# Electrocardiographic Predictors of Incident Congestive Heart Failure and All-Cause Mortality in Postmenopausal Women

## The Women's Health Initiative

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***Background***—Information is limited about ECG predictors of the risk of incident congestive heart failure (CHF), particularly in women without overt manifestations of cardiovascular disease (CVD).

***Methods and Results***—We evaluated hazard ratios for incident CHF and all-cause mortality using Cox regression in 38 283 participants of the Women's Health Initiative (WHI) during a 9-year follow-up. All risk models were adjusted for demographic and available clinical and therapeutic variables (multivariable-adjusted models). A backward selection procedure was used to identify dominant predictors among those that were significant as individual ECG predictors. Eleven ECG variables were significant predictors of incident CHF, with none of them having a significant interaction with baseline CVD status. From 6 dominant ECG predictors, wide QRS/T angle had a nearly 3-fold increased risk in multivariable-adjusted single ECG variable models. Two other repolarization variables, $STV_5$ depression and high $TV_1$ amplitude, and 2 QRS-related variables, QRS non-dipolar voltage and myocardial infarction (MI) by ECG, were all associated with ≈2-fold increase of incident CHF risk. Overall, 11 of the 12 ECG variables were significant predictors of all-cause mortality. Four variables had a significant interaction with CVD status requiring stratification. Three among these 4 were strong, dominant predictors in the CVD group: ECG MI, wide QRS/T angle, and low $TV_5$ amplitude had risk increase from >2-fold to 3-fold, with considerably lower risks in the CVD-free group.

***Conclusions***—Several repolarization variables in postmenopausal women are predictors of the risk of incident CHF and all-cause mortality as important as old ECG MI. **(*Circulation*. 2006;113:481-489.)**

**Key Words:** electrocardiography ■ epidemiology ■ menopause ■ women

There is lack of information about the value of ECG abnormalities in prediction of future congestive heart failure (CHF), particularly in women without history or clinical manifestations of coronary heart disease (CHD) or hypertensive heart disease, both important precursors of CHF. An accompanying article in this issue[1] reported risk data for combined fatal and nonfatal CHD events and CHD mortality associated with ECG variables in the participants of the Women's Health Initiative (WHI). The special objective of the present investigation was to evaluate the risk of incident CHF and all-cause mortality associated with ventricular repolarization abnormalities in addition to the predictive value expected from depolarization (QRS) abnormalities such as old myocardial infarction (MI) by ECG criteria.

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## Methods

### Study Design and Population

WHI is a 40-center national US study of risk factors and prevention of common causes of mortality, morbidity, and impaired quality of life in women. Details of elements such as study design, protocol sampling procedures, selection, and exclusion criteria have been published previously.[2] The women initially chosen for the present study (n=40 786) were the participants in the dietary modification trial (n=68 133) with the exclusion of 27 347 women who were enrolled in randomized trials on hormone therapy. After additional exclusions of 1087 women with major ventricular conduction defects (QRS ≥120 ms) and 1345 women because of ECG with inadequate quality or incomplete data from various ECG programs used for ECG processing, waveform analysis,

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and derivation of secondary ECG variables for the present investigation, 38 283 women were left for the present study.

The study group was stratified by baseline cardiovascular disease (CVD) status at baseline into women with CVD (n=2568) and those who were CVD free (n=35 715). Baseline CVD was defined by the presence of a history or clinical diagnosis of MI, angina pectoris, coronary artery bypass surgery, coronary angioplasty, or stroke at the time the women entered the WHI.

Incident CHF and all-cause mortality were the outcomes considered in the present investigation. Incident CHF was determined in the course of active follow-up and was defined as hospitalization for CHF as diagnosed by a physician with the patient receiving medical treatment for CHF, with corroboration of pertinent abnormalities in diagnostic testing by a review (noncentralized) of the medical records. There were 233 women with prevalent CHF in the CVD group at the study baseline. These cases were excluded in risk analyses in the incident CHF risk model. The follow-up period for the study group was up to 9.2 years (mean, 6.2 years).

## ECG Methodology

Strictly standardized procedures were used for recording of the standard 12-lead ECGs. Identical ECG equipment (MAC PC, Marquette Electronics) was used in all clinical centers. Special attention was paid to locating the chest electrodes in precise positions.[3] All ECGs were processed in a central laboratory (EPICARE Center, Wake Forest University, NC), and they were all visually inspected for technical errors and inadequate quality. ECGs were initially processed by the Dalhousie ECG program,[4] and processing was later repeated for the present study by the 2001 version of the Marquette 12-SL program (GE Marquette). The variables of key interest considered as initial candidates for risk prediction included some ECG waveform descriptors derived by the Novacode program.[5] The procedures for deriving ST and T waveform variables were described in earlier communications.[6,7] Modified orthogonal Chebyshev polynomials were calculated for the XYZ orthogonal components that were derived by a transformation matrix from the standard 12-lead ECG.[8] Subsequently, an inverse matrix transformation was used to calculate the projections of waveform vectors on standard leads $V_5$, aVF, and $V_1$.

