Electrocardiographic Abnormalities That Predict Coronary Heart Disease Events and Mortality in Postmenopausal Women

The Women's Health Initiative

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Background—Information is limited about the independent prognostic value of repolarization abnormalities in women.

Methods and Results—We evaluated hazard ratios for ECG variables for combined fatal and nonfatal coronary heart disease (CHD) events and for CHD mortality using Cox regression in 38 283 Women's Health Initiative (WHI) participants during up to 9.2 years of follow-up. All risk models were adjusted for demographic, clinical, and therapeutic variables. Evaluated as single ECG variables, wide QRS/T angle and ECG-demonstrated myocardial infarction (ECG-MI) were the strongest predictors of CHD events, with hazard ratios (95% CI) of 1.90 (1.50 to 2.42) and 1.62 (1.29 to 2.03), respectively. Six other repolarization variables were also significant, strong predictors of CHD events. Wide QRS/T angle, ECG-MI, and QT prolongation appeared as dominant predictors when evaluated simultaneously with other ECG variables in a multiadjusted risk model. QRS/T angle, ECG-MI, and high QRS nondipolar voltage were the strongest predictors of CHD mortality, with hazard ratios of 2.70, 2.41, and 2.18, respectively. The risk increase ranged from 63% to 95% for the other 4 significant predictors. Five ECG abnormalities were identified as dominant mortality risk predictors: wide QRS/T angle, ECG-MI, high QRS nondipolar voltage, reduced heart rate variability, and QT prolongation (in the cardiovascular disease–free group only).

Conclusions—Ventricular repolarization abnormalities in postmenopausal women are as important predictors of CHD events and CHD mortality as ECG-MI and other QRS abnormalities. Repolarization variables and QRS nondipolar voltage warrant attention in future investigations. **(*Circulation*. 2006;113:473-480.)**

Key Words: cardiovascular diseases ■ electrocardiography ■ morbidity ■ mortality ■ women

Population studies have in general found a low or nonsignificant prognostic value for ECG abnormalities in women.[1–4] This may be because many studies have not had an adequate statistical power to evaluate the risk in women, particularly the cause-specific mortality and morbidity in subsamples stratified by gender and coronary heart disease (CHD) or cardiovascular disease (CVD) status at baseline. The Women's Health Initiative (WHI) provides a unique opportunity to investigate the risk of fatal and nonfatal adverse events for a variety of ECG abnormalities in a large population of postmenopausal women. The specific objective of this investigation was to evaluate the contribution of ventricular repolarization abnormalities to CHD events and CHD mortality prediction compared with ventricular depolarization–related ECG abnormalities such as myocardial infarction (MI) by ECG criteria (ECG-MI).

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Methods

Study Design and Population

The 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 the study design, protocol sampling procedures, and selection and exclusion criteria, among other things, have been published elsewhere.[5] The women initially chosen for the present study (n=40 786) were participants in the dietary modification trial (n=68 133), which the exclusion of 27 347 women who were enrolled in randomized trials on hormone therapy. After the additional exclusion 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, and derivation of secondary ECG variables for the present investigation, 38 283 women remained in the present study.

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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)
STV5 (μV)	Mean ST amplitude in V_5	22 (2, 43)	32 (13, 52)
Square root (E2/E1) (%)	T-wave roundness index (square root of the ratio of the second and first T eigenvectors)	33 (21, 48)	30 (20, 43)
TV1 (μV)	Mean T-wave amplitude in V_1	19 (−15, 55)	20 (−10, 49)
TV5 (μV)	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)
STV5 gradient (μV)	ST gradient in V_5 (increase from beginning to end)	12 (7, 17)	14 (9, 20)
TNDPV (μV)	T-wave nondipolar 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 (μV)	Cornell voltage (RaVL+SV3)	1317 (1005, 1689)	1152 (864, 1468)
RNDPV (μV)	QRS nondipolar 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)

RMS indicates root mean square.

