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ARTICLE

QT_c interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up

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Abstract
Aims/hypothesis We evaluated the association of QT interval corrected for heart rate (QT_c) and resting heart rate (rHR) with mortality (all-causes, cardiovascular, cardiac, and ischaemic heart disease) in subjects with type 1 and type 2 diabetes.
Methods We followed 523 diabetic patients (221 with type 1 diabetes, 302 with type 2 diabetes) who were recruited between 1974 and 1977 in Switzerland for the WHO Multinational Study of Vascular Disease in Diabetes. Duration of follow-up was 22.6±0.6 years. Causes of death were obtained from death certificates, hospital records, post-mortem reports, and additional information given by treating physicians.
Results In subjects with type 1 diabetes QT_c, but not rHR, was associated with an increased risk of: (1) all-cause mortality (hazard ratio [HR] 1.10 per 10 ms increase in QT_c, 95% CI 1.02–1.20, p=0.011); (2) mortality due to cardiovascular (HR 1.15, 1.02–1.31, p=0.024); and (3) mortality due to cardiac disease (HR 1.19, 1.03–1.36, p=0.016). Findings for subjects with type 2 diabetes were different: rHR, but not QT_c was associated with mortality due to: (1) all causes (HR 1.31 per 10 beats per min, 95% CI 1.15–1.50, p<0.001); (2) cardiovascular disease (HR 1.43, 1.18–1.73, p<0.001); (3) cardiac disease (HR 1.45, 1.19–1.76, p<0.001); and (4) ischaemic heart disease (HR 1.52, 1.21–1.90, p<0.001). Effect modification of QT_c by type 1 and rHR by type 2 diabetes was statistically significant (p<0.05 for all terms of interaction).
Conclusions/interpretation QT_c is associated with long-term mortality in subjects with type 1 diabetes, whereas rHR is related to increased mortality risk in subjects with type 2 diabetes.

Keywords Cardiovascular disease · Diabetes mellitus · Heart rate · Mortality · QT interval · Risk factors

Abbreviations

bpm	beats per min
HR	hazard ratio
QT_c	QT interval corrected for heart rate
rHR	resting heart rate
V	ventral

Introduction

Compared with the non-diabetic population, subjects with type 1 and type 2 diabetes mellitus are reported to have an increase in all-cause mortality [1]. Cardiovascular disease has been found to be the main reason for this excess mortality [1–4]. In an effort to identify easily available and reliable predictors for cardiovascular risk and mortality in diabetes mellitus, the evaluation of parameters reflecting myocardial ventricular repolarisation has been of particular

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interest. In subjects with type 1 diabetes, prolongation of the QT interval corrected for heart rate (QT_c) and heart rate variability have both been shown to be associated with increased risk of arrhythmia and death, whereas QT dispersion has been suggested to be less reliable [5]. However, the association between QT_c and cardiovascular mortality in type 2 diabetes is controversial. Some reports suggest that QT_c correlates with an increase in cardiovascular mortality [6–9]. Others have indicated that QT dispersion might more accurately predict cardiovascular mortality in this patient group [10–12].

Increased resting heart rate (rHR), which is easily measurable in clinical practice, has been shown to be an independent risk factor for cardiovascular death in a non-diabetic population [13–16]. Recently, rHR has also been shown to be valuable in estimating the risk of cardiovascular death in patients with type 2 diabetes [8, 10]. However, data directly comparing the role of QT_c and rHR in subjects with type 1 and type 2 diabetes are lacking. Based on a 23-year follow-up of the Swiss cohort of the WHO Multinational Study of Vascular Disease in Diabetes [17], the present study aimed to evaluate the long-term association of QT_c and rHR with mortality in patients with type 1 and type 2 diabetes within the same study framework.

