

# Prolonged QT interval predicts cardiac and all-cause mortality in the elderly

## The Rotterdam Study

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**Aims** To examine the association between heart-rate corrected QT prolongation and cardiac and all-cause mortality in the population-based Rotterdam Study among men and women aged 55 years or older and to compare the prognostic value of the QT interval, using different formulas to correct for heart rate.

**Methods and Results** After exclusion of participants with arrhythmias or bundle branch block on the ECG, the study population consisted of 2083 men and 3158 women. The QT interval was computed by the Modular ECG Analysis System (MEANS). Data were analysed using Cox' proportional hazards model. Participants in the highest quartile of the heart-rate corrected QT interval had about a 70% age- and sex-adjusted increased risk for both all-cause mortality (hazard ratio (HR) 1.8; 95%CI:1.3–2.4) and cardiac mortality (HR 1.7; 95%CI:1.0–2.7) compared to those in the lowest quartile. In women, the increased risk

associated with prolonged QT for cardiac death was more pronounced than in men. These risk estimates did not change after adjustment for potential confounders, including history of myocardial infarction, hypertension and diabetes mellitus.

**Conclusion** A prolonged heart-rate corrected QT interval is an independent predictor for cardiac and all-cause mortality in older men and women. The risk associated with prolonged QT is hardly affected by the heart-rate correction formula used.

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**Key Words:** Electrocardiogram, coronary heart disease, mortality, aged, risk factor, prolonged QTc interval.

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## Introduction

The prolonged heart-rate corrected QT interval on the 12-lead electrocardiogram (ECG) is associated with an increased risk for ventricular arrhythmias, sudden death, and coronary heart disease. This relationship has been reported in patients with the long QT syndrome<sup>[1]</sup>, in patients after myocardial infarction<sup>[2,3]</sup>, and in diabetic patients with autonomic neuropathy<sup>[4]</sup>. Few studies have been performed in the population at large<sup>[5–7]</sup> and they have shown controversial results. In the Dutch Civil Servants Study<sup>[5]</sup>, men and women with a prolonged heart-rate corrected QT had a twofold increased risk for

death from coronary heart disease. In the Zutphen Study<sup>[6]</sup>, a two- to fourfold increased risk for coronary heart disease mortality associated with a prolonged heart-rate corrected QT was observed in middle-aged men and a threefold increased risk in elderly men. In contrast to these findings, prolonged heart-rate corrected QT was not associated with total mortality, sudden cardiac death or coronary artery disease mortality in either men or women in the Framingham Heart Study<sup>[7]</sup>.

The duration of the QT interval is strongly correlated with heart rate. Previous studies on the prognostic implications of the prolonged QT interval all used Bazett's formula<sup>[8]</sup> to correct QT for heart rate, but its adequacy has been questioned. Several new correction formulas have been proposed<sup>[9–12]</sup>. In clinical practice, the formula which best predicts heart disease will be the most valuable<sup>[13]</sup>. In analogy, the definition of prolonged

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QT should be based on prognostic implications for clinical endpoints, for example a two- or threefold risk for cardiac mortality.

Until now, the threshold value for prolonged QT, notably the value that distinguishes between normal and prolonged QT, was often based on the distribution of QT interval duration in the male population. As women have systematically longer heart-rate corrected QT intervals, clinically useful threshold values for prolonged QT in men and women may differ.

In the present study we examined the association between heart-rate corrected QT prolongation and cardiac and all-cause mortality in men and women aged 55 years or older, participating in the population-based Rotterdam Study. We compared the prognostic value of the heart-rate corrected QT interval, applying different formulas to correct for heart-rate.

## Methods

### *Study population and baseline data collection*

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors for chronic diseases in the elderly. Objectives and methods of the Rotterdam Study have been described in detail elsewhere<sup>[14]</sup>. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Ommoord district of the city of Rotterdam, were invited to participate (response rate 78%). Of 7129 participants, the baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, established cardiovascular risk factors, and use of medications.

