Prediction of Mortality Using Measures of Cardiac Autonomic Dysfunction in the Diabetic and Nondiabetic Population

The MONICA/KORA Augsburg Cohort Study

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OBJECTIVES — To evaluate whether reduced heart rate variability (HRV), prolonged corrected QT (QTc) interval, or increased QT dispersion (QTD) are predictors of mortality in the general diabetic and nondiabetic population.

RESEARCH DESIGN AND METHODS — Nondiabetic (n = 1,560) and diabetic (n = 160) subjects aged 55–74 years were assessed to determine whether reduced HRV, prolonged QTc interval, and increased QTD may predict all-cause mortality. Lowest quartiles for the maximum-minimum R-R interval difference (max-min, as measured at baseline from a 20-s standard 12-lead resting electrocardiogram without controlling for depth and rate of respiration), QTc >440 ms and QTD >60 ms, were used as cutpoints.

RESULTS — During a 9-year follow-up, 10.5% of the nondiabetic and 30.6% of the diabetic population deceased. In the nondiabetic individuals, multivariate Cox proportional hazard models adjusted for cardiovascular risk factors and demographic variables showed that prolonged QTc interval (hazard ratio 2.02 [95% CI 1.29–3.17]; P = 0.002) but not low max-min (0.93 [0.65–1.34]; P = 0.700), and increased QTD (0.98 [0.60–1.60]; P = 0.939) were associated with increased mortality. In the diabetic subjects, prolonged QTc was also a predictor of mortality (3.00 [1.34–6.71]; P = 0.007), while a trend for an increased risk was noted in those with low max-min (1.74 [0.95–3.18]; P = 0.075), whereas increased QTD did not predict mortality (0.42 [0.06–3.16]; P = 0.402).

CONCLUSIONS — Prolonged QTc interval, but not increased QTD, is an independent predictor of a twofold and threefold increased risk of mortality in the nondiabetic and diabetic elderly general population, respectively. Low HRV during spontaneous breathing tends to be associated with excess mortality in the diabetic but not nondiabetic population.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CAN, cardiovascular autonomic neuropathy; CVD, cardiovascular disease; ECG, electrocardiogram; HRV, heart rate variability; KORA, Cooperative Health Research in the Region of Augsburg; max-min, maximum-minimum R-R interval difference; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; SDNN, SD of R-R intervals.

Cardiovascular autonomic neuropathy (CAN) is a serious complication of diabetes that may lead to severe postural hypotension, exercise intolerance, enhanced intraoperative instability, and, presumably, increased incidence of silent myocardial infarction and ischemia (1). A number of prospective studies have demonstrated increased mortality among diabetic patients with CAN diagnosed by reduced heart rate variability (HRV) (2). In a meta-analysis of 15 studies, the pooled relative risk of mortality in studies that defined CAN by the presence of two or more abnormalities was 3.45 (95% CI 2.66–4.47) and, in studies that used more than one measure, 1.20 (1.02–1.41) (3). However, these were clinic-based studies (3,4) and, hence, subject to referral bias. Moreover, in several of these studies no appropriate adjustment for important confounding variables was performed. Autonomic dysfunction may also be found in the absence of diabetes as a consequence of cardiac diseases and is an independent indicator of poor prognosis in these patients (1,2,5).

The mechanisms by which CAN may lead to increased mortality remain a matter of debate. A meta-analysis revealed a 2.3-fold increased risk of CAN in diabetic patients showing a prolonged QT interval (6), leading to the speculation that CAN might also predispose to malignant ventricular arrhythmias and sudden death (7).

QT dispersion (QTD), which has been defined as the difference between the longest and shortest QT intervals on a standard 12-lead electrocardiogram (ECG), is considered to reflect regional variation in ventricular recovery times. This spatial dispersion of repolarization could offer an electrophysiological substrate for malignant ventricular arrhythmias (8,9).

