Prognostic Value of Ischemic Electrocardiographic Findings for Cardiovascular Mortality in Men and Women

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Objectives. The aim of this study was to investigate the independent prognostic value of ischemic electrocardiographic (ECG) findings for cardiovascular mortality and to evaluate a possible sex-differential in this regard.

Background. In previous reports, ST segment and T wave changes on the resting ECG were described as independent risk factors for development of coronary heart disease. Although more prevalent in women, they are often given less clinical importance than in men.

Methods. Ten-year follow-up data from the Belgian Interuniversity Research on Nutrition and Health study were used. The results presented here are based on ECGs of the 4,797 men and 4,320 women, aged 25 to 74 years, who were free of angina pectoris at the start of follow-up, had no history of myocardial infarction (MI) and showed no Q wave evidence of an old MI on their ECG.

Results. At baseline, the age-standardized prevalence of an “ischemic ECG” (Minnesota codes I, IV, V1–3, or VII1) was 8.4% in men and 10.6% in women. Cardiovascular mortality rates in men and women with an ischemic ECG were respectively 7.7 and 2.6 per 1,000 person-years, compared with 2.3 and 1.0 in those with no such ECG findings. After correction for the potential confounding effects of established cardiovascular disease (CVD) risk factors, the multivariately adjusted risk ratios were 2.45 (95% confidence interval [CI]: 1.70 to 3.53) for men and 2.16 (95% CI: 1.30 to 3.58) for women. Testing the interaction between an ischemic ECG and sex on CVD mortality revealed that the risk ratios were not significantly changed (p = 0.95). The etiologic fraction of CVD deaths attributable to an ischemic ECG was estimated as 19.3% for men and 22.4% for women. Both men and women with major ischemic findings in their baseline electrocardiogram (Minnesota codes IV1,2, V1,2 or VII1) had a fourfold increased risk of CVD death.

Conclusion. These results support the hypothesis that women with ischemic ECG findings are at the same increased risk for CVD mortality as men.

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Gender differences in diagnosis, treatment and prognosis of cardiovascular disease (CVD) has received increasing attention in preventive cardiology. This study focuses on gender differences in the prognostic value for CVD mortality of repolarization abnormalities considered to represent various degrees of myocardial ischemia.

Because of important differences in CVD mortality and morbidity rates between the sexes, epidemiologic studies have dealt with the potential sex differential in certain CVD risk factors and their impact. For instance, it is documented that serum triglycerides have greater predictive value for coronary heart disease (CHD) in women compared to men (1). One of the established risk factors for CVD, ST-T abnormalities on the resting electrocardiogram (ECG), is independently associated with subsequent development of CHD (2–11). Most of the studies, however, were carried out in men and cohort studies on this issue in women are rare. Nevertheless, in clinical practice the presence of ST-T findings is given less weight in women despite their higher prevalences.

The aims of our study were 1) to study the independent prognostic value of ischemic ECG findings for CVD mortality in men and women free of CHD at baseline and 2) to study whether there is a gender difference in this prognostic value.

Methods

Study population. The results are based on observations made in the men and women who took part in the Belgian Interuniversity Research on Nutrition and Health (BIRNH) study. This study, in which baseline measurements were made in the years 1981 to 1984, focuses on the distribution of cardiovascular risk factors and nutritional habits in Belgium and their relation to total and cause-specific mortality. The detailed methodology and results were published elsewhere...
After 10 years, 144 men and 67 women were identified as CVD mortality were defined as those with ICD-codes 410 to 414. Cases of CHD from CVD all codes ranging from 390 to 459. Information on the exact cause of death was collected from hospital completed the death certificate. Where appropriate, more infor-
tained from the family doctor and/or the doctor who com-
local community registers and causes of death were ascer-
in 99% of the participants. Vital status was checked through
follow-up.

Follow-up. The global sample was followed for at least 10 years for cause-specific mortality, the follow-up being complete in 99% of the participants. Vital status was checked through local community registers and causes of death were ascer-
tained from the family doctor and/or the doctor who com-
pleted the death certificate. Where appropriate, more information on the exact cause of death was collected from hospital or medical records. According to the International Classification of Diseases (ICD) (15), we considered as cause of death from CVD all codes ranging from 390 to 459. Cases of CHD mortality were defined as those with ICD-codes 410 to 414. After 10 years, 144 men and 67 women were identified as CVD deaths; 66 men and 27 women died from CHD.