The study group was stratified by CVD status at baseline into women with baseline 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, congestive heart failure, or stroke at the time the women entered the WHI.

Two outcomes were considered in the present investigation: CHD events (fatal and nonfatal) and CHD mortality. A CHD event in CVD-free women implies incident CHD, defined by clinical diagnosis of an MI or CHD death. In the CVD group, CHD events included 48 women with a recurrent MI among the 681 women with a prior clinically recognized MI. CHD mortality was defined by CHD death (no known non-CHD cause and either chest pain within 72 hours before death or a history of chronic ischemic heart disease in the absence of valvular heart disease. The follow-up period for the study group was up to 9.2 years (mean 6.2 years), and among those with any end-point event, the mean time until the first event was 3.5 years.

ECG Methodology

Standard 12-lead ECGs were recorded in all women by strictly standardized procedures in all clinical centers. Special attention was paid to locating the chest electrodes in precise positions.[6] All ECGs were processed in a central laboratory (EPICARE Center, University of Alberta, Edmonton, Canada, and later Wake Forest University, Winston-Salem, NC), where they were visually inspected for technical errors and inadequate quality. ECGs were initially processed by the Dalhousie ECG program,[7] and processing was later repeated for the present study with the 2001 version of the Marquette 12-SL program (GE Marquette). Many ECG variables of interest are contained in matrix 2 of the Marquette program, derived from the median QRS complex, ST segment, and T wave.

Most of the key variables, described in Table 1, are familiar to electrocardiographers. For the benefit of nonelectrocardiographers, most of these variables are described in schematics in Figures I and II of the online-only Data Supplement. The variables considered as initial candidates for risk prediction included some ECG waveform descriptors derived by the Novacode program,[8] including some repolarization (ST and T) waveform variables described in previous communications.[9,10] The program uses modified orthogonal Chebyshev polynomials calculated for the XYZ orthogonal components that were derived by a transformation matrix from the standard 12-lead ECG.[11] Subsequently, an inverse matrix transformation was used to calculate the projections of waveform vectors on standard leads V_5, aVF, and V_1.

The waveform amplitudes from orthonormal expansion are the mean and not the peak values of the waves, which explains their ostensibly smaller values. Variables from such an orthonormal expansion are statistically independent, thus reducing the colinearity problem that is common with variables used in ECG classification criteria. In the V_5 lead, T_{mean} and T_{peak} are correlated at level $r=0.93$, and the peak value can be estimated if needed ($TV5_{peak}=2.24\times TV5_{mean}-47$ μV). Low TV5 amplitude (amplitude of T wave in V_5) turned out to be an important risk predictor, and both peak and mean values are listed for TV_5 in tables for risk model data. For TV1 amplitude (amplitude of T wave in V_1), it is important to use the mean T value, because the waveform is commonly biphasic. QRS/T angle, the spatial angle between the QRS and T vectors, is determined with best accuracy using the mean QRS and T vectors, although the angle between the maximal QRS and T vectors (shown in Figure II of the data supplement) gives closely similar results. QTrr is the rate-adjusted QT as a linear function of the RR interval, used to evaluate QT prolongation.[12]

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 nondipolar components. The voltage ratio of the second and the first principal components is at times called T-wave complexity.[13] 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 relatively narrow. T-wave and QRS nondipolar 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 more than 1 maximum and minimum in body-surface ECG maps signifies the presence of

nondipolar components. These components are also projected in part on the standard 12-lead ECG, although their presence is more difficult to visualize because of the dimensionality problem.

Old MI was defined by codes 5.1 to 5.4 of the Novacode criteria.[8] ST was classified as depressed if the mean value of the ST segment in V_5 was negative or 0 μV (prevalence 14%), where the ST segment was defined as 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 cutpoints for the reference groups often differ from those used to define normal limits for diagnostic classification (for instance, for 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 colinearity problems, in order to facilitate interpretation as to why certain ECG variables were selected or not selected into multiple ECG variable models. To account for the potential differences on the effect of the ECG markers of the outcomes between the baseline CVD and CVD-free groups, a series of single ECG variable proportional hazards models were 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 derived for the combined group.

