

# QT Interval Prolongation and Mortality in Type 1 Diabetic Patients

## A 5-year cohort prospective study

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**OBJECTIVE** — The aim of the study was to assess the relationship between QT interval prolongation and mortality in type 1 diabetic patients.

**RESEARCH DESIGN AND METHODS** — Data on survival after 5 years were obtained from 316 of 379 patients (83.3%) who took part in a study on the prevalence of diabetic neuropathy and QT interval prolongation.

**RESULTS** — Mortality at 5 years was 6.32%. Patients who survived were significantly younger ( $P=0.04$ ), had a shorter duration of diabetes ( $P=0.01$ ), had lower systolic ( $P=0.004$ ) and diastolic ( $P=0.03$ ) blood pressure levels, and had a shorter QT interval corrected for the previous cardiac cycle length (QTc) ( $P=0.000005$ ) than subjects who died. In univariate analysis, patients had a higher risk of dying if they had a prolonged QTc (odds ratio [OR] 20.14 [95% CI 5.7–70.8]) or if they were affected by autonomic neuropathy (3.55 [1.4–8.9]). QTc prolongation was the only variable that showed a significant mortality OR in multivariate analysis (24.6 [6.51–92.85];  $P=0.000004$ ).

**CONCLUSIONS** — This is the first cohort-based prospective study indicating that QTc prolongation is predictive of increased mortality in type 1 diabetic patients.

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An excess mortality risk has been reported in normal subjects with QT interval prolongation (1,2). In diabetes, the association of QT interval prolongation with resting electrocardiogram (ECG), autonomic neuropathy, poor survival prognosis, and sudden death has been suggested by studies performed on selected series of patients (3–8). Recently, 1 cohort-based retrospective study reported that QT interval prolongation predicted mortality in a group of 182 newly diagnosed type 2 diabetic patients representing the Dundee

cohort of the U.K. Prospective Diabetes Study (9). A similar study in type 1 diabetic patients has not yet been conducted.

**RESEARCH DESIGN AND METHODS** — A random sample of 379 of all 766 type 1 diabetic patients attending 22 outpatient clinics in Piemonte, Italy, and 118 healthy subjects matched for sex and age were studied in 1989 to assess the prevalence of diabetic neuropathy. Because all type 1 diabetic patients in Italy must attend diabetes clin-

ics for insulin and syringe prescriptions, this sample was representative of the type 1 diabetic population in the area of the study and met the requirements to permit inferences on the prevalence of neuropathy (10) and QT prolongation (11) in the type 1 diabetic population.

Details on the study population, the sampling and screening procedures, and disease staging have been reported elsewhere (10,11). The diabetic patients included 196 males and 183 females (age distribution 15–29 years,  $n=174$ ; 30–44 years,  $n=155$ ; 45–59 years,  $n=50$ ). The control subjects included 59 males and 58 females (age distribution 15–29 years,  $n=45$ ; 30–44 years,  $n=40$ ; 45–59 years,  $n=33$ ). No patients abused alcohol, and they were asked to abstain from drinking any alcoholic beverages and from smoking on the evening before the day of testing. All of the patients gave their informed consent to participate in the study.

None of the patients was affected by renal failure. None of the patients was treated with antiarrhythmic drugs or cisapride. Less than 10% of the patients were treated with drugs affecting the cardiovascular system.

The presence of autonomic neuropathy was defined on the basis of the results of heart rate calculation on the same ECG used to assess QT interval and 2 cardiovascular tests: 1) the response of heart rate to deep breathing at the rate of 6 respiratory cycles/min (deep breathing test [DBT]) and 2) the response of blood pressure to the changing of posture from lying to standing (postural blood pressure test [PBPT]). Heart rate was defined abnormal if it was  $>100$  beats/min (12).

