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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Running title: Cardiac autonomic dysfunction and mortality

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ABSTRACT

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

**Research Design and Methods:** Nondiabetic (n=1560) 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 max-min R-R interval difference (max-min) as measured from a 20 second standard 12-lead ECG without controlling for depth and rate of respiration, QTc>440ms, and QTD>60ms determined from 12-lead resting ECG at baseline 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 [95% CI]: 2.02[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 QT dispersion, is an independent predictor of a 2-fold and 3-fold 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.
Cardiovascular autonomic neuropathy (CAN) is a serious complication of diabetes which may lead to severe postural hypotension, exercise intolerance, enhanced intraoperative instability, and presumably to an increased incidence of silent myocardial infarction and ischemia (1). A number of prospective studies have demonstrated an 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 1.20(1.02-1.41) in studies that used one measure (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 has been 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 an 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).

The QT dispersion (QTD) which has been defined as the difference between the longest and shortest QT intervals on a standard 12-lead 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, QTc, and QTD in diabetic and nondiabetic subjects at the population level. Therefore, these indices of cardiac autonomic function were measured in the population-based MONICA/KORA Augsburg cohort 1989/90 (S2), 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

Study sample. The MONICA survey S2 was part of the multinational WHO MONICA project (10). In 1989/90, 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 55-74 year old study participants were included in the present analysis, of whom n=160 were classified as having diabetes mellitus if they reported a diagnosis of diabetes or if they were taking antidiabetic medication, while n=1560 subjects were considered nondiabetic if they did not meet these criteria. All participants were prospectively followed within the framework of the Cooperative Health Research in the Region of Augsburg (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.

Data collection. 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 1 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 and in winter for more than 1 hour per week in at least 1 season. Prevalent cardiovascular disease was defined as the need for hospital treatment of myocardial infarction or stroke (13). Obesity was defined as a BMI ≥30 kg/m². Hypertension was defined as a blood pressure of 160/95 mm Hg or higher or use of antihypertensive medication, given that the subject was aware of having hypertension. Dyslipidemia was defined as a total/HDL cholesterol ratio ≥5 (14).

**ECG-based variables.** ECG examination was performed in a standardized manner as described previously (14,15). In brief, 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 standard deviation 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 8 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 study (18), and Fridericia (19). QT dispersion (QTD) was measured as the difference between longest and shortest QT interval in 12-lead ECG. The cut points were the lowest quartiles for SDNN, CV, and max-min difference, while those for the QT indices were QTc>440 ms and QTD>60 ms.

For the calculation of the autonomic function indices 241/26 non-diabetic/diabetic subjects had to be excluded due to atrial fibrillation or flutter (n=37), left (n=38) and right (n=63) bundle-branch block, 2nd and 3rd degree AV block or SA block (n=12), treatment with antiarrhythmic agents or treatment with agents known to prolong the QT interval (n=48) (multiple nominations were possible). Additional 47/8 non-diabetic/diabetic subjects were excluded in the HRV assessment, respectively, and 64/9 non-diabetic/diabetic subjects were excluded in the QTc interval analyses due to multiple supraventricular or ventricular extrasystoles, pacemaker therapy or missing data. Thus, 1,513 non-diabetic and 152 diabetic subjects were included in the multiple logistic regression analyses of HRV, while 1,496 non-diabetic and 151 diabetic subjects were included in the QTc interval model. The QTD model comprised 1,433 non-diabetic and 140 diabetic subjects due to incomplete 12 leads.

**Statistical Methods.** All continuous variables were described by mean±standard deviation, differences between groups were evaluated by t-tests. Categorical variables were described by frequency tables and
Cardiac autonomic dysfunction and mortality 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 logrank 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 non-diabetic subjects. The SAS statistical software package version 8.2 TS2M0 was used for statistical analyses.

RESULTS

Baseline characteristics. Compared with nondiabetic persons, diabetic subjects were significantly older, had a higher BMI, faster resting heart rate, higher systolic blood pressure, lower HDL cholesterol, higher cholesterol/HDL 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 as compared with the nondiabetic group (all $p<0.05$). The use of $\beta$ 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, and 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 second standard 12-lead ECG without controlling for depth and rate of respiration” at 1st quartile vs 2nd-4th quartile ($p=0.0447$)(Fig. 1A), whereas no significant difference was noted in the nondiabetic group ($p=0.4227$)(Fig. 1C). The corresponding mortality rates were 30/79(38.0%) vs 19/80(23.8%) in diabetic subjects and 42/366(11.5%) vs 119/1179(10.1%) in nondiabetic participants, respectively. In subjects who had a QTc interval >440 vs those $\leq$440 ms survival probability was significantly lower in both the diabetic ($p<0.0001$)(Fig. 1B) and nondiabetic ($p=0.0026$) group (Fig. 1D).

