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EDITORIAL COMMENT

QTc Prolongation and Sudden Cardiac Death

The Association Is in the Detail*

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In their paper in this issue of the *Journal*, Straus et al. (1) have clarified a somewhat controversial area involving the association of QTc prolongation with the risk of sudden cardiac death (SCD) in an adult population. Straus et al. (1) determined the risk relationship between QTc duration and the probability of SCD in 6,134 subjects age 55 years and older who were enrolled in a prospective, population-based Rotterdam study in which the average follow-up was 6.7 years. Subjects with an abnormally prolonged QTc interval had a more than three-fold increased risk for SCD after adjustment for relevant covariates.

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Why the controversy? In brief, good-quality epidemiologic studies investigating the QTc-risk question have come up with different results regarding the mortality risk posed by QTc prolongation in a general population. For example, the Framingham study was unable to demonstrate an association of baseline QTc prolongation with total mortality or sudden death (2), yet positive findings have been reported in the longitudinal Zutphen study from the Netherlands involving middle-aged and elderly men (3), in the Strong Heart Study that enrolled American Indians (4), and in the Cardiovascular Health Study involving community-dwelling elderly subjects (5). The negative Framingham study is of particular concern because it is well appreciated that the Framingham investigators have consistently provided excellent scientific studies. In brief, why is the Framingham study different from all other studies or, better still, why the difference between the Rotterdam study and the Framingham study? Both were population-based studies, with the Rotterdam study involving men and women age 55 years and older who were followed on average for more than 6 years, whereas the Framingham study involved subjects ages 30 to 65 years at entry into the study in 1948 with follow-up extending over a 30-year period. This important design difference in the two studies may explain a good portion of the discrepant results. In the Framingham study, the baseline electrocardiogram (ECG) was recorded in a majority of the subjects at a relatively young age, probably before the development of subclinical cardiac disease; the Rotterdam study recorded the first of two baseline ECGs when the subjects were enrolled in the study at age 55 years, an age when subclinical cardiac disease is likely to be present in many of the subjects.

There are some important details in the categorized QTc interval cutoffs used in the Straus et al. (1) study that warrant specific attention. Straus et al. (1) subdivided the Bazett-corrected QTc interval into gender-specific groupings for women and men and further subdivided the QTc interval into normal, borderline, and prolonged categories. Their QTc classification approach is essentially identical to the classification that we developed in 1992 (6) and that was subsequently adopted as part of the European Guidelines on QT Interval Prolongation (7). Using this approach, the Rotterdam investigators were able to show a dose-response effect between the duration of the QTc interval (borderline and abnormally prolonged categories relative to normal QTc duration) and the risk of SCD in the entire population in two age groups (55 to 68 years and >68 years) and separately for men and women after adjustment for relevant covariates. This dose-response effect adds considerable strength and significance to the association of QTc prolongation and the risk of SCD in older adults.

What are some of the possible mechanisms for the observed risk association? The simplest explanation is that QTc prolongation, whatever the cause, is proarrhythmic, and this alone contributes to an increased probability of arrhythmic SCD. It is possible that the length of the QTc interval is just a marker for the severity of underlying subclinical cardiac disease (coronary, hypertension, nonischemic cardiomyopathy, and so forth) and that the risk is related to the latent underlying cardiac problem. The authors tried to adjust for some of the relevant covariate risk factors, but, as in any observational study, adjustment is never complete. Could the QTc prolongation in a general adult population reflect genetic variability, with the increased risk for SCD being a direct consequence of gene-related, modest QTc prolongation? It is possible that the presence of one or more ion-channel gene polymorphisms could cause minor alterations in ion-channel function that contributes to modest prolongation in cardiac repolarization and an increased probability for fatal arrhythmias. For example, a D85N polymorphism in the KCNE1 gene, the beta-subunit of the I_{Ks}, has been associated with drug-induced QTc prolongation (8). The frequency of this polymorphism is approximately 2% to 3% in the general population. In vitro cellular expression studies have substantiated the functional effect of this polymorphism on ventricular repolarization. Alone, this polymorphism might have only negligible effects on the QTc duration in a general population. However, the presence of additional unrecognized ion-channel polymorphisms may have additive effects on the QTc duration such that individuals who carry several

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of these polymorphisms, as postulated in the carriership model (9), might be at increased risk for SCD. Such polymorphisms are being investigated as modifier genes to explain the normal variation in the QTc interval that exists among overtly healthy individuals (10).

In summary, the Rotterdam group has enhanced our understanding of the relationship between QTc duration and the risk of SCD in older adults. The question is whether this well-crafted risk-stratification study can be translated into effective management strategies to reduce SCD and improve survival in subjects with prolonged ventricular repolarization.

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