A digitally stored ECG was available in 6160 (86%) participants. An ECG was missing in 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as  $\text{weight} \cdot \text{length}^{-2}$  in  $\text{kg} \cdot \text{m}^{-2}$ . Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication of hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above  $11.1 \text{ mmol} \cdot \text{l}^{-1}$  or use of antidiabetic medication. History of myocardial infarction was defined as self-reported myocardial infarction with hospital admission, or myocardial infarction on the ECG<sup>[15]</sup>. Presence of angina pectoris was established through the Rose questionnaire<sup>[16]</sup>.

After exclusion of participants with arrhythmias ( $n=256$ ) or complete left or right bundle branch block ( $n=290$ ), and of subjects without follow-up data, mainly because they moved to unknown addresses ( $n=345$ ), the

study population consisted of 2093 men and 3176 women.

### *Follow-up procedures*

The follow-up period, starting at the baseline examination and for the present analysis lasting until April 1996, comprised 3 to 6 (mean 4) years. With respect to the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners working in the study district of Ommoord. These 20 general practitioners, covering about 85% of the cohort, all have their practice computerized and report possible non-fatal and fatal events of participants on computer file to the Rotterdam Study data-centre on a regular basis. All possible events reported by the general practitioner are verified by research physicians from the Rotterdam Study through patient records of the participating general practitioners and medical specialists. In April 1996, the medical records of participants with general practitioners outside the Ommoord area, about 15% of the cohort, were checked by research physicians and all possible events plus additional information was collected for coding. Causes and circumstances of death were obtained shortly after the report of a death by the municipal health service or the general practitioner, by questionnaire from the general practitioner and by scrutinizing information from hospital discharge records in case of admittance or referral.

Overall, follow-up information was available for 94% of the population of the present study. Participants in whom no follow-up information was available were similar to those included in the present study. Those without follow-up were on average 3.5 years older (73.9 vs 70.4 years), had a lower prevalence of hypertension (25% vs 30%) and diabetes (10% vs 14%). No other differences in baseline characteristics were found.

Classification of events was based on the International Classification of Diseases, 10th edition (ICD-10)<sup>[17]</sup>. We defined cardiac mortality as death from myocardial infarction (ICD-10: I21–24), chronic ischaemic heart disease (ICD-10: I25), pulmonary embolism or other pulmonary heart disease (ICD-10: I26–28), cardiomyopathy (ICD-10: I42–43), cardiac arrest (ICD-10: I46), arrhythmias (ICD-10: I47–49), heart failure (ICD-10: I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within 1 h after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded<sup>[18,19]</sup>.

All events were classified independently by two research physicians. If there was disagreement, a consensus was reached in a separate session. Finally, all events were verified by a medical expert in the field of cardiovascular disease. In case of discrepancies, the judgment by this expert was considered definite.

### ECG interpretation and measurements

A 12-lead resting ECG was recorded on an ESAOTE-ACTA cardiograph, at a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements and diagnostic interpretations. The MEANS program has been extensively evaluated<sup>[20-22]</sup>.

The MEANS program determines the overall QT interval for all 12 leads together on a representative beat, which results from selective averaging of dominant beats. To correct QT for heart rate we used five formulas that have also been used in other population-based studies:

- (1) Bazett's formula<sup>[8]</sup>:  $QT_c = QT \times \sqrt{(1/RR)}$ ;
- (2) Fredericia's cubic root<sup>[23]</sup>:  $QT_c = QT \times (1/RR)^{1/3}$ ;
- (3) Linear regression formula<sup>[10]</sup>:  $QT_c = QT + \beta \times (1-RR)$  with  $\beta = 0.140$  in men and  $\beta = 0.163$  in women.
- (4) The normogram method<sup>[12]</sup>:  $QT_c = QT + \beta \times (1-RR)$ , with  $\beta = 0.116$  for heart rates less than 60 beats  $\cdot \text{min}^{-1}$ ,  $\beta = 0.156$  for heart rates from 60 through 99 beats  $\cdot \text{min}^{-1}$  and  $\beta = 0.384$  for heart rates of 100 beats  $\cdot \text{min}^{-1}$  or more.
- (5) QT index (QTI)<sup>[11]</sup>:  $QTI = QT/QT_p$ , where  $QT_p$  is the predicted interval and equals  $QT_{max}/(1 + 0.01 \times HR)$ , with  $QT_{max} = 0.656$  s, and HR is the heart rate in beats  $\cdot \text{min}^{-1}$ .

