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Comparison of the Prognostic Significance of the Electrocardiographic QRS/T Angles in Predicting Incident Coronary Heart Disease and Total Mortality (from the Atherosclerosis Risk In Communities Study)

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Abstract

Spatial QRS/T angle and the spatial T wave axis have been shown to be strong independent predictors of incident coronary heart disease (CHD) and total mortality, but they are not routinely available. We evaluated whether the frontal plane QRS/T angle, easily obtained as the difference between frontal plane axes of QRS and T, provides a suitable substitute for the spatial QRS/T angle as a risk predictor. Our study consisted of 13,973 participants from the Atherosclerosis Risk In Communities Study. The outcome variables were incident CHD and total mortality during a median follow-up of 14 years. The ECG variables were categorized as: abnormal ($\geq 95^{\text{th}}$ percentile), borderline ($\geq 75^{\text{th}}$ and $< 95^{\text{th}}$ percentile), and normal ($< 75^{\text{th}}$ percentile), separately for men and women. Cox regression was used to assess the effect of the ECG variables on the risk of each outcome. The normal category was considered the reference cell. With adjustment for demographic and clinical characteristics, both QRS/T angles were approximately equally strong predictors of total mortality with an over 50% increased risk. The spatial QRS/T angle was a stronger predictor of incident CHD in women with a 114% increased risk, but it was not significantly associated with the risk of incident CHD in men. Similarly, the frontal plane QRS/T angle was only statistically significant for women with a 74% increased risk of incident CHD. In conclusion, the frontal plane QRS/T angle as an easily derived risk measure is a suitable clinical substitute for the spatial QRS/T angle for risk prediction.

Keywords

electrocardiography; QRS/T angle; cardiovascular diseases; mortality

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INTRODUCTION

Recent studies have demonstrated that the spatial QRS/T angle, defined as the angle between the mean QRS and T vectors is a strong independent predictor of incident coronary heart disease (CHD) and total mortality (1–8). However, most clinicians are not familiar with the measurement of the spatial QRS/T angle and it is not routinely available in clinical electrocardiogram (ECG) reports, which potentially limits a wider use and validation of these reports (9). In contrast, the frontal plane axes of QRS and T are readily available in ECG reports printed by most current electrocardiographs, and these angles are understood and easily interpreted by clinicians. The difference between the two axes is the frontal plane QRS/T angle which may provide a simpler, independent prognostic tool for clinicians than the spatial QRS/T angle. The specific objective of this investigation was to compare the prognostic significance of the frontal plane QRS/T angle, the spatial QRS/T angle and the spatial T wave axis.

METHODS

The data for the present study were from the Atherosclerosis Risk In Communities Study (10), a population-based, multicenter prospective study designed to investigate the natural history and etiology of atherosclerotic and cardiovascular disease events from 4 U.S. communities in Maryland, Minnesota, Mississippi, and North Carolina (n = 15,792 men and women aged 45–64 years). Eligible participants were interviewed at home, and then invited to a baseline clinical examination (1987–1989). They attended three further clinical examinations at approximately three-year intervals, and received a follow-up telephone call yearly. Details of the Atherosclerosis Risk In Communities Study design, protocol sampling procedures, and selection and exclusion criteria have been published elsewhere (10). From this study, 15,582 had complete ECG and clinical data available. The ECG was recorded at the baseline examination. After excluding 458 ECGs of the participants with an external pacemaker, Wolff-Parkinson-White pattern, or complete bundle branch block (QRS duration ≥ 120 ms), and 1,006 participants who had ECG evidence or a history of myocardial infarction (MI), coronary bypass surgery, or angioplasty, and 145 with ECGs of inadequate quality, ECGs of 13,973 participants considered free of CHD were available for the present study.

Two outcomes were considered in the present investigation: Incident CHD events (fatal and nonfatal) and all cause mortality. After baseline, deaths and hospitalization events were ascertained by annual follow-up calls to the cohort members, review of vital records, and community surveillance of hospitalized and fatal events. CHD death was defined as lacking a probable non-CHD cause, and occurring in the context of a recent myocardial infarction, chest pain within 72 hours of death. Events were classified independently by a separate committee (11). The present study included CHD events occurring between the baseline examination and December 31, 2002. The median follow-up time was 14.3 years (maximum of 16.1 years). CHD incidence on follow-up included fatal and non-fatal events was defined as a definite, probable, silent MI, or a definite CHD death. Silent MI defined between examinations ascertained by ECGs of a major Q wave, or a minor Q wave with ischemic ST-T changes by computerized Minnesota Code criteria (12).

