Is OT interval prolongation a strong or a weak predictor for cardiac death?

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Letters to the Editor

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Is QT Interval Prolongation a Strong or a Weak Predictor for Cardiac Death?

In Ahnve's Editorial Comment in *Circulation*,[1] based in part on our own papers,[2,3] he discusses the prognostic value of QT_c prolongation. We agree with his conclusion that QT_c duration of >440 msec is associated with increased risk for cardiac death. However, we would like to draw attention to the observed difference between men and women.

Among women, the prevalence of QT_c prolongation is two to three times higher than among men.[2-6] However, we found that QT_c of ≥440 msec is much less predictive of coronary heart disease mortality or sudden death in women than in men. In the 28-year follow-up study of >3,000 civil servants, men with QT_c of ≥440 msec had twice the risk of coronary heart disease mortality as men with QT_c of <420 msec. Among women, the relative risk was only 1.1.[2] The risk for cardiovascular disease mortality was somewhat higher but not significant. Choosing a cut off of 450 or 460 msec did not make any difference. The discrepancy also was reported in the 2-year follow-up study among 6,693 patients who had 24-hour ambulatory ECG. Men with QT_c of >440 msec had a relative risk of sudden death of 3.3 compared with men with QT_c <440 msec. For women, the relative risk was 1.7.[3]

The association between QT_c duration and cardiac death clearly seems to vary by sex. Of course, this implies that data from men and women should be processed and reported separately. If not, the increased risk among men may be obscured. In studies in which women make up a large part of the prolonged QT_c category,[5] this may have diluted the relative risks reported. Most previous studies did not report results for men and women separately. Some did not describe the sex distribution of the subjects either.

Several other ECG characteristics have proved to be different between men and women.[7,8] What causes these differences between men and women? It might be the smaller size of the female heart or some effect of hormonal differences or of the autonomic regulation of the heart. This may be an interesting topic for future physiological and ECG studies. Whatever the physiological background, the sex discrepancy should be taken into consideration in the analysis and interpretation of ECG data.

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Joint Effects of Serum Triglycerides and LDL and HDL Cholesterol

In a further analysis of the Helsinki Heart Study, Manninen et al[1] have attempted to elucidate the troublesome relation between serum triglyceride levels and coronary heart disease. Although their analysis is intriguing, several problems remain.

First, and most importantly, we should be cautious about implications for drug treatment in populations of people who do not have clinical disease. As the authors note, there was no significant decrease in all-cause mortality in the gemfibrozil-treated group, even in the highest-risk stratum. In fact, when data from the first 1.5 years of poststudy follow-up are included, there was an almost significant increase in noncardiac deaths in the treatment group (43 versus 27, $p=0.056$) and no significant difference in total mortality overall (59 versus 55, $p=0.7$).[2] Data from 2 more years of follow-up presented at the NIH Conference on HDL and Triglycerides (Bethesda, Md., February 26–28, 1992) revealed a trend toward increasing total mortality in the gemfibrozil group, with 101 deaths in the treatment arm versus 83 deaths in the placebo arm ($p=0.16$). This information, combined with other recent data,[3] raises further questions about the wisdom of drug treatment for altering blood lipids in otherwise healthy individuals.

Second, although a stratified analysis avoids the modeling assumptions of regression analysis, it does not fully "eliminate the effects of multicollinearity." When subsamples defined by high density lipoprotein (HDL) levels (or the ratio of low density lipoprotein [LDL] to HDL) are again stratified by triglyceride levels, the result is four strata that differ in levels of HDL, since stratification does not eliminate the correlation between triglyceride and HDL. That is, the highest-risk group in the article's Figure 3, defined by the combination of a low HDL/LDL ratio and a high triglyceride level, is also unique in having the lowest mean HDL level of the four strata. This fact is verified by reference to Table 7, which reveals a monotonic increase in the proportion of subjects in the lowest tertile of HDL.

Third, an analysis of the heterogeneity of the odds ratios does not support the presence of a statistically significant interaction. Using the data from Figure 3 and Table 6, we performed a χ^2 test for interaction that yielded a value of $p=0.22$. The authors should