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Electrocardiograms of Menopausal Women With Coronary Heart Disease or at Increased Risk for Its Occurrence

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Abstract

Little is known about electrocardiographic (ECG) characteristics of menopausal women with or at increased risk of coronary heart disease (CHD). Data from 10,101 participants in the Raloxifene Use for The Heart (RUTH) trial were used to correlate baseline ECG abnormalities with clinical characteristics. Baseline characteristics that were statistically significantly associated ($p \leq 0.05$) with ECG findings in univariate analyses were used to derive multivariate model selection. Of 59% normal electrocardiograms, 50% were from women with CHD and 69% from women at increased risk of CHD. In the women with CHD, 59% reported a previous myocardial infarction (MI); 43% had a normal electrocardiogram, and 49% had a definite ECG Q-wave MI. Women in the increased-risk group had not reported a previous MI, yet 11% had a definite ECG Q-wave MI. Of women reporting hypertension, 35% had ECG evidence of left ventricular hypertrophy, but 58% did not have an abnormal electrocardiogram. Significantly more women with diabetes in the increased-risk and documented CHD cohorts had abnormal electrocardiograms ($p < 0.01$ for the 2 cohorts). Percent abnormal electrocardiograms increased with increasing age (55 to 64, 65 to 74, and ≥ 75 years, $p < 0.01$) in all cohorts. Angina and coronary artery bypass graft surgery, but not percutaneous coronary intervention, predicted an abnormal electrocardiogram. In conclusion, there were high percentages of normal electrocardiograms in the increased-risk and documented CHD groups of RUTH participants, with substantial discrepancy between MI history and ECG MI

documentation, and increasing age was the predominant correlate with an abnormal electrocardiogram in all 3 cohorts.

Limited information is available about electrocardiographic (ECG) characteristics of menopausal women with documented coronary heart disease (CHD) or at increased risk of CHD. The Raloxifene Use for The Heart (RUTH) study offers a database for correlation of baseline ECG abnormalities with clinical characteristics of the study population. The objective of the RUTH trial was to ascertain whether raloxifene 60 mg/day versus placebo decreased the occurrence of coronary death, nonfatal myocardial infarction (MI), hospitalization due to acute coronary syndrome, and invasive breast cancer. Study results were previously published.¹ Briefly, raloxifene decreased the incidence of invasive breast cancer but had no significant effect on coronary events. The purpose of the present study was to ascertain the relation of baseline ECG abnormalities to coronary risk characteristics and previous coronary events, with particular attention to MI, hypertension, and age, to assess whether ECG abnormalities offer added clinical value.

Methods

The RUTH trial enrolled 10,101 women (≥ 55 years old) at 177 sites in 26 countries. Participants were 5,070 women with increased risk of CHD and 5,031 women with documented CHD. Characteristics of the RUTH population are presented in Table 1 and described in detail elsewhere.²

Documented CHD required evidence of MI, myocardial revascularization, or angina with $\geq 50\%$ angiographic obstruction of a major coronary artery. Increased CHD risk status required 4 points using a predefined scale that encompassed older age, diabetes mellitus, hypertension, hyperlipidemia, and current cigarette smoking (Table 2).

A 12-lead baseline electrocardiogram was recorded for all women randomly assigned to treatment in RUTH; electrocardiograms were available for 10,087 women (99.9%). Of these, 178 were not assessable and were excluded from analysis, leaving 9,909 electrocardiograms (98%) in the present analyses (total cohort). Electrocardiograms were assessed for 5 variables: definite Q-wave MI, pathological ST-T changes (not ST-T changes associated with ventricular hypertrophy), conduction disturbances, atrial fibrillation and/or atrial flutter, and left ventricular hypertrophy (LVH). Criteria for ECG abnormalities are listed in Table 3. If all 5 abnormalities were absent, electrocardiograms were classified as normal. All electrocardiograms were read manually by 1 electrocardiographer (RS) who was blinded to patient data and were archived at the central ECG laboratory.

Chi-square tests were used to analyze ECG findings with respect to baseline characteristics. Reported p values are 2-sided. All continuous variables were defined as categorical, using widely accepted breakpoints or by calculating tertiles. Baseline characteristics that were statistically significantly associated with ECG findings at an alpha level equal to 0.05 in univariate analyses were considered for multivariate model selection. Logistic regression with stepwise model selection was used to determine potential predictors of abnormal electrocardiograms, with an alpha value equal to 0.10 used as the criterion for variables to enter and stay in the model at each step. Correlated variables, such as diabetes status and fasting glucose, were not included in the same model to avoid multicollinearity. Models were generated for overall abnormal electrocardiograms and for each major abnormality category. All statistical analyses were conducted for the documented CHD cohort, the increased-risk cohort, and the total cohort. Analyses were performed using SAS 8.2 or a subsequent version (SAS Institute, Cary, North Carolina).