In formulas 1 to 4,  $QT_c$  is standardized for an RR of 1.0 s or heart rate of 60 beats  $\cdot \text{min}^{-1}$  and can be interpreted as the length of the QT interval at a heart rate of 60 beats  $\cdot \text{min}^{-1}$ . Formulas 1 and 2 have an implicit 1 s under the root sign and thus the ratio (1/RR) is unitless. In formula 5, QTI reflects the length of the measured QT interval relative to the predicted QT interval. For example, a QTI of 110 can be interpreted as a 10% prolongation of the QT interval. Left ventricular hypertrophy was determined using voltage as well as repolarization criteria. Negative T-waves were defined as negative T-wave deflections of at least 1.0 mm in any of leads I-III, aVR, aVF, and  $V_2-V_6$ .

### Data analysis

Differences in baseline characteristics between those with and without follow-up data were examined by means of one way analysis of covariance, adjusting for age and gender when appropriate. To evaluate whether certain patient characteristics could confound the relationship between  $QT_c$  and the end-points studied, differences in the distribution of cardiovascular risk indicators between subjects in quartiles of Bazett's  $QT_c$  interval were examined through the use of one-way analysis of covariance, adjusting for age and gender.

For the five correction formulas under study, heart-rate corrected QT values were categorized in sex-specific quartiles. By means of Cox' proportional

hazards analysis, age- and sex-adjusted hazards ratios for cardiac and all-cause mortality for subjects in the three highest quartiles, with the lowest quartile as a reference group, were calculated for each formula separately. We adjusted for two sets of confounders: (1) age and sex, and (2) all potential confounders resulting from the analysis of covariance.

Influence of age and history of myocardial infarction on the risk for cardiac death associated with prolonged  $QT_c$  was examined through Cox' proportional hazards analysis within the strata of these possible effect modifiers.

To estimate the risk associated with published threshold values for the prolonged  $QT_c$  interval, we studied risk for cardiac and all-cause mortality of subjects with Bazett's  $QT_c$  intervals above 420 ms, 440 ms, and 460 ms, relative to those with Bazett's  $QT_c$ -intervals below 420 ms. All analyses were performed for men and women separately.

## Results

The participants of the present study were, on average, 68 years old. Most cardiovascular risk indicators under study, apart from serum cholesterol and history of angina pectoris, showed a positive association with heart-rate corrected QT-interval duration (Table 1).

### Predictive value of heart-rate corrected QT interval obtained with different correction formulas

Risk for all-cause mortality (Table 2) and cardiac mortality (Table 3) in the three upper quartiles of the heart-rate corrected QT interval, relative to those in the lowest quartile, was hardly influenced by the correction formula used. For men, the highest age-adjusted hazard ratios (HR) in the fourth quartile were obtained for QTI, both for all-cause mortality (HR 1.8; 95%CI 1.2-2.9) and cardiac mortality (HR 1.7; 95%CI 0.8-3.6). For women, the highest hazard ratios in the fourth quartile were obtained for Bazett's formula, both for all-cause mortality (HR 1.9; 95%CI 1.3-2.9) and cardiac mortality (HR 2.4; 95%CI 1.1-5.3). In all formulas, although least pronounced in Bazett's formula, the risk for cardiac mortality in the second quartile of the heart-rate corrected QT interval seemed to be lower than in the first quartile, suggesting a J- or U-shaped curve, especially in women.

Depending on the correction formula used, men in the highest quartile of the heart-rate corrected QT interval had a 50 to 80% increased risk for all-cause mortality and a non statistically significant 30 to 70% increased risk for cardiac mortality. In women in the highest quartile of the heart-rate corrected QT interval the increased risks for cardiac mortality were more pronounced than in men. All risk estimates were