It should be noted that the waveform amplitudes from orthonormal expansion are the mean and not the peak values of the waves, explaining their ostensibly smaller values. Variables from such an orthonormal expansion are statistically independent, thus reducing the collinearity problem, common with variables used in ECG classification criteria. In $V_5$ lead, the mean and the peak values of the T wave were correlated at level $r=0.93$. Low $TV_5$ amplitude was found to be an important risk predictor, and both the mean and the estimated peak values are listed for $TV_5$ in tables for risk model data. For $TV_1$ amplitude, it is better to use the mean rather than the peak T value because the waveform is commonly biphasic.

Most of the ECG variables used are familiar to the electrocardiographers. Figures I and II in the online-only Data Supplement illustrate some of the key variables. QRS/T angle, the spatial angle between QRS and T, was determined for better accuracy with the use of the mean QRS and T vectors, although the angle between the maximal QRS and maximal T vectors shown in Figure II gives closely similar results. QTrr is the rate-adjusted QT as a linear function of the RR interval, used to evaluate QT prolongation.[9] Ultrashort heart rate variability was determined from the 10-second ECG record as the root-mean-square value of successive differences of the RR intervals of normally conducted QRS complexes, excluding intervals immediately preceding and following ectopic ventricular complexes.

The parameters chosen from singular value decomposition were the voltage ratio of the second and the first principal components (square root of (E2/E1) of the T wave and the magnitudes of the T wave and QRS non-dipolar components. The voltage ratio of the second and the first principal components is at times called T wave complexity.[10] It is an index of the roundness of the T vector loop, as depicted in Figure II. It attains the maximal value (100%) for a completely round configuration of the T loop, in contrast to a normal T loop, which is narrow. T wave and QRS non-dipolar voltage quantify the residual variance of the higher-order components that are not contained in the first 3 (XYZ) components of the 12-lead ECG signal. The presence of >1 maximum and minimum in body surface ECG maps signifies the presence of non-dipolar components.

Old MI by ECG was defined by codes 5.1 to 5.4 of the Novacode criteria.[5] These MI criteria use the presence of major Q waves or smaller Q waves with ST-T abnormalities. ST depression was defined as the ST segment mean value in $V_5$ negative or 0 $\mu$V (prevalence 14%), where the ST segment was determined in the interval from 20 ms past the J-point to J +80 ms or the beginning of the T wave, whichever occurred later. For other continuous variables, the cutpoints were set to obtain 10% prevalence at the high and low end of the distribution. These cut points for the reference groups often differ from those used to define normal limits for diagnostic classification, eg, for the Cornell voltage.

## Statistical Methods

Frequency distributions of the variables were first inspected to rule out anomalies and outliers possibly due to measurement artifacts. Correlations between ECG variables were evaluated to examine possible collinearity problems to facilitate interpretation as to why certain ECG variables were selected or not selected into multiple ECG variable models. Full correlation matrix was presented in the accompanying article.[1] To account for the potential differences between the baseline CVD and CVD-free groups on the effect of the ECG markers of the outcomes, a series of single ECG variable proportional hazards models was evaluated. Each model was stratified by baseline CVD status and included as explanatory variables the ECG variable of interest, an interaction term between the ECG variable and baseline CVD status, and any adjustment variables. For those individual ECG markers for which the interaction was not significant, a second model without the interaction term was evaluated for the combined group.

Following the single ECG variable analyses, all ECG variables as well as those interactions with a significant association with outcome events were entered simultaneously into risk prediction models, and a backward selection procedure was used to identify significant independent risk predictors (criterion for removal=$P>0.05$). These models were labeled multiple ECG variable models. All models considered in the present report were adjusted for demographic variables (age, ethnicity, systolic blood pressure, body mass index) and the following clinical and therapeutic variables: smoking, hormone therapy use at baseline, self-report of the use of cholesterol-lowering drugs, self-report of diabetes control or the use of cardioactive drugs (antiarrhythmics, calcium channel blockers, $\beta$-blockers, diuretics, antidepressants, psychotherapeutic drugs). These models were labeled multivariable-adjusted. Age-adjusted models were included in the online-only Data Supplement only. The proportional hazards assumption of the Cox model was checked graphically for each of the candidate variables. All analyses were performed with the SAS system for Windows, version 9.0.