Subjects and methods

Study population The WHO Multinational Study of Vascular Disease in Diabetes is a multicentre international study with a central protocol applied by 14 centres in 13 countries [18]. For the original study, each centre recruited stratified samples of 250 men and 250 women with a clinical diagnosis of diabetes, aged between 35 and 54 years at time of recruitment. The present analysis was based on the Swiss cohort of this study [17], which included 533 subjects randomly selected according to the central protocol by 231 local practitioners [17, 18]. The sample was representative of a large area including almost the entire country. The diagnosis of diabetes mellitus was made on a clinical basis. Subjects were eligible if diabetes had been diagnosed at least 1 year prior to study entry and anti-diabetic treatment (diet, oral glucose-lowering drugs, insulin) had been initiated by their physicians. If insulin was needed for treatment within 1 year of diagnosis, subjects were considered to have type 1 diabetes [18], the remaining subjects were classified as having type 2 diabetes. These comparably simple clinical definitions with acknowledged inadequacies were used because of the constraints on information available and the need for consistency with earlier reports [19–21]. At baseline, a standardised clinical examination was performed, including a detailed questionnaire with information on diabetes diagnosis, the duration and treatment, as well as on symptoms of vascular and cardiac disease. Previous medical history also included the use of other medication (including diuretics, lipid-lowering drugs and blood pressure-lowering drugs). Central randomisation to the cohort was stratified according to sex, age (35–41 years, 42–48 years, 49–54 years) and duration of diabetes (1–6 years, 7–13 years, 14 years and more). In addition, height and weight were recorded, and blood pressure was measured after 30 min of rest; hypertension being defined as a systolic blood pressure of ≥160 mmHg, and/or a diastolic blood pressure ≥95 mmHg, and/or the use of antihypertensive medication including diuretics. Urine was tested semiquantitatively for proteinuria using the salicylsulfonic acid method, blood samples were drawn to measure fasting plasma glucose, cholesterol, triacylglycerol and creatinine, and a 12-lead ECG was recorded. These baseline investigations were carried out between February 1974 and May 1977. All subjects gave informed consent. Analyses were carried out in accordance with the Declaration of Helsinki and the Swiss laws regarding data security. Data used were made fully anonymous before the analyses.

ECG recordings Standard 12-lead resting ECGs were recorded with the patient supine and resting for at least 30 min. Analyses were performed according to the Minnesota code [22]. All tracings were evaluated by the same two experienced readers. The following items were derived from the ECG code results: 'ECG coronary probable' consisting of code 1.1, 1.2 and 7.1; 'ECG coronary possible' consisting of codes 1.3, 4.1, 4.2, 4.3, 5.1, 5.2 and 5.3; all other recordings were rated as 'ECG coronary unlikely' [22]. QT and RR intervals were measured by an experienced cardiologist, blinded to the diagnosis and outcome of the individual patients. QT interval length was usually measured in the ventral (V)2 and V3 leads using a digitiser (CalComp, Newbury, Berks, UK). Measurements in V2 and V3 were chosen, since they provide a close approximation of maximal QT [23]. QT interval length was measured from the onset of the QRS to the end of the T wave. In the presence of U waves, the end of the QT interval was set at the nadir of the curve between T and U wave. Maximal QT interval was corrected for the respective heart rate using the Bazett formula [24] $\left(QT_{c\,Bazett} = QT/RR^{1/2}\right)$. In addition, the formulas suggested by Fridericia $\left(QT_{c\,Fridericia}=QT/RR^{1/3}\right)$ [25] and the Framingham formula derived by linear regression $\left[QT_{c\,Sagie}= QT + 0.154(1 - RR)\right]$ were used [26].

Follow-up and outcome definition The status (alive/dead) and date of death of each subject were ascertained as per 1 January 1998 on the basis of data obtained from population

registries. In deceased patients, the underlying cause of each death was determined from a copy of the death certificate, hospital records, post-mortem reports (where available), and additional information given by the treating physicians. Causes of death were coded according to the International Classification of Disease (ICD-9). Cardiovascular mortality included codes 390 to 459 and 798.1, cardiac mortality codes 390 to 429 and 798.1, and mortality due to ischaemic heart disease codes 410 to 414.

Statistical analysis Statistical assessment of potential differences in baseline characteristics between patients with type 1 and type 2 diabetes mellitus was carried out using the two-tailed unpaired Student's *t* test for continuous variables and the Pearson's chi-squared test for proportions. The impact of QT_c interval and rHR on mortality rates was assessed by time-to-event analysis using Cox proportional hazards models. Date of last clinical contact or documented date of leaving Switzerland was used for censored subjects, and exact date of death for subjects who had died. Analyses were conducted separately for subjects with type 1 and type 2 diabetes respectively, regarding all-cause, cardiovascular and cardiac mortality, and death due to ischaemic heart disease. Univariable analyses were performed before adjusting the regression model for age and sex. Then a 'full model' was fitted including the following explanatory variables: age, sex, BMI, duration of diabetes, total cholesterol, triacylglycerol, fasting plasma glucose, presence of hypertension/antihypertensive medication, history of coronary heart disease, history of microvascular disease, smoking, alcohol consumption, treatment with insulin (subjects with type 2 diabetes) and treatment with diuretics. QT_c was included in the analysis of rHR and vice versa. The model's assumptions (proportionality) were regularly checked. Analyses were then repeated using cut-off values corresponding to the lower limits of the upper quartiles (QT_c interval ≥450 ms or <450 ms in type 1, rHR ≥90 beats per min [bpm] or <90 bpm in type 2 diabetes). Comparable cut-off values have been suggested in earlier reports [13, 27, 28]. Based on these cut-off values, Kaplan–Meier survival analyses were performed for the main endpoint (overall mortality) and differences were statistically assessed using log-rank test. To formally assess effect modification of QT_c and rHR by diabetes type a confirmatory analysis was performed including terms of interaction in an analysis by Cox regression. Finally, regression models using the Bazett formula for QT_c were compared with models using the formula suggested by Fridericia [25] and by Sagie [26]. All analyses were performed using Stata version 8.2 (Stata Corporation, College Station, TX, USA). Results are given as mean±SD and as hazard ratio (HR) with 95% CI. p values <0.05 were considered statistically significant.