**Table 1** General characteristics of the study population. Values are means (standard deviation) or percentages. P-values are presented for equality of values in sex-specific quartiles of Bazett's QTc interval, adjusted for age and sex using one-way analysis of covariance

| Characteristics                             | All          | Q1*   | Q2†   | Q3‡   | Q4§   | P-value |
|---|--------------|-------|-------|-------|-------|---------|
| Age (years)                                 | 68.2 (8.7)   | 67.2  | 68.2  | 68.2  | 71.4  | <0.01   |
| Heart rate (beats . min <sup>-1</sup> )     | 70.1 (11.9)  | 62.3  | 68.2  | 72.2  | 77.2  | <0.01   |
| Systolic blood pressure (mmHg)              | 139.1 (22.2) | 136.9 | 138.6 | 138.9 | 141.6 | <0.01   |
| Diastolic blood pressure (mmHg)             | 73.6 (11.5)  | 71.9  | 73.1  | 73.8  | 75.3  | <0.01   |
| Body mass index (kg . m <sup>-2</sup> )     | 26.3 (3.7)   | 26.0  | 26.1  | 26.5  | 26.8  | <0.01   |
| Current cigarette smoking (%)               | 21.4         | 19.0  | 20.2  | 24.1  | 22.3  | <0.01   |
| Serum cholesterol (mmol . l <sup>-1</sup> ) | 6.7 (1.2)    | 6.6   | 6.6   | 6.7   | 6.7   | ns      |
| Hypertension (%)                            | 29.1         | 26.6  | 27.1  | 27.3  | 35.1  | <0.01   |
| Diabetes mellitus (%)                       | 11.9         | 9.6   | 9.6   | 11.7  | 16.2  | <0.01   |
| History of MI (%)                           | 12.2         | 11.1  | 9.3   | 11.5  | 16.7  | <0.01   |
| History of angina pectoris (%)              | 6.5          | 6.6   | 6.9   | 6.2   | 6.2   | ns      |
| Electrocardiographic LVH (%)                | 4.7          | 5.7   | 4.1   | 3.5   | 5.6   | <0.01   |
| Negative T-wave (%)                         | 7.4          | 9.3   | 6.2   | 6.7   | 7.6   | <0.05   |

\*Q1=lowest quartile of QTc (<406 ms in men; <418 ms in women).

†Q2=second quartile of QTc (406-421 ms in men; 418-432 ms in women).

‡Q3=third quartile of QTc (421-437 ms in men; 432-446 ms in women).

§Q4=highest quartile of QTc (>437 ms in men; >446 ms in women).

MI=myocardial infarction; LVH=left ventricular hypertrophy.

**Table 2** Age-adjusted hazard ratios for all-cause mortality of men and women in the three highest quartiles of heart-rate corrected QT, relative to those in the lowest quartile, using five different formulas to correct the QT interval for heart rate

| Formula                              | Group | Percentile |       |       | Hazard ratio  |               |               |
|--------------------------------------|-------|------------|-------|-------|---------------|---------------|---------------|
|                                      |       | 25th       | 50th  | 75th  | Q2*           | Q3†           | Q4‡           |
| 1. Bazett <sup>[8]</sup>             | M     | 406        | 421   | 437   | 0.9 (0.6-1.4) | 1.2 (0.8-1.9) | 1.5 (1.0-2.3) |
|                                      | F     | 418        | 432   | 446   | 1.3 (0.8-2.0) | 1.5 (1.0-2.3) | 1.9 (1.3-2.9) |
|                                      | All   |            |       |       | 1.2 (0.8-1.6) | 1.4 (1.0-2.0) | 1.8 (1.3-2.4) |
| 2. Fredericia <sup>[23]</sup>        | M     | 401        | 413   | 426   | 1.0 (0.6-1.6) | 1.4 (0.9-2.2) | 1.6 (1.1-2.4) |
|                                      | F     | 408        | 420   | 432   | 1.0 (0.7-1.5) | 1.1 (0.7-1.7) | 1.6 (1.1-2.3) |
|                                      | All   |            |       |       | 1.0 (0.7-1.3) | 1.2 (0.9-1.7) | 1.6 (1.2-2.1) |
| 3. Linear regression <sup>[10]</sup> | M     | 400        | 411   | 424   | 0.9 (0.5-1.4) | 1.5 (1.0-2.3) | 1.5 (1.0-2.3) |
|                                      | F     | 410        | 421   | 433   | 1.0 (0.7-1.6) | 1.1 (0.7-1.7) | 1.7 (1.2-2.4) |
|                                      | All   |            |       |       | 0.9 (0.7-1.3) | 1.3 (1.0-1.7) | 1.6 (1.2-2.1) |
| 4. Normogram <sup>[12]</sup>         | M     | 403        | 414   | 427   | 1.1 (0.7-1.7) | 1.6 (1.0-2.5) | 1.7 (1.1-2.6) |
|                                      | F     | 410        | 421   | 433   | 1.1 (0.7-1.7) | 1.2 (0.8-1.9) | 1.7 (1.2-2.5) |
|                                      | All   |            |       |       | 1.1 (0.8-1.5) | 1.4 (1.0-1.9) | 1.7 (1.3-2.2) |
| 5. QT index <sup>[11]</sup>          | M     | 98.3       | 101.5 | 104.8 | 1.3 (0.8-2.1) | 1.8 (1.1-2.9) | 1.8 (1.2-2.9) |
|                                      | F     | 100.5      | 103.4 | 106.6 | 1.0 (0.6-1.5) | 1.2 (0.8-1.8) | 1.8 (1.2-2.6) |
|                                      | All   |            |       |       | 1.1 (0.8-1.5) | 1.4 (1.1-2.0) | 1.8 (1.3-2.3) |