Results

In the total cohort, 59% of women had a normal electrocardiogram; 69% of the increased-risk population and 50% of women with documented CHD had normal electrocardiograms ($p < 0.01$). Statistically significant differences between the increased-risk and documented CHD cohorts were found for definite Q-wave MI (higher for documented CHD), overall conduction disturbances (greater in the increased-risk cohort for left anterior fascicular block), atrial fibrillation and/or flutter (higher rates in the increased CHD risk cohort), and presence of LVH (larger proportion of the increased-risk cohort, $p < 0.01$ for all).

Age was categorized as 55 to 64, 65 to 74, and ≥ 75 years. Abnormal electrocardiograms increased with increasing age in all 3 cohorts ($p < 0.01$ for all; Table 4). Age-related ECG abnormalities included conduction disturbances and atrial fibrillation ($p < 0.01$) for the total cohort and documented CHD cohort ($p = 0.01$ for the 2 comparisons in increased-risk cohort). Pathologic ST-T depression decreased with increasing age in the total cohort ($p = 0.01$) and documented CHD cohort ($p < 0.01$). These disparities were equally apparent when age was categorized as ≥ 70 or < 70 years; LVH was not age-related.

Women in the documented CHD cohort reporting a previous MI were more likely to have an abnormal electrocardiogram (Table 5) and to have specific ECG abnormalities: definite Q-wave MI, pathologic ST-T depression, conduction disturbances, atrial fibrillation or flutter ($p < 0.01$ for all), and LVH ($p < 0.01$). Of the 57% in the documented CHD cohort reporting a previous MI, 43% had a normal electrocardiogram, 49% had definite ECG Q-wave MI, 15% had pathologic ST-T depression, and 28% had conduction disturbances. However, in the increased-risk cohort (with no reported previous MI), 31% had an abnormal electrocardiogram, 11% had definite Q-wave MI, 18% had pathologic ST-T depression, and 42% had conduction disturbances. LVH was present in 37%.

Women with previous coronary artery bypass grafting (CABG; 33% of documented CHD group) had a greater likelihood of abnormal electrocardiogram ($p < 0.01$) and definite Q-wave MI ($p < 0.01$), conduction disturbances ($p < 0.01$), and atrial fibrillation or flutter ($p < 0.01$). Previous percutaneous coronary intervention (34% of documented CHD group) did not significantly affect ECG normality, although patients with abnormal electrocardiograms and previous percutaneous coronary intervention were more likely to have a definite Q-wave MI ($p < 0.01$); patients without percutaneous coronary intervention were more likely to have conduction disturbances ($p = 0.01$), atrial fibrillation and/or flutter ($p = 0.01$), and LVH ($p < 0.01$).

In the documented CHD group, 66% of patients reported previous angina pectoris and were more likely to have an abnormal electrocardiogram ($p < 0.01$), specifically definite Q-wave MI ($p < 0.01$), pathologic ST-T depression ($p < 0.01$), conduction disturbances ($p < 0.01$), atrial fibrillation and/or flutter ($p < 0.01$), and LVH ($p < 0.01$).

History of systemic hypertension was reported by 85% of patients in the increased-risk cohort and 71% in the documented CHD cohort. These patients were more likely to have an abnormal electrocardiogram ($p < 0.01$), atrial fibrillation and/or flutter ($p < 0.01$), and LVH ($p < 0.01$) and were less likely to have definite Q-wave MI ($p < 0.01$). Of women reporting hypertension, 58% did not have abnormal electrocardiograms; only 1/3 of hypertensive patients with abnormal electrocardiograms (15% of all hypertensive patients) had ECG evidence of LVH, 40% in the increased-risk cohort and 32% in the documented CHD cohort. In the increased-risk and documented CHD groups, increased systolic blood pressure (categorized as ≤ 136.5 , ≤ 151.5 , and > 151.5 mm Hg) was significantly associated with abnormal electrocardiogram and LVH ($p < 0.01$ for the 2 comparisons). Increased definite Q-wave MI was also associated with increased systolic blood pressure in the documented

CHD cohort ($p = 0.01$) but not in the increased-risk cohort. Of patients with abnormal electrocardiograms, LVH was present in 25% of patients in the lowest systolic blood pressure tertile, in 31% in the mid tertile, and in 40% in the highest tertile. The only relation observed between diastolic blood pressure (categorized as ≤ 78 , ≤ 85 , and > 85 mm Hg) and abnormal electrocardiograms was a greater likelihood of LVH with increasing diastolic blood pressure ($p < 0.01$ for all comparisons). In patients with abnormal electrocardiograms, LVH was present in 28% of the lowest diastolic blood pressure tertile, 30% of the mid tertile, and 39% of the highest tertile.

