Prolonged QT Interval:
A Tricky Diagnosis?

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Prolonged heart-rate adjusted QT intervals on the electrocardiogram (ECG) are associated with an increased risk for coronary heart disease and sudden death. However, the diagnosis of the prolonged QT interval is hampered by lack of standards. We studied variations in the prevalence of prolonged QT, based on different common definitions, in a large nonhospitalized population, and compared our results with other studies applying the same definitions. The study population consisted of 2,200 men and 3,366 women participants of the Rotterdam Study, ≥55 years old. The QT interval was computed by our Modular ECG Analysis System (MEANS). Three different formulas to adjust QT for heart rate were used: Bazett’s formula (QTc), a linear regression equation (QTlr), and the QT index (QTI). Prolonged QT occurred frequently in both men and women, and its prevalence increased with age. Women had longer heart-rate adjusted QT intervals than men (mean QTc 433 ms vs 422 ms), and mean values for QTc were lower than for QTlr (mean QTlr 422 ms in men and 412 ms in men). Prevalence was highest for prolonged QTc (31% in men and 26% in women) and lowest for prolonged QTI (6% in men and 9% in women). Comparison with other studies applying the same correction formulas showed large discrepancies in prevalence estimates of prolonged QTc and QTlr, and to a lesser degree of prolonged QTI, possibly due to differences in measurement techniques. Future research is needed to relate QT interval to prognosis, to obtain measurement technique specific reference values of heart-rate adjusted QT measurements, and to obtain age- and sex-specific threshold values for prolonged QT. Such data are needed to use the QT interval with confidence.

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ACTA cardiograph (Florence, Italy) with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain electrocardiographic measurements and diagnostic interpretations. The QT interval was determined over all leads in 1 representative complex, which resulted from selective averaging of dominant beats. To adjust QT for heart rate, 3 different methods were used. First, we calculated the corrected QT interval (QTc) according to Bazett’s formula: QTc = QT / \sqrt{RR}, where RR is the RR interval.

METHODS

Study population and data collection: This study is part of the Rotterdam Study,14 a population-based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere.14 Briefly, in the Rotterdam Study, all men and women ≥55 years old and living in the Rotterdam district of Ommoord, were invited to participate. Of the 7,129 participants who took part in the study (response rate 69%), baseline data, collected from 1990 to 1993, included an electrocardiogram (ECG), history of cardiovascular disease, established cardiovascular risk factors, and use of medications. A digitally stored ECG was available for 6,160 participants (86%). Fourteen percent of the ECGs were missing due to temporary technical problems with the electrocardiographic recorder. Participants with arrhythmias (n = 290) and those with complete left or right bundle branch block (n = 304) were excluded, leaving 2,200 men and 3,366 women in the present study.

QT measurement and correction for heart rate: A 12-lead ECG at rest was recorded with an ESAOTE-ACTA cardiograph (Florence, Italy) with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain electrocardiographic measurements and diagnostic interpretations. The QT interval was determined over all leads in 1 representative complex, which resulted from selective averaging of dominant beats. To adjust QT for heart rate, 3 different methods were used. First, we calculated the corrected QT interval (QTc) according to Bazett’s formula: QTc = QT / \sqrt{RR}, where RR is the RR interval.

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interval in seconds. Second, we used a linear regression equation that was also applied in the Framingham Study: $QT_{tr} = QT + 0.140*(1-RR)$ in men and $QT_{tr} = QT + 0.163*(1-RR)$ in women. In the Framingham Study, application of the linear regression equation had very similar results: $QT_{tr} = QT + 0.147*(1-RR)$ in men and $QT_{tr} = QT + 0.167*(1-RR)$ in women. Examination of the linear regression that QTc, QTlr, and QT with RR showed a negative association of QTc (regression coefficient $r = -0.08$, $p < 0.001$) and QTI ($r = -0.01$, $p < 0.001$) with RR. Consequently, QTc and QTI do not completely correct QT for heart rate. As expected, there was no significant linear association of QTlr with RR.

**Distribution of heart-rate adjusted QT intervals:** In Table II, the mean values of QT, RR, QTc, QTlr, and QTI and the prevalence of prolonged heart-rate adjusted QT, defined in 4 different ways, were assessed in men and women separately and in different age groups. In addition, we studied whether QTc, QTlr, and QTI were still associated with the RR interval using a linear regression model. In this case, this would indicate that the correction for heart rate with the formula is not complete. Prevalences from published reports were compared with adjusted results from our study, using the same exclusion rules and, if necessary, adjusting for age using linear regression analysis. All analyses were performed for men and women separately, using BMDP statistical software (version 7, 1990, Los Angeles, California).
ms, respectively. Overall, QTc ranged from 345 to 628 ms in men and from 329 to 538 ms in women. In both men and women, mean QTpr was about 10 ms shorter than the adjusted mean QTc in the Rotterdam Study, which was 425 ms (SD 22). Mean QTpr was about 375 ms in men and 388 ms in women participating in the Framingham Study, whereas the adjusted mean values of QTpr were 401 ms (SD 19) in men and 416 ms (SD 18) in women in the Rotterdam Study. Prevalences of prolonged QTc and prolonged QTpr were markedly higher in the Rotterdam Study than in other published studies using the same formulas. Prevalence of prolonged QTc was lower in women in the Rotterdam Study compared with women in the Cardiovascular Health Study, except for the highest age group, but estimates for men were similar.