To the best of our knowledge, no study has hitherto systematically evaluated the predictive value of HRV, corrected QT (QTc), and QTD in diabetic and nondiabetic subjects at the population level. Therefore, these indexes of car-

Table 1—*MONICA Survey 1989–1990 (S2): baseline characteristics*

	Nondiabetic participants	Diabetic participants
n	1,560	160
Sex (male/female)	51.3/48.7	51.3/48.8
Age (years)	63.7 ± 5.4	65.2 ± 5.5*
BMI (kg/m²)	27.9 ± 3.9	29.4 ± 3.8*
Heart rate (bpm)	65.3 ± 10.7	71.6 ± 12.8*
Systolic blood pressure (mmHg)	140 ± 19	148 ± 20*
Diastolic blood pressure (mmHg)	81 ± 11	79 ± 12
Total cholesterol (mg/dl)	253.5 ± 44.7	254.2 ± 55.0
LDL cholesterol (mg/dl)	163.8 ± 42.4	161.5 ± 45.1
HDL cholesterol (mg/dl)	56.9 ± 15.9	49.3 ± 15.4*
Total–to–HDL cholesterol ratio	4.81 ± 1.81	5.60 ± 2.14*
Fibrinogen (g/l)	4.30 ± 0.89	4.76 ± 1.24*
Hypertension	36.60	60.63*
CVD (MI or stroke)	5.83	12.50*
Regular smokers	15.65	16.25
High alcohol intake	20.67	10.63*
Physically active	28.84	20.00*
Use of ß-blockers	11.35	16.25†
All-cause mortality	10.51	30.63*
CAD mortality	3.21	11.25*
Diabetes duration (years)	—	8.11 ± 7.01

Data are means ± SD or percentages unless otherwise indcated. *$P < 0.05$; †$P = 0.072$. CAD, coronary artery disease; MI, myocardial infarction.

diac autonomic function were measured in the population-based Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)/Cooperative Health Research in the Region of Augsburg (KORA) cohort 1989–1990, Augsberg, Germany, to elucidate to which extent these markers of autonomic dysfunction may independently contribute to excess mortality in the diabetic and nondiabetic general population.

RESEARCH DESIGN AND METHODS

— The MONICA survey S2 was part of the multinational World Health Organization MONICA project (10). In 1989–1990, a random sample aged 25–74 years ($n = 4,940$) was selected from an original population of $n = 349,050$ in the Augsburg region in southern Germany. All study participants aged 55–74 years were included in the present analysis, of whom $n = 160$ were classified as having diabetes if they reported a diagnosis of diabetes or if they were taking antidiabetes medication, while $n = 1,560$ subjects were considered nondiabetic if they did not meet these criteria. All participants were prospectively followed within the framework of KORA. After a follow-up period of 9 years, all-cause mortality and cardiovascular mortality were assessed. The survey was approved by the local authorities, and all participants gave written informed consent.

Blood pressure, body height, and body weight, were determined by trained medical staff (mainly nurses). All measurement procedures have been described elsewhere in detail (11–13). Information concerning sociodemographic variables, smoking habits, physical activity, and alcohol intake was assessed by standardized personal interviews. A regular smoker was defined as a subject who regularly smoked at least one cigarette per day. Alcohol consumption on the previous workday and during the previous weekend was calculated in grams per day. High alcohol intake was defined as ≥40 g/day in men and ≥20 g/day in women. A participant was considered physically active if he or she participated in sports in summer or winter for >1 h/week. Prevalent cardiovascular disease (CVD) was defined as the need for hospital treatment of myocardial infarction or stroke (13). Obesity was defined as BMI ≥30 kg/m^2. Hypertension was defined as a blood pressure of 160/95 mmHg or higher or use of antihypertensive medication, given that the subject was aware of having hypertension. Dyslipidemia was defined as a total–to–HDL cholesterol ratio ≥5 (14).

ECG-based variables

ECG examination was performed in a standardized manner as described previously (14,15). In brief, a 12-lead resting ECG was recorded over 20 consecutive seconds in the supine position using the digital stand-alone ECG data acquisition and analysis system SICARD 803 (Siemens Medizintechnik, Erlangen, Germany). Time domain measures including the SD of R-R intervals (SDNN), coefficient of variation (CV) of R-R intervals, and the difference between the maximum and minimum R-R interval (max-min difference) were computed (16). This approach was limited by not controlling for respiration and not using an index of HRV during deep breathing. QT intervals were determined from the 12-lead ECG strips. From each lead, three QT intervals were measured and, of these, the median values were computed. The longest of the 12 QT medians obtained was used as the representative QT interval for further analysis. Measurable QT intervals in eight leads were required as an acceptable minimum for this definition. QTc interval correction formulas for heart rate included the approaches by Bazett (17), the Framingham Heart Study (18), and Fridericia (19). QTD was measured as the difference between the longest and shortest QT intervals in 12-lead ECG. The cut points were the lowest quartiles for SDNN, CV, and max-min difference, while those for the QT indexes were QTc >440 ms and QTD >60 ms.