Identical electrocardiographs (MAC PC, Marquette Electronics) were used in all clinic centers, and Standard 12-lead ECGs were recorded in all participants by strictly standardized procedures. All ECGs were processed in the central ECG laboratory, EPICARE (Epidemiological Cardiology Research Center at Wake Forest University, Winston-Salem, NC), where they were visually inspected for technical errors and inadequate quality. The ECGs were initially processed by the Dalhousie ECG program (13,14) and later processing was repeated for the present study with the 2001 version of the GE Marquette 12-SL program ('Marquette 12SL ECG Physician' Guide at www.gehealthcare.com). The variables considered

as initial candidates for risk prediction included some ECG waveform descriptors derived by the Minnesota Code (MC) and Novacode programs (12–14).

The frontal plane QRS/T angle (QRS/T_{Frontal}) was defined as the absolute value of the difference between the frontal plane QRS axis and T axis, and was adjusted to the minimal angle by $[360 \text{ degrees} - \text{angle}]$ if angle > 180 degrees. (The range of axis measurement is from -89 degrees to $+270$ degrees in the GE-Marquette ECG program).

The spatial QRS/T angle (QRS/T_{Spatial}) is the angle between the mean QRS vector and T vector. The mean spatial QRS and T vectors were calculated from quasi-orthogonal X, Y and Z leads reconstructed from the standard ECG leads by a matrix transformation method (15).

The spatial T-wave axis was calculated as previously described (4,15). The mean spatial axis was based on the areas of the wave components of the QRS complex and T wave. ST-T abnormalities were classified according to the Minnesota Code (MC 4.1 or 4.2 as major ST depression, MC 4.3 or 4.4 as minor ST depression, MC 5.1 or 5.2 as major T abnormality, and MC 5.3 or 5.4 as minor T abnormality) (12). Left ventricular hypertrophy on ECG was defined by the Cornell voltage index ($R_{aVL} + SV_3 \geq 2200$ uV for women, ≥ 2600 uV for men) (16). QTrr interval is the rate-adjusted QT as a linear function of the RR interval, used to evaluate QT prolongation ($QT_{rr} \geq 445$ ms for women, $QT_{rr} \geq 439$ ms for men) (17).

Frequency distributions of all variables were first inspected to rule out anomalies and outliers possibly due to measurement artifacts. Descriptive statistics were used to determine mean, standard deviations, and percentiles for continuous variables, and frequencies and percents for categorical variables. Differences in characteristics by gender were assessed using Chi-square tests and nonpaired T-tests.

Cox's proportional hazards analysis was used to assess the effects of spatial QRS/T angle, frontal plane QRS/T angle, and spatial T wave axis on the risk of cardiovascular events and total mortality, unadjusted and adjusted for demographic and clinical characteristics and ST abnormalities. Age was used as the timescale and birth cohort was used as a stratification factor in all analyses. Each ECG variable was initially included as a continuous variable. The relative risk was calculated to demonstrate the incremental risk per one standard deviation (SD) change in each measure. Then each ECG variable was trichotomized at defined cut points to establish prognostic indices with practical clinical utility. We categorized the ECG variables as: abnormal ($\geq 95^{\text{th}}$ percentile), borderline ($\geq 75^{\text{th}}$ and $< 95^{\text{th}}$ percentile), and normal ($< 75^{\text{th}}$ percentile), separately for men and women. The normal category was considered the reference cell in the analyses. Adjustment was made for demographic and clinical variables and is listed in Table 3. SAS version 9.1 (SAS Institute, Inc, Cary, NC) was used in all analyses.

RESULTS

Of a total 13,973 participants, 58% were women and 27% were black (Table 1). The average age of the study group at baseline was 54.4 years (\pm SD 5.7 years) and 33% had hypertension, 11% diabetes, 4.2% angina by Rose questionnaire, 2.1% left ventricular hypertrophy by Cornell voltage, and 4.2% had major ST-T abnormalities. Statistics for the ECG variables of the study population show that the spatial QRS/T angle was 14 degrees smaller in women than in men, 75 degrees versus 61 degrees, respectively ($p < 0.0001$). The gender difference in the frontal plane QRS/T angle, although significant ($p < 0.0004$), was considerably smaller, 23 degrees in women and 25 degrees in men. The mean values of both QRS/T angles were larger in blacks than whites, and while there was no significant sex difference in the spatial T wave axis, blacks had a significantly larger value than whites.