The cardiovascular tests were performed and evaluated as previously described (3). The cutoff values for abnormality were assessed as the means + 2 SD in healthy control subjects (10). DBT was abnormal if it was  $<15$  beats/min in subjects 15–29 years of age,  $<11$  beats/min in subjects 30–44 years of age, and  $<10$  beats/min in subjects 45–59 years of age. PBPT was abnormal if a fall in systolic arterial blood pressure  $>30$  mmHg was observed for all

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**Abbreviations:** DBT, deep breathing test; ECG, electrocardiogram; OR, odds ratio; PBPT, postural blood pressure test; QTc, QT interval corrected for the previous cardiac cycle length.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical characteristics

	Alive	Dead	P	Available at follow-up	Lost at follow-up	P
n	296	20	—	316	63	—
Male sex (%)	77.5	50	0.90	51.2	53.9	0.96
Age (years)	31.4 ± 11.1	36.7 ± 10.6	0.040	31.8 ± 11.2	33.4 ± 10.6	0.30
Duration of diabetes (years)	13.5 ± 8.7	18.7 ± 10.9	0.012	13.9 ± 8.9	15.5 ± 8.4	0.18
BMI (kg/m <sup>2</sup> )	22.6 ± 3.1	22.5 ± 2.9	0.87	22.6 ± 3.1	22.9 ± 2.7	0.47
Waist-to-hip ratio (cm/cm <sup>1</sup> )	0.8 ± 0.1	0.8 ± 0.06	0.59	0.8 ± 0.1	0.8 ± 0.07	0.80
Systolic blood pressure (mmHg)	123.9 ± 20.0	138.0 ± 35.6	0.004	124.8 ± 21.5	129.8 ± 15.4	0.08
Diastolic blood pressure (mmHg)	80.4 ± 11.4	86.2 ± 11.4	0.032	80.8 ± 11.7	81.8 ± 6.4	0.81
Heart rate (beats/min <sup>1</sup> )	84.3 ± 13.5	83.6 ± 11.2	0.80	84.3 ± 13.4	85.3 ± 14.6	0.60
QTc (s)	0.41 ± 0.03	0.45 ± 0.02	0.000005	0.42 ± 0.03	0.42 ± 0.02	0.33
Autonomic neuropathy (% affected)	22	50	0.004	25	26	0.67

Data are means ± SD unless otherwise indicated.

age-groups. Patients with 2 or more abnormal results for the cardiovascular tests and heart rate were considered to be affected by autonomic neuropathy (11).

QT and RR intervals were measured as described by Gonin et al. (13). The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to the formula proposed by Taran and Szilagyl (14), which known as “Bazett’s formula” (15):  $QTc = QT/(RR)^{1/2}$ . Although QTc does not vary much within individuals (16), 5 consecutive QT intervals and their corresponding RR intervals were measured because a single cardiac cycle may be insufficient to represent a person’s long-term QTc interval length. Two independent observers unaware of the grouping of any subject measured all the intervals, the QTc for each subject was calculated as the mean value of the 5 calculated intervals, and the mean of the readings of the 2 observers was used to minimize interobserver variability and to reduce the bias introduced by errors in manual measurements. All of the ECGs were recorded at the same paper speed (50 mm/s<sup>1</sup>), and lead 1 or lead 2 was chosen for QT analysis in each patient. QTc >0.44 s was considered abnormally prolonged in accordance with the criteria commonly used in the literature (1,17,18).

We have previously reported that the prevalence of QTc prolongation was 25.6% in the diabetic population and 7.6% in the control subjects. Furthermore, QTc prolongation was significantly associated with autonomic neuropathy in diabetic patients (diabetic patients with autonomic neuropathy vs. patients without QTc:  $0.43 \pm 0.033$  vs.  $0.417 \pm 0.034$  s, respectively;  $P < 0.01$ ).

Data on survival after 5 years were obtained by analyzing the patients’ files in the clinics for 316 of the 379 patients (83.3%) and 106 of 118 control subjects (90.5%). Clinical characteristics of patients available and lost to follow-up are shown in Table 1.

Statistical analysis was performed using the StatView software program (Abacus Concepts, Berkeley, CA). Data are means ± SD. The  $\chi^2$  test was used for comparison among groups of noncontinuous variables; otherwise, the Student’s *t* test was used. A logistical regression model that included systolic blood pressure, diastolic blood pressure, age, duration of diabetes, autonomic neuropathy (present vs. absent), QTc (categorized according to the duration of QTc interval: >0.44 vs. <0.44 s), smoking, personal history of ischemic heart disease, and hypertension and/or treatment with drugs was used to assess the relationship between variables and the risk of dying.