The risk models retained for presentation for each of the 2 outcomes were multivariable-adjusted single ECG variable models and multivariable-adjusted multiple ECG variable models. Risk model data for age-adjusted models are included in the online-only Data Supplement only. The tables in Results were partitioned so that hazard ratios for those ECG variables with a significant interaction with baseline CVD status are listed first, separately for each group, and then for the combined groups for those variables with no significant interaction.

# Results

## Study Group Characteristics

The mean age of the study group was 62.1 years (SD 6.8). The distribution of race/ethnicity in the study group was white (82.3%), black (10.2%), Hispanic (3.3%), Asian (including Pacific Islanders) (2.5%), and other or unknown (1.7%). Slightly more than one half (51.4%) were current

users of hormone therapy, 6.2% were current smokers, 51.6% had never smoked, 1.8% had a history of MI, 1.1% had a previous coronary angioplasty or bypass operation, and 3.4% had angina pectoris at baseline. Thirty percent of the women were using cardioactive drugs, with >75% of the women taking antihypertensives. The mean systolic blood pressure was 127 mm Hg (SD 17), and mean diastolic blood pressure was 76 mm Hg (SD 9). The distributions (medians and the limits for interquartile range) of the 11 continuous ECG variables (Table 1) are relatively similar in both baseline groups with no clinically relevant differences, although some of the mean values were statistically significant (not shown) in this large group of women. The significance of interaction between baseline CVD and some of these ECG variables in risk models is considered in connection with risk evaluation results.

## Correlations Between ECG Variables

The correlations in women with and without baseline CVD were similar, and they were subsequently evaluated in the combined group. Full correlation matrix was presented in the accompanying article[1] and is not reproduced here. QRS/T angle appeared to be the common denominator in the correlations among other ECG variables that reflect altered sequence of ventricular repolarization (T wave roundness, $TV_1$ amplitude, $TV_5$ amplitude, $STV_5$ gradient), with correlations ranging from −0.26 for ST segment gradient to 0.52 for the mean $TV_1$ amplitude. QRS/T angle was also correlated with Cornell voltage ($r$=0.44). Other correlations were smaller.

## ECG Predictors in Age-Adjusted Models

The age-adjusted risk model data are shown only in the online-only Data Supplement because they are of lesser importance in the context of the present report.

## Risk of Incident CHF and All-Cause Mortality Associated With Demographic and Clinical Factors

Several non-ECG factors were associated with the risk of incident CHF and all-cause mortality (not shown). Age was a significant predictor of the risk of incident CHF. Evaluated as a continuous variable, each 5-year increment in age was associated with a 44% increase of the risk of incident CHF and with a 52% risk of all-cause mortality. As expected, diabetes and the use of cardioactive drugs were both strong predictors of incident CHF, with a >2-fold increase in risk. As noted, 30% of the women were using some cardioactive drug at the baseline, largely antihypertensives (>75% of the women). Women who were current smokers also had a >2-fold increased risk of incident CHF, and pronounced overweight (upper quartile of body mass index) was associated with a nearly 2-fold increased risk. In regard to ethnic factors, Asians were at reduced risk of incident CHF, with a hazard ratio only one quarter that of white women.

Each 5-year increment of age was associated a 52% increase in the risk of all-cause mortality. In the group aged 76 to 79 years, the risk increase was >7-fold compared with the group aged 50 to 54 years. Whereas diabetes, current smoking, and use of cardioactive drugs were strong predictors of all-cause mortality, the all-cause mortality risk was slightly reduced (by 15%) in current users of hormone therapy.

**TABLE 1. Definitions, Median Values, and Limits for Interquartile Range (25th, 75th Percentiles) for ECG Variables by Baseline CVD Status**