During a median follow-up of 14.3 years, there were 1,793 total deaths and 1,627 had incident CHD (fatal plus non-fatal) events. Cox regression was used to assess the effect of the ECG variables on the risk of incident CHD and total mortality. Age-adjusted hazard ratios (HR) with 95% confidence intervals are provided in Table 2 for the ECG variables, separately for men and women. Almost all of the key demographic, clinical, and electrocardiographic variables shown in Table 2 are significantly associated with the risk of incident CHD events and death.

The risk for incident CHD or total mortality associated with an abnormal QRS/T spatial or frontal angle was greater for women than for men. The hazard ratios decreased, as expected, in Cox regression models adjusted for demographic and clinical variables (Table 3). With adjustment for demographic and clinical characteristics, the spatial QRS/T angle was a strong predictor of incident CHD in women with a 114% increased risk, with no significant increase of CHD risk in men. Similarly, the frontal plane QRS/T angle was associated with a 74% increased risk of incident CHD in women, with no significant risk increase in men. In women as well as in men, both QRS/T angles were approximately equally strong predictors of total mortality, with an over 50% increased risk. After an additional adjustment for ST-T abnormalities in the risk models for the other ECG predictors, the risk of incident CHD and total mortality decreased slightly for both QRS/T angles, but remained significant. When all clinical and ST-T abnormalities were entered in a model that simultaneously included both QRS/T angles and spatial T wave axis, the spatial QRS/T angle retained significant predictive power for incident CHD and total mortality in women only. The frontal QRS/T angle had marginally significant HR for CHD incidence and total mortality for women. The spatial T wave axis was no longer significantly associated with CHD risk.

DISCUSSION

The key results from the present investigation from the multivariable-adjusted risk models demonstrate that spatial QRS/T angle is a significant, strong independent predictor of incident CHD in women, with a hazard ratio of 2.14 (95% confidence interval 1.62–2.82), but that it is not a significant predictor of incident CHD in men. The frontal plane QRS/T angle, when considered separately from the spatial QRS/T angle was equally predictive of total mortality and like the spatial QRS/T angle was predictive of incident CHD in women but not men. When both the spatial QRS/T and frontal QRS/T angle were considered together in a multivariable model, both were associated about equally with significantly increased risk of total mortality but for incident CHD only in women.

Normal repolarization in the free wall of the left ventricle occurs in reverse sequence to that of depolarization. However, in later phases of repolarization this relationship changes and as a consequence the spatial angle between the QRS and T axes is not zero, as would be expected if the whole repolarization process mirrored exactly the reverse of excitation. The QRS/T spatial angle in normal adult men and women is 68 degree (18). An abnormally wide angle indicates a patho-physiological change in ionic channel mechanisms in some myocardial region, and that in turn alters the regional sequence of ventricular repolarization. A number of previous studies have shown repeatedly that the repolarization abnormalities such as ST depression, T wave inversion and QT prolongation are significant and independent predictors for cardiac morbidity and mortality (19–29). More recently, there has been increasing interest in evaluation of the prognostic value of the spatial angle between the QRS and T vectors (1–8). A large QRS/T angle reflects an abnormal sequence of ventricular repolarization. Recently, Kardys et al (2–4) revealed that the spatial QRS/T angle was a strong and independent predictor of cardiac death and total mortality in 6,134 men and women aged 55 years and over from the Rotterdam Study in Netherlands. More recently, Rautaharju et al (6,7) evaluated the predictive value of the spatial QRS/T angle in 38,283 women in the Women's Health Initiative (WHI) participants, and demonstrated that a wide spatial QRS/T angle was the strongest predictor of

incident CHD events and total mortality. Yamazaki et al (8) also demonstrated in a large clinical population that the spatial QRS/T angle adjusted for age, gender and heart rate was a significant and independent predictor of cardiovascular mortality.

