >57 | 1.41 (1.14 to 1.73) | 0.0013 |
| Θ(R\|STT) (°)‡‡ | Q5 | >79 | 1.52 (1.29 to 1.78) | <0.001 | Q5 | >89 | 1.86 (1.54 to 2.25) | <0.001 |
| $\Theta(T_p\|T_{ref})$ (°)§§ | Q5 | >25 | 1.51 (1.28 to 1.78) | <0.001 | Q5 | >36 | 2.10 (1.74 to 2.54) | <0.001 |
| $\Theta(T_{init}\|T_{term})$ (°)‖‖ | Q5 | >21 | 1.44 (1.22 to 1.70) | <0.001 | Q5 | >25 | 1.70 (1.40 to 2.03) | <0.001 |
| STJV, μV¶¶ | Q5 | >45 | 1.13 (0.94 to 1.36) | 0.1982 | Q5 | >50 | 1.61 (1.31 to 1.96) | <0.001 |
| $T_oV$, μV¶¶ | Q5 | >132 | 0.95 (0.78 to 1.16) | 0.6057 | Q5 | >128 | 1.34 (1.09 to 1.66) | 0.0066 |
| $T_pV$, μV¶¶ | Q5 | >437 | 0.83 (0.67 to 1.03) | 0.0841 | Q5 | >413 | 1.06 (0.83 to 1.34) | 0.6594 |
| $T_oV/T_pV$## | Q5 | >0.36 | 1.93 (1.42 to 2.63) | <0.001 | Q5 | >0.41 | 1.87 (1.47 to 2.38) | <0.001 |
| STJaVR, μV*** | Q5 | >−5 | 1.37 (1.16 to 1.61) | <0.001 | Q5 | >4 | 1.64 (1.34 to 1.99) | <0.001 |
| STJ aVL, μV*** | Q1 | <−10 | 1.16 (0.97 to 1.39) | 0.1088 | Q1 | <−10 | 1.33 (1.09 to 1.61) | <0.001 |
| STJ V1, μV | Q5 | >14 | 1.41 (1.19 to 1.67) | <0.001 | Q5 | >19 | 1.51 (1.24 to 1.84) | <0.001 |
| STJ V6, μV | Q1 | <0 | 1.15 (0.97 to 1.37) | 0.0979 | Q1 | <−10 | 2.01 (1.66 to 2.42) | <0.001 |
| Tam aVR, μV | Q5 | >−166 | 1.49 (1.26 to 1.75) | <0.001 | Q5 | >−122 | 1.96 (1.62 to 2.37) | <0.001 |
| Tam aVL, μV | Q1 | <19 | 1.45 (1.23 to 1.71) | <0.001 | Q1 | <−19 | 1.58 (1.30 to 1.91) | <0.001 |
| Tam V1, μV | Q5 | >83 | 1.29 (1.09 to 1.52) | 0.0033 | Q5 | >102 | 1.60 (1.32 to 1.95) | <0.001 |
| Tam V6, μV | Q1 | <41 | 1.60 (1.36 to 1.88) | <0.001 | Q1 | <87 | 1.89 (1.56 to 2.29) | <0.001 |

CHD indicates coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiographic; HR, hazard ratio.

*Test group threshold for the quintile (Q) listed with the remaining 4 quintiles as the reference group.

†Single ECG variable model was multivariable-adjusted for study arm, age, race, smoke status, diabetes, hypertension, family history of CHD/stroke, body mass index, and total cholesterol; ECG variables with low correlations were entered simultaneously into the multiple ECG variable model, adjusting each of them to the other ECG variables and subsequently multivariable-adjusted to the same set of demographic/clinical variables as the single ECG variable model.

‡*P* value from Student *t* test for differences between the means or from *z* test for proportions.

§$QT_{ea}$, $QT_{pa}$, and $QT_{oa}$=rate adjusted QTend ($QT_e$), QTpeak ($QT_p$), and QTonset ($QT_o$) whereby $QT_{ea}=QT_e+184\times(1-RR)$, $QT_{pa}=QT_p+135\times(1-RR)$, and $QT_{oa}=QT_o+113\times(1-RR)$.

‖$T_pT_{xd}=T_pT_{xd}$ interval representing dispersion of the initial left ventricular lateral wall repolarization time (RT) or crossmural RT gradient.

¶$(T_pT_e)_a$=global repolarization time dispersion (interval from $QT_{pa}$ to $QT_{ea}$).

#$RT_{epi}$=ECG estimate of epicardial repolarization time. (see Methods section).