\*Q2=second quartile; †Q3=third quartile; ‡Q4=fourth quartile.

M=male; F=female; All=combining sex-specific quartiles.

independent of other cardiovascular risk indicators, as additional adjustment for body-mass index, cigarette smoking, hypertension, diabetes mellitus, history of myocardial infarction, electrocardiographic left ventricular hypertrophy, and presence of negative T-waves did not materially change the results. Although there was a residual association of corrected QT with heart rate (Table 1), inclusion of heart rate in the multiple regression model did not materially change the results.

Subgroup analysis showed that the risk for all-cause mortality associated with heart-rate corrected QT was more pronounced in those under 70 years of age than in older subjects (HR of the highest vs the lowest quartile 2.8; 95%CI 1.5-5.2 vs 1.5; 1.1-2.0). A history of myocardial infarction did not modify the association of heart-rate corrected QT with all-cause and cardiac mortality but the number of cases of cardiac death was too small to allow for conclusions.

**Table 3** Age-adjusted hazard ratios for cardiac mortality of men and women in the three highest quartiles of heart-rate corrected QT, relative to those in the lowest quartile, using five different formulas to correct the QT interval for heart rate

| Formula                              | Group | Percentile |       |       | Hazard ratio  |               |               |
|--------------------------------------|-------|------------|-------|-------|---------------|---------------|---------------|
|                                      |       | 25th       | 50th  | 75th  | Q2*           | Q3†           | Q4‡           |
| 1. Bazett <sup>[8]</sup>             | M     | 406        | 421   | 437   | 0.7 (0.3–1.5) | 0.7 (0.3–1.5) | 1.3 (0.7–2.4) |
|                                      | F     | 418        | 432   | 446   | 1.0 (0.4–2.6) | 1.8 (0.8–4.1) | 2.4 (1.1–5.3) |
|                                      | All   |            |       |       | 0.8 (0.5–1.5) | 1.1 (0.6–1.9) | 1.7 (1.0–2.7) |
| 2. Fredericia <sup>[23]</sup>        | M     | 401        | 413   | 426   | 1.0 (0.4–2.2) | 1.1 (0.5–2.5) | 1.6 (0.8–3.3) |
|                                      | F     | 408        | 420   | 432   | 0.5 (0.2–1.3) | 1.2 (0.5–2.5) | 1.9 (0.8–4.4) |
|                                      | All   |            |       |       | 0.7 (0.4–1.3) | 1.1 (0.7–2.0) | 1.7 (1.1–2.8) |
| 3. Linear regression <sup>[10]</sup> | M     | 400        | 411   | 424   | 0.9 (0.4–2.1) | 1.2 (0.6–2.7) | 1.6 (0.8–3.3) |
|                                      | F     | 410        | 421   | 433   | 0.5 (0.2–1.4) | 1.3 (0.6–2.9) | 2.1 (1.1–4.2) |
|                                      | All   |            |       |       | 0.7 (0.4–1.4) | 1.3 (0.7–2.2) | 1.8 (1.1–3.0) |
| 4. Normogram <sup>[12]</sup>         | M     | 403        | 414   | 427   | 1.0 (0.5–2.3) | 1.0 (0.5–2.2) | 1.5 (0.5–2.3) |
|                                      | F     | 410        | 421   | 433   | 0.6 (0.2–1.6) | 1.3 (0.6–2.9) | 2.1 (1.0–4.1) |
|                                      | All   |            |       |       | 0.8 (0.5–1.5) | 1.3 (0.7–2.2) | 1.7 (1.1–2.9) |
| 5. QT index <sup>[11]</sup>          | M     | 98.3       | 101.5 | 104.8 | 1.2 (0.6–2.7) | 1.1 (0.5–2.5) | 1.7 (0.8–3.6) |
|                                      | F     | 100.5      | 103.4 | 106.6 | 0.4 (0.2–1.2) | 1.1 (0.5–2.3) | 1.7 (0.9–3.3) |
|                                      | All   |            |       |       | 0.8 (0.5–1.5) | 1.1 (0.6–1.9) | 1.7 (1.0–2.7) |