Resting ECG. Using a 3-channel Hewlett-Packard device type 1516B, a 12-lead ECG lasting, on average, 16 s, was taken in supine position in accordance with classical recommendations. All tracings were coded by a trained physician on the basis of Minnesota criteria (16). Signs of an ischemic ECG were defined as the presence of either a borderline Q wave (code I₃), significant or borderline ST-segment depres-

### Abbreviations and Acronyms

- **BIRNH**: Belgian Inteuniversity Research on Nutrition and Health
- **BMI**: body mass index
- **CHD**: coronary heart disease
- **CI**: confidence interval
- **CVD**: cardiovascular disease
- **ECG**: electrocardiogram, electrocardiographic
- **ICD**: international classification of diseases
- **RR**: risk ratios

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(12,13). An age- and sex-stratified population sample of subjects 25 to 74 years old was selected at random from 42 of the 43 Belgian geographic districts. To achieve a sufficient sample size under circumstances in which little pressure was put on invited eligible subjects, a sample of more than 30,000 persons was selected. The participation rate was 36.5%, resulting in 11,302 subjects taking part in the study (5,949 men and 5,353 women). A 10% random sample of the nonparticipants was selected and invited to answer a number of questions related to smoking and nutritional habits, which revealed that no differences exist between participants and nonparticipants with respect to lifestyle (13). It was not feasible, however, to compare participants and nonparticipants with regard to their ECG pattern.

Data used in the present analysis are those from the 4,797 men and 4,320 women free of prevalent CHD at baseline, defined as being free of angina pectoris or a positive history of acute myocardial infarction according to the Rose questionnaire (14), and having no Q wave evidence of an old myocardial infarction on their resting ECG at baseline (Q and QS patterns, Minnesota coding criteria I₁₋₃).

The study design and methodology was approved by the ethical committees of the University of Ghent and the Free University of Brussels.

Follow-up. The global sample was followed for at least 10 years for cause-specific mortality, the follow-up being complete in 99% of the participants. Vital status was checked through local community registers and causes of death were ascertained from the family doctor and/or the doctor who completed the death certificate. Where appropriate, more information on the exact cause of death was collected from hospital or medical records. According to the International Classification of Diseases (ICD) (15), we considered as cause of death from CVD all codes ranging from 390 to 459. Cases of CHD mortality were defined as those with ICD-codes 410 to 414. After 10 years, 144 men and 67 women were identified as CVD deaths; 66 men and 27 women died from CHD.

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### Statistical methods.

Age-standardized cardiovascular mortality rates were obtained using the method of direct standardization using 10-year age-strata with the male and female sample of subjects with no ECG ischemia as reference (17). Statistical analysis of the association between ischemic ECG findings and CVD mortality was performed by fitting Cox proportional hazard models (18) with additional covariates of age (years), BMI (kg/m²), current smoking (yes/no), systolic blood pressure (mm Hg), total serum cholesterol (mg/dl), uric acid (mg/dl), diabetic status (yes/no) and antihypertensive drug use (yes/no). The statistical significance of a variable in the model was determined according to the Wald chi-square statistic. Statistical interaction between ECG findings and gender was evaluated by fitting their multiplicative effect. All models were checked on the assumption of proportionality of hazards. The global level for statistical significance was taken as alpha = 0.05 and all analyses were performed using SAS software (SAS System for Windows, Release 6.11, SAS Institute Inc., Cary, NC.) The proportion of CVD deaths in the global sample that could be attributed to the presence of an ischemic ECG was expressed as the population etiologic fraction Pₑ(RR-1)/RR, where RR is the risk ratio and Pₑ the proportion of deceased subjects that had a baseline ischemic ECG (17).

### Results

In Figure 1 the prevalences of an ischemic ECG finding are shown stratified by age group and gender. As expected, these prevalences are clearly age-related, giving subjects in the highest age group a tenfold higher prevalence than the youngest individuals in the sample. The overall age-standardized prevalence of an ischemic ECG was 8.4% in men and 10.6% in women. This higher prevalence in women was consistently observed in all age groups. Differences between sexes were not
present, however, for so-called major ischemic abnormalities (codes IV_{1,2}, V_{1,2} and VII_{1}) with age-standardized prevalences of, respectively, 1.9% in men and 1.8% in women (age-specific prevalences shown in Fig. 1 as the horizontal line within bars). Consequently, the gender difference in prevalence of ischemic ECG findings was largely due to differences in the occurrence of Minnesota codes IV_{3} and V_{3}, both known to be more prevalent in women.

Table 1 shows that ischemic ECG findings are mainly negative T-waves (code V_{1–3}) either occurring alone or in conjunction with ST-segment depressions (code IV_{1–3}). The latter are found relatively more often in women, while borderline Q wave patterns (code I_{3}) and left bundle branch blocks (code VII_{1}) are more often observed among men. Isolated ST-segment depression was found only in one man.