Results

Study characteristics The entire cohort comprised 533 patients and baseline ECGs were available in 523 patients (221 type 1 diabetes, 302 type 2 diabetes). During follow-up 18 patients left the country and were censored accordingly. This translated into a drop-out rate of 3.4%. Baseline ECG was normal in more than three-quarters of all patients (85% and 77% for types 1 and 2 diabetes, respectively). The mean difference of repeated determinations of QT_c was 2.8%. Mean follow-up was 22.6±0.6 years corresponding to a total of 11,815 person-years. Baseline characteristics are shown in Table 1. The proportion of women in the type 1 diabetes group was 54%, that for type 2 diabetes was lower (44%). Overall there were slightly more men than women (278, 255). Subjects with type 1 diabetes were generally younger, but had a longer duration of diabetes and a higher prevalence of retinopathy as well as higher mean values for fasting glucose at baseline. In contrast, subjects with type 2 diabetes showed higher values for BMI, blood pressure, and lipids, with coronary heart disease reported more frequently. Only a minority of subjects with type 2 diabetes were being treated with diet alone; two-thirds were using oral glucose-lowering drugs (e.g. sulfonylureas and/or biguanides), and less than one-third were being treated with insulin. In contrast, all patients with type 1 diabetes used insulin, with a minority also receiving oral glucose-lowering drugs (e.g. biguanides). While the proportion of subjects treated with antihypertensive drugs other than diuretics as well as with lipid-lowering drugs was comparable for the two types of diabetes, the use of diuretics was more frequent in subjects with type 2 diabetes. At baseline rHR tended to be higher and QT_c interval was significantly longer in patients with type 1 diabetes than in those with type 2 diabetes.

All-cause mortality During the study period 107 subjects with type 1 diabetes and 158 subjects with type 2 diabetes died. In subjects with type 1 diabetes, QT_c was positively associated with overall mortality. The unadjusted HR was 1.07 per 10 ms increase of QT_c (95% CI 1.01–1.15, p=0.033). This was not substantially altered when the model was adjusted for age and sex (HR 1.10, 95% 1.02–1.18, p=0.009). The association persisted after additional inclusion of further explanatory variables as stated in Subjects and methods ('full model', HR 1.10, 1.02–1.20, p=0.011). In contrast, no association of rHR with this endpoint was detected in type 1 diabetes (p=0.924) (Fig. 1, Tables 2 and 3). Subjects with type 2 diabetes revealed a strong positive association between rHR and mortality due to all causes. The unadjusted HR was 1.27 per 10 bpm (95% CI 1.14–1.41, p<0.001). Again, adjustment for age and sex revealed a similar HR (1.28, 1.16–1.42, p<0.001),

Table 1 Study characteristics

	Type 1 diabetes	Type 2 diabetes
Demographic		
Total number of patients (*n*)	225	308
Age (years)	43±6	46±6[b]
Female patients (*n*)	121 (54%)	134 (44%)[a]
Clinical		
BMI (kg/m^2)	24±4	28±5[b]
Duration of diabetes (years)	15±10	9±6[b]
Systolic blood pressure (mmHg)	136±20	141±21[a]
Diastolic blood pressure (mmHg)	86±11	89±11[b]
Nicotine consumption (no. cigarettes per day)	4±8	4±8
Alcohol consumption (g/day)	8±17	12±28
ECG performed	221 (98%)	302 (98%)
ECG normal	187 (85%)	234 (77%)
Resting heart rate (bpm)	79±13	77±14
QTc (ms)	433±30	426±32[a]
Biochemical		
Total cholesterol (mmol/l)	6.1±1.4	6.5±1.4[a]
Triacylglycerol (mmol/l)	1.4±1.2	2.4±2.7[b]
Fasting glucose (mmol/l)	11.7±6.5	10±4.1[b]
Serum creatinine (μmol/l)	91.9±43.3	86.6±27.4
Micro- and macrovascular disease		
Presence of retinopathy	117 (52%)	68 (22%)[b]
Presence of proteinuria	51 (23%)	75 (24%)
Presence of coronary heart disease	45 (20%)	96 (31%)[a]
Medication		
Diet alone as glucose-lowering treatment	0 (0%)	27 (9%)[b]
Use of oral glucose-lowering drugs	27 (12%)	188 (62%)[b]
Use of insulin	225 (100%)	90 (29%)[b]
Use of any antihypertensive drug*	33 (15%)	68 (22%)
Use of lipid-lowering drugs	4 (2%)	15 (5%)
Use of diuretics	22 (10%)	60 (20%)[a]