**DISCUSSION**

The results of this study show that a prolonged heart-rate adjusted QT interval is more frequent in women than in men and that the prevalence in both sexes increases markedly with age. Mean values of heart-rate adjusted QT interval and prevalence of prolonged heart-rate adjusted QT vary substantially according to the correction formulas and threshold values used. Comparison of our findings with data presented from other studies showed that even if the same formulas to adjust QT for heart rate are used, large differences in estimates of prevalence of prolonged QT can be observed.

Because QTpr was the only formula without a residual linear association with the RR interval, this formula may be preferable to QTc and QTI when linear associations of QT with cardiovascular determinants are examined. The linear regression coefficients estimated from the Framingham Study were very similar to our estimates. Thus, in studies with a relatively small number of participants, regression coefficients need not be derived, but coefficients from the Framingham Study or from the present study can be used.

Comparison with previous studies showed that marked differences in prevalence estimates of prolonged QT were present between studies using the same correction formulas. These discrepancies may at least partly be explained by differences in measure-
The definition of prolonged heart-rate adjusted QT, depending on the threshold value used to distinguish between normal and prolonged QT, can be based on prognostic implications for clinical end points. Depending on the purpose of diagnosing prolonged QT, higher or lower thresholds and associated risk levels may be considered relevant, which also influences the number of subjects detected with prolonged QT. Instead of dichotomous thresholds, multilevel risk groups or continuous estimates associated with heart-rate adjusted QT may be studied. Because women have systematically longer (about 10 ms) heart-rate adjusted QT intervals, it seems that the threshold value for prolonged QTc and QTlr should be higher in women than in men.

Using data from large population-based follow-up studies, such as the Rotterdam Study,14 may offer an opportunity to circumvent the problem of the lack of standards by establishing specific reference values for each electrocardiographic computer program or manual measurement technique separately. For each method, age- and sex-specific normal values of QT interval can be assessed, together with threshold values for the prolonged heart-rate adjusted QT interval. Thresholds should depend on the additional risk associated with a certain length of the heart-rate adjusted QT interval, for example, a two- or threefold risk for cardiovascular morbidity or mortality. This would facilitate uniform diagnoses of those with prolonged heart-rate adjusted QT intervals, and link them to established levels of risk. Consequently, prevalence of prolonged heart-rate adjusted QT can be compared between different populations. More importantly, this would enable physicians to target preventive measures at patients with QT intervals, inferring increased cardiovascular risk. At present, in the absence of these measurement technique specific reference values, the prolonged QT interval remains a tricky diagnosis.

5. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J.

### TABLE III Prevalence of Prolonged QT in the Rotterdam Study Compared With Three Population-Based Studies

<table>
<thead>
<tr>
<th>Definition</th>
<th>Men, age 65–64</th>
<th>Men, age 65–84</th>
<th>Men, age 29–62</th>
<th>Women, age 65–74</th>
<th>Women, age 65–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt;420 ms*</td>
<td>720 (31.4–38.5)</td>
<td>573 (44.6–60.2)</td>
<td>2,239 (9.3–16.4)</td>
<td>1,71 (15.7–18.5)</td>
<td></td>
</tr>
<tr>
<td>QTc &gt;420 ms†</td>
<td>2,779 (21.9–31.9)</td>
<td>14.7 (13.1–16.4)</td>
<td>2,779 (21.9–31.9)</td>
<td>17.1 (15.7–18.5)</td>
<td></td>
</tr>
<tr>
<td>QTc &gt;432 ms†</td>
<td>2,779 (21.9–31.9)</td>
<td>14.7 (13.1–16.4)</td>
<td>2,779 (21.9–31.9)</td>
<td>17.1 (15.7–18.5)</td>
<td></td>
</tr>
</tbody>
</table>

*QTc = QT/√RR.
†QTc = QT/√(656/(1 + 0.01*heart rate)).
§Adj. prevalence after applying the same exclusion criteria as in the comparison study and adjusting for age using linear regression if necessary.

Numbers of participants in different age groups in the Rotterdam Study are presented in Table II.