Figure 2 shows the estimated actuarial survival curves by gender and presence of ischemic signs on the baseline ECG. As expected, CVD mortality is much higher in men compared to women but an ischemic ECG at baseline increases the risk of cardiovascular death in both sexes. In our sample, cumulative mortality in men with an initial ischemic ECG was about 14% after 10 years. The form of these curves also suggests that the effect of ischemia on the baseline ECG on CVD mortality is not specifically short- or long-term but is rather constant over the whole follow-up period. Even after a longer period, subjects showing signs of ischemia on their initial ECG are dying faster from CVD than those with no ischemic ECG.

The age-standardized CVD mortality rates experienced over the whole follow-up period are 7.65 and 2.56 per 1,000 person-years in men and women having ischemic ECG findings (Table 2). For the men and women not showing signs of ischemia on their ECG at the start of the follow-up period, the mortality rates are, respectively, 2.28 and 1.02 per 1,000 person-years. For the major ST-T findings, CVD mortality is about eightfold higher in men and sixfold higher in women, with age-adjusted mortality rates of 18.00 and 5.86 per 1,000 person-years in men and women, respectively.

According to Cox regression analyses shown in Table 3, the multivariately adjusted RR related to an initial ischemic ECG are 2.16 in women and 2.45 in men, both RR being significantly different from one, concluded from their 95% confidence intervals (CI). Modeling the multiplicative effect in a Cox model between gender and presence of a baseline ischemic ECG revealed no interaction between these variables (p = 0.95); hence, both RR were not significantly different. In our sample, a sex differential of ischemic ECG findings in predicting CVD mortality could not be demonstrated. We reached the
same conclusion comparing the etiologic fractions related to an ischemic ECG. The proportion of CVD deaths attributed to ECG ischemia is 19.3% in men and 22.4% in women.

In our multivariate analysis, ischemic ECG findings at baseline were among the strongest predictors for cardiovascular mortality. In both men and women only the effect of age was more pronounced, contrasted with the effect of other classical CVD risk factors such as systolic blood pressure, smoking, BMI and total cholesterol. Entering minor and major ischemic ECG findings simultaneously in a multivariate model with adjustment for the other risk factors revealed again a similarity of RR between genders. Men and women with major ischemic-like changes on their baseline ECG had a more than fourfold risk of CVD death. The risk for those subjects with minor ischemic ECG findings was much less and in both sexes failed to reach statistical significance at the 5% level.

In an extra analysis with exclusion of persons with ECG codes I3 and VII1, we performed a Cox regression analysis relating combined ST-T changes and isolated T wave abnormalities to later CVD mortality. Interaction testing failed to detect a sex differential for both these ECG classifications. The result of this analysis, pooling men and women, was that combined ST-T changes were most predictive with a multivariate RR of 5.11 (95% CI: 3.40 to 7.68), while the independent prognostic value of isolated T wave abnormalities was much less pronounced and only of borderline significance (RR = 1.49 [95% CI: 0.95 to 2.31]).

**CHD mortality.** In men, 45.8% of all CVD deaths were labeled as CHD deaths while for women this proportion was 40.3%. Modeling the association between all ischemic ECG changes and CHD mortality, adjusting for the same list of covariates, showed again the similarity of the impact of an ischemic ECG on CHD death for men and women. The adjusted RR for men was 2.03 (95% CI: 1.15 to 3.56) while for women it was 2.15 (95% CI: 0.96 to 4.84). The interaction term between gender and initial ischemic ECG changes was once more not statistically significant (p = 0.52). Mortality rates after 10 years were too low to perform a powerful analysis of the relation between major ischemic ECG changes and CHD death.