Data are mean values±SD
QT_c QT interval corrected for heart rate according to the formula suggested by Bazett
*Diuretics excluded
[a] $p<0.05$ for difference between type 1 and type 2 diabetes
[b] $p<0.001$ for difference between type 1 and type 2

which was not substantially altered in the fully adjusted model (HR 1.31, 1.15–1.50, $p<0.001$). A comparable effect was not detected for QT_c in these patients ($p=0.380$). The analysis of an effect modification of QT_c and rHR by diabetes type revealed a statistically significant association between QT_c and type 1 diabetes and between rHR and type 2 diabetes ($p=0.026$ and $p=0.014$ for terms of interaction; Fig. 1), thereby underscoring the differences between the two types of diabetes. Subjects with type 1 diabetes and a QT_c ≥450 ms had a twofold increased mortality risk compared with those with a QT_c <450 ms (HR 2.04, 95% CI 1.27–3.25, $p=0.003$). In type 2 diabetes, a comparable increase in risk was observed when subjects with a rHR ≥90 bpm were compared with those with rHR <90 bpm (HR 2.23, 95% CI 1.43–3.46, $p<0.001$). Results of Kaplan–Meier survival analysis are shown in Fig. 2 (p values for log-rank test 0.019 and 0.001 for type 1 and type 2 diabetes, respectively).

Cardiovascular mortality In 50 subjects with type 1 and in 76 subjects with type 2 diabetes, death was classified as due to cardiovascular disease. As for all-cause mortality, QT_c but not rHR was positively associated with cardiovascular mortality in type 1 diabetes (Fig. 1, Table 2). HRs for QT_c tended to be lower in the unadjusted model and after inclusion of age and sex when compared with the fully adjusted model, although conventional levels of significance were reached only in the latter (Table 3). Inverse findings were observed in subjects with type 2 diabetes, where rHR but not QT_c was related to this endpoint (Fig. 1, Table 2). Again, the HR in the unadjusted model was similar to those after adjustment for age and sex and to the 'full model' (Table 3). Confirmatory analysis using interaction terms revealed that the differences between the two types of diabetes were unlikely to be a chance finding ($p=0.008$ and $p=0.008$ for interaction, respectively; Fig. 1). In type 1 diabetes, mortality risk for a QT_c ≥450 ms was again increased twofold compared with a QT_c <450 ms (HR 2.34, 95% CI 1.16–4.71, $p=0.018$). In type 2 diabetes a rHR ≥90 bpm was even associated with a threefold increased risk (HR 3.27, 95% CI 1.76–6.09, $p<0.001$).

Cardiac mortality Cardiac mortality was confirmed in 43 type 1 and 71 type 2 diabetic patients. In the former, QT_c

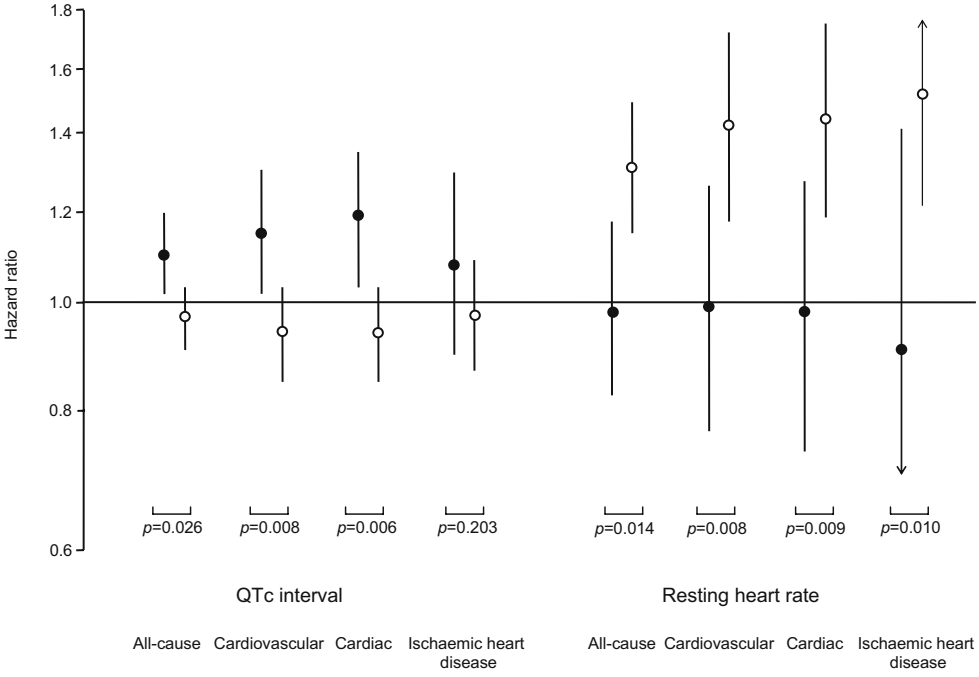

Fig. 1 Hazard ratios for mortality due to all causes, cardiovascular disease, cardiac disease, and ischaemic heart disease per incremental 10 ms prolongation of QT_c interval and per 10 bpm increase in resting heart rate, respectively. *p* values are for effect modification by type of diabetes (*closed circles*, type 1 diabetes; *open circles*, type 2 diabetes)