Although the spatial QRS/T angle could be incorporated in ECG reports by modern computer-based ECG machines, it is presently not generally available and most clinical users are not familiar with this measurement. In contrast, QRS and T axes are routinely reported, and the frontal plane QRS/T angle can be easily calculated from them. Both QRS/T angles were significant when considered jointly, therefore, the frontal plane QRS/T axis gives additional information and is a convenient substitute for the spatial QRS/T angle for identification of increased risk of incident CHD and death, especially in women.

The adoption of the frontal plane QRS/T angle index is a single independent addition for risk evaluation for clinicians. Regardless of other abnormalities (including ST-T wave abnormalities) an abnormal frontal plane QRS/T angle (≥ 73 degrees for men and ≥ 67 degrees for women) confers an added increase in risk of future CHD. This in turn should assist the clinician in instituting vigorous risk factor reduction behavior or further diagnostic testing.

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Table 1
Baseline Characteristics of the Study Population Including Key Demographic, Clinical and Electrocardiographic Variables of Interest by Gender

Variables	All Participants (N=13,973)	Men (N=5,908)	Women (N=8,065)	P Value ⁶
Percent (%)				
Gender (Women)	57.7%			
Race (Black)	26.7%	22.9%	29.6%	<0.001
Hypertension ¹	33.4%	32.1%	34.4%	0.004
Diabetes Mellitus	10.9%	10.7%	11.1%	0.406
Angina Pectoris by Rose questionnaire	4.2%	2.5%	5.4%	<0.001
LVH by Cornell Voltage ²	2.1%	2.6%	1.8%	0.001
Major_ST Depression ³	1.2%	1.3%	1.2%	0.710
Major_STT Abnormality ³	4.2%	3.5%	4.7%	<0.001
Mean + Standard Deviation				
Age (years)	54.4±5.7	54.8±5.8	54.2±5.7	<0.001
Heart Rate (beats/per min)	66.4±10.2	64.7±10.2	67.6±10.1	<0.001
QTrr (ms)	415.1±15.8	414.1±13.9	415.9±17.1	<0.001
Frontal plane QRS axis (degree) ⁵	30.9±31.6	27.6±33.0	33.3±30.3	<0.001
Frontal plane T axis (degree) ⁵	37.9±28.6	36.3±30.1	39.1±27.4	<0.001
QRS/T_{Spatial} (degree)				
At 75 th , 90 th , 95 th percentiles ⁷	84, 104, 117	93, 112, 123	77, 96, 110	
All Participants	67.2±28.0	75.2±27.7	61.4±26.8	<0.001
Black ⁸	69.1±31.0	81.8±29.1	61.8±29.7	<0.001
White ⁸	66.5±26.8	73.2±27.0	61.2±25.5	<0.001
QRS/T_{Frontal} (degree)				
At 75 th , 90 th , 95 th percentiles ⁷	31, 51, 69	32, 54, 73	31, 50, 67	
All Participants	23.9±24.0	24.7±25.1	23.3±23.1	0.001
Black ⁸	26.0±27.8	26.9±29.2	25.5±27.0	0.118
White ⁸	23.1±22.3	24.1±23.7	22.3±21.1	<0.001
T wave Axis_{Spatial} (degree)				
At 75 th , 90 th , 95 th percentiles ⁷	32, 43, 54	32, 41, 51	32, 45, 56	
All Participants	26.0±16.1	25.8±14.4	26.1±17.3	0.377
Black ⁸	31.8±18.9	32.3±17.4	31.4±19.8	0.158
White ⁸	23.8±14.4	23.9±12.8	23.8±15.6	0.793

(1) Note: Hypertension at baseline (Systolic blood pressure \geq 140 or diastolic blood pressure \geq 90), or on antihypertensive medication.

(2) Left Ventricular Hypertrophy by Cornell Voltage (CV = RaVL + SV3): LVH_CV cut point at CV \geq 2200 for Women, and CV \geq 2600 for Men.