| Table 2. Age-Specific Number of CVD Deaths and Age-Standardized CVD Mortality Rates in Subgroups According to Ischemic ECG Findings in Men and Women |
|---|---|---|---|---|---|
| Age Group | 25–35 yr | 35–44 yr | 45–54 yr | 55–64 yr | 65–74 yr |
| **Men** | | | | | |
| No ischemic ECG changes | 0/917 (9,203)* | 4/1,083 (10,846) | 8/978 (9,599) | 37/870 (8,227) | 48/545 (4,736) |
| Ischemic ECG changes | 0/21 (212) | 0/42 (407) | 9/85 (786) | 15/125 (1,085) | 23/131 (1,067) |
| Major ischemic ECG changes | 0/2 (20) | 0/6 (61) | 3/16 (134) | 10/30 (205) | 10/39 (315) |
| Minor ischemic ECG changes‡ | 0/19 (192) | 0/38 (367) | 7/75 (705) | 6/102 (942) | 16/105 (863) |
| **Women** | | | | | |
| No ischemic ECG changes | 0/818 (8,225) | 1/1,017 (10,236) | 2/931 (9,288) | 18/712 (7,018) | 18/384 (3,588) |
| Ischemic ECG changes | 0/23 (232) | 0/54 (540) | 1/102 (1,005) | 6/139 (1,357) | 21/140 (1,302) |
| Major ischemic ECG changes | 0/1 (10) | 0/5 (50) | 0/14 (141) | 3/27 (255) | 10/30 (252) |
| Minor ischemic ECG changes‡ | 0/22 (222) | 0/52 (520) | 1/92 (905) | 5/122 (1,194) | 14/121 (1,143) |

CVD = cardiovascular disease; ECG = electrocardiographic. *Cell entries are number of CVD deaths over the number of subjects in that cell at the start of the follow-up period (number of person-years are given between parentheses). †Age-standardized mortality rates per 1,000 person-years. ‡Subjects with major ischemic ECG abnormalities excluded.

**Table 3. Adjusted Risk Ratios (+95% CI) for CVD Mortality According to Ischemic ECG Findings in Both Men and Women**

<table>
<thead>
<tr>
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<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
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<tr>
<td><strong>Age-adjusted</strong></td>
<td></td>
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<tr>
<td>Ischemic ECG changes</td>
<td>2.83</td>
<td>(1.98–4.03)</td>
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<tr>
<td>Minor ischemic ECG changes*</td>
<td>1.43</td>
<td>(0.93–2.18)</td>
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<tr>
<td>Major ischemic ECG changes†</td>
<td>4.55</td>
<td>(2.85–7.27)</td>
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<tr>
<td><strong>Multivariately adjusted‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic ECG changes</td>
<td>2.45</td>
<td>(1.70–3.53)</td>
</tr>
<tr>
<td>Minor ischemic ECG changes*</td>
<td>1.26</td>
<td>(0.82–1.93)</td>
</tr>
<tr>
<td>Major ischemic ECG changes†</td>
<td>4.21</td>
<td>(2.60–6.82)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CVD = cardiovascular disease; ECG = electrocardiographic; RR = risk ratio. *Additional adjustment for major ischemic ECG changes. †Additional adjustment for minor ischemic ECG changes. ‡Adjustment for age, body mass index, systolic blood pressure, total cholesterol, smoking, uric acid, diabetes, left ventricular hypertrophy and use of antihypertensive drugs.
**Discussion**

**Ischemic ECG changes and CVD: Reported results.** In the epidemiologic literature many studies deal with the prognostic value of ECG ST-T changes for CVD or CHD mortality. However, until more recently most of these studies have concentrated on men (2,3). According to 5-year follow-up data of 5,738 men aged 30 to 59 years, Reunanen et al. (4) reported in one of the earlier studies that subjects with a baseline Minnesota code IV_{1-3} or V_{1-2} had about five times more risk of dying from CHD. In a more recent study (10) from data in 9,139 men aged 40 to 80 years without CHD at baseline taking part in the Reykjavik study and followed-up for up to 24 years, an adjusted relative risk of 2 was found for CHD in subjects with silent ST-T changes on their initial ECG. Schouten et al. (9) reported on a Dutch study of 1,583 men aged 40 to 65 years in which after a 15-year follow-up, CVD mortality rates were elevated by 90% (RR = 1.9) in those with ST-segment depression greater than 0.25 mm.

In one of the earliest reports on signs of ischemia on the ECG among women as well as men, Liao et al. (6) looked in more detail at sex differences in the relationship of ECG ST-T findings to risk of CHD based on data from the Chicago Heart Association Detection Project in Industry. In the 9,203 men and 7,818 women, aged 40 to 64 years and free of CHD at baseline, the age-standardized prevalences of ST-T changes were 8.1% in men and 12.3% in women. Based on these baseline observations and after a follow-up period of 11.5 years, they found a relative risk for CHD mortality of 2.6 (p < 0.0001) in men and 1.4 in women (not significant). In their multivariate analysis, the sex difference in risk ratios turned out to be at borderline significance (p = 0.09). Nevertheless, the authors concluded that with the use of the same criteria for ST-segment depression and T wave abnormality for both sexes, it may be that more women than men are misclassified as abnormal. They considered whether it might be appropriate to use different criteria for ST-T abnormalities for the two sexes.