Diabetes mellitus was reported by 46% of patients in the overall cohort, 64% at increased risk, and 27% with documented CHD. Patients without diabetes having abnormal electrocardiograms were more likely to have definite Q-wave MI ($p < 0.01$). Patients with diabetes were more likely to have conduction disturbances ($p = 0.01$), atrial fibrillation or flutter ($p = 0.01$), and LVH ($p < 0.01$). There were significantly more abnormal electrocardiograms for patients with diabetes in the increased-risk ($p = 0.01$) and documented CHD ($p < 0.01$) cohorts; however, atrial fibrillation or flutter was not statistically significant in the increased-risk and documented CHD cohorts despite differences in the overall cohort. Baseline increased fasting glucose level (> 7.8 ml/L) was more likely to be associated with abnormal electrocardiogram ($p = 0.01$) and with pathologic ST-T depression ($p = 0.01$), LVH ($p = 0.01$), atrial fibrillation or flutter ($p = 0.01$), and decreased definite Q-wave MI ($p < 0.01$). Increased hemoglobin A_{1c} was associated with a greater likelihood of abnormal electrocardiogram, decreased Q-wave MI, and increased LVH ($p < 0.01$ for all comparisons).

Increased total cholesterol and low-density lipoprotein failed to predict ECG abnormalities except in patients with documented CHD ($p = 0.01$). High levels of high-density lipoprotein cholesterol were more likely to be associated with a normal electrocardiogram (all cohorts, $p < 0.01$). Increased triglyceride levels were more likely to be associated with an abnormal electrocardiogram ($p < 0.01$), pathologic ST-T depression ($p = 0.01$), and LVH ($p < 0.01$). Increased triglycerides were also associated with decreased definite Q-wave MI ($p < 0.01$) and conduction disturbances ($p = 0.03$) in patients with abnormal ECG findings.

Body mass index ≥ 27 kg/m² was reported in 60% of the total cohort; body mass index categorized as < 25 , < 30 , and ≥ 30 kg/m² did not correlate with ECG abnormalities, even when categorized as ≥ 27 versus < 27 kg/m². Although no between-cohort differences in the association of abnormal electrocardiograms and body mass index were observed, there was a statistically significant increase in Q-wave MI in patients with body mass index < 25 kg/m² ($p = 0.01$). These findings were consistent when body mass index was categorized as ≥ 27 or < 27 kg/m². Increased waist circumference correlated only to decreased definite Q-wave MI ($p < 0.01$) when divided into ≤ 89 -, ≤ 97.5 -, and > 97.5 -cm tertiles, which is consistent with the present MI findings related to body mass index, which are counterintuitive.

In the total cohort, 12% of patients were current smokers and 26% reported exposure to secondary smoke. Current smoking was associated with a greater likelihood of abnormal electrocardiogram ($p < 0.01$); exposure to secondary smoke exerted no influence. Increased abnormal electrocardiograms occurred in patients who consumed ≥ 1 drink/week compared to < 1 drink/week ($p < 0.01$). No specific ECG abnormality was statistically significantly different between alcohol drinkers and nondrinkers.

There was no direct relation between intensity of physical activity and ECG abnormalities; minimally demanding and highly demanding physical activities were less likely to be associated with a normal electrocardiogram than moderately demanding activities in the overall cohort ($p < 0.01$). When categorized as ≤ 2 or > 2 weekly episodes of vigorous

physical activity, those without such activity were more likely to have abnormal electrocardiogram; this finding was consistent in all 3 cohorts, particularly so in the documented CHD group ($p < 0.01$). There was a significant relation between cardiac rehabilitation and abnormal electrocardiograms in the total cohort ($p < 0.01$), but not in the increased-risk cohort or documented CHD cohort. However, for women with abnormal electrocardiograms, cardiac rehabilitation was more prominently associated with definite Q-wave MI ($p < 0.01$).

Mean number of years after menopause was 19.4. Increased number of years after menopause (categorized as ≤ 16 , ≤ 22 , and > 22 years) was more likely to be associated with an abnormal electrocardiogram, but this finding (and an association with conduction disturbances and atrial fibrillation or flutter) may be a surrogate for older age and not related to menopausal influence. In an exploratory analysis, age and years after menopause were found to have a high Pearson correlation coefficient of 0.729 ($p < 0.01$). Indeed, ECG findings for years after menopause mirror those for increasing age. Hysterectomy was reported by 23% of patients; hysterectomy status was unrelated to ECG abnormality.

Increased heart rate (divided into tertiles ≤ 67 , ≤ 74 , and > 74 beats/min) was not related to abnormal electrocardiogram in general; however, increased heart rate was associated with an increase in atrial fibrillation or flutter ($p < 0.01$ for all cohorts) and with a decrease in conduction disturbances in the total cohort ($p = 0.02$) and in the documented CHD cohort ($p = 0.01$).