**$RT_{endo}$=ECG estimate of endocardial repolarization time.

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

‡‡Θ(R|STT)=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.

¶¶Symbol "V" in STJV, $T_oV$ and $T_pV$ refers to spatial magnitudes of STJ, $T_o$, and $T_p$ vectors.

##$T_oV/T_pV$=ratio of $T_oV$ and $T_pV$ vector magnitudes.

***STJ refers to ST onset (J point) amplitudes in the leads listed.

Diabetes was a strong predictor of CHD death, with a 2.7-fold increased multivariable-adjusted risk in both groups of women. Hypertension in CVD-free women had a 1.59-fold multivariable-adjusted increased risk for CHD death and a 1.81-fold increased risk in women with CVD. Of interest is that ventricular ectopic complexes and left atrial enlargement

**Table 3.** Correlations Between Electrocardiographic Variables Selected for Evaluation of Independent Predictors of Coronary Heart Disease Death

| ECG Variables | $\Theta(T_p \mid T_{ref})$ | $\Theta(T_{init} \mid T_{term})$ | STJV6 | $QT_{pa}$ | TaVR | TV1 | Heart Rate | QRS Duration |
|---|---|---|---|---|---|---|---|---|
| $\Theta(T_p \mid T_{ref})$* | 1.00 | | | | | | | |
| $\Theta(T_{init} \mid T_{term})$† | 0.30 | 1.00 | | | | | | |
| STJV6‡ | −0.30 | −0.17 | 1.00 | | | | | |
| $QT_{pa}$§ | 0.09 | −0.07 | −0.10 | 1.00 | | | | |
| TaVR | 0.56 | 0.27 | −0.44 | 0.22 | 1.00 | | | |
| TV1 | 0.16 | 0.25 | −0.10 | −0.09 | 0.27 | 1.00 | | |
| Heart rate | 0.03 | −0.05 | −0.17 | −0.04 | 0.16 | 0.12 | 1.00 | |
| QRS duration | 0.10 | 0.08 | −0.26 | 0.13 | 0.03 | 0.02 | −0.11 | 1.00 |

*$\Theta(T_p \mid T_{ref})$=spatial angle between T peak ($T_p$) and normal T reference ($T_{ref}$) vectors.
†$\Theta(T_{init} \mid T_{term})$=spatial angle between initial and terminal T vectors from the initial 3 and terminal 2 quintiles of repolarization, respectively.
‡STJV6=STJ-point amplitude.
§$QT_{pa}$=rate-adjusted QT peak interval.

were both significant predictors of CHD risk in both groups of women.

## Discussion

Key results of this investigation can be summarized as follows: (1) A majority of the ECG variables were significant predictors of CHD death in women when evaluated as single ECG variables and remained significant in multivariable-adjusted risk models; (2) 2 sets were considered as candidates for independent predictors of CHD death: Set 1, spatial angles between Tpeak ($T_p$) and normal T reference ($T_{ref}$) vectors and between the initial and terminal T vectors ($\Theta(T_p \mid T_{ref})$ and $\Theta(T_{init} \mid T_{term})$, respectively), STJ depression in V6 and rate-adjusted $QT_p$ interval ($QT_{pa}$); and Set 2, TaVR and TV1 amplitudes, heart rate and QRS duration; (3) The strongest independent predictors in women with and without CVD with

**Table 4.** Hazard Ratios With 95% Confidence Intervals for 2 Sets of Independent Predictors of CHD Death With Common Test Group Cut-Off Points at 95th or 5th Percentiles in CVD-Free Women by CVD Status at Baseline