| ECG Variable | | Median (25th, 75th Percentile) | |
|---|---|---|---|
| Acronyms (Units) | Description | Baseline CVD (n=2568) | CVD-Free (n=35 715) |
| Variables related to ventricular repolarization (ST-T) | | | |
| QRS/T angle, ° | Spatial angle between mean QRS and T vectors | 61 (42, 85) | 56 (40, 73) |
| $STV_5$, $\mu$V | Mean ST amplitude in $V_5$ | 22 (2, 43) | 32 (13, 52) |
| Sqr(E2/E1), % | T wave roundness index (square root of the ratio of the second and first T eigenvectors) | 33 (21, 48) | 30 (20, 43) |
| $TV_1$, $\mu$V | Mean T wave amplitude in $V_1$ | 19 (−15, 55) | 20 (−10, 49) |
| $TV_5$, $\mu$V | Mean T wave amplitude in $V_5$ | 123 (78, 171) | 151 (110, 194) |
| QTrr, ms | Rate-adjusted QT as a linear function of RR interval | 416 (407, 429) | 413 (405, 423) |
| STgrad $V_5$, $\mu$V | ST gradient in $V_5$ (increase from beginning to end) | 12 (7, 17) | 14 (9, 20) |
| TNDPV $\mu$V | T non-dipolar voltage (not contained in XYZ signal) | 9 (8, 10) | 9 (8, 10) |
| Variables related to ventricular depolarization (QRS) | | | |
| ECG MI | Defined by Novacode criteria | ... | ... |
| CV, $\mu$V | Cornell voltage ($RaVL+SV_3$) | 1317 (1005, 1689) | 1152 (864, 1468) |
| RNDPV, $\mu$V | QRS non-dipolar voltage (not contained in XYZ signal) | 40 (31, 53) | 38 (30, 49) |
| Other ECG variables | | | |
| HRV, ms | Ultrashort heart rate variability (rms value of successive differences of normally conducted sinus RR intervals) in 10-second ECG record | 17 (10, 27) | 16 (11, 27) |

### ECG Predictors of Incident CHF

None of the ECG variables had a significant interaction with CVD status in these CHF risk models, and the risk data are shown for the combined CVD group (Table 2). All ECG variables evaluated except T wave non-dipolar voltage were significant predictors of incident CHF in multivariable-adjusted single ECG variable models, with 6 of them identified as dominant predictors. Wide QRS/T angle was the strongest among the dominant predictors, with incident CHF risk increase approaching 3-fold. Two other dominant repolarization variables, ST depression in $V_5$ and tall $TV_1$, and QRS non-dipolar voltage were associated with a ≥2-fold increase in the risk of incident CHF. It was noted that ECG MI was not among the dominant predictors, although in the single ECG variable model it had a 2-fold increase in incident CHF risk.

### ECG Predictors of All-Cause Mortality

Overall, 11 of the 12 ECG variables evaluated were significant predictors of all-cause mortality. In contrast to the incident CHF risk models, 4 ECG variables had a significant interaction with baseline CVD in the risk models for all-cause mortality (Table 3). Three among these 4 were strong, dominant predictors in the CVD group: ECG MI, wide QRS/T angle, and low $TV_5$ amplitude had risk increase from >2-fold to 3-fold, with substantially lower risks in the CVD-free group.

### Relative Risks in Relation to Absolute Risk

Relative risks for ECG predictors viewed side by side with absolute risks (Table 4) are particularly relevant for considering ECG findings in relation to possible preventive efforts. The annual risk for incident CHF in our study population was 18.95/10 000 and was 46.63/10 000 for all-cause mortality. Only incident CHF rates for 6 dominant risk predictors were considered here. The annual new event rate difference per 10 000 was 43 for QRS/T angle and 37 for ECG MI. For the other 4 significant ECG predictors of incident CHF, the difference ranged from 18 to 26 events. For wide QRS/T angle, the annual rate of incident CHF was over 4-fold greater than that of women in the corresponding reference group.

## Discussion

The results of the present study show that a variety of repolarization abnormalities are predictive of incident CHF. The presence of these repolarization abnormalities as well as ECG MI, high Cornell voltage, and QRS non-dipolar voltage may be potentially important subclinical indicators of pending evolution of this high-risk clinical condition. Dominant among all these incident CHF predictors was wide QRS/T angle, indicating an abnormal sequence of ventricular repolarization. Altered temporal/spatial sequence of repolarization and abnormal heterogeneity of action potential durations with aberrations of ionic channel function are also mechanisms for 3 other repolarization abnormalities: $STV_5$ depression, high $TV_1$ amplitude, and prolonged QT. They were all among the dominant predictors of incident CHF, with increased risk equal to that for ECG MI and QRS non-dipolar voltage. All of these abnormalities were significant predictors of incident CHF in women, with no significant difference in relation to baseline CVD status, and they warrant special attention.

Left ventricular hypertrophy and ischemic heart disease are common clinical conditions associated with the evolution of CHF and with the evolution of the abnormalities in several of the repolarization variables, and this may explain at least in part their association with the risk of incident CHF. These same pathophysiological mechanisms may be responsible for the fact that they were also significant predictors of all-cause mortality, with several of them dominant, possibly independent predictors. From QRS variables, ECG MI and QRS non-dipolar voltage were among the dominant predictors of death from all causes.