- (3) Major ST Depression: Minnesota Code in 4.1 or 4.2. Major_STT Abnormality: Minnesota Code in 5.1 or 5.2; or 4.1 or 4.2;
- (4) The ECG variables were categorized as: abnormal ($\geq 95^{\text{th}}$ percentile), borderline ($\geq 75^{\text{th}}$ and $< 95^{\text{th}}$ percentile), and normal ($< 75^{\text{th}}$ percentile), separately for men and women.
- (5) For Frontal plane QRS-axis or Frontal plane T-axis from the GE Marquette Program.
- (6) For significant statistical test between men and women.
- (7) The values of spatial QRS/T angle, frontal QRS/T angle and T wave axis at 75^{th} , 90^{th} , 95^{th} percentiles.
- (8) Among total 13,973 participants, 10,236 for White (45.5% for Men and 55.5% for Women), and 3,737 for Black (36.2% for Men and 63.8% for Women)

Table 2

Age-adjusted Hazard Ratios and 95% Confidence Intervals of QRS/T Angles and Selected Electrocardiographic and Key Clinic Variables for Incident Coronary Heart Disease and All-cause Mortality

Variables	Incident CHD		Total Mortality	
	Men N=1018/5908	Women N=609/8065	Men N=927/5908	Women N=866/8065
(Adjusted for age)				
Male- vs. - Female	2.31 (2.09–2.56)		1.43 (1.30–1.57)	
Black - vs. - N-Black	0.91 (0.79–1.07)	1.46 (1.24–1.73)	2.02 (1.76–2.31)	1.97 (1.72–2.25)
Hypertension (Yes vs. No)	1.54 (1.36–1.74)	2.31 (1.96–2.71)	1.73 (1.52–1.97)	1.87 (1.63–2.14)
Diabetes Mellitus (Yes vs. No)	2.42 (2.08–2.83)	3.82 (3.21–4.53)	2.01 (1.71–2.37)	3.15 (2.71–3.65)
Angina Pectoris by Rose questionnaire (Yes vs. No)	2.29 (1.74–3.02)	1.91 (1.47–2.50)	2.08 (1.55–2.78)	1.61 (1.27–2.04)
LVH by Cornell Voltage (Yes vs. No)	1.30 (0.92–1.85)	3.30 (2.31–4.72)	1.82 (1.33–2.50)	3.06 (2.26–4.13)
Heart Rate (per 10 beats)	1.13 (1.07–1.20)	1.31 (1.21–1.41)	1.30 (1.23–1.38)	1.34 (1.26–1.42)
QT _{Tr} (per SD [§])	1.05 (0.98–1.11)	1.12 (1.05–1.19)	1.18 (1.11–1.26)	1.13 (1.08–1.19)
QRS/T _{Spatial} (per SD [§])	1.16 (1.09–1.23)	1.47 (1.37–1.57)	1.21 (1.14–1.29)	1.36 (1.28–1.45)
QRS/T _{Frontal} (per SD [§])	1.12 (1.05–1.18)	1.27 (1.20–1.35)	1.20 (1.14–1.26)	1.27 (1.21–1.34)
T _{Axis} _{Spatial} (per SD [§])	1.16 (1.10–1.22)	1.14 (1.07–1.22)	1.21 (1.15–1.27)	1.22 (1.16–1.28)
Heart Rate - Increase vs. Normal [‡]	1.58 (1.22–2.05)	2.54 (1.96–3.29)	2.85 (2.32–3.51)	2.52 (2.04–3.12)
QT _{Tr} - Prolongation vs. Normal [‡]	1.27 (0.91–1.78)	1.77 (1.26–2.50)	2.00 (1.45–2.74)	1.59 (1.20–2.10)
Major_STT abnormality [*]	1.94 (1.48–2.54)	2.28 (1.72–3.01)	2.66 (2.09–3.37)	2.64 (2.13–3.28)
QRS/T _{Spatial} - Abnormal vs. Normal [‡]	1.59 (1.24–2.04)	3.87 (3.08–4.84)	2.16 (1.73–2.70)	3.08 (2.51–3.78)
QRS/T _{Frontal} - Abnormal vs. Normal [‡]	1.63 (1.28–2.08)	2.52 (1.95–3.25)	2.30 (1.86–2.84)	2.57 (2.09–3.16)
T _{Axis} _{Spatial} - Abnormal vs. Normal [‡]	1.84 (1.44–2.35)	1.61 (1.19–2.19)	2.43 (1.97–3.01)	2.02 (1.60–2.55)