For the calculation of the autonomic function indexes, 241/26 nondiabetic/diabetic subjects had to be excluded due to atrial fibrillation or flutter ($n = 37$), left ($n = 38$) and right ($n = 63$) bundle-branch block, second- and third-degree atrioventricular or sinoatrial block ($n = 12$), treatment with antiarrhythmic agents, or treatment with agents known to prolong the QT interval ($n = 48$) (multiple nominations were possible). An additional 47/8 nondiabetic/diabetic subjects were excluded in the HRV assessment, respectively, and 64/9 nondiabetic/diabetic subjects were excluded in the QTc interval analyses because of multiple supraventricular or ventricular extrasystoles, pacemaker therapy, or missing data. Thus, 1,513 nondiabetic and 152 diabetic subjects were included in the multiple logistic regression analyses of HRV, while 1,496 nondiabetic and 151 diabetic subjects were included in the QTc interval model. The QTD model comprised 1,433

nondiabetic and 140 diabetic subjects as a resulut of incomplete 12 leads.

Statistical methods

All continuous variables were described as means ± SD, and differences between groups were evaluated by *t* tests. Categorical variables were described by frequency tables and compared between groups using Fisher's exact test. All tests were performed two sided, and the level of significance was set at $\alpha = 0.05$. Survival curves were estimated by the Kaplan-Meier method. The log-rank test was used to compare different survival curves. Multiple Cox regression models were fitted to analyze risk factors of mortality and potential confounders. Different models using fixed sets of independent variables were estimated and stratified for diabetic and nondiabetic subjects. The SAS statistical software package (version 8.2) TS2M0 was used for statistical analyses.

RESULTS

Baseline characteristics

Compared with nondiabetic individuals, diabetic subjects were significantly older, had a higher BMI, faster resting heart rate, higher systolic blood pressure, lower HDL cholesterol, higher total–to–HDL cholesterol ratio, and higher fibrinogen levels as well as significantly higher proportions of hypertension and myocardial infarction or stroke (all $P < 0.05$) (Table 1). Furthermore, rates of death from all causes and coronary artery disease were significantly higher, while the percentages of physically active subjects and those with high alcohol intake were significantly lower in the diabetic compared with the nondiabetic group (all $P < 0.05$). The use of β-blocking agents tended to be higher in diabetic subjects ($P = 0.072$). No significant differences between the groups were noted for sex, diastolic blood pressure, total cholesterol, LDL cholesterol, or the percentage of regular smokers.

Kaplan-Meier survival estimates

In the diabetic group, survival probability was significantly lower in subjects with the max-min R-R interval difference "as measured from a 20 s standard 12-lead ECG without controlling for depth and rate of respiration" (see RESEARCH DESIGN AND METHODS) at the 1st quartile vs. 2nd–4th quartiles ($P = 0.0447$)(Fig. 1*A*), whereas no significant difference was noted in the nondiabetic group ($P = 0.4227$)(Fig. 1*C*). The corresponding mortality rates were 30 of 79 (38.0%) vs. 19 of 80 (23.8%) in diabetic subjects and 42 of 366 (11.5%) vs. 119 of 1,179 (10.1%) in nondiabetic participants, respectively. In subjects who had a QTc interval >440 vs. those with a QTc interval ≤440 ms, survival probability was significantly lower in both the diabetic ($P < 0.0001$) (Fig. 1*B*) and nondiabetic ($P = 0.0026$) groups (Fig. 1*D*).