### Comparison With Previous Studies

Little is known about ECG predictors of incident CHF, which was the major focus of the present investigation. It is known that patients with clinically overt CHF may have ECG manifestations of CHD or left ventricular hypertrophy. However, ≥50% of the adults with CHF have normal left ventricular ejection fraction with no systolic dysfunction. In the Strong Heart Study of 3184 American Indians, 50 of the 95 subjects with CHF had a normal ejection fraction (>54%).[11] These 50, compared with those with no CHF, were older and overweight and had renal dysfunction, and they were predominantly women. Those with CHF and severe left ventricular dysfunction were more often men with lower body mass index and eccentric left ventricular hypertrophy. Non–insulin-dependent diabetes was found in the Strong Heart Study population to be associated with adverse cardiac effects such as increased left ventricular mass and wall thickness, reduced systolic chamber and myocardial function, and increased arterial stiffness, independent of increases in obesity level and arterial pressure.[12] These alterations are likely to accelerate development of CHF.

In general, a low or nonsignificant prognostic value of ECG abnormalities in women has been found in many epidemiological studies.[13–17] Lower age range of the women and a shorter follow-up time in many of these studies may account at least in part for the difference from the results in the present investigation.

There is more information available about the association of abnormal repolarization and other prevalent ECG abnormalities with morbidity and mortality. A recent report from the aforementioned Strong Heart Study examined the association of ST depression and C-reactive protein, a marker of systemic inflammation, with CVD and all-cause mortality.[18] The results indicated that these 2 variables were additively predictive of mortality. The presence of both factors (upper quartile of each) was associated with >3-fold increased risk of CVD death and a nearly 4-fold increased risk of all-cause mortality in multivariable-adjusted risk models. The presence of either predictor was associated with a >2-fold increase of the risk of CVD death and with a 50% increase of the risk of all-cause mortality.

Among other reports on repolarization abnormalities and mortality risk, the health survey of Amsterdam civil servants and their spouses aged 40 to 65 years evaluated the association between ST waveform in lead I and CHD and all-cause

**TABLE 2. Hazard Ratios and 95% CIs for Incident CHF* from Multivariable-Adjusted Single and Multiple ECG Variable Models†**

| ECG Variables/(Cutpoints)† | Multivariable-Adjusted Single ECG Variable Models | Multivariable-Adjusted Multiple ECG Variable Models |
|---|---|---|
| QRS/T angle | | |
| Reference (0–56°) | 1 | 1 |
| Increased (57–96°) | 1.59‖ (1.26, 2.02) | 1.51‖ (1.17, 1.94) |
| Wide (≥97°) | 2.73‖ (2.06, 3.60) | 1.95‖ (1.41, 2.70) |
| ECG MI/ischemic injury | | |
| No MI | 1 | RM |
| MI | 1.99‖ (1.53, 2.59) | |
| Isolated ST-T abnormalities or minor Q waves | 1.55‖ (1.21, 1.99) | |
| $STV_5$ mean amplitude | | |
| Reference (>0 μV) | 1 | 1 |
| Depressed (≥0 μV) | 2.11‖ (1.62, 2.52) | 1.49§ (1.17, 1.89) |
| $TV_1$ mean amplitude | | |
| Reference ( −41–80 μV) | 1 | 1 |
| Low (<−41 μV) | 1.07 (0.75, 1.51) | 1.31 (0.91, 1.90) |
| High (>80 μV) | 2.16‖ (1.68, 2.78) | 1.56§ (1.19, 2.05) |
| QRS non-dipolar voltage | | |
| Reference (<65 μV) | 1 | 1 |
| Increased (≥65 μV) | 2.00‖ (1.51, 2.65) | 1.64‖ (1.23,2.19) |
| $TV_5$ mean amplitude | | |
| Reference (73–235 μV) | 1 | RM |
| Low (<73 or <117 μV) | 1.85‖ (1.46, 2.35) | |
| High (>235 μV) | 0.86 (0.54, 1.38) | |
| $STV_5$ gradient | | |
| Reference (≥3 μV) | 1 | RM |
| Low or negative (<3 μV) | 1.72‖ (1.28, 2.30) | |
| QTrr | | |
| Reference (<437 ms) | 1 | 1 |
| Prolonged (≥437 ms) | 1.80‖ (1.40, 2.31) | 1.60§ (1.25, 2.07) |
| Cornell voltage | | |
| Reference (<1800 μV) | 1 | RM |
| High (≥1800 μV) | 1.64‖ (1.28, 2.10) | |
| T wave roundness index | | |
| Reference (<31%) | 1 | RM |
| Oblong (31%–57%) | 1.33§ (1.06, 1.66) | |
| Round (>57%) | 1.62‖ (1.20, 2.19) | |
| Heart rate variability | | |
| Reference (8–44 ms) | 1 | 1 |
| Low (<8 ms) | 1.27 (0.96, 1.69) | 1.19 (0.89, 1.58) |
| High (>44 ms) | 1.53§ (1.15, 2.04) | 1.44‡ (1.08, 1.92) |
| T non-dipolar voltage | | |
| Reference (<13 μV) | 1 | RM |
| Increased (≥13 μV) | 1.30 (0.97, 1.75) | |