In the total, increased-risk, and documented CHD cohorts, aspirin use was reported by 58%, 32%, and 84% of patients, and lipid-lowering drug therapy was reported by 54%, 40%, and 68% of patients, respectively. Aspirin use was more likely to be associated with an abnormal electrocardiogram ($p < 0.01$), definite Q-wave MI ($p < 0.01$), and pathologic ST-T depression ($p < 0.01$) and was less likely to be associated with conduction disturbance ($p < 0.01$) and atrial fibrillation and/or flutter ($p < 0.01$). Lipid-lowering drug therapy was more likely to be associated with definite Q-wave MI ($p < 0.01$) and pathologic ST-T depression ($p < 0.01$) and less likely with conduction disturbances ($p = 0.01$), atrial fibrillation and/or flutter ($p < 0.01$), and LVH ($p < 0.01$). Beta blockers were used by 47%, 31%, and 65% of patients and calcium antagonists were used by 34%, 34%, and 35% of patients in the total, increased-risk, and documented CHD cohorts, respectively. Beta blockers were more likely to be associated with an abnormal electrocardiogram ($p < 0.01$), definite Q-wave MI ($p < 0.01$), and pathologic ST-T depression ($p = 0.02$) and were less likely to be associated with conduction disturbances ($p < 0.01$). Calcium antagonists were slightly more likely to be associated with an abnormal electrocardiogram ($p = 0.03$) and less likely to be associated with definite Q-wave MI ($p < 0.01$). Diuretic use, reported by 35% of the total cohort, 35% of those at increased risk, and 34% with documented CHD, was more likely to be associated with an abnormal electrocardiogram, atrial fibrillation and/or flutter, and LVH ($p < 0.01$ for all). Angiotensin-converting enzyme inhibitors were used by 41% of the total population, 45% of those at increased risk, and 38% with documented CHD; in patients with diabetes, the rates were 22%, 49%, and 49%, respectively. Use of angiotensin-converting enzyme inhibitors was more likely to be associated with an abnormal electrocardiogram ($p < 0.01$), pathologic ST-T disturbance ($p = 0.01$), atrial fibrillation or flutter ($p = 0.01$), and LVH ($p < 0.01$). Patients with and those without diabetes had comparable findings for association of angiotensin-converting enzyme with abnormal electrocardiograms (with or without diabetes, $p < 0.01$), pathologic ST-T depression (with diabetes, $p < 0.01$; without diabetes, $p = 0.01$), and LVH (with or without diabetes, $p < 0.01$). In patients without diabetes, use of angiotensin-converting enzyme was associated with increased rates of definite Q-wave MI ($p < 0.01$) and atrial fibrillation and/or flutter ($p = 0.02$). Selection bias (Table 2) could have confounded between-group differences in this cross-sectional analysis.

In an examination of characteristics predictive of abnormal ECG findings, the following were most prominent: for the total cohort, previous MI, previous CABG, and age; for the increased-risk cohort, age, diabetes, and hypertension; and for the documented CHD cohort, previous MI, previous CABG, increased fasting glucose, and age (Table 6).

In the total cohort, previous MI and previous angina best predicted ECG evidence of definite Q-wave MI. In the increased-risk cohort, smoking was a predictor of definite Q-wave MI, along with negatively associated diabetes and low-density lipoprotein cholesterol. In women with documented CHD, previous MI was the predominant predictor followed by previous angina (Table 7).

Atrial fibrillation and/or flutter were strongly predicted by heart rate in all patient groups. In the total cohort, important predictors also included age, high-density lipoprotein, and hypertension, with a negative association with previous angina and previous MI. In the increased-risk group, age was also an important predictor, as was high-density lipoprotein cholesterol. In the documented CHD group, age and hypertension were also important predictors (Table 7).

Systolic blood pressure was an important predictor of LVH in all 3 cohorts. In the total cohort, there was important predictive value for hypertension, diabetes, and triglyceride levels; in the increased risk group, hypertension and diabetes were also predictors (Table 7).

Discussion

A larger percentage of women (59% of total cohort, 69% at increased risk of CHD, and 50% with documented CHD) had normal baseline electrocardiograms, illuminating the lack of reassurance offered by a normal electrocardiogram for absence of coronary risk or established CHD.

Previous MI and CABG surgery were more significant determinants of ECG abnormality in the total and documented CHD cohorts; however, about 43% of women in the total cohort who reported previous MI had a normal electrocardiogram and <50% with abnormal electrocardiogram had definite Q-wave MI. This finding was not surprising given the predominance of non-ST-segment elevation (non-Q-wave) MI in women. Importantly, in patients at increased risk of CHD, 11% had a definite Q-wave MI, likely representing silent or unrecognized MI. There was a similar finding in the Framingham Study, in which women 55 to 94 years of age had a 30% to 45% occurrence of unrecognized MI.³ Patients with previous angina pectoris were also more likely to have an abnormal electrocardiogram and definite Q-wave MI, raising the question of silent or unrecognized MI. Of note, in the documented CHD cohort of this study, angina, MI, percutaneous coronary intervention, and CABG were not mutually exclusive and frequently overlapped.

