Increased QT Interval Dispersion Predicts 15-Year Cardiovascular Mortality in Type 2 Diabetic Subjects

The population-based Casale Monferrato Study

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OBJECTIVE—To evaluate the predictive role of increased corrected QT (QTc) and QT interval dispersion (QTd) on all-cause and cardiovascular mortality in a large, unselected type 2 diabetic population.

RESEARCH DESIGN AND METHODS—The prospective study included 1,357 type 2 diabetic patients from the Casale Monferrato Study. At baseline, QTc intervals >0.44 s and QTd intervals >0.08 s were considered abnormally prolonged. Both all-cause and cardiovascular mortality were assessed 15 years after the baseline examination.

RESULTS—During the follow-up period, 862 subjects per 12,450 person-years died. Multivariate analysis showed that the hazard ratio (HR) of cardiovascular mortality was significantly increased in subjects with prolonged QTd (1.26 [95% CI 1.02–1.55]) and was only slightly reduced after multiple adjustments. Conversely, prolonged QTc did not increase the HRs for all-cause or cardiovascular mortality.

CONCLUSIONS—Increased QTd predicts cardiovascular mortality after a long-term follow-up period in a large, unselected population of type 2 diabetic subjects.

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D iabetes is a known cardiovascular risk factor, and there is much interest in the identification of factors that may improve cardiovascular risk stratification in diabetic subjects, possibly by using noninvasive low-cost approaches. In the general population, prolonged corrected QT (QTc) and increased QT interval dispersion (QTd), reflecting abnormalities of ventricular myocardial repolarization, are independent predictors of mortality (1). However, in type 2 diabetic subjects, the predictive role of QTc and QTd on all-cause and cardiovascular mortality remains controversial because studies addressing this issue were performed on small cohorts and/or had relatively short follow-up periods and/or focused on populations representative of specific ethnic groups (2–9). Therefore, we performed a prospective study to assess the predictive role of increased QTc and QTd on all-cause and cardiovascular mortality in an unselected, large population of type 2 diabetic subjects after a long-term follow-up period.

RESEARCH DESIGN AND METHODS—The study base included 1,540 type 2 diabetic subjects residing in Casale Monferrato (93,477 inhabitants) in 1991 who were identified through diabetes clinics, general practitioners, hospital discharges, prescriptions, and sales records of reagent strips/syringes (10,11). Electrocardiogram (ECG) records suitable for QTc/QTd evaluation were available for 1,359 (88%) patients (580 male and 779 female). R-R and QT intervals were measured blindly by two observers on the resting ECG tracing, using five consecutive beats on a lead V5. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to the Bazett equation (12). A QTc >0.44 s was considered abnormally prolonged. R-R and QT intervals also were measured for three consecutive cardiac cycles on the six thoracic leads. QTc dispersion was calculated using the difference between the maximum and the minimum QTc in any thoracic leads. A QTd >0.080 s was considered abnormally increased (10).

The relevant time scale for the analysis was the time since diabetes diagnosis to death or to 31 December 2006 (11). During the follow-up period (1991–2006), patients were regularly evaluated (three to four times per year) at the diabetes clinic or by general practitioners. Information on both deaths and the causes of death was obtained from the demographic files of towns of residence, hospital discharges, and autopsy records. Causes of death were derived and coded according to the ICD-9 classification (11) by two independent observers.

The role of QTc and QTd as independent predictors of cardiovascular and all-cause mortality was assessed using multivariate Cox proportional hazards models. The test for nonproportional hazard was performed using Shoenfeld residuals. The *P* value was two-sided and considered statistically significant when <0.05.

RESULTS—As previously reported (10), at the baseline examination subjects with increased QTc (*n* = 354) or QTd (*n* = 448) were older and had higher systolic and/or diastolic blood pressure. Patients with increased QTd also had greater creatinine and fibrinogen levels. Of 1,359 subjects recruited at baseline, information on vital status at follow-up was available for 1,357 patients (99.8%). During follow-up, 862 patients per 12,450 person-years died. Of these, 440 subjects died of cardiovascular disease. Relative to the

Table 1—*Mortality rates and results of Cox regression analyses in the Casale Monferrato Study by QTc and QTd*