MI indicates myocardial infarction; RM, removed in backward selection procedure. ECG variables are defined in Table 1.

*There were 375 incident CHF events.

†Cutpoints for continuous variables partition the distributions so that the highest decile is always selected as a comparison group (for $TV_1$ and $TV_5$, both the highest and lowest deciles). Prevalent CHF at baseline (233 subjects) was excluded from incident CHF risk models.

‡$P<0.05$; §$P<0.01$; ‖$P<0.001$.

**TABLE 3. Hazard Ratios and 95% CIs for All-Cause Mortality* From Multivariable-Adjusted Single and Multiple ECG Variable Models by CVD Status at Baseline†**

| | Multivariable-Adjusted Single ECG Variable Models | | Multivariable-Adjusted Multiple ECG Variable Models | |
|---|---|---|---|---|
| ECG Variables/(Cutpoints)† | CVD Group | CVD-Free Group | CVD Group | CVD-Free Group |
| $TV_5$ mean amplitude | | | | |
| Reference (73–235 $\mu$V) | 1 | 1 | 1 | 1 |
| Low (<73 or <117 $\mu$V) | 2.42‖ (1.68, 3.48) | 1.10 (0.89, 1.37) | 1.60‡ (1.07, 2.37) | 0.82 (0.63, 1.05) |
| High (>235) | 1.79 (0.89, 3.61) | 1.14 (0.90, 1.45) | 2.00 (0.99, 4.04) | 1.24 (0.97, 1.59) |
| $TV_1$ mean amplitude | | | | |
| Reference (−41–80 $\mu$V) | 1 | 1 | RM | |
| Low (<−41 $\mu$V) | 0.57 (0.28, 1.18) | 0.90 (0.70, 1.16) | | |
| High (>80 $\mu$V) | 1.91§ (1.28, 2.86) | 1.13 (0.91, 1.40) | | |
| ECG MI/ischemic injury | | | | |
| No MI | 1 | 1 | 1 | |
| MI | 3.08‖ (2.05, 4.64) | 1.36§ (1.10, 1.68) | 1.40‖ (1.15, 1.70) | |
| Isolated ST-T abnormalities or minor Q waves | 1.72‡ (1.08, 2.75) | 1.15 (0.96, 1.39) | 1.11 (0.93, 1.33) | |
| QRS/T angle | | | | |
| Reference (0–56°) | 1 | 1 | 1 | |
| Increased (57–96°) | 1.63‡ (1.05, 2.55) | 1.17‡ (1.01, 1.36) | 1.21§ (1.05, 1.40) | |
| Wide (≥97°) | 2.98‖ (1.90, 4.70) | 1.28‡ (1.02, 1.61) | 1.36‡ (1.07, 1.74) | |
| $STV_5$ mean amplitude | | | | |
| Reference (>0 $\mu$V) | 1 | | RM | |
| Depressed (≤0 $\mu$V) | 1.29§ (1.10, 1.52) | | | |
| $STV_5$ gradient | | | | |
| Reference (≥3 $\mu$V) | 1 | | 1 | |
| Low or negative (<3 $\mu$V) | 1.55‖ (1.26, 1.90) | | 1.32‡ (1.06, 1.65) | |
| Heart rate variability | | | | |
| Reference (8–44 ms)1 | 1 | | | |
| Low (<8 ms) | 1.43‖ (1.20, 1.71) | | 1.40‖ (1.17, 1.67) | |
| High (>44 ms) | 1.08 (0.87, 1.33) | | 1.04 (0.84, 1.29) | |
| QTrr | | | | |
| Reference (<437 ms) | 1 | | 1 | |
| Prolonged (≥437 ms) | 1.35§ (1.12, 1.63) | | 1.28‡ (1.06, 1.55) | |
| Cornell voltage | | | | |
| Reference (<1800 $\mu$V) | 1 | | RM | |
| High (≥1800 $\mu$V) | 1.30§ (1.08, 1.56) | | | |
| QRS non-dipolar voltage | | | | |
| Reference (<65 $\mu$V) | 1 | | 1 | |
| Increased (≥65 $\mu$V) | 1.46‖ (1.19, 1.79) | | 1.33§ (1.08, 1.64) | |
| T wave roundness index | | | | |
| Reference (<31) | 1 | | RM | |
| Borderline (31–57) | 1.13 (0.98, 1.30) | | | |
| Large (>57) | 1.21 (0.98, 1.49) | | | |
| T non-dipolar voltage | | | | |
| Reference (<13 $\mu$V) | 1 | | RM | |
| Increased (≥13 $\mu$V) | 1.25‡ (1.03, 1.53) | | | |