\*Q2=second quartile; †Q3=third quartile; ‡Q4=fourth quartile.  
M=male; F=female; All=combining sex-specific quartiles.

### *Risk associated with published threshold values for prolonged heart-rate corrected QT*

Participants with Bazett's QTc intervals above 420 ms had an increased risk for all-cause mortality (HR 1.6; 95%CI 1.2–2.1 in men and HR 1.6; 95%CI 1.1–2.2 in women). For this threshold value, the positive association between QT interval and cardiac mortality was not statistically significant in either men or women (HR 1.3; 95%CI 0.8–2.2 in men and HR 1.5; 95%CI 0.9–2.9 in women). Increasing the threshold for prolonged QTc to 440 ms resulted in higher risk estimates for all-cause mortality (HR 1.8; 95%CI 1.3–2.5 in men and HR 1.7; 95%CI 1.2–2.5 in women) and cardiac mortality (HR 1.6; 95%CI 0.9–2.9 in men and HR 1.9; 95%CI 1.0–3.7 in women). Those with Bazett's QTc intervals above 460 ms had a more than twofold risk for all-cause mortality (HR 2.4; 95%CI 1.5–3.8 in men and HR 2.1; 95%CI 1.4–3.2 in women) and cardiac mortality (HR 2.2; 95%CI 1.0–5.2 in men and HR 2.3; 95%CI 1.1–5.1 in women).

Overall, the risk for all-cause mortality associated with a certain threshold value was somewhat higher in men than in women, while the risk for cardiac mortality associated with a certain threshold value was higher in women than in men.

## Discussion

Results from the present study show that the prolonged heart-rate corrected QT interval predicts all-cause and cardiac mortality in older men and women, independent of other cardiovascular risk indicators. The risk for

all-cause and cardiac mortality associated with heart-rate corrected QT is hardly influenced by the formula used for correction.

Our results support the association between prolonged heart-rate corrected QT and cardiac mortality reported in two previous studies in non-hospitalized populations in the Netherlands<sup>[5,6]</sup>. In these studies, measurement of the QT interval was performed manually in a subset of leads, and absolute values of the QTc interval were systematically smaller than those measured by the MEANS program in the population of the Rotterdam Study. In the Zutphen Study<sup>[6]</sup>, elderly men with Bazett's QTc intervals above 420 ms had a threefold risk for coronary heart disease death (HR 3.1; 95%CI 1.3–7.6). This is even higher than the risk for cardiac mortality associated with prolonged QTc above 460 ms in men in the Rotterdam Study. This may partly be explained by the definition of end-points, as our definition of cardiac mortality is wider than the definition of coronary heart disease mortality in the Zutphen Study. In the Dutch Civil Servants Study<sup>[5]</sup> among 3000 healthy middle-aged men and women, Bazett's QTc above 440 ms was associated with a twofold risk for both all-cause mortality (odds ratio (OR) 1.8 in men and OR 1.9 in women) and cardiac mortality (OR 2.0 in men and OR 1.9 in women), after 15 years. No clear differences in risk estimates between men and women, such as we found, were reported. This may partly be explained by differences in population characteristics, as our population is older and selective survival may play a role, especially in men. Men with heart disease die younger than women, and the men who survive until older age may be healthier than women of the same age.