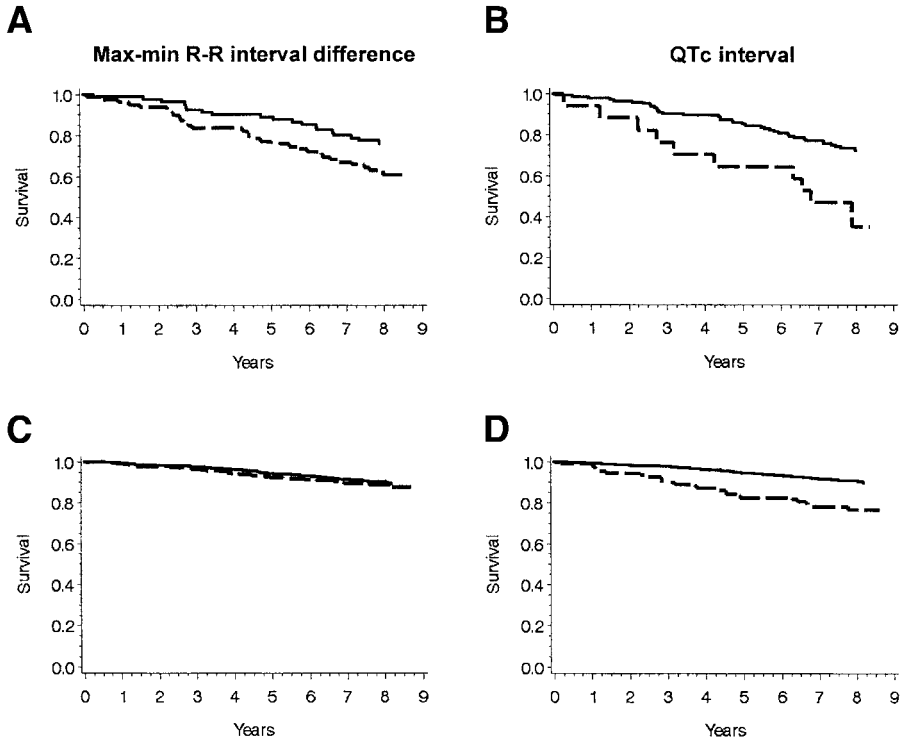

Figure 1—*Kaplan-Meier survival probability for the max-min R-R interval difference (1st quartile [broken line] vs. 2nd–4th quartiles [continuous line]) in the diabetic* (A) *and nondiabetic* (C) *cohorts and QTc interval (>440 ms [broken line] vs. ≤440 ms [continuous line]) in the diabetic* (B) *and nondiabetic* (D) *cohorts.*

Association between HRV and mortality

In the nondiabetic group, male sex, age, regular smoking, low physical activity, and hypertension (all $P < 0.05$), but not low max-min difference, were significant predictors of mortality, while CVD tended to predict mortality ($P = 0.06$) (Table 2). Among diabetic individuals, only low physical activity and dyslipidemia were significant predictors of mortality (both $P < 0.05$), while low max-min difference, male sex, CVD, and regular smoking tended to predict mortality ($P = 0.067$ to $P = 0.089$). The increase in relative risk of mortality for the 1st quartile of max-min was 73% in diabetic persons. The results were similar when using the SDNN and CV as alternative indexes of HRV (data not shown).

Association between QT variables and mortality

In the nondiabetic group, prolonged QTc interval, male sex, age, regular smoking, low physical activity, and hypertension (all $P < 0.05$) were significant predictors of mortality, while CVD tended to predict mortality ($P = 0.076$) (Table 2). Among diabetic individuals, prolonged QTc interval, male sex, age, and low physical activity were significant predictors of mortality (all $P < 0.05$), while a trend to predict mortality was noted for regular smoking and dislipidemia ($P = 0.087$, to $P = 0.081$). The increase in relative risk of 9-year mortality in subjects with QTc >440 ms was twofold and threefold in the nondiabetic and diabetic group, respectively. The results were similar when using the Framingham Heart Study and Fridericia formulas for QTc (data not shown).

In the nondiabetic group, male sex, age, high alcohol intake, regular smoking, low physical activity, and hypertension (all $P < 0.05$), but not increased QTD, were significant predictors of mortality (Table 2*C*). In the diabetic group, age and low physical activity (both $P < 0.05$), but not increased QTD, were significant predictors of mortality.