| | CVD-Free Women | | Women With CVD | |
|---|---|---|---|---|
| Variable (Cut Point) | Model 1* | Model 2* | Model 1* | Model 2* |
| Set 1 | | | | |
| $\Theta(T_p T_{ref})$ (>42°)† | 2.13 (1.72 to 2.64) | 1.73 (1.36 to 2.21) | 2.03 (1.68 to 2.46) | 1.49 (1.20 to 1.87) |
| $\Theta(T_{init} \mid T_{term})$ (>30°)‡ | 1.49 (1.19 to 1.86) | 1.40 (1.08 to 1.80) | 1.42 (1.14 to 1.75) | 1.40 (1.11 to 1.78) |
| STJampl.V6 (<−25 μV) | 1.30 (1.00 to 1.67) | 1.07 (0.79 to 1.44) | 1.62 (1.32 to 1.98) | 1.75 (1.39 to 2.20) |
| $QT_{pa}$ (≥360 ms)§ | 1.49 (1.27 to 1.76) | 1.37 (1.13 to 1.65) | 1.29 (1.07 to 1.56) | 1.23 (0.99 to 1.52) |
| Set 2‖ | | | | |
| Tampl. aVR (>−100) | 2.27 (1.86 to 2.77) | 1.81 (1.44 to 2.27) | 2.09 (1.75 to 2.49) | 1.71 (1.40 to 2.10) |
| Tampl. V1 (>175 μV) | 1.56 (1.25 to 1.96) | 1.41 (1.09 to 1.83) | 1.85 (1.49 to 2.29) | 1.54 (1.21 to 1.96) |
| Heart rate (>84/min) | 2.25 (1.80 to 2.83) | 1.78 (1.38 to 2.30) | 1.30 (0.96 to 1.76) | 1.14 (0.82 to 1.59) |
| QRS duration (≥100 ms) | 1.64 (1.31 to 2.05) | 1.35 (1.04 to 1.75) | 1.45 (1.17 to 2.49) | 1.45 (1.14 to 1.84) |

CHD indicates coronary heart disease; CVD, cardiovascular disease.
*A set of ECG variables with low correlations ($r$<0.4) was entered simultaneously into the risk model, and each was adjusted for the other ECG variables with no further adjustment (Model 1) and with additional adjustment for demographic and clinical factors (Model 2).
†$\Theta(T_p \mid T_{ref})$=spatial angle between T peak ($T_p$) and T reference ($T_{ref}$) vectors signifying deviation of repolarization direction in normal repolarization.
‡$\Theta(T_{init} \mid T_{term})$=spatial angle between the mean initial and terminal T vectors from quintiles 1 to 3 and 4 to 5, respectively.
§$QT_{pa}$=rate-adjusted QT peak interval.
‖($T_p \mid T_{ref}$, $\Theta(T_{init} \mid T_{term})$) and STJ V6 were replaced in Set 2 by T amplitudes in aVR and V1.

**Table 5.** Hazard Ratios With 95% Confidence Intervals for CHD Death for Clinical and Related Electrocardiographic Findings in Women With/Without CVD at Baseline

| | CVD Free Group (N=52 092) | | CVD Group (N=12 569) | |
|---|---|---|---|---|
| Clinical Classification | Unadjusted | Multivariable Adjusted* | Unadjusted | Multivariable Adjusted* |
| Hypertension (yes vs no)† | 1.98 (1.73 to 2.26) | 1.59 (1.36 to 1.87) | 2.25 (1.89 to 2.68) | 1.81 (1.43 to 2.30) |
| Diabetes (yes vs no)‡ | 3.20 (2.66 to 3.86) | 2.70 (2.20 to 3.31) | 3.35 (2.80 to 4.01) | 2.69 (2.16 to 3.36) |
| AF by self-report (yes vs no) | 7.31 (3.28 to 16.3) | 4.27 (1.86 to 9.79) | 1.01 (0.83 to 1.24) | 1.10 (0.86 to 1.39) |
| Ectopic complexes (yes vs no) | 1.43 (1.09 to 1.89) | 1.41 (1.03 to 1.94) | 1.90 (1.45 to 2.47) | 1.75 (1.28 to 2.38) |
| Left atrial enlargement (yes vs no)§ | 1.61 (1.37 to 2.17) | 1.24 (0.92 to 1.66) | 1.94 (1.53 to 2.45) | 1.59 (1.22 to 2.08) |
| AF at baseline ECG (yes vs no) | — | — | 2.19 (1.46 to 3.26) | 2.61 (1.62 to 4.20) |
| Major ST depression (yes vs no)‖ | — | — | 2.76 (2.13 to 3.57) | 2.10 (1.65 to 2.68) |
| ECG-LVH & ST-T (yes vs no)¶ | — | — | 2.68 (1.96 to 3.67) | 2.16 (1.53 to 3.05) |
| ECG-MI by MC (yes vs no)# | — | — | 1.62 (1.33 to 1.98) | 1.62 (1.29 to 2.03) |