It has been suggested that the absence of the association between Bazett's QTc interval and cardiac

death in the Framingham Heart Study<sup>[7]</sup> may be explained by a U-shaped relationship, conferring increased mortality in those with short and in those with prolonged QT intervals. Although we did find a U-shaped relationship between heart-rate corrected QT and cardiac mortality in women with all correction formulas, this was least pronounced in Bazett's formula, and virtually absent for all formulas in men. In an additional analysis (data not shown) we found a statistically significant positive linear association between Bazett's QTc interval and all-cause and cardiac mortality in men and women. This suggests that the U- or J-shaped association is weak and the risk associated with QT prolongation is valid over the whole range of QT interval duration.

The relationship between prolonged heart-rate corrected QT and future cardiac mortality may be attributed to ventricular electrical instability and dispersion of repolarization, which give rise to early afterdepolarizations<sup>[24]</sup>. As in these mechanisms parasympathetic activity exhibits beneficial effects, an unfavourable balance in sympathetic and parasympathetic activity may play an important role. This is in accordance with the positive association between the QTc interval and blood pressure and heart rate. In addition, patchy myocardial fibrosis, with or without clinical symptoms, may lead to ventricular electrical instability and dispersion of repolarization. This is supported by the positive association of the heart-rate corrected QT interval with a history of myocardial infarction in our study.

Women have longer heart-rate corrected QT intervals than men (median of Bazett's QTc 432 ms vs 421 ms in the present study). It has been suggested that, based on the distribution of the heart-rate corrected QT interval, the threshold for prolonged QT should be higher in women than in men. However, the risk for cardiac mortality associated with certain threshold levels of prolonged QTc is at least as high in women as in men. Therefore, the threshold for prolonged heart-rate corrected QT in women should be comparable with that in men.

As the prevalence of prolonged heart-rate corrected QT is higher and the relative risk for cardiac mortality is somewhat higher in women than in men, the proportion of cardiac deaths attributable to the prolonged QT interval is greater in women than in men. It should be emphasized, however, that the absolute risk for cardiac death is greater in men than in women.

The risk associated with the heart-rate corrected QT interval is hardly influenced by the correction formula used. In an additional analysis (data not shown) the uncorrected QT interval itself had hardly any prognostic value for cardiac mortality. When we added the RR interval as an independent variable to the model, we found hazard ratios similar to those for Bazett's formula. Apparently heart rate is a confounder which plays an important role in prediction of mortality by QT. This is illustrated by our finding that both corrected QT (using a correction formula) and adjusted QT (using

a multivariate model to adjust for heart rate) had similar predictive values. This is not explained by heart rate or RR by itself (data not shown), which has little prognostic value in this elderly population. Although all formulas may be used for risk stratification, there is no reason to discard Bazett's formula, which is most frequently used in reported studies as well as in clinical practice.

In this study we used the extensively validated MEANS computer program<sup>[22,25]</sup> to measure the QT interval, without supervision of human ECG interpreters. The use of a computer program offers a standardized and efficient way to interpret ECGs, without the intra- and inter-observer variation of human observers measuring and interpreting ECGs. The results of the present study imply that the heart-rate corrected QT interval obtained with the MEANS program can be used to identify subjects at risk for future cardiac and all-cause mortality in the population at large and in a clinical setting. As system-specific thresholds for prolonged QT interval corrected with Bazett's formula, obtained by the MEANS program, 440 or 460 ms can be used. If another measurement technique is used, absolute values of the QTc interval and the precision of the QT measurement may differ systematically from our method<sup>[21]</sup>, and this would require modifications of the thresholds applied.

In conclusion, the QTc interval is an independent predictor of cardiac and all-cause mortality in men and women. In clinical practice, the prolonged heart-rate corrected QT can be easily determined, manually as well as by computer, and may be used to identify subjects at increased risk for future mortality.

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