Table 2—*Relative risk (RR) (95% CI) for the associations of reduced HRV (max-min), prolonged QTc interval, QTD, cardiovascular risk factors, and demographic variables with 9-year all-cause mortality in nondiabetic and diabetic individuals*

	Nondiabetic group		Diabetic group	
	RR (95% CI)	*P*	RR (95% CI)	*P*
HRV*				
Max-min (1st quartile)	0.93 (0.65–1.34)	0.700	1.74 (0.95–3.18)	0.075
Male sex	2.59 (1.77–3.78)	0.000	1.79 (0.91–3.52)	0.089
Age	1.11 (1.08–1.15)	0.000	1.05 (0.99–1.12)	0.088
CVD	1.64 (0.98–2.74)	0.060	1.69 (0.73–3.89)	0.218
High alcohol intake	1.33 (0.93–1.89)	0.117	0.66 (0.19–2.23)	0.499
Use of β-blockers	1.01 (0.63–1.63)	0.969	0.79 (0.32–1.95)	0.603
Regular smokers	2.02 (1.40–2.91)	0.000	1.95 (0.95–3.99)	0.067
Physically active	0.60 (0.40–0.88)	0.010	0.21 (0.06–0.69)	0.010
Hypertension	1.60 (1.15–2.22)	0.005	0.85 (0.43–1.69)	0.645
Obesity	0.97 (0.92–1.01)	0.164	0.97 (0.88–1.05)	0.434
Dyslipidemia	0.99 (0.90–1.08)	0.762	1.13 (1.00–1.27)	0.043
Prolonged QTc interval†				
QTc (>440 ms [ref. 17])	2.02 (1.29–3.17)	0.002	3.00 (1.34–6.71)	0.007
Male sex	2.60 (1.78–3.80)	0.000	2.16 (1.05–4.42)	0.036
Age	1.12 (1.08–1.15)	0.000	1.07 (1.01–1.13)	0.033
CVD	1.59 (0.95–2.66)	0.076	1.18 (0.47–2.93)	0.728
High alcohol intake	1.35 (0.94–1.92)	0.103	0.52 (0.15–1.79)	0.299
Use of β-blockers	1.08 (0.67–1.73)	0.765	1.04 (0.40–2.67)	0.936
Regular smokers	1.97 (1.37–2.85)	0.000	1.89 (0.91–3.91)	0.087
Physically active	0.62 (0.42–0.92)	0.018	0.24 (0.07–0.80)	0.020
Hypertension	1.55 (1.11–2.16)	0.011	0.87 (0.44–1.70)	0.684
Obesity	0.96 (0.92–1.01)	0.110	0.96 (0.88–1.05)	0.380
Dyslipidemia	0.97 (0.89–1.06)	0.480	1.12 (0.99–1.28)	0.081
QTD‡				
QTD (>60 ms)	0.98 (0.60–1.60)	0.939	0.42 (0.06–3.16)	0.402
Male sex	2.32 (1.56–3.45)	0.000	1.67 (0.82–3.40)	0.157
Age	1.11 (1.08–1.15)	0.000	1.07 (1.00–1.14)	0.034
CVD	0.97 (0.48–1.95)	0.934	1.56 (0.56–4.35)	0.400
High alcohol intake	1.54 (1.07–2.23)	0.021	0.71 (0.21–2.46)	0.592
Use of β-blockers	1.12 (0.68–1.86)	0.649	0.77 (0.27–2.17)	0.615
Regular smokers	2.13 (1.46–3.11)	0.000	1.52 (0.62–3.74)	0.360
Physically active	0.64 (0.43–0.97)	0.036	0.16 (0.04–0.66)	0.012
Hypertension	1.58 (1.10–2.26)	0.012	1.01 (0.48–2.16)	0.973
Obesity	0.97 (0.92–1.01)	0.152	0.95 (0.86–1.06)	0.368
Dyslipidemia	1.02 (0.93–1.12)	0.648	1.11 (0.97–1.27)	0.140

*HRV: nondiabetic group, $n = 1,513$; nondiabetic group, $n = 152$. †Prolonged QTc interval: nondiabetic group, $n = 1,496$; diabetic group, $n = 151$. ‡QTD: nondiabetic group, $n = 1,433$; diabetic group, $n = 140$.

After introducing both the max-min difference and QTc interval and their possible interaction into the model, QTc interval prolongation remained a significant predictor of all-cause mortality showing risk ratio 2.23 (95% CI 1.32–3.75), $P = 0.003$, in the nondiabetic group and 7.09 (1.80–27.94), $P = 0.005$, in the diabetic group, respectively. In contrast, low max-min difference did not predict mortality in the nondiabetic group (0.96 [0.64–1.42]; $P = 0.829$) but tended to in the diabetic group (1.96 [0.99–3.89]; $P = 0.054$). There was no interaction between these two variables in predicting mortality (data not shown).