In contrast to their findings, several other studies found that having an initial ischemic ECG carries the same prognostic value for CVD or CHD in men and women. In the Busselton study (8), for example, the age-standardized relative risks for CVD mortality in subjects aged 40 to 79 years after a follow-up period of 13 years, were 2.1 and 2.2 for men and women having a code IV_{2} abnormality on their baseline ECG and 3.5 and 5.2 for those with a code V_{2}. Also for less pronounced T wave abnormalities (code V_{3}), women had a higher relative risk for CVD mortality than men (3.0 vs. 2.3). Because of the limited sample size (1,056 men, 1,063 women), a powerful analysis of the predictive value of other specific ST-T changes proved impossible. Similar results were obtained by Kannel et al. (5) in their analysis of the 30-year follow-up data in the Framingham study. They report that nonspecific ST-T abnormalities (ST-segment depression \(>1\) mm and/or T wave flattening or inversion) have a higher prognostic value for CHD in women compared to men, after adjustment for age, systolic blood pressure and total cholesterol (relative risks of 1.3 in middle-aged men and 1.6 in middle-aged women). In the Renfrew and Paisley Survey (11), relative risks for ischemic heart disease mortality related to ECG “evidence of ischemia” at baseline (Minnesota codes I_{1-3}, IV_{1-4}, V_{1-3} and VII_{1}) were also comparable between sexes. The RR, obtained after a 15-year follow-up of 7,058 men and 8,353 women aged 45 to 64 years (adjusted for age, diastolic blood pressure, total cholesterol and smoking), were 2.5 in men and 2.3 in women, both RR being significantly different from one but not from each other.

**Definition of ischemic ECG changes and statistical power.** The definition of ischemic findings as used in this study may seem arbitrary although comparable to those adopted in the studies mentioned earlier, as it includes less meaningful codes which we grouped separately as “minor” ischemic abnormalities. In our study, these so-called minor ECG changes are indeed shown to be of lesser importance for future cardiovascular mortality. The association between major ischemic ECG stigmata and CVD mortality is strong. The association between major ischemic changes and CHD mortality was not studied in detail due to the insufficient number of CHD and natural deaths. To consider the second main objective of our study (no sex-differential in predictive value) with sufficient statistical power, we used the broader definition of ECG ischemia and concentrated mainly on cardiovascular mortality rather than CHD mortality. So, to gain sensitivity (statistical power), some specificity of the issue was given up. In the group with a normal ECG the sex ratio in age-standardized CVD mortality rates was about 2.5, which is in line with what is known from mortality statistics in Belgium. Power calculations based on the number of CVD deaths as observed over the complete follow-up period showed that the likelihood of detecting a true similar sex effect (RR = 2.5) in CVD mortality risk in the group of individuals with a baseline ischemic ECG was 82%.

**Specificity of the impact of ischemic ST-T changes.** The question arises whether the association is confounded by the presence of other abnormalities on the initial ECG. In our data set, ischemic ECG changes were significantly associated only with arrhythmias (Minnesota code VIII_{1-6}) in men and women. However, adding the presence of arrhythmias on the baseline ECG as a covariate in our multivariate model did not change the estimated RR.

Apart from borderline Q wave and left bundle branch block (codes I_{3} and VII_{1}), about one third of the ischemic findings in our study were combined ST-segment and T wave abnormalities and two thirds were isolated T wave changes. These two categories may carry a different meaning in relation to ischemia, and also their risk may substantially differ. In an extra analysis with exclusion of subjects with borderline Q wave changes or left bundle branch block, we observed strongly elevated CVD death rates in the group with combined ST-T changes compared to the rather moderate risk in subjects showing T wave changes only on their baseline ECG.

**Selection bias and external validity.** The BIRNH study is not characterized by a high participation rate and hence could be subject to selection bias. However, analysis of a 10% nonrespondent sample revealed no major differences in...
lifestyle-related characteristics between participants and non-participants. Another argument favoring acceptable external validity for our study can be found in the mortality experience over the 10 years of follow-up. The age- and sex-specific total mortality rates for the BIRNH participants were very comparable to the estimates from official age- and sex-specific national mortality statistics in Belgium.

Conclusions. In conclusion, the results from our study indicate that, first, in subjects clinically free of CHD, the prevalence of ischemic ECG findings is higher in women than in men over all age groups. Second, a baseline ischemic ECG is associated in both sexes with a higher risk for CVD mortality independent of other classical risk factors, this effect being not specifically short- or long-term. And finally, this prognostic value is comparable between the sexes. From this we conclude that the clinical judgment of major ischemic findings on the resting ECG should not be different for men and women.

References