After the single ECG variable analyses, all ECG variables and 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 were first adjusted for age only and then additionally for demographic variables (age, ethnicity, systolic blood pressure, and 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 (antiarrhythmic drugs, calcium channel blockers, β-blockers, diuretics, antidepressants, or psychotherapeutic drugs). These models were labeled as multiadjusted, which implies adjustment for multiple exposures. 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 multiadjusted single ECG variable models and multiadjusted multiple ECG variable models. Risk model data for age-adjusted models are included only in the data supplement. The results tables 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 distribution of race/ethnicity in the study group was white (82.3%), black (10.2%), Hispanic (3.3%), and other or unknown (4.2%). The mean age of the study group was 62.1 years (SD 6.8 years). Concerning smoking status, 6.2% were current smokers and 51.6% had never smoked. Slightly more than one half (51.4%) were current users of hormone therapy, 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. The mean systolic blood pressure was 127 mm Hg (SD 17 mm Hg), and diastolic blood pressure was 76 mm Hg (SD 9 mm Hg). The distributions (medians and limits for interquartile range) of the 11 continuous ECG variables (Table 1) indicate no notable clinically significant differences between women with and without prior CVD, although some of the mean values were statistically significant (not shown) in this large group of women. More directly relevant is the significance of interaction between baseline CVD and some of these ECG variables in risk models, considered in connection with risk evaluation results.

Correlations Between ECG Variables

The correlations were first analyzed separately in women with and without baseline CVD, but given the similarity of the correlations, only the correlation matrix for the entire cohort is presented (Table 2). QRS/T angle appeared to be the common denominator in the correlations among those variables that reflected altered sequence of ventricular repolarization (T-wave roundness, TV1, TV5, and ST gradient in V_5 [STV5 gradient]), with correlations ranging from −0.26 for ST-segment gradient in V_5 to 0.52 for the mean TV1 amplitude. QRS/T angle was also correlated with Cornell voltage (r=0.39). Other correlations were smaller.

TABLE 2. Correlations Between ECG Variables in Combined Group of Women With and Without Prior CHD

	QRS/T Angle	T-Wave Roundness	TV1	TV5	STV5	STV5 Gradient	CV	RNDPV	TNDPV	QTrr	HRV
QRS/T angle	1										
T-wave roundness	0.47	1									
TV1	0.52	0.36	1								
TV5	−0.45	−0.45	−0.15	1							
STV5	−0.34	−0.34	−0.15	0.75	1						
STV5 gradient	−0.26	−0.42	−0.24	0.74	0.66	1					
CV	0.44	0.19	0.04	−0.26	−0.14	0.02	1				
RNDPV	0.02	0.08	0.11	0.08	0.03	0.09	0.14	1			
TNDPV	0.01	0.01	0.00	0.10	0.04	0.07	0.08	0.20	1		
QTrr	0.09	0.11	−0.01	−0.17	−0.17	−0.12	0.14	0.06	0.05	1	
HRV	0.03	0.02	−0.01	−0.04	−0.05	−0.03	−0.00	0.04	0.08	0.02	1

Acronyms and units for the variables are given in Table 1.

ECG Predictors in Age-Adjusted Models

Age-adjusted risk model data are of lesser importance here and are of interest mainly for initial consideration of the significance of interaction between ECG variables and baseline CVD status. These data are shown only in the data supplement.