but not rHR was significantly associated with cardiac mortality (Fig. 1, Table 2). HRs tended to be slightly higher in the fully adjusted model compared with the unadjusted analysis (Table 3). In type 2 diabetes, rHR was found to predict cardiac mortality, whereas QT_c was not (Fig. 1, Table 2). Adjustment for age and sex and inclusion of further explanatory variables did not affect HRs (Table 3). Again, effect modification showed that QT_c was related to type 1 and rHR to type 2 diabetes ($p=0.006$ and $p=0.009$ for interaction, respectively; Fig. 1). HR for subjects with type 1 diabetes and QT_c ≥450 ms was 2.90 (95% CI 1.36–6.16, $p=0.006$). In subjects with type 2 diabetes, risk of cardiac mortality was comparably increased for those with a rHR ≥90 bpm (HR 3.51, 95% CI 1.86–6.64, $p<0.001$).

Death due to ischaemic heart disease There were 25 and 52 deaths due to ischaemic heart disease in subjects with type 1 and type 2 diabetes, respectively. In the former, no statistically significant association was found for either QT_c nor rHR (Fig. 1, Tables 2 and 3). In subjects with type 2 diabetes, a strong positive association persisted for rHR but not for QT_c ($p=0.010$ for interaction; Fig. 1, Tables 2 and 3). Type 2 diabetic subjects with a rHR of ≥90 bpm had a more than threefold increased risk of dying from ischaemic heart disease (HR 3.33, 95% CI 1.63–6.77, $p=0.001$).

Different formulas for correcting QT interval for heart rate Similar results were obtained using the formulas proposed by Fridericia [25] or Sagie [26] when compared with Bazett's formula [24]. For example, in subjects with type 1 diabetes, HR for all-cause mortality was 1.10 using Bazett's model. Applying Fridericia's or Sagie's approach the corresponding values were 1.12 and 1.13, respectively (Table 2). The same additional explanatory variables were used for all three analyses. The current literature is mainly based on Bazett's formula. In order to compare the present findings with previous reports, the formula suggested by Bazett was included in the final model.

Discussion

The main finding of this 23-year follow-up was a difference in the prognostic value of rHR and QT_c between the two types of diabetes. In subjects with type 1 diabetes QT_c, but not rHR was associated with an increased risk of all-cause mortality and mortality due to cardiovascular and cardiac disease. In contrast, in type 2 diabetes rHR, but not QT_c was consistently related to mortality due to all causes, cardiovascular, cardiac, and ischaemic heart disease. Interestingly, in type 1 diabetes a QT_c interval ≥450 ms translated into a twofold increase in all-cause mortality and a threefold increase in cardiac mortality. In subjects with type 2 diabetes a comparable increase in mortality risk was found for a rHR of ≥90 bpm compared with a rHR <90 bpm.

To our knowledge, this is the first study to prospectively assess the role of QT_c and rHR in both types of diabetes within the same study framework. Its findings confirm the prognostic value of QT_c as an independent risk factor for all-cause mortality in type 1 diabetes [5, 28–30]. In addition to the results of Rossing et al. [5], the present

Table 2 Hazard ratios (95% CI) for mortality due to all causes, cardiovascular, cardiac, and ischaemic heart disease