Values are hazard ratio (95% CI). MI indicates myocardial infarction; RM, removed in backward selection procedure. ECG variables are defined in Table 1.

*There were 914 deaths from all causes.

†Data for ECG variables with a significant interaction with baseline CVD status are listed first, separately for both groups; cutpoints for continuous variables partition the distributions so that the highest decile is always selected as a risk group (for $TV_1$ and $TV_5$, both the highest and lowest deciles).

‡$P<0.05$; §$P<0.01$; ‖$P<0.001$.

**TABLE 4. Annual Rate per 10 000 of Incident CHF in Women With Specified ECG Abnormalities and Difference in Number of Events Between Reference and Abnormal Groups***

| | QRS/T Angle | ECG MI | $STV_5$, Mean | QRS Non-dipolar Voltage | $TV_1$, Mean | QTrr |
|---|---|---|---|---|---|---|
| Age-adjusted relative risk | 3.71 | 2.62 | 2.31 | 1.98 | 2.51 | 2.20 |
| Multivariable-adjusted relative risk† | 2.73 | 1.99 | 2.02 | 2.00 | 2.16 | 1.80 |
| Annual events per 10 000 women in high-risk group | 55.1 | 49.7 | 43.0 | 35.4 | 42.3 | 42.7 |
| Annual events per 10 000 in reference group | 12.3 | 13.1 | 15.2 | 17.5 | 17.5 | 16.5 |
| Annual difference per 10 000 women | 43 | 37 | 28 | 18 | 25 | 26 |

*Total annual event rate was 18.95/10 000 women.

†Hazard ratios from multivariable-adjusted single ECG variable models for incident CHF.

mortality in a 15-year mortality follow-up of this apparently healthy population sample.[19] With flat, closely isoelectric ST (between 25 and −25 $\mu$V at J 80 ms) as the reference group, the CHD mortality risk in multivariable-adjusted models for ST depression >25 $\mu$V was increased ≈2-fold in both men and women, but the hazard ratio was significant in men only. Similarly, a slight ST elevation with a well-shaped, upwardly sloping ST (≥25 $\mu$V at J 80 ms) was associated with 60% reduced CHD mortality risk, which was significant in men only. The risk of all-cause mortality for ST depression was significantly increased in women only, with a hazard ratio 1.7, and the risk for ST elevation was significantly reduced in men only (by 60%).

Data from a risk evaluation study with a methodology perhaps more comparable to that in the present study, although in a younger cohort, are from the 2002 report of the Copenhagen City Heart Study on a large cohort of men and women aged 35 to 74 years evaluated for 5 groups of mutually exclusive ECG abnormalities.[20] No significant interaction was found in that study between gender and ECG abnormalities in the individual categories of ECG abnormalities evaluated. The multivariable-adjusted relative risk (7-year follow-up) for ischemic heart disease in the pooled gender group for high-amplitude QRS combined with abnormal ST-T was 3.62, and that for high QRS voltage combined with abnormal T wave was 1.89. However, the prevalence of these combinations was only 1.2% for each. The prevalence was 2.3% for isolated ST abnormalities and 7.3% for isolated abnormal T wave, and the relative risk for them was still significantly increased: 2-fold for ST depression and 56% for isolated T wave abnormalities.

In a previous WHI report, several repolarization variables were identified as strong predictors of incident CHD.[1] Among these, wide QRS/T angle, ECG MI, and prolonged QT were dominant predictors, and they were also dominant predictors of CVD mortality. Wide QRS/T angle was also reported to be associated with excess CHD mortality risk in another previous study,[21] and 2 previous investigations reported increased mortality risk for abnormal T axis deviation,[22,23] related to a wide QRS/T angle. The mechanism of generation of abnormally wide QRS/T angle is inherently associated with structural and functional myocardial changes inducing aberrations in ionic channel functions and regionally heterogeneous shortening of action potential durations. Widening of the QRS/T angle is frequently associated with an anterior shift of the T axis,[23] suggesting preferential action potential shortening in the anterior wall (epicardial) regions.