ECG Predictors of CHD Events

Multiadjusted risk model data with adjustment for demographic, clinical, and treatment variables are of primary interest in the present context (Table 3). Single ECG variable models identify significant ECG predictors, and dominance

TABLE 3. Hazard Ratios and 95% CIs for Combined Fatal and Nonfatal CHD Events From Multiadjusted Single and Multiple ECG Variable Risk Models

	Multiadjusted* Single ECG Variable Models		Multiadjusted* Multiple ECG Variable Models	
ECG Variables (Cutpoints)	CVD Group	CVD-Free Group	CVD Group	CVD-Free Group
T nondipolar voltage				
Normal (<13 μV)	1	1	1	1
Increased (≥13 μV)	0.59 (0.29, 1.21)	1.29 (0.97, 1.72)	0.46* (0.21, 0.99)	1.24 (0.93, 1.66)
QRS/T angle				
Reference (0–56°)	1		1	
Increased (57–96°)	1.24* (1.03, 1.50)		1.21* (1.00, 1.46)	
Wide (≥97°)	1.90‡ (1.50, 2.42)		1.68‡ (1.32, 2.16)	
ECG-MI/ischemic injury				
No ECG-MI	1		1	
ECG-MI	1.62‡ (1.29, 2.03)		1.42† (1.12, 1.80)	
Isolated ST-T abnormalities or minor Q waves	1.34† (1.09, 1.66)		1.24 (1.00, 1.54)	
STV5 mean amplitude			Removed in backward-selection procedure	
Reference (>0 μV)	1			
Depressed (≤0 μV)	1.46‡ (1.20, 1.78)			
STV5 gradient			Removed in backward-selection procedure	
Reference (≥3 μV)	1			
Downsloping or horizontal (<3 μV)	1.42* (1.09, 1.86)			
TV5 mean amplitude			Removed in backward-selection procedure	
Reference (73–235 μV)	1			
Low (<73 μV) (T_{peak} <117 μV)	1.37† (1.10, 1.71)			
High (>235 μV)	0.77 (0.54, 1.10)			
QTrr				
Reference (<437 ms)	1		1	
Prolonged (≥437 ms)	1.37† (1.08, 1.73)		1.29* (1.02, 1.64)	
TV1 mean amplitude			Removed in backward-selection procedure	
Reference (−41 to 80 μV)	1			
Low (< −41 μV)	0.89 (0.66, 1.20)			
High (>80 μV)	1.35* (1.06, 1.72)			
T-wave roundness index			Removed in backward-selection procedure	
Reference (<31%)	1			
Oblong (31%–57%)	1.27* (1.06, 1.52)			
Wide (>57%)	1.35* (1.03, 1.76)			
QRS nondipolar voltage			Removed in backward-selection procedure	
Reference (<65 μV)	1			
Increased (≥65 μV)	1.28 (0.98, 1.68)			
Heart rate variability			Removed in backward-selection procedure	
Reference (8–44 ms)	1			
Low (<8 ms)	1.21 (0.96, 1.54)			
High (>44 ms)	0.88 (0.66, 1.18)			
Cornell voltage			Removed in backward-selection procedure	
Reference (<1800 μV)	1			
High (≥1800 μV)	1.07 (0.84, 1.37)			

ECG variable acronyms and units are defined in Table 1. Values are hazard ratios (95% CIs). There were 545 CHD events. Adjusted for demographic, clinical, and therapeutic variables.

*P<0.05; †P<0.01; ‡P<0.001.

among these significant predictors is revealed by relative risks in multiple ECG variable models when all ECG variables are considered simultaneously.

Only T-wave nondipolar voltage had a significant interaction with CVD status at baseline, with a significantly reduced relative risk in the CVD group in the multiadjusted multiple ECG model. Nine of the 12 ECG variables were significant predictors of CHD events in single ECG variable models. The strongest ECG predictor was QRS/T angle, with a nearly 2-fold increased risk. ECG-MI was also a strong predictor, with relative risk increased 62%. For the 6 other repolarization variables that were significant CHD event predictors in

TABLE 4. Hazard Ratios and 95% CIs for CHD Mortality From Fully Adjusted Single and Multiple ECG Variable Risk Models by CVD Status at Baseline