	Number of deaths	Rate per 1,000 person-years (95% CI)	Model 1	Model 2	Model 3	Model 4
All-cause mortality						
QTc (s)						
≤0.44	589	67.5 (62.3–73.2)	1.00	1.00	1.00	1.00
>0.44	273	73.2 (65.0–82.4)	1.08 (0.93–1.24)	1.05 (0.91–1.21)	1.08 (0.93–1.26)	1.04 (0.89–1.23)
QTd (s)						
≤0.08	635	67.1 (62.1–72.6)	1.00	1.00	1.00	1.00
>0.08	227	75.4 (66.2–85.8)	1.11 (0.95–1.29)	1.06 (0.91–1.24)	1.10 (0.94–1.29)	1.06 (0.90–1.26)
Cardiovascular mortality						
QTc (s)						
≤0.44	300	34.5 (30.8–38.6)	1.00	1.00	1.00	1.00
>0.44	140	37.5 (31.8–44.3)	1.07 (0.88–1.31)	1.04 (0.85–1.28)	1.08 (0.88–1.34)	1.02 (0.81–1.27)
QTd (s)						
≤0.08	313	33.1 (29.6–37.0)	1.00	1.00	1.00	1.00
>0.08	127	42.2 (35.4–50.2)	1.26 (1.02–1.55)	1.21 (0.99–1.49)	1.27 (1.02–1.57)	1.23 (0.97–1.54)

Model 1: unadjusted; model 2: adjusted for age and sex; model 3: model 2 plus hypertension, apoB-to-apoA1 ratio, HbA_{1c}, micro-/macroalbuminuria, and smoking; and model 4: model 3 plus coronary heart disease.

reference category with QTd ≤0.08 s, the hazard ratio (HR) for cardiovascular mortality was 1.26 (95% CI 1.02–1.55) in patients with increased QTd and only was slightly reduced after multiple adjustment for age, sex, hypertension, smoking, apolipoprotein (apo)B-to-apoA1 ratio, HbA_{1c}, coronary heart disease, and micro-/macroalbuminuria (Table 1). Conversely, prolonged QTc did not increase the HRs for all-cause or cardiovascular mortality. Tests for nonproportional hazard resulted as nonsignificant in all analyses.

CONCLUSIONS—This study provides evidence that, in a large population-based cohort of type 2 diabetic patients, increased QTd confers increased long-term cardiovascular mortality risk, independently of other cardiovascular risk factors. Previous reports have suggested a similar conclusion. However, they were performed on small clinic-based type 2 diabetic cohorts (2,8,9) and had a relatively short follow-up period (3).

A previous prospective study on an unselected type 2 diabetic population of American Indians showed the predictive value of ventricular repolarization abnormalities on cardiovascular mortality (4). Our results are in line with these findings and extend them to a European type 2 diabetic population.

Unlike previous reports (2–6,9,12), the current study did not identify QTc as a predictor of all-cause (4–6,12) and/or cardiovascular (2,3,9,12) mortality,

possibly because of differences in the study design (2–6,9,12) and prolonged QTc cutoff values (4). Compared with population-based studies, clinic-based studies (2,3,5,6,9,12) notoriously have a potential for a selection bias, such as selecting patients with more severe illness. Nevertheless, findings from the current study are consistent with the view that QTd is a better cardiovascular risk predictor than QTc in type 2 diabetic subjects (3).

The prospective study design; the large population sample; the representativeness of the study base with regard to the Italian diabetic population; the high estimated completeness of ascertainment; the recruitment of subjects cared for by both general practitioners and diabetes clinics, thus limiting the effect of selection bias; and the centralized assessment of measurements are key strengths of our study.

The main limitation is represented by the manual assessment of the QT interval. However, ECGs potentially interfering with accurate QT interval measurements were excluded, and analyses were performed blindly. Furthermore, the QTc for each subject was considered as the mean of the readings of two observers to minimize interobserver variability (10).

The possibility that changes in QTc/QTd abnormalities occurred during follow-up cannot be excluded. However, QT abnormalities do not change significantly over time in type 2 diabetic patients (2). Furthermore, changes in repolarization later in time with respect to baseline

would have resulted in an underestimation bias of HRs of QTc and QTd.

Finally, coronary heart disease, micro-/macroalbuminuria, HbA_{1c}, and the apoB-to-apoA1 ratio (10,13–15) have been found to be associated with increased QTc or QTd and/or cardiovascular morbidity/mortality. Therefore, adjustment for these factors could result in an overadjustment bias that would ultimately reduce the statistical significance of the HRs in the fully adjusted model 4.

In conclusion, we found that increased QTd predicts cardiovascular mortality in type 2 diabetic subjects. This observation is of clinical relevance because it may help in identifying people at higher cardiovascular risk by using a noninvasive and low-cost tool.

for the integrity of the data and the accuracy of the data analysis.

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