Note: Incident-CHD: including incident MI, ECG MI, non-fatal CHD or Fatal CHD.^{*} Major_STT abnormality: MC in 5.1 or 5.2; or 4.1 or 4.2; Minor_STT abnormality: MC in 5.3 or 5.4, or 4.3 or 4.4.[‡] The ECG variables were categorized as: abnormal ($\geq 95^{\text{th}}$ percentile), borderline ($\geq 75^{\text{th}}$ and $< 95^{\text{th}}$ percentile), and normal ($< 75^{\text{th}}$ percentile), separately for men and women.[§]SD = Standard Deviation;

Table 3
Hazard Ratios and 95% Confidence Intervals of QRS/T Angles and Selected Electrocardiographic and Key Clinic Variables for Incident Coronary Heart Disease and All-cause Mortality (Multivariable Model)

Variables	Incident CHD		Total Mortality	
	Men	Women	Men	Women
Multivariable (Adjusted for Clinical[*])				
QRS/T _{Spatial} - Abnormal vs. Normal [‡]	1.22 (0.92–1.62)	2.14 (1.62–2.82)	1.54 (1.20–1.99)	1.67 (1.30–2.15)
QRS/T _{Frontal} - Abnormal vs. Normal [‡]	1.15 (0.86–1.52)	1.74 (1.29–2.34)	1.58 (1.23–2.02)	1.62 (1.26–2.09)
T_Axis _{Spatial} - Abnormal vs. Normal [‡]	1.31 (0.98–1.76)	1.11 (0.78–1.57)	1.63 (1.26–2.11)	1.36 (1.03–1.80)
Major_STT abnormality (MC_4 or MC_5)	1.17 (0.85–1.61)	1.43 (1.03–1.99)	1.63 (1.23–2.16)	1.59 (1.22–2.07)
Multivariable (Adjusted for Clinical[*] and additional ECG variables)				
<i>Adjustment for Clinical[*] and STT abnormality (MC_4 or MC_5)</i>				
QRS/T _{Spatial} - Abnormal vs. Normal [‡]	1.18 (0.87–1.61)	2.22 (1.63–3.01)	1.33 (1.00–1.79)	1.53 (1.15–2.04)
QRS/T _{Frontal} - Abnormal vs. Normal [‡]	1.09 (0.78–1.51)	1.71 (1.23–2.39)	1.37 (1.03–1.83)	1.46 (1.10–1.95)
T_Axis _{Spatial} - Abnormal vs. Normal [‡]	1.33 (0.91–1.93)	0.79 (0.50–1.27)	1.39 (0.98–1.99)	1.01 (0.69–1.47)
<i>Adjustment for Clinical[*], STT abnormality, and all QRS/T angles and T Wave Axis in simultaneously</i>				
QRS/T _{Spatial} - Abnormal vs. Normal [‡]	1.10 (0.79–1.54)	2.07 (1.48–2.89)	1.17 (0.85–1.62)	1.42 (1.04–1.95)
QRS/T _{Frontal} - Abnormal vs. Normal [‡]	1.03 (0.72–1.46)	1.31 (1.00–1.88)	1.27 (0.93–1.73)	1.26 (1.00–1.73)
T_Axis _{Spatial} - Abnormal vs. Normal [‡]	1.28 (0.87–1.89)	0.67 (0.42–1.08)	1.28 (0.88–1.87)	0.91 (0.62–1.34)

Note: Incident-CHD: including incident ECG myocardial infarction, non-fatal CHD or Fatal CHD.

#Age is used as the time scale in the multivariable models and birth cohort is used as a stratification factor

* Adjusted for Clinical variables: By the key demographic and clinical variables: gender, race, body mass index, education, family history of stroke, family history of CHD, smoking status, alcohol use, asthma, cancer, diabetes mellitus, hypertension, Rose angina, Rose intermittent claudication, sport index, forced expiratory volume (FEV1), high density lipoprotein, high density lipoprotein, total triglycerides, total cholesterol, systolic blood pressure, diastolic blood pressure, hematocrit, white blood cell, total calories, dietary cholesterol, ankle brachial index, baseline fasting blood glucose, insulin, creatinine, fibrinogen, and uric acid.

‡ The ECG variables were categorized as: abnormal ($\geq 95^{\text{th}}$ percentile), borderline ($\geq 75^{\text{th}}$ and $< 95^{\text{th}}$ percentile), and normal ($< 75^{\text{th}}$ percentile), separately for men and women.