AF indicates atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiographic; MC, Minnesota code; MI, myocardial infarction.
*Multivariable single ECG variable model adjusted for age, ethnicity, body mass index, smoking status, hypertension, diabetes mellitus, CVD status at baseline, hypercholesterolemia, family history of CHD, systolic blood pressure, heart rate, and study component/arm groups (hormone therapy/dietary modification/calcium and vitamin D).
†Hypertension defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or on medication for hypertension.
‡Diabetes defined as self-report of physician diagnosis and treatment with insulin or oral antidiabetic drugs.
§MC 9.6.
‖Major ST depression=MC 4.1 or 4.2.
¶ECG-LVH & major ST-T=Left ventricular hypertrophy by Cornell Voltage (RaVL+SV3) ≥2200 μV) & MC 4.1/4.3.
#MC 1.1/1.2 or MC 1.3 & MC 5.1/5.2.

an over 2-fold increased risk were $\Theta(T_p|T_{ref})$ >42° in Set 1 and TaVR amplitude less negative than −100 μV in Set 2; (4) Among Set 2 variables also heart rate >84 had an over 2-fold increased risk in CVD-free women; (5) The risk for these strong CHD death predictors remained significant after multivariable adjustment for demographic/clinical factors; and (6), Set 2 variable TaVR was as strong predictor as the computationally more complex Set 1 best predictor $\Theta(T_p|T_{ref})$.

## Possible Mechanisms for the Association of ECG Predictors With the Risk of CHD Death

Three mechanisms possibly accounting for increased risk for CVD death are summarized in Table 6. The first mechanism is related to myocardial ischemia in chronic CHD. Myocardial ischemia most commonly located in left-anterior-descending coronary artery perfusion area shortens action potential duration and alters spatial direction of the repolarization sequence during the initial LV lateral wall repolarization. A previous report from the Cardiovascular Health Study demonstrated that anterior-right rotation of the $T_p$ vector is associated with QRS|T angle widening in CVD free men and women.[17] Anterior-right rotation of the $T_p$ vector also accounts for the increased (less negative) amplitude in aVR and increased V1 amplitude (Figure 2). Thus, same pathophysiological mechanisms relating to altered regional repolarization times may account for increased risk of CHD death associated with Set 1 main predictor $\Theta(T_p|T_{ref})$ and Set 2 main predictor TaVR. The second mechanism in Table 6 is related to LV overload in hypertensive heart disease. In LVH, with increased epicardial excitation time ($ET_{epi}$) and $RT_{epi}$ due to increased LV mass and possibly also with slowed myocardial conduction velocity leads into widening of $\Theta(T_p|T_{ref})$ and

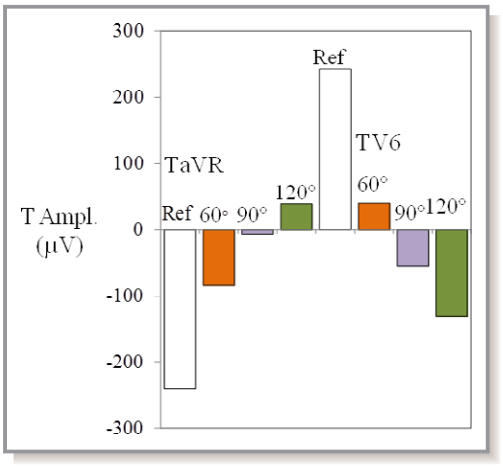


**Figure 2.** T wave amplitude changes in leads aVR (left) and V6 (right) with anterior-right rotation of the T vector in the horizontal plane from the direction in normal depolarization (Ref, blank white columns) by 60, 90 and 120 degrees (orange, purple and green columns, respectively). TV6 amplitudes decrease and TaVR amplitudes increase progressively with increasing rotation of the T vector to anterior-right.

**Table 6.** Main Parameters of the Repolarization Model Associated With Mechanisms Accounting for Increased Risk of CHD Death

| Main Parameters of the Repolarization Model | | Plausible Mechanisms |
|---|---|---|
| Rate-adjusted QT peak interval | $QT_{pa}$ | 1. $APD_{epi}$ and $RT_{epi}$ shorten in chronic ischemic CHD most commonly in LAD perfusion area, widen $\Theta(T_p\|T_{ref})$ and induce abnormal T waves in left-lateral and anterior-right chest leads and aVR (Figure 2) associated with increased risk for CVD death (Table 4). |
| Rate-adjusted QT end | $QT_{ea}$ | 2. Prolonged LV overload in hypertensive heart disease slows myocardial conduction velocity, increases $ET_{epi}$ and $RT_{epi}$, widens $\Theta(T_p\|T_{ref})$ and repolarization sequence changes from normal predominantly reverse to predominantly concordant with respect to depolarization sequence (LV strain pattern); abnormalities associated with increased risk of CHD death and heart failure. |
| Spatial T peak vector deviation angle from normal reference direction | $\Theta(T_p\|T_{ref})$ | 3. Regional QT prolongation (increased $QT_{pa}$, $RT_{epi}$) or diffuse global QT prolongation for any reason; associated with increased CHD death. |
| LV epicardial excitation time | $ET_{epi}$; $ET_{epi}$=QR peak time | |
| LV epicardial repolarization time; Derived from $QT_{pa}$, modified by $\Theta(T_p\|T_{ref})$ | $RT_{epi}$ | |
| LV epicardial action potential duration | $APD_{epi}$; $APD_{epi}=RT_{epi}-ET_{epi}$ | |

