

COMMENTS AND RESPONSES

Prediction of Mortality Using Measures of Cardiac Autonomic Dysfunction in the Diabetic and Nondiabetic Population: The MONICA/KORA Augsburg Cohort Study

Response to Ziegler et al.

A recent article by Ziegler et al. (1) on the value of electrocardiogram (ECG) parameters (corrected QT [QTc] interval and heart rate variability) in identifying diabetic subjects at increased risk of mortality showed that QT interval corrected for heart rate using Bazett's formula (QTcB) >440 ms was associated with higher mortality. While these results are clinically very relevant, the title of the paper suggests that QTc prolongation is caused by cardiac autonomic neuropathy. In fact, other factors may also prolong QTc interval in diabetic subjects (2,3).

We analyzed baseline ECGs of 189 diabetic subjects participating in two phase II drug studies. A total of 65 were with and 124 without clinically manifest peripheral neuropathy. As found by Ziegler et al., the mean \pm SD heart rate was higher in diabetic subjects with ($70 \pm$

8 bpm) and without neuropathy (75 ± 9 bpm) than in healthy control subjects (57 ± 10 bpm; $P < 0.05$) (4). QTcB was also longer in diabetic subjects with (416 ± 24 ms) and without neuropathy (410 ± 66 ms) than in control subjects (393 ± 23 ms) ($P < 0.01$ vs. diabetic subjects). QTcB >440 ms (the cutoff found to be associated with increased mortality in the Ziegler et al. study) was seen in 31% of diabetic subjects without neuropathy, 18.5% of diabetic subjects with neuropathy ($P = 0.06$ vs. diabetics without neuropathy), and 4% of healthy control subjects ($P < 0.01$ vs. both groups of diabetic subjects) (4), suggesting that QTc prolongation may occur even in diabetic subjects without peripheral neuropathy. Besides subclinical cardiac autonomic neuropathy, other mechanisms that could contribute to QTc prolongation include acute hyperglycemia (2) or hypoglycemia (3), altered cytosolic calcium content (2), electrolyte disturbances (2), and oxidant-induced changes in expression of cardiac membrane rapidly activating delayed rectifier potassium ion (I_{Kr}) channels (3).

Ziegler et al. also found that decreased difference between the maximum and minimum R-R intervals on a 20-s ECG tracing was associated with increased risk of death (1). We analyzed the difference between the maximum and minimum R-R intervals in 10-s ECG recordings in our subjects and found that this was significantly lower in diabetic subjects with (median 32 ms [interquartile range 17–59.5]) and without neuropathy (30 ms [18–52]) than in normal subjects (73 ms [46–133.5]; $P < 0.001$ by Mann-Whitney U test). There was no significant difference between the two diabetic groups ($P = 0.721$). Ziegler et al. analyzed risk of death for the lower quartile versus that for the upper three quar-

tiles without mentioning a cutoff value below which decreased heart rate variability is associated with increased mortality. Defining a cutoff value for heart rate variability would have made their observations more clinically relevant.

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