Cardiovascular mortality

Prolonged QT interval predicted cardiovascular mortality in the entire cohort and in the nondiabetic group (3.91 [95% CI 2.14–7.14]) $P < 0.001$, and 4.47 [2.44–9.22], $P < 0.001$, respectively) but not in the diabetic group (1.39 [0.26–7.43], $P = 0.698$). The max-min difference and QTD did not predict cardiovascular mortality in either of the groups studied, possibly because of the relatively small number of cases (data not shown).

CONCLUSIONS — The results of this study suggest that prolonged QTc interval is an independent predictor of mortality over 9 years in the nondiabetic and diabetic elderly general population, respectively. Diabetic patients with a QTc prolongation >440 ms had a threefold increased risk of mortality. In contrast, increased QT dispersion did not predict mortality in nondiabetic or diabetic subjects. Low HRV showed a trend toward an increased risk of mortality by 73% in the diabetic but not the nondiabetic elderly general population. Thus, while QTc interval prolongation represents a general prognostic index independent of the presence of diabetes, reduced HRV appears to be a more specific marker only in the context of diabetes.

Several studies have previously reported that QTc interval prolongation predicts the risk of mortality in the elderly (20) and middle-aged (21) general population, although in apparently healthy subjects this risk was weak (21). Likewise, an increased QTD has been identified as a predictor of increased cardiac mortality at the population level (22,23). However, recent studies evaluating the predictive role of prolonged QTc or increased QTD in diabetic patients have reported conflicting results. In a 23-year follow-up of the World Health Organization Multinational Study of Vascular Disease in Diabetes, QTc was associated with long-term mortality in subjects with type 1 diabetes but not in those with type 2 diabetes (24). In contrast, in the Strong Heart Study, including American Indians with type 2 diabetes, QTc predicted all-cause mortality after a mean follow-up of 4.7 years (25), and in the Dundee cohort of the UK Prospective Diabetes Study, including newly diagnosed type 2 diabetic patients, both QTD and QTc predicted cardiac mortality after a mean follow-up of 12.7 years (26). Moreover, QTD was identified as an independent predictor for total cardiovascular events and for cardiac deaths among type 2 diabetic patients with arterial hypertension (27). However, another study found that QTc but not QTD was an independent predictor of all-cause and cardiovascular mortality in type 2 diabetic patients (28). However, these were clinic-based studies and, hence, not representative of any certain population. We confirm at the population level that prolonged QTc but not increased QT dispersion is a predictor of all-cause mortality in both elderly nondiabetic and diabetic subjects. However, there is ongoing controversial discussion about the value of measuring QT dispersion (29,30). Among the reasons for the divergent study results are difficulties in determining the end of the T-wave, the absence of standards for this method, circadian rhythm, and the lack of normative data.

Whether reduced HRV is a predictor of mortality has previously been addressed at the population level in two studies (31,32). We suggest that low HRV is not an independent predictor of mortality in the nondiabetic population. This is in line with the results of the Hoorn study (31) and the Atherosclerosis Risk in Communities (ARIC) study (32). On the other hand, in the Zutphen study (33) the 5-year age-adjusted relative rate of total mortality was 2.1 (95% CI 1.4–3.0) in middle-aged men and 1.4 (0.9–2.2) in elderly men with low HRV. This finding does not necessarily contradict ours, since that study included only a male population. We found that male sex is an independent predictor of mortality in the nondiabetic population, and the prognostic value of low HRV may therefore differ between male and female or mixed cohorts. However, as shown above, the risk associated with low HRV was considerably lower and no longer significant in elderly men.

The Hoorn study (31) followed a population aged 50–75 years over 9 years similar to our cohort aged 55–74 years. The results of our study are compatible with those of the Hoorn study, demonstrating that diminished HRV is a predictor of mortality in the diabetic as opposed to the nondiabetic population. In contrast, in the ARIC study (32), low HRV did not predict fatal coronary artery disease or non–coronary artery disease mortality in diabetic subjects after an average of 8 years of follow-up. However, in the ARIC cohort the age range of 45–64 years was considerably lower than in our cohort. The findings of the Hoorn study (31) and ours indicate that after adjustment for the various confounding factors, the value of low HRV in predicting excess mortality is only moderate. In line with the borderline independent effect of low max-min difference on mortality observed in our study, in the Hoorn study the increased risk of mortality in the diabetic subjects was noted in only two of six indexes of HRV measured (31). This risk level may be underestimated because this and other epidemiologic surveys have performed less extensive assessment compared with the majority of the clinic-based studies. Indeed, it has been suggested in a meta-analysis that the pooled relative risk of mortality in clinic-based studies that used more than one index was considerably higher than that observed in studies that used one measure only (3).