	Multiadjusted Single ECG Variable Models		Multiadjusted Multiple ECG Variable Models	
ECG Variables (Cutpoints)	CVD Group	CVD-Free Group	CVD Group	CVD-Free Group
Cornell voltage				
Reference (<1800 μV)	1	1	1	1
High (≥1800 μV)	0.48 (0.17, 1.37)	1.91 (1.09, 3.36)	0.36 (0.12, 1.05)	1.25 (0.69, 2.26)
QTrr				
Reference (<437 ms)	1	1	1	1
Prolonged (≥437 ms)	0.47 (0.14, 1.54)	2.17 (1.24, 3.73)	0.45 (0.14, 1.50)	1.90* (1.09, 3.33)
QRS/T angle				
Reference (0–56°)	1		1	
Borderline (57–96°)	1.32 (0.85, 2.04)		1.23 (0.79, 1.93)	
High (≥97°)	2.70‡ (1.65, 4.39)		2.12† (1.25, 3.62)	
ECG- MI/ischemic injury				
No MI	1		1	
MI	2.41‡ (1.52, 3.81)		1.87* (1.15, 3.03)	
Isolated ST-T abnormalities or minor Q waves	1.50 (0.93, 2.42)		1.24 (0.76, 2.02)	
QRS nondipolar voltage				
Reference (<65 μV)	1		1	
Increased (≥65 μV)	2.18† (1.33, 3.57)		1.85* (1.11, 3.08)	
Heart rate variability				
Reference (8–44 ms)	1		1	
Low (<8 ms)	1.95† (1.24, 3.07)		1.87† (1.19, 2.95)	
High (>44 ms)	1.04 (0.55, 1.97)		0.97 (0.51, 1.83)	
TV5 mean amplitude				
Normal (73–235 μV)	1		Removed in backward-selection procedure	
Low (<73 μV) (T_{peak} <117 μV)	1.80† (1.16, 2.81)			
High (>235 μV)	1.22 (0.61, 2.45)			
STV5 mean amplitude				
Reference (>0 μV)	1		Removed in backward-selection procedure	
Depressed (≤0 μV)	1.63* (1.07, 2.47)			
TV1 mean amplitude				
Reference (−41 to 80 μV)	1		Removed in backward-selection procedure	
Low (< −41 μV)	1.14 (0.62, 2.10)			
High (>80 μV)	1.59 (0.98, 2.59)			
T-wave roundness index				
Reference (<31%)	1		Removed in backward-selection procedure	
Oblong (31%–57%)	1.19 (0.79, 1.80)			
Round (>57%)	1.60 (0.93, 2.73)			
STV5 gradient				
Reference (≥3 μV)	1		Removed in backward-selection procedure	
Downsloping or horizontal (<3 μV)	1.47 (0.83, 2.58)			
T nondipolar voltage				
Reference (<13 μV)	1		Removed in backward-selection procedure	
Increased (≥13 μV)	1.12 (0.64, 1.98)			

ECG variable acronyms and units are defined in Table 1. Values are hazard ratios (95% CIs). There were 112 CHD mortality events.
*P<0.05; †P<0.01; ‡P<0.001.

TABLE 5. Annual Rate of CHD Events in Women With Specified ECG Abnormalities per 10 000 Women and Difference in Number of Events Between Reference and Abnormal Groups*

	QRS/T Angle	ECG-MI	STV5 Mean	STV5 Gradient	TV5 Mean	QTrr
Age-adjusted relative risk†	2.31	1.91	1.65	1.57	1.57	1.49
Multiadjusted relative risk†	1.90	1.62	1.46	1.42	1.37	1.37
Annual events/10 000 women in high-risk group	61.1	60.2	49.3	53.5	50.2	44.1
Annual events/10 000 women in reference group	20.8	21.6	24.1	25.8	25.6	25.8
Annual difference/10 000	40	39	25	28	25	18

*Total annual event rate was 27.5/10 000 women.

†Hazard ratios from the age-adjusted and multiadjusted single ECG variable models for CHD events.