Previous CABG, known to be associated with increased atherosclerotic burden, predicted a greater likelihood of abnormal electrocardiogram and definite Q-wave MI; in contrast, previous percutaneous coronary intervention did not significantly alter ECG abnormality. Percutaneous coronary intervention is more often performed earlier in the clinical course of atherosclerotic coronary disease than CABG, which may explain this difference. Of 368,000 women in the dietary modification trial of the Women's Health Initiative, those with baseline cardiovascular disease were more likely to have ST-T and repolarization changes (Cornell voltage LVH) than women without cardiovascular disease.⁴

In the RUTH trial, women with a history of systemic hypertension at baseline were more likely to have abnormal ECG findings, particularly LVH, which was evident in the increased-risk and documented CHD cohorts. More women at increased risk of CHD were

likely to have hypertension, reflecting the point system for selection criteria for this cohort, which oversampled risk factors. Even so, >50% of women in the increased-risk cohort who reported hypertension did not have an abnormal electrocardiogram; only 35% of them (representing 15% of all hypertensive patients) had ECG evidence of LVH. This finding confirms the well-known lack of sensitivity of electrocardiography for the presence of LVH, despite its relatively high specificity. With and without LVH, women have lower QRS voltages and shorter QRS durations than men.⁵ In apparently healthy menopausal women in the Women's Health Initiative, LVH indexes were derived from computer measurements for hypertrophied left ventricular mass, Cornell voltage, and Minnesota Code items. Age and factors associated with metabolic syndrome were related to these indexes.⁶ The increase in ECG LVH associated with increasing systolic blood pressure likely reflects a greater degree of LVH associated with higher systolic blood pressure levels. LVH correlated with tertile of diastolic blood pressure, without correlation between diastolic blood pressure and other ECG abnormalities.

Diabetes mellitus was also over-represented in the increased-risk cohort owing to selection criteria. The predominance of definite Q-wave MI in patients with abnormal electrocardiograms who did not have diabetes is counterintuitive. Increased baseline fasting glucose was more likely associated with an abnormal electrocardiogram, a finding not concordant with the diabetes data. In this study, of interest is the high prevalence of LVH in women with diabetes, increased fasting glucose, and abnormal hemoglobin A_{1c}; an association has been reported previously among LVH, diabetes, abnormal glucose tolerance, and insulin levels.⁷

ECG associations with increased total cholesterol levels are likely substantially confounded by concomitant lipid-altering therapies, including statins. Increased high-density lipoprotein is postulated as more protective for women and in this study was associated with normal electrocardiograms. Increased triglycerides impose greater risk for women and in this study were associated with an abnormal electrocardiogram.

Anomalous findings include the increase in Q-wave MI in the lowest body mass index subgroup and the decreasing risk of Q-wave MI with increasing waist circumference. Smoking had an expected association with greater likelihood of abnormal electrocardiogram. No ECG abnormality was statistically significantly different between women who consumed ≥ 1 versus < 1 alcoholic drink/week. Physical activity data suggested that the lowest levels were more likely associated with an abnormal electrocardiogram, buttressing the potential benefit of physical activity. The association of cardiac rehabilitation with abnormal electrocardiogram may reflect a referral bias because cardiac rehabilitation is also more prominently associated with definite Q-wave MI.

The increased association of aspirin use with abnormal electrocardiogram and definite Q-wave MI is concordant with clinical practice guidelines. The negative correlation of aspirin use with atrial fibrillation and/or flutter may reflect warfarin (and, consequently, less aspirin) use. That lipid-lowering drugs were more likely associated with definite Q-wave MI and less likely associated with atrial fibrillation and LVH may reflect increased prescription of such drugs in the documented CHD cohort compared to the increased-risk cohort (68% vs 40%, respectively). Beta-blocker use was more likely associated with an abnormal electrocardiogram and definite Q-wave MI, which likely reflects adherence to clinical practice guidelines, as does the use of calcium antagonists. These 2 medications may also be used to treat hypertension. The association of angiotensin-converting enzyme inhibitors with abnormal electrocardiogram may reflect its increased use in patients with diabetes, particularly in the documented CHD cohort. It is uncertain what proportion of angiotensin-converting enzyme inhibitor use is for coronary versus hypertension treatment. The

association of abnormal electrocardiogram and LVH with hypertension may also reflect the use of diuretic medication.

Increasing age was a powerful determinant of ECG abnormality in the total cohort, the major determinant in the increased-risk group, and a feature in the documented CHD cohort. An exploratory analysis of years after menopause and age showed these to be highly correlated, so much so that years after menopause may be a surrogate for age. Previous hormone therapy was more likely associated with a normal electrocardiogram, potentially reflecting a cardio-protective effect. That age is highly predictive of atrial fibrillation and/or flutter is well-established in the clinical literature.