	Type 1 diabetes		Type 2 diabetes	
All-cause mortality				
$QT_{c\ Bazett}$ (model with rHR)	1.10 (1.02–1.20)	p=0.011	0.97 (0.91–1.03)	p=0.380
rHR (model with $QT_{c\ Bazett}$)	0.98 (0.83–1.18)	p=0.924	1.31 (1.15–1.50)	p<0.001
$QT_{c\ Fridericia}$ (model with rHR)	1.12 (1.03–1.21)	p=0.011	0.97 (0.91–1.03)	p=0.343
rHR (model with $QT_{c\ Fridericia}$)	1.09 (0.93–1.28)	p=0.307	1.28 (1.13–1.46)	p<0.001
$QT_{c\ Sagie}$ (model with rHR)	1.13 (1.03–1.23)	p=0.012	0.97 (0.90–1.04)	p=0.366
rHR (model with $QT_{c\ Sagie}$)	1.10 (0.94–1.30)	p=0.241	1.28 (1.13–1.46)	p<0.001
Cardiovascular mortality				
$QT_{c\ Bazett}$ (model with rHR)	1.15 (1.02–1.31)	p=0.024	0.94 (0.85–1.03)	p=0.160
rHR (model with $QT_{c\ Bazett}$)	0.99 (0.77–1.27)	p=0.917	1.43 (1.18–1.73)	p<0.001
$QT_{c\ Fridericia}$ (model with rHR)	1.16 (1.02–1.32)	p=0.026	0.93 (0.84–1.02)	p=0.140
rHR (model with $QT_{c\ Fridericia}$)	1.12 (0.88–1.42)	p=0.346	1.35 (1.12–1.63)	p=0.002
$QT_{c\ Sagie}$ (model with rHR)	1.18 (1.02–1.36)	p=0.023	0.91 (0.82–1.02)	p=0.100
rHR (model with $QT_{c\ Sagie}$)	1.14 (0.90–1.46)	p=0.272	1.34 (1.11–1.61)	p=0.002
Cardiac mortality				
$QT_{c\ Bazett}$ (model with rHR)	1.19 (1.03–1.36)	p=0.016	0.94 (0.85–1.03)	p=0.182
rHR (model with $QT_{c\ Bazett}$)	0.98 (0.74–1.28)	p=0.865	1.45 (1.19–1.76)	p<0.001
$QT_{c\ Fridericia}$ (model with rHR)	1.19 (1.03–1.38)	p=0.018	0.93 (0.84–1.03)	p=0.163
rHR (model with $QT_{c\ Fridericia}$)	1.13 (0.88–1.46)	p=0.336	1.37 (1.13–1.66)	p=0.001
$QT_{c\ Sagie}$ (model with rHR)	1.21 (1.03–1.42)	p=0.017	0.92 (0.82–1.02)	p=0.115
rHR (model with $QT_{c\ Sagie}$)	1.16 (0.90–1.51)	p=0.256	1.36 (1.12–1.66)	p=0.002
Death due to ischaemic heart disease				
$QT_{c\ Bazett}$ (model with rHR)	1.08 (0.90–1.30)	p=0.397	0.97 (0.87–1.09)	p=0.617
rHR (model with $QT_{c\ Bazett}$)	0.91 (0.58–1.42)	p=0.678	1.52 (1.21–1.90)	p<0.001
$QT_{c\ Fridericia}$ (model with rHR)	1.09 (0.90–1.32)	p=0.399	0.97 (0.86–1.09)	p=0.581
rHR (model with $QT_{c\ Fridericia}$)	0.98 (0.64–1.49)	p=0.914	1.48 (1.18–1.85)	p=0.001
$QT_{c\ Sagie}$ (model with rHR)	1.09 (0.89–1.34)	p=0.401	0.96 (0.84–1.09)	p=0.531
rHR (model with $QT_{c\ Sagie}$)	0.99 (0.64–1.51)	p=0.946	1.47 (1.18–1.84)	p=0.001

Data are given per incremental 10 ms prolongation of QT_c interval and 10 bpm increase in rHR, respectively Formulas for calculation of QT_c: Bazett [24], Fridericia [25], Sagie [26], as indicated by subscript All models adjusted for age, sex, BMI, duration of diabetes, total cholesterol, triacylglycerol, fasting plasma glucose, presence of hypertension, history of coronary heart disease, history of microvascular disease, smoking, alcohol consumption, treatment with insulin (subjects with type 2 diabetes) and treatment with diuretics.

analysis found QT_c to be associated not only with overall mortality but also with cardiovascular and cardiac mortality. Moreover, it also reproduced the findings of Sawicki and colleagues, which were made in subjects with nephropathy [28] in a more general sample of subjects with type 1 diabetes. The HR for overall mortality found in the present analysis was comparable to that in Rossing's report [5], but tended to be lower than the risk ratio found in subjects with overt nephropathy [28] (1.10 and 1.47 per 10 ms, respectively). Earlier reports have suggested that the association between QT_c and cardiovascular disease was stronger in male than in female subjects with type 1 diabetes [30]. The present study had slightly more female subjects in the group with type 1 diabetes, thereby potentially underestimating the prognostic value of QT_c for this patient group.

An increased rHR has been found to be related to all-cause mortality and cardiovascular death in several trials of non-diabetic subjects [13, 31–34], and in subjects with type 2 diabetes [8, 10]. Our analysis confirmed the role of rHR as an easily measurable factor for risk assessment of all-cause and cardiovascular mortality in subjects with type 2 diabetes, and had comparable HRs. In addition to findings of previous reports, we also observed a relation between elevated rHR and both cardiac mortality and mortality due to ischaemic heart disease. On the other hand, the present analysis did not confirm an association between QT_c and any of the endpoints in type 2 diabetes as has been reported previously [6, 7, 9, 10, 35]. Given previous hypotheses that prolongation of QT_c as a marker of cardiac autonomic neuropathy could be of greater importance in type 1 than in type 2 diabetes [5], our findings on this count are intriguing, and it can only be speculated on the underlying mechanisms.