Hazard ratios presented are lower than differences in events owing to adjustment in the models and positive correlation between risk factors.

addition to wide QRS/T angle, the risk increase ranged from 35% for high TV1 amplitude to 46% for STV5 depression. The multiadjusted multiple ECG variable model confirmed the dominant role of QRS/T angle and ECG-MI as predictors of CHD events, with risk increases by 68% and 42%, respectively. Prolonged QT interval (QTrr ≥437 ms) was also retained as a significant, dominant predictor, with a 29% risk increase. Because of correlations between the ECG predictors, the risk levels in the multiple ECG variable models were somewhat lower than in the single ECG variable models.

ECG Predictors of CHD Mortality

Among the significant CHD mortality predictors, prolonged QT had a significant interaction with baseline CVD status, with a significant risk in the CVD group only (risk increase nearly 2-fold; Table 4). QRS/T angle and ECG-MI were the strongest predictors of CHD mortality, with hazard ratios of 2.70 and 2.14, respectively. The risk increase was more than 2-fold for high QRS nondipolar voltage, 95% for low heart rate variability, 80% for low TV5 amplitude, and 63% for STV5 depression.

Five ECG abnormalities were identified as dominant among the significant predictors of CHD mortality when evaluated simultaneously with the other ECG variables and with multiple adjustment for demographic, clinical, and therapeutic variables. These dominant, strong mortality risk predictors were wide QRS/T angle, ECG-MI, high QRS nondipolar voltage, reduced heart rate variability, and QT prolongation (in the CVD-free group only). In the latter model, there was more than a 2-fold increased risk for wide QRS/T angle, and it ranged from 85% to 87% for the other 4 dominant predictors.

Relative Risks in Relation to Absolute Risk

Relative risks for ECG predictors shown in the context of absolute risks (Table 5) are particularly relevant for the consideration of ECG findings in relation to possible preventive efforts. The annual risk for CHD events in the present study population was 27.50/10 000 and 5.97/10 000 for CHD mortality. Only CHD event rates for the 6 most significant predictors were considered here. The annual new event rate difference per 10 000 was 40 events for QRS/T angle and 39 for ECG-MI. For the other 4 ECG predictors of CHD, the difference ranged from 18 to 28 events.

Discussion

Wide QRS/T angle and 6 other repolarization variables were significant predictors of CHD events in addition to ECG-MI. Dominant among these individually significant predictors of CHD events were wide QRS/T angle, prolonged QT, and ECG-MI.

Wide QRS/T angle and 3 other repolarization variables, ECG-MI, increased QRS nondipolar voltage, and low heart rate variability, were significant predictors of CHD mortality. Of these, wide QRS/T angle, ECG-MI, and prolonged QT (in CVD-free women only) were dominant ECG predictors of mortality risk.

Overall, the results indicate that several repolarization variables are significant CHD event and CHD mortality predictors, with excess risk particularly strong for wide QRS/T angle, comparable to the risk associated with ECG-MI. QRS/T angle becomes wide when repolarization sequence becomes abnormal either as a primary abnormality or secondary to an altered ventricular repolarization sequence such as takes place in bundle-branch blocks. The latter abnormalities were excluded from the present study. Prolonged QT is known to be associated with excess risk of malignant arrhythmias in hereditary and acquired long-QT syndrome and is generally associated with abnormal heterogeneity of ventricular repolarization. The predictive value of moderate QT prolongation in asymptomatic women is less clear.

Comparison With Previous Studies

As noted already, previous studies have in general found a low or nonsignificant prognostic value for ECG abnormalities in women.[1–4] 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.

Two previous studies have documented an increased risk for abnormal T-axis deviation,[14,15] a variable closely related to QRS/T angle. A wide QRS/T angle in women without clinical evidence of CHD can be considered as a subclinical abnormality. A large QRS/T angle reflects an abnormal sequence of ventricular repolarization. When the ventricular excitation sequence is relatively normal, a wide QRS/T angle commonly

reflects an anterior shift of the T wave, which also induces increased TV1 amplitude and reduced TV5 amplitude.[15]