QT prolongation is well known clinically as an arrhythmogenic mechanism in hereditary and drug-induced long-QT syndrome. The predictive value of moderate QT prolongation and its mechanism as a substrate for arrhythmogenic risk in asymptomatic women is less clear. Some studies have reported increased mortality risk for a moderate QT prolongation in men as well as in women,[24–27] and in some QT prolongation has been found to have a nonsignificant association with mortality when evaluated specifically in women without CHD.[28,29] In the present study moderately prolonged QT (QTrr ≥437 ms) was a significant predictor of incident CHF as well as all-cause mortality in women with and without prior CVD in study baseline. Glucose intolerance has been associated with QT prolongation in a population-based study,[30] and case-control studies found a strong association between QT prolongation and sudden cardiac death among diabetic patients, including those without heart disease.[31,32]

QRS non-dipolar voltage was a significant predictor of incident CHF and all-cause death in the present study. Its value as a risk predictor has to our knowledge not been previously investigated. Its presence probably reflects secondary minor alterations in ventricular conduction due to fibrotic damage or collagen tissue formation in subclinical ischemic myocardial damage or in left ventricular hypertrophy. T wave non-dipolar voltage was previously reported to be the strongest ECG predictor of all-cause mortality in men.[33] In the present study increased T wave non-dipolar voltage was a significant although rather weak predictor of all-cause mortality in women.

There is voluminous literature on mortality risk associated with reduced heart rate variability in Holter ECGs. Some studies have also observed a significant association with mortality for decreased heart rate variability when evaluated from very short (10-second to 2-minute) ECG recordings.[34,35] In the present study low heart rate variability was a strong predictor of all-cause mortality in both single and multiple multivariable-adjusted ECG variable models. High heart rate variability was a significant predictor of incident CHF.

## Limitations of This Investigation

This study was limited to postmenopausal women who were mainly relatively healthy at the time they were enrolled in WHI, and the results may not be generalizable to other female

populations. Other studies are also needed to evaluate CHF and all-cause mortality risk in men compared with women.

Risk evaluation results were presented as multivariable-adjusted models, including adjustment for demographic and therapeutic variables. The latter adjustment variables included self-report of the use of cholesterol-lowering drugs and self-report of diabetes control. It is recognized that self-report data for some of the therapeutic variables may have weakened the risk models. Although self-report of cholesterol-lowering drugs is probably reasonably satisfactory, we did not have test data available about the adequacy of diabetes control. To some extent more satisfactory criteria were used to define incident CHF (hospitalization with a physician's diagnosis of CHF and pertinent abnormalities in diagnostic testing corroborated by a review [although noncentralized] of the medical records).

There were no data available for the assessment of peripheral arterial disease because the ankle pressure measurement was not available. Women with this condition are generally included within the CHD-free group.

Finally, the question of adjustment of the probability values for multiple testing needs to be considered. We note that most of the significant predictors, particularly those that were dominant predictors, were significant with probability values clearly $<0.05$. Any possible adjustment for multiple comparisons would likely have caused relatively minor adjustment of probability values. In addition, there is no general agreement on a method to correct for multiple comparisons when variables for the final models are selected with the use of backward selection.

### Clinical Significance and Implications and Avenues for Future Research

ECG is among the first tests readily available to physicians caring for postmenopausal women. The results of the present investigation suggest that repolarization abnormalities are prognostic predictors of CHF and all-cause mortality as important as ECG MI, and their presence in women with and without CVD should not be overlooked. The presence of repolarization abnormalities, particularly wide QRS/T angle, may make a substantial difference in the number of new CHF events and may warrant consideration of possibly intensified prevention efforts in these postmenopausal women.

Evaluation of repolarization abnormalities and particularly QRS/T angle for their predictive value is suggested as a potentially fertile topic in future investigations. Spatial QRS/T angle or its frontal plane counterpart is presently not routinely reported in clinical ECG. It is also suggested that the value of QRS non-dipolar voltage as a risk predictor may warrant special attention in future studies.

The importance of the conventional risk factors, particularly the age of the patient, smoking, obesity, and any clinical condition necessitating the use of cardioactive drugs, should not be overlooked in risk evaluation when focusing on the role of ECG factors, the main objective of the present investigation.

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## Disclosures

None.

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