One limitation of this study is the relatively short period (20 s) of ECG recording without control for respiration. However, since we have not employed frequency domain indexes of HRV, we believe that computing time domain indexes from these recordings is relatively accurate. Relatively short recordings of ECG leads have been reliably used in several other epidemiological studies, e.g., three or more consecutive cycles (34) or recordings over 10 s in the Rotterdam Study (6) and the Diabetes Prevention Program (35) or 15–30 s in the Zutphen-Study (33). Nonetheless, adding indexes of vagal function obtained during controlled deep breathing would have likely strengthened the HRV results.

In conclusion, after adjustment for various well-known prognostic factors such as male sex, age, smoking, physical activity, hypertension, obesity, dyslipidemia, and CVD prolonged QTc interval and, to a lesser degree, without controlling for respiration as a result of the restricted setting of an epidemiological study, diminished HRV represent independent predictors of 9-year mortality in the diabetic elderly general population. In contrast, increased QT dispersion did not predict mortality in nondiabetic or diabetic individuals. Low HRV showed a trend of borderline significance toward an increased risk of mortality by 73% in the diabetic population but was not a predictor of mortality in the nondiabetic elderly general population. Thus, cardiac autonomic dysfunction characterized by prolonged QTc and/or diminished HRV is associated with a high risk of excess mortality particularly in diabetic subjects. Recent studies indicate that some cardioprotective agents may increase diminished HRV (36) and shorten prolonged QT interval (37) and, hence, have the potential to improve or worsen prognosis in selected patient populations. Against this background, the findings of the present study may have consequences for treatment of diabetic patients with CAN provided that the simple measures of HRV and QTc interval described herein are being used for risk stratification in clinical routine. Measurement of the QTc interval may be favored in this context given that it is simple to do and may represent a stronger prognostic marker than HRV.