The association between old ECG-MI and mortality risk in women has generally been found to be weak or nonsignificant. Some studies, even with a relatively large number of women, have reported too few fatal end points for this category to perform a meaningful risk analysis.[1,2] Mortality risk can be expected to be higher for incident ECG-MI. The Framingham study reported a 30% 10-year mortality rate in women with incident unrecognized Q-wave MI, double the rate in the general Framingham Study population.[16]

A 2002 report from the Copenhagen City Heart Study on a large cohort of men and women aged 35 to 74 years compared predictive value for 5 groups of mutually exclusive ECG abnormalities.[17] No significant interaction was found between gender and ECG abnormalities in the individual categories of ECG abnormalities evaluated. The multivariable-adjusted 7-year risk of ischemic heart disease in the pooled gender group was significantly increased for isolated negative T waves and for ST depression with negative T waves, by 56% for the former and by more than 2-fold for the latter abnormality. The corresponding risk increases for all-cause mortality were 61% for isolated negative T waves and 68% for ST depression with negative T waves.

Reported results for the association of QT prolongation with excess mortality in women are conflicting.[18–22] In the present study, moderately prolonged QT (QTrr $\geq$437 ms) was among the dominant repolarization variables as a CHD mortality predictor in CVD-free women, and it was a significant predictor of CHD events in all women.

QRS nondipolar voltage was a strong predictor of CHD mortality in the present study. To the best of our knowledge, QRS nondipolar voltage has not been evaluated for risk previously.

The Copenhagen Heart Study[17] and a recent report from the Cardiovascular Health Study[23] have provided new evidence that there is no significant difference between men and women with regard to mortality risk for repolarization abnormalities. In the latter report, the ECG methodology used was similar to that used in the present study.

Study Limitations

The present study evaluated the risk for ECG variables in postmenopausal women. The risk levels and significant variables will differ in younger age groups of women and in men. The majority of WHI participants are relatively healthy women, and caution should be exercised before the risk data are generalized to other populations. This investigation did not evaluate possible variation of the findings by ethnicity or the risk in men.

Risk evaluation results were presented as multiadjusted models, including adjustment for a long list of standard coronary risk factors and medications. Although some of these adjustment variables were collected by direct examination (blood pressure, body mass index, and medication use), it is recognized that self-report data for some of these variables may have weakened the risk models, but access to each subject's physician's records or hospital records was not feasible in this massive study.

Finally, the question of adjustment of the probability values for multiple testing needs to be considered. We note that most of the significant variables in the risk models were significant, with probability values clearly smaller than 0.05, and possible adjustment for multiple comparisons would likely cause relatively minor adjustment of probability values. Also, there is no generally agreed on method to correct for multiple comparisons when variables for the final models are selected by backward selection, and Bonferroni correction would be overly conservative.

Clinical Implications and Avenues for Future Research

It is becoming increasingly recognized that physicians tend to underestimate the risk of adverse cardiovascular events in women.[24] Repolarization abnormalities in women are often ignored as inconsequential. The results from the present study suggest that in women with and without prior CVD, an old ECG-MI and a wide QRS/T angle indicating an abnormal sequence of ventricular repolarization are among the dominant ECG predictors of future CHD events and CHD death. The annual difference in event rates among women with wide QRS/T angle or ECG-MI was substantial compared with women in the corresponding reference groups (40 and 39 events/10 000, respectively), and the event rate difference for the other dominant ECG predictors was still considerable, ranging from 18 to 28 events/10 000 women. QRS/T angle is presently not routinely reported in clinical electrocardiography. The value of QRS/T angle and other repolarization variables should prove a potentially fertile area for future research; in addition, the significance of QRS nondipolar voltage needs to be confirmed in independent studies.

The objective of primary prevention is to prevent the disease or at least slow down its evolution into adverse events. The objective of secondary prevention is also to slow down the progression of the disease and to prevent recurrent nonfatal adverse events. In view of the severity of this health problem in postmenopausal women, the presence of ECG abnormalities may warrant serious consideration for a possibly intensified primary or secondary prevention effort.

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Disclosures

None.

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