In subjects with type 1 diabetes an increased prevalence of prolonged QT_c has been reported before [30, 36], in particular in subjects with autonomic neuropathy [36–38]. This may indicate that increased QT_c relates to diabetic autonomic neuropathy [39]. QT_c prolongation has been suggested to result from a reduction in vagal activity and an

Table 3 Hazard ratios (95% CI) for mortality due to all causes, and to cardiovascular, cardiac and ischaemic heart disease

		All-cause mortality		Cardiovascular mortality		Cardiac mortality		Death due to ischaemic heart disease	
Type 1 diabetes									
QTc	Crude/unadjusted	1.07 (1.01–1.15)	p=0.033	1.08 (0.99–1.19)	p=0.098	1.10 (0.99–1.22)	p=0.084	1.04 (0.91–1.19)	p=0.610
	Adjusted for age and sex	1.10 (1.02–1.18)	p=0.009	1.10 (1.00–1.22)	p=0.057	1.12 (1.00–1.25)	p=0.055	1.06 (0.92–1.23)	p=0.410
	Full model*	1.10 (1.02–1.20)	p=0.011	1.15 (1.02–1.31)	p=0.024	1.19 (1.03–1.36)	p=0.016	1.08 (0.90–1.30)	p=0.397
Type 2 diabetes									
rHR	Crude/unadjusted	1.27 (1.14–1.41)	p<0.001	1.35 (1.15–1.57)	p<0.001	1.36 (1.16–1.60)	p<0.001	1.42 (1.18–1.70)	p<0.001
	Adjusted for age and sex	1.28 (1.16–1.42)	p<0.001	1.36 (1.18–1.57)	p<0.001	1.37 (1.18–1.59)	p<0.001	1.41 (1.19–1.68)	p<0.001
	Full model*	1.31 (1.15–1.50)	p<0.001	1.43 (1.18–1.73)	p<0.001	1.45 (1.19–1.76)	p<0.001	1.52 (1.21–1.90)	p<0.001

Results are shown from a three-step approach in regression modelling (unadjusted, adjusted for age and sex, and 'full model'). Data are given per incremental 10 ms prolongation of QT_c interval for type 1 and 10 bpm increase in rHR for type 2 diabetes, respectively.

*Full model adjusted for: age, sex, BMI, diabetes duration; levels of fasting glucose, triacylglycerol and cholesterol; presence or absence of microvascular disease, hypertension, coronary heart disease; treatment with diuretics, insulin (for type 2 diabetes); alcohol consumption, smoking. QT_c was included in the analysis of rHR and vice versa.

increased sympathetic tonus, thereby reflecting myocardial autonomic instability and an increased risk of arrhythmia and cardiac death [9, 28, 36, 40]. Compared with previous publications reporting an association of QT_c with mortality in type 2 diabetes [9, 10, 35], subjects with type 2 diabetes were substantially younger in the present study. It should also be noted that some earlier reports revealing an association between QT_c and mortality were cross-sectional [35] or based on a case–control design [9] and in the case of prospective trials [6, 7, 10] had a considerably shorter follow-up.

In type 2 diabetes hyperglycaemia is often associated with a pro-inflammatory state including obesity, dyslipidaemia and hypertension, thereby promoting the development of atherosclerosis [41]. Interestingly, impaired myocardial oxygen supply has also been shown to influence QT interval [28, 30]. As has been pointed out before [6, 10], QT_c is possibly a composite marker, reflecting abnormal ventricular repolarisation due to ischaemia, fibrosis, left ventricular hypertrophy and dilatation, autonomic neuropathy, and vascular damage, conditions frequently present in diabetic myocardium. Although the models used in this analysis were adjusted for the pre-existence of coronary heart disease, we could not fully rule out a potential interference due to silent heart disease in subjects with diabetes, since invasive cardiac procedures were not performed.