APD indicates action potential duration; CHD, coronary heart disease; CVD, cardiovascular disease; LV, left ventricle.

the repolarization sequence changes progressively from normal predominantly reverse to predominantly concordant with respect to depolarization sequence generating the so called LV strain pattern. A predominantly concordant repolarization sequence results in increase (less negative) aVR amplitude, again suggesting that widened $\Theta(T_p|T_{ref})$ angle and decreased TaVR amplitude are produced by the same pathophysiological mechanism. Increasing dyssynchrony of depolarization [11,12] may in turn, lead into dyssynchrony of ventricular relaxation with impairment of diastolic function.[18] These ECG abnormalities are associated with increased risk of CHD death and heart failure. The third mechanism postulated is associated with derailed ionic channel dynamics due to possible adverse effects of cardioactive drugs and a multiplicity of other factors inducing regional QT prolongation (increased $QT_{pa}$, $RT_{epi}$) or diffuse global QT prolongation, known to be associated with increased risk of CHD death, including sudden cardiac death.

$\Theta(T_{init}|T_{term})$ was the second spatial angle as a significant predictor of CHD death. $\Theta(T_{init}|T_{term})$ reflects increased difference in the spatial direction of repolarization during initial and terminal repolarization as a manifestation of a widened, rounder T vector loop related to T wave complexity which has been suggested as an indicator of subclinical myocardial ischemia in asymptomatic adults.[19]

## Relation of the Present Study With Previous Investigations

The risk of CHD death in CVD-free men and women 45 to 65 years old was evaluated in a report from the Atherosclerosis Research in Communities Study excluding men and women with a history or clinical manifestations of CHD or other CVD.[3] ECG-based exclusions from the CVD-free group included QRS duration 120 ms or longer or major Q waves by Minnesota Code[20] (MC 1.1). In women, independent predictors of the risk of CHD death were $(QRS_m|T_m)$ and $(T_p|T_{ref})$, with a 2-fold increased risk for the former, and with a 1.7-fold increased risk for the latter variable. $QT_{ea}$ was an independent predictor in men but not in women. A notable finding in the Atherosclerosis Research in Communities Study was that the risk levels for independent predictors for CHD death were stronger in women than in men. In the present investigation $\Theta(T_p|T_{ref})$ and $\Theta(T_{init}|T_{term})$ were independent predictors of CHD death in addition to heart rate. In the selection of CHD-free women in the present study a more extensive set of ECG-based exclusions were made, including ECG evidence of an old MI, atrial fibrillation in baseline ECG, high-amplitude QRS (Cornell voltage) with even minor T-wave abnormalities (MC 5.1 to 5.3) so that the repolarization measures used can be considered as isolated independent predictors of CHD death.

A report from the Seven Countries Study in a male cohort with no manifest cardiac diseases at baseline evaluated the risk of CHD death for isolated inverted T waves with no other codable ECG abnormalities.[5] The risk of CHD death for inverted T waves was over 3-fold in 5-year follow-up, decreasing with the length of follow-up but still significant at 40-year follow-up.

Laukkanen et al evaluated the association of isolated T wave inversion and widened QTS|T angle with the risk of SCD in a male cohort from a general Finnish population with a 20-year follow-up.[4] In a multivariable adjusted single ECG variable model, T wave inversion and widened QRS|T angle were both associated with an over 3-fold risk for SCD. QRS duration from 110 to 119 ms was also a significant predictor of SCD compared to men with QRS duration <110 ms. Anttila et al, in another report from a nationally representative sample of the general Finnish population of adult men and

women, documented that a positive T wave in aVR was a strong predictor of CVD death in fully adjusted risk models.[7] TaVR was also reported in an earlier study to be a predictor of CVD death in a large clinical male population.[21]

## Clinical Implications

$\Theta(T_p|T_{ref})$ was a strong predictor of CHD death in women with CVD as well as in CVD-free women. From a practical clinical point of view, a potentially more important observation was that ECG variables such as TV1 and TaVR amplitudes (from the alternative Set 2 in Table 4) were practically as strong predictors of CHD death as the computationally more complex angular measures of deviant repolarization. This finding suggests that these simple variables may be potentially useful clinical tools for identification of high-risk women for preventive intervention on CHD death.