In menopausal women enrolled in the RUTH trial, ECG abnormalities were only modestly associated with clinical characteristics of CHD and increased risk of CHD and with previous MI, previous CABG, and previous percutaneous coronary intervention. The ECG findings substantially underestimated presence of MI, although an ECG Q-wave MI likely indicated an undiagnosed coronary event in women at increased risk of CHD, particularly in women who smoke and in those with angina. Increasing age was the factor most highly associated with abnormal electrocardiograms.

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Table 1

Baseline characteristics of RUTH participants

Variable	All Patients (n = 10,101)	Increased CHD Risk (n = 5,070)	Documented CHD (n = 5,031)
Age (years)	67.6 ± 6.7	67.5 ± 6.8	67.6 ± 6.5
Age ≥70 years	3,931 (39%)	2,033 (40%)	1,898 (38%)
Height (cm)	158.0 ± 6.8	157.6 ± 6.8	158.5 ± 6.8
Weight (kg)	71.9 ± 13.9	72.9 ± 14.7	70.9 ± 12.9
Body mass index (kg/m ²)	28.8 ± 5.1	29.3 ± 5.5	28.2 ± 4.8
Body mass index ≥27 kg/m ²	5,994 (60%)	3,185 (63%)	2,809 (56%)
Waist circumference (cm)	93.9 ± 13.2	95.5 ± 13.5	92.2 ± 12.6
Systolic blood pressure (mm Hg)	146 ± 21	147 ± 20	144 ± 21
Diastolic blood pressure (mm Hg)	82 ± 10	83 ± 10	81 ± 10
Heart rate (beats/min)	71 ± 10	73 ± 10	69 ± 11
Ethnicity			
Caucasian	8,481 (84%)	4,128 (81%)	4,353 (87%)
Hispanic	520 (5%)	414 (8%)	106 (2%)
East Asian	505 (5%)	246 (5%)	259 (5%)
Afro-Caribbean	129 (1%)	75 (1%)	54 (1%)
West Asian	77 (1%)	23 (<1%)	54 (1%)
Other	391 (4%)	181 (4%)	210 (4%)
Current smoker	1,256 (12%)	884 (17%)	372 (7%)
Exposure to secondary smoke	2,598 (26%)	1,359 (27%)	1,239 (25%)
Alcohol consumption			
≥1 drink/week	1,746 (17%)	770 (15%)	976 (19%)
<1 drink/week	2,581 (26%)	1,262 (25%)	1,319 (26%)
None	5,329 (57%)	3,034 (60%)	2,295 (54%)
Physical activity at work/leisure			
High	808 (8%)	403 (8%)	405 (8%)
Moderate	5,350 (53%)	2,615 (52%)	2,735 (55%)
Minimum	3,937 (39%)	2,013 (40%)	1,924 (38%)
Vigorous activity >2 times/week	2,477 (25%)	1,092 (22%)	1,385 (28%)
History of cardiac rehabilitation	1,462 (14%)	136 (3%)	1,326 (26%)
Number of years postmenopausal	19.4 ± 8.8	19.1 ± 9.0	19.7 ± 8.6
Hysterectomy	2,319 (23%)	1,180 (23%)	1,139 (23%)
Previous use			
Estrogen replacement therapy	1,399 (14%)	603 (12%)	796 (16%)
Estrogen/progestin replacement therapy	605 (6%)	301 (6%)	304 (6%)
Oral contraceptives	1,930 (19%)	777 (15%)	1,153 (23%)
Number of years using estrogen or estrogen/progestin	4.1 ± 5.4	3.9 ± 4.9	4.3 ± 5.7
Diabetes mellitus	4,607 (46%)	3,265 (64%)	1,342 (27%)
Systemic hypertension	7,863 (78%)	4,310 (85%)	3,553 (71%)
Previous myocardial infarction	2,950 (29%)	0 (0%)	2,950 (59%)

Variable	All Patients (n = 10,101)	Increased CHD Risk (n = 5,070)	Documented CHD (n = 5,031)
Previous coronary bypass graft	1,654 (16%)	0 (0%)	1,654 (33%)
Previous percutaneous intervention	1,690 (17%)	0 (0%)	1,690 (34%)
Previous angina pectoris*	3,341 (33%)	0 (0%)	3,341 (66%)
Lower extremity arterial disease	1,083 (11%)	683 (13%)	400 (8%)
Abnormal electrocardiogram [†]	7,448 (41%)	4,978 (31%)	2,470 (50%)
Electrocardiographic Q-wave myocardial infarction	1,116 (11%)	170 (3%)	946 (19%)
Total cholesterol (mg/dl)	218.7 ± 44.5	224.5 ± 44.0	212.8 ± 44.2
Low-density lipoprotein cholesterol (mg/dl)	121.9 ± 37.3	125.4 ± 37.1	118.4 ± 37.1
High-density lipoprotein cholesterol (mg/dl)	52.4 ± 14.3	53.0 ± 15.0	51.9 ± 13.6
Triglycerides (mg/dl)	159.0 ± 110.8	163.7 ± 114.4	154.2 ± 106.8
Fasting glucose (mmol/L)	7.7 ± 3.5	8.4 ± 3.8	6.9 ± 3.0
Hemoglobin A _{1c} [‡]	7.2 ± 1.6	7.5 ± 1.8	6.8 ± 1.4
Fibrinogen (mg/L) [§]	355.3 ± 81.1	353.3 ± 80.8	358.0 ± 81.7

Values are presented as mean ± SD or number of patients (percentage).