RESULTS — The patients lost to follow-up were not significantly different regarding

age, duration of disease, BMI, blood pressure, heart rate, prevalence of autonomic neuropathy, and QTc values versus subjects included in the follow-up study (Table 1). Mortality at 5 years was 6.32% (20/316) in diabetic patients and 0.9% (1/106) in the control group ( $P < 0.001$ ).

Patients who survived were significantly younger ( $31.4 \pm 11.1$  vs.  $36.7 \pm 10.7$  years;  $P = 0.04$ ), had a shorter duration of diabetes ( $13.6 \pm 8.7$  vs.  $18.7 \pm 10.9$  years;  $P = 0.01$ ), had lower systolic ( $123.9 \pm 20.0$  vs.  $138.0 \pm 35.6$  mmHg;  $P = 0.004$ ) and diastolic ( $80.5 \pm 13.6$  vs.  $83.6 \pm 11.2$  mmHg;  $P = 0.03$ ) blood pressure levels, and had a shorter QTc ( $0.41 \pm 0.03$  vs.  $0.45 \pm 0.02$  s;  $P = 0.000005$ ) than subjects who died (Table 1).

In univariate analysis, patients had a higher risk of dying if they had a prolonged QTc (odds ratio [OR] 20.14 [95% CI 5.7–70.8]) or were affected by autonomic neuropathy (3.55 [1.4–8.9]). QTc prolongation was the only variable that showed a highly significant mortality OR in multivariate analysis (Table 2).

Table 2—Relative risk of death associated with QTc interval prolongation in type 1 diabetic patients

Variable	OR (95% CI)	P
Systolic blood pressure (per additional mmHg)	1.01 (0.95–1.02)	0.45
Diastolic blood pressure (per additional mmHg)	1.05 (0.98–1.12)	0.11
Age (per additional year)	0.99 (0.93–1.06)	0.85
Personal history of ischemic heart disease (positive vs. negative)	1.67 (0.78–5.65)	0.45
Duration of diabetes (per additional year)	1.05 (0.97–1.14)	0.19
Autonomic neuropathy (present vs. absent)	2.21 (0.62–7.84)	0.22
QTc prolongation (>0.44 vs. ≤0.44 s)	24.6 (6.51–92.85)	0.000004

The results were obtained from logistical regression analysis.

**CONCLUSIONS** — This is the first cohort-based prospective study indicating that QTc prolongation is the most predictive factor of increased mortality in type 1 diabetic patients, even when other variables such as age, duration of disease, and blood pressure are taken into account.

The study was conducted on a random sample representative of the type 1 diabetic population in Piemonte in northwest Italy. Our results confirm similar observations in nondiabetic subjects (1,2), in patients who underwent Holter monitoring for various diseases (18), in diabetic patients with nephropathy (19), and in a cohort of newly diagnosed type 2 diabetic patients (9). Unfortunately, ascertaining causes of death in the sample was not possible because of restrictions on accessing personal data in Italy. Therefore, we are not able to calculate the relationship between QTc interval duration and specific causes of death, particularly sudden death.

Autonomic imbalance (11,20) and ischemic heart disease (21) seem to be the main causes of QT prolongation in diabetic patients. Both conditions are associated with an excess mortality together with nephropathy. Moreover, some drugs other than hypoglycemic agents and drugs that cause electrolyte disturbances may play an additional role in QTc lengthening. Therefore, the mechanism linking QTc prolongation and the excess mortality is probably complex and remains to be elucidated. In this study, the number of patients taking drugs affecting the cardiovascular system was small, and thus the role of drugs in QTc lengthening is negligible. We do not have information on incipient nephropathy and subclinical ischemic heart disease, so we cannot exclude the possibility that both of these factors had a role in the excess mortality among patients with prolonged QTc and thus confounded the relationship between QTc prolongation and mortality.

However, measurements of QTc interval are easily obtained without the need for patient compliance, and QTc analysis is a simple, inexpensive, and noninvasive test that could be used to stratify the death risk in diabetic patients, particularly those who are candidates for surgery or kidney and/or pancreas transplantation.

These preliminary results are stimulating for further prospective studies to evaluate the relevance of those factors known to influence QT duration and those factors potentially contributing to mortality in type 1 diabetes such as the degree of metabolic control, nephropathy, and ischemic heart disease.

## APPENDIX

### The Neuropathy Study Group of the Italian Society of the Study of Diabetes, Piemonte Affiliate

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