## Limitations of the Study

Data were not available from echocardiographic evaluation of cardiac function to permit a more refined identification of silent CVD. T waves, particularly in women, are considered to be sensitive to variations in sympathetic tone as reflected by increased heart rate. However, the correlations between heart rate and the angular measures of deviant spatial direction of repolarization and also $QT_{pa}$ were low ($r<0.4$). Since the primary focus of our study was on a limited number of independent predictors of CHD death, no provision was made to adjust for multiple comparisons for mean differences between CVD and CVD-groups. No competing risk analysis was done to evaluate additional risk of CHD death for ECG variables beyond the risk information contained in diabetes, hypertension, and other clinical conditions. The primary aim of our study was not diagnostic discrimination but rather an exploratory analysis to establish associations as the first-line predictors of CHD death and to consider possible mechanisms accounting for the observed excess risk found for them.

## Acknowledgments

The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

## Sources of Funding

The WHI Sequencing Project is funded by the National Heart, Lung, and Blood Institute (HL-102924) as well as the National Institutes of Health (NIH), U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

## Disclosures

None.

## References

1. Zhang Y, Post WS, Blasco-Colmenares E, Blasco-Colmenares E, Dalal D, Tomaaaelli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22:660–670.
2. 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.
3. Rautaharju PM, Zhang ZM, Warren J, Haisty WK, Prineas RJ, Kurcharska-Newton AM, Rosamond WD, Soliman EZ. Electrocardiographic predictors of coronary heart disease and sudden cardiac deaths in men and women free from cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Heart Assoc*. 2013;2:e000061 doi: 10.1161/JAHA.113.000061.
4. Laukkanen JA, Di Angelantonio E, Khan H, Kurl S, Ronkainen K, Rautaharju PM. T wave inversion, QRS duration and QRS/T-angle as electrocardiographic predictors of the risk for sudden cardiac death. *Am J Cardiol*. 2014;113:1178–1183.
5. Rautaharju PM, Menotti A, Blackburn H, Parapid B, Kircanski B. Isolated negative T waves as independent predictors of short-term and long-term coronary heart disease mortality in men free of manifest heart disease in the Seven Countries Study. *J Electrocardiol*. 2012;45:717–722.
6. Kumar A, Prineas RJ, Arnold AM, Psaty BM, Furberg CD, Robbins J, Lloyd-Jones DM. Prevalence, prognosis, and implications of isolated minor nonspecific ST-segment and T-wave abnormalities in older adults: Cardiovascular Health Study. *Circulation*. 2008;118:2790–2796.
7. 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.
8. 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.
9. 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. *Circulation*. 2012;125:2588–2594.
10. Rautaharju PM, Prineas RJ, Wood J, Zhang ZM, Crow R, Heiss G. Electrocardiographic predictors of new-onset heart failure in men and in women free of coronary heart disease (from the Atherosclerosis in Communities [ARIC] Study). *Am J Cardiol*. 2007;100:1437–1441.
11. Rautaharju PM, Gregg RE, Zhou SH, 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.
12. 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 not evident from global QT. *Am J Cardiol*. 2011;107:744–750.
13. The Women's Health Initiative Study Group. Design paper: design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61–109.
14. Rautaharju PM, Park L, Rautaharju FS, Crow R. A standardized procedure for locating and documenting ECG chest electrode positions: consideration of the effect of breast tissue on ECG amplitudes in women. *J Electrocardiol*. 1998;31:17–29.
15. Horáček BM, Warren JW, Field DQ, Feldman CL. Statistical and deterministic approaches to designing transformations of electrocardiographic leads. *J Electrocardiol*. 2002;35(suppl):41–52.

16. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13:S122–S128.

17. 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.

18. 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.

19. Al-Zaiti SS, Runco KN, Carey MG. Increased T wave complexity can indicate subclinical myocardial ischemia in asymptomatic adults. *J Electrocardiol*. 2011;44:684.

20. Blackburn H, Keys A, Simonson E, Rautaharju PM, Punsar S. The electrocardiogram in population studies: a classification system. *Circulation*. 1960; 21:1160–1175.

21. 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.