* With angiographically confirmed coronary heart disease.

[†] Definite Q-wave myocardial infarction; pathologic ST-T depression; conduction disturbances excluding first-degree atrioventricular block, atrial fibrillation or flutter; or ventricular hypertrophy.

[‡] n = 9,795, 4,910, and 4,885 for overall, increased risk for coronary heart disease, and documented coronary heart disease, respectively.

[§] n = 520, 302, and 218 for overall, increased coronary heart disease risk, and documented coronary heart disease, respectively.

Table 2**Inclusion criteria for participation in RUTH trial***

Points for coronary heart disease [†]	
Myocardial infarction 3–36 months before randomization	4
Angina pectoris with coronary disease documented by angiogram	4
Catheter-based coronary revascularization 6–36 months before randomization	4
Coronary artery bypass grafting 3–36 months before randomization	4
Myocardial infarction >36 months before randomization	2
Catheter-based coronary revascularization >36 months before randomization	2
Coronary artery bypass grafting >36 months before randomization	2
Points for coronary heart disease risk factors	
Lower extremity arterial disease documented by symptoms, ankle/brachial index <0.9, revascularization, or nontraumatic amputation	4
Current smoker + systemic hypertension + hyperlipidemia [‡]	4
Diabetes mellitus [§]	3
Age ≥70 years	1
Age ≥65–<70 years	1
Hyperlipidemia	1
Current smoker by self-report ^{//}	1
Systemic hypertension [¶]	1

* At least 4 risk points required for enrollment.

[†] Can be additive to points for coronary heart disease risk factors.

[‡] Low-density lipoprotein cholesterol >160 mg/dl or high-density lipoprotein cholesterol <45 mg/dl with triglycerides >250 mg/dl or on medication.

[§] Fasting plasma glucose >140 mg/dl or on medication.

^{//} At least 10 cigarettes/day for 6 months before enrollment.

[¶] Systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg or on medication.

Table 3

Criteria for electrocardiographic abnormality

1	definite Q-wave myocardial infarction: pathologic Q-waves (>0.03 second in duration) in ≥ 2 contiguous leads; leads II, III, and aVF for inferior infarction, leads I aVL and V_2 - V_6 or a QS pattern in ≥ 2 leads of leads V_1 - V_3 for anterior infarction
2	pathologic ST-T depression: ST-segment depression >0.5 mm at ST junction, with horizontal or downward ST-segment depression and/or T-wave inversion in leads where this should not occur (Minnesota Code IV, 1, 2 or V 1, 2)
3	left bundle branch block, right bundle branch block, left anterior fascicular block, left posterior fascicular block, atrial ventricular block higher than first degree—standard definitions
4	atrial fibrillation and/or atrial flutter—absence of P waves and presence of atrial fibrillation or flutter wave
5	left ventricular hypertrophy: Cornell gender-specific voltage criteria, R wave in lead aVL + S wave in lead V_3 >2.0 mV without (left ventricular hypertrophy only) or with secondary ST-T abnormalities (lateral ST-segment depression and/or T-wave inversion)

Table 4

Summary of abnormal electrocardiographic rates by age category

Study Cohort	Age (years)			p Value
	55-64	65-74	≥75	
All patients				
Number of patients	3,675	4,906	1,316	
Abnormal electrocardiogram	1,312 (36%)	2,045 (42%)	674 (51%)	<0.01
Increased risk				
Number of patients	1,897	2,415	661	
Abnormal electrocardiogram	495 (26%)	782 (32%)	288 (44%)	<0.01
Documented coronary heart disease				
Number of patients	1,778	2,491	655	
Abnormal electrocardiogram	817 (46%)	1,263 (51%)	386 (59%)	<0.01

Table 5

Summary of abnormal electrocardiographic rates by previous myocardial infarction status

Study Cohort	Previous MI		p Value
	Yes	No	
All patients			
Number of patients	2,891	7,018	
Abnormal electrocardiogram	1,653 (57%)	2,383 (34%)	<0.01
Increased risk			
Number of patients	0	4,978	
Abnormal electrocardiogram	0 (—)	1,566 (31%)	—
Documented coronary heart disease			
Number of patients	2,891	2,040	
Abnormal electrocardiogram	1,653 (57%)	817 (40%)	<0.01

Table 6

Characteristics predictive of abnormal electrocardiographic findings: risk ratios (confidence intervals)