The strength of the present study lies in the long follow-up period, the well-defined cohort of diabetic subjects (Swiss cohort [17] of the WHO Multinational Study of Vascular Disease in Diabetes [18, 22]), the evaluation of pre-specified endpoints, and the small drop-out rate. Considerable efforts were undertaken to adjust for relevant factors known to affect cardiovascular risk and/or myocar-

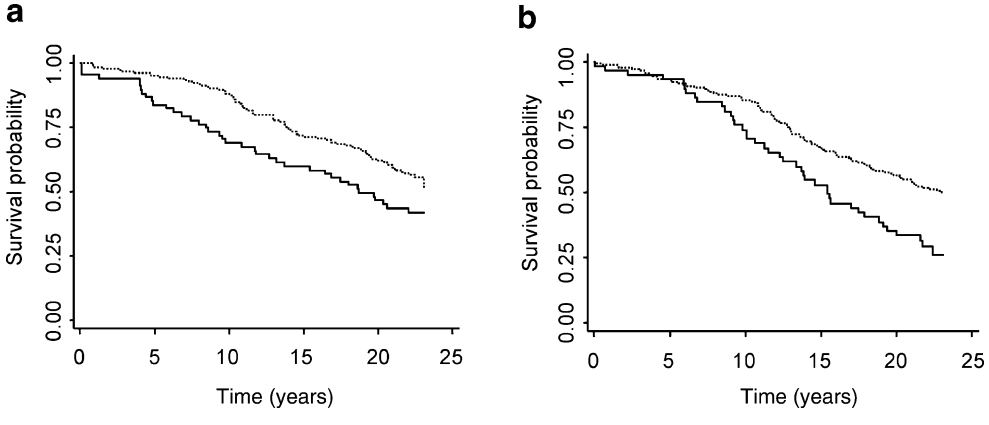

Fig. 2 Kaplan–Meier estimation of survival probabilities for overall mortality. **a** The survival probabilities for type 1 diabetes, comparing patients with a QTc interval ≥450 ms (*solid line*) with those with a QTc interval <450 ms (*dotted line*). p=0.019 for difference by log-rank test. **b** Survival probabilities for type 2 diabetes comparing patients with a resting heart rate ≥90 bpm (*solid line*) with those with rHR <90 bpm (*dotted line*). p=0.001 for difference by log-rank test

dial ventricular repolarisation This allowed inclusion of parameters that earlier reports had not been adjusted for, despite their known influence on mortality (e.g. alcohol consumption) [42]. Moreover, as the use of Bazett's formula [24] to calculate QT_c has been questioned before [8, 26, 43], possible differences in effect were taken into account by performing sensitivity analyses using the formulas suggested by Fridericia [25] and by Sagie [26]. In contrast to earlier reports [8], inclusion of different calculations of QT_c did not substantially alter our results (Table 2). As a consequence, Bazett's formula was included in the final model to allow for comparisons with other reports.

Nevertheless, we must acknowledge some limitations to our findings. Thus rHR was determined from ECG recordings, whereas in clinical practice it is usually measured by pulse palpation, rendering it subject to variation due to circumstantial factors (medical setting, circadian rhythm, body position etc.). In addition, QT_c and rHR can potentially be influenced by specific medication. Although the use of antihypertensive medication and diuretics was recorded in the present trial, data did not allow to specifically adjust for the use of beta blockers. Since it is known that treatment with these agents can influence both QT_c [44], and rHR, a potential interfering effect on the present findings cannot be fully excluded. It should, however, be noted that at the time of study entry only a limited number of beta blockers was available in Switzerland. Moreover, in another study [9] adjustment for use of beta blockers only modestly attenuated the association between QT_c and the risk of primary cardiac arrest. Another known factor to influence rHR is physical training [45]. Tachycardia may be a marker of decreased physical fitness, which in turn may be associated with an increased risk of mortality [46]. Interestingly, increased rHR was found to be an independent prognostic factor of cardiovascular mortality in studies controlling for energy expenditure as an indicator of physical fitness [31].

In deceased patients, the underlying cause of death was determined from a copy of the death certificate, hospital records, post-mortem reports, and additional information given by the treating physicians. Despite intensive efforts to collect comprehensive data, the cause of death may, in some cases, have been misclassified, especially if based only on death certificates, which are a comparatively unreliable source of information. Thus, our findings regarding all-cause mortality are clearly more robust than those for cause-specific mortality.

Glycaemic control has been shown to be related to macrovascular complications [47, 48], and was, therefore, included in the present analysis. Importantly, information on glycaemic control had to be based on fasting glucose, since HbA_{1c} was not available at the time of study entry, thereby potentially limiting the accuracy of adjustment. With regard to this, however, Veglio et al. did not report a significant influence of HbA_{1c} levels on QT_c [35].

In summary, this study, performed in a large, diabetic cohort followed over 23 years, confirms that in subjects with type 1 diabetes prolonged QT_c is associated with an increased mortality risk due to all causes, and to cardiovascular and cardiac disease, whereas no association was found for rHR. In contrast, in subjects with type 2 diabetes, elevated rHR, but not QT_c, is associated with an increased risk of all-cause mortality as well as risk of death due to cardiovascular, cardiac and ischaemic heart disease. The underlying pathophysiological mechanisms are probably complex and remain to be fully elucidated.

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