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References

1. Vinik AI, Ziegler D: Diabetic cardiovascular autonomic neuropathy. *Circulation* 115:387–397, 2007
2. Ziegler D: Cardiovascular autonomic neuropathy: clinical manifestations and measurement. *Diabetes Rev* 7:342–357, 1999
3. Maser RE, Mitchell BD, Vinik AI, Freeman R: The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 26:1895–1901, 2003
4. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH: Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 29:334–339, 2006
5. Suarez GA, Clark VM, Norell JE, Kottke TE, Callahan MJ, O'Brien PC, Low PA, Dyck PJ: Sudden cardiac death in diabetes mellitus: risk factors in the Rochester diabetic neuropathy study. *J Neurol Neurosurg Psychiatry* 76:240–245, 2005
6. Whitsel EA, Boyko EJ, Siscovick DS: Reassessing the role of QTc in the diagnosis of autonomic failure among patients with diabetes: a meta-analysis. *Diabetes Care* 23:241–247, 2000
7. Veglio M, Sivieri R, Chinaglia A, Scaglione L, Cavallo-Perin P: QT interval prolongation and mortality in type 1 diabetic patients: a 5-year cohort prospective study. *Diabetes Care* 23:1381–1383, 2000
8. Chen A, Kusumoto FM: QT dispersion: much ado about something? *Chest* 125: 1974–1977, 2004
9. Manttari M, Oikarinen L, Manninen V, Viitasalo M: QT dispersion as a risk factor for sudden cardiac death and fatal myocardial infarction in a coronary risk population. *Heart* 78:268–272, 1997
10. WHO MONICA Project Principal Investigators: The World Health Organization MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease): a major international collaboration. *J Clin Epidemiol* 34:105–114, 1988
11. Keil U, Cairns V, Döring A: MONICA-Project, Region Augsburg, Manual of Operations, Survey. In *GSF-Bericht 20*. Munich, Germany, Forschungszentrum für Gesundheit und Umwelt, 1985
12. Hense HW, Filipiak B, Döring A: Ten-year trends of cardiovascular risk factors in the MONICA Augsburg Region in Southern Germany: results from the 1984/85, 1989/90 and 1994/1995 surveys. *Cardiovasc Dis Prev* 1:318–327, 1998
13. Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Löwel H: Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med* 162:82–89, 2002
14. Ziegler D, Zentai C, Perz S, Rathmann W, Haastert B, Meisinger C, Löwel H: Selective contribution of diabetes and other cardiovascular risk factors to cardiac autonomic dysfunction in the general population. *Exp Clin Endocrinol Diabetes* 114: 153–159, 2006
15. Perz S, Pöppl SJ, Stieber J: ECG data management and analysis in the MONICA Survey Augsburg. In *Lecture Notes in Medical Informatics 25, Medical Informatics Europe 1985*. Reichertz PL, Lindberg DAB, Eds. Heidelberg, Germany, Springer, 1985, p. 811
16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 93:1043–1065, 1996
17. Bazett HC: An analysis of the time-relations of electrocardiograms. *Heart* 7:353–370, 1920
18. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D: An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol* 70:797–801, 1992
19. Fridericia LS: Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 53: 469–486, 1920 [article in German]
20. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE: Prolonged QT interval predicts cardiac and all-cause mortality in the elderly: the Rotterdam Study. *Eur Heart J* 20:278–284, 1999
21. Karjalainen J, Reunanen A, Ristola P, Viitasalo M: QT interval as a cardiac risk factor in a middle aged population. *Heart* 77:543–548, 1997
22. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE: QTc dispersion predicts cardiac mortality in the elderly: the Rotterdam Study. *Circulation* 97:467–472, 1998
23. Okin PM, Devereux RB, Howard BV, Fabsitz RR, Lee ET, Welty TK: Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: the Strong Heart Study. *Circulation* 101:61–66, 2000
24. Stettler C, Bearth A, Allemann S, Zwahlen M, Zanchin L, Deplazes M, Christ ER, Teuscher A, Diem P: 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. *Diabetologia* 50:186–194, 2007
25. Okin PM, Devereux RB, Lee ET, Galloway JM, Howard BV: Electrocardiographic repolarization complexity and abnormality predict all-cause and cardiovascular mortality in diabetes: the Strong Heart Study. *Diabetes* 53:434–440, 2004
26. Rana BS, Lim PO, Naas AA, Ogston SA, Newton RW, Jung RT, Morris AD, Struthers AD: QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. *Heart* 91:44–50, 2005
27. Salles GF, Deccache W, Cardoso CR: Usefulness of QT-interval parameters for cardiovascular risk stratification in type 2 diabetic patients with arterial hypertension. *J Hum Hypertens* 19:241–249, 2005
28. Christensen PK, Gall MA, Major-Pedersen A, Sato A, Rossing P, Breum L, Pietersen A, Kastrup J, Parving HH: QTc interval length and QT dispersion as predictors of mortality in patients with non-insulin-dependent diabetes. *Scand J Clin Lab Invest* 60:323–332, 2000
29. Coumel P, Maison-Blanche P, Badilini F: Dispersion of ventricular repolarization: reality? Illusion? Significance? *Circulation* 97:2491–2493, 1998
30. Rautaharju PM: A farewell to QT dispersion: are the alternatives any better? *J Electrocardiol* 38:7–9, 2005
31. Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, Heethaar RM, Stehouwer CD: Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care* 24:1793–1798, 2001
32. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G: Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes* 51: 3524–3531, 2002
33. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D: Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: the Zutphen Study. *Am J Epidemiol* 145:899–908, 1997
34. Deyneli O, Ersoz HO, Yavuz D, Fak AS, Akalin S: QT dispersion in type 2 diabetic patients with altered diurnal blood pressure rhythm. *Diabetes Obes Metab* 7:136–143, 2005
35. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME, the Diabetes Prevention Program Research Group: The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care* 29: 914–919, 2006
36. Aronson D: Pharmacologic modulation of autonomic tone: implications for the diabetic patient. *Diabetologia* 40:476–481, 1997
37. Ebbehøj E, Arildsen H, Hansen KW, Mogensen CE, Mølgaard H, Poulsen PL: Effects of metoprolol on QT interval and QT dispersion in type 1 diabetic patients with abnormal albuminuria. *Diabetologia* 47: 1009–1015, 2004