All Patients (n = 9,909)	Increased Risk (n = 4,978)	Documented CHD (n = 4,931)			
Previous myocardial infarction	2.489 (2.21–2.80)	2.359 (1.89–2.95)	Previous myocardial infarction	2.160 (1.83–2.55)	
Previous coronary artery bypass grafting	2.232 (1.95–2.55)	1.420 (1.21–1.66)	Previous coronary artery bypass grafting	1.884 (1.57–2.26)	
Age*	1.960 (1.69–2.28)	1.420 (1.13–1.78)	Increased fasting glucose	1.550 (1.15–2.08)	
Hemoglobin A _{1c} *	1.438 (1.29–1.61)	≥1 alcoholic drink/week*	0.787 (0.63–0.98)	Previous percutaneous coronary intervention	0.670 (0.57–0.79)
Hypertension	1.327 (1.17–1.50)	Systolic blood pressure*	1.330 (1.11–1.60)	Hypertension	1.365 (1.15–1.62)
≥1 alcoholic drink/week*	0.850 (0.74–0.98)	Vigorous activity	0.784 (0.64–0.96)	Age*	1.518 (1.18–1.96)
High-density lipoprotein*	1.345 (1.18–1.54)			Ethnicity: Afro-Caribbean versus Caucasian†	2.408 (1.14–5.10)
Systolic blood pressure*	1.225 (1.09–1.38)			Triglycerides*	1.342 (1.10–1.63)
Previous hormone use	0.830 (0.75–0.92)			Previous hormone use	0.828 (0.70–0.97)
Ethnicity: Asian vs Caucasian†	2.336 (1.56–3.49)			Hemoglobin A _{1c} *	1.203 (0.90–1.62)
Vigorous activity	0.871 (0.77–0.98)				

* For characteristics with >2 levels, the risk ratio presented is for the highest and lowest levels. For example, age is divided into 55 to 64, 65 to 74, and ≥75 years; the risk ratio presented is for the ≥75-year-old group compared to the 55- to 64-year-old group.

† Risk ratio is presented for the ethnicity with the highest risk compared with to Caucasian patients (the most common) in the dataset.

Table 7

Characteristics predictive of particular electrocardiographic findings in patients with abnormal electrocardiograms: risk ratios (confidence intervals)

All patients (n = 4,036)	Increased risk (n = 1,566)	Documented CHD (n = 2,470)
Definite Q-wave myocardial infarction		
Previous myocardial infarction	Diabetes mellitus	Previous myocardial infarction
6.382 (5.26–7.75)	0.572 (0.39–0.85)	5.984 (4.65–7.69)
Previous angina	Low density lipoprotein*	Hypertension
1.367 (1.13–1.65)	0.375 (0.20–0.72)	0.739 (0.58–0.94)
≥1 alcoholic drink/week*	Smoking	Previous angina
0.779 (0.59–1.03)	1.646 (1.03–2.63)	1.336 (1.04–1.72)
Diabetes mellitus		Years after menopause*
0.788 (0.65–0.96)		0.726 (0.56–0.94)
Hypertension		
0.781 (0.62–0.98)		
Atrial fibrillation and/or flutter		
Heart rate*	Heart rate*	Heart rate*
3.104 (2.08–4.64)	3.380 (2.00–5.71)	3.104 (1.87–5.16)
Age*	Age*	Age*
2.944 (1.84–4.71)	2.877 (1.69–4.90)	4.187 (2.05–8.55)
Previous angina	High-density lipoprotein*	Hypertension
0.535 (0.37–0.78)	1.995 (1.27–3.14)	2.192 (1.21–3.98)
Previous myocardial infarction		Previous coronary artery bypass grafting
0.520 (0.33–0.82)		0.625 (0.39–1.00)
High-density lipoprotein*		
1.825 (1.24–2.69)		
Hypertension		
1.751 (1.07–2.87)		
Left ventricular hypertrophy		
Systolic blood pressure*	Hypertension	Systolic blood pressure*
1.786 (1.47–2.17)	2.179 (1.48–3.22)	1.845 (1.40–2.43)
Diabetes mellitus	Systolic blood pressure*	
1.313 (1.12–1.54)	1.694 (1.28–2.25)	
Hypertension	Diabetes mellitus	
1.430 (1.15–1.77)	1.383 (1.09–1.76)	
Previous percutaneous coronary intervention	Age*	
0.716 (0.58–0.88)	0.663 (0.48–0.92)	
Triglycerides*	Hysterectomy	
1.251 (1.05–1.50)	0.740 (0.57–0.96)	
Hysterectomy		
0.819 (0.68–0.98)		

* For characteristics with >2 levels, the risk ratio presented is for the highest and lowest levels. For example, age is divided into 55 to 64, 65 to 74, and ≥75 years; the risk ratio presented is for the ≥75-year-old group compared to the 55- to 64-year-old group.