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 “as measured from a 20 second standard 12-lead ECG without controlling for depth and rate of respiration” were significant predictors of mortality, while CVD tended to predict mortality ($p=0.06$) (Table 2A). Among diabetic persons 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 2B). Among diabetic persons 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 2-fold and 3-fold in the nondiabetic and diabetic group, respectively. The results were similar when using the Framingham and Fridericia formulas for QT correction (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 2C). In the diabetic group age and low physical activity (both p<0.05), but not increased QTD were significant predictors of mortality.

After introducing both the max-min difference “as measured from a 20 second standard 12-lead ECG without controlling for depth and rate of respiration” and QTc interval and their possible interaction into the model, QTc interval prolongation remained a significant predictor of all-cause mortality showing a RR (95% CI) of 2.23(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 predict mortality in the diabetic group (1.96[0.99-3.89]; p=0.054), respectively. There was no interaction between these two variables in predicting mortality (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 3-fold increased risk of mortality. In contrast, increased QT dispersion neither predicted mortality in nondiabetic nor in diabetic subjects. Low HRV, “as measured from a 20 second standard 12-lead ECG without controlling for depth and rate of respiration”, showed a trend towards an increased risk of mortality by 73% in the diabetic but not in 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 WHO 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 UKPDS including newly diagnosed Type 2 diabetic patients both QTc 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). Amongst 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 (1.4-3.0) in middle-aged men and 1.4 (0.9-2.2) in elderly men with low HRV. This finding is not necessarily contradicting 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 therefore the prognostic value of low HRV may 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 CAD or non-CAD 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 2 out of 6 indexes of HRV measured (31). This risk level may be underestimated as this and other epidemiologic surveys have performed less extensive assessment compared to 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 of 20 sec ECG recording without control for respiration. However, since we have not employed frequency domain indices of HRV, we believe that computing time domain indices from these recordings is relatively accurate. Relatively short recordings of ECG leads have been reliably used in several other
epidemiological studies, i.e. ≥3 consecutive cycles (34) or recordings over 10 sec in the Rotterdam-Study (6) and the Diabetes Prevention Program (35) or 15-30 sec 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 due to 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 neither predicted mortality in nondiabetic nor in diabetic individuals. Low HRV “as measured from a 20 second standard 12-lead ECG without controlling for depth and rate of respiration” showed a trend of borderline significance towards 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 the 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.

ACKNOWLEDGMENTS

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REFERENCES

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.
TABLE 1. MONICA Survey 1989/90 (S2): baseline characteristics

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<tr>
<th></th>
<th>Nondiabetic Participants</th>
<th>Diabetic Participants</th>
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<td>160</td>
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<tr>
<td>Sex (m/f) (%)</td>
<td>51.3/48.7</td>
<td>51.3/48.8</td>
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<tr>
<td>Age (years)</td>
<td>63.7±5.4</td>
<td>65.2±5.5*</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.9±3.9</td>
<td>29.4±3.8*</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>65.3±10.7</td>
<td>71.6±12.8*</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>140±19</td>
<td>148±20*</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81±11</td>
<td>79±12</td>
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<td>HDL cholesterol (mg/dl)</td>
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<td>Total cholesterol/HDL ratio</td>
<td>4.81±1.81</td>
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<td>Fibrinogen (g/l)</td>
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<tr>
<td>Hypertension (%)</td>
<td>36.60</td>
<td>60.63*</td>
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<tr>
<td>CVD (MI or stroke) (%)</td>
<td>5.83</td>
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<td>High alcohol intake (%)</td>
<td>20.67</td>
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<td>Physically active (%)</td>
<td>28.84</td>
<td>20.00*</td>
</tr>
<tr>
<td>Use of ß blockers (%)</td>
<td>11.35</td>
<td>16.25+</td>
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<tr>
<td>All-cause mortality (%)</td>
<td>10.51</td>
<td>30.63*</td>
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<td>CAD mortality (%)</td>
<td>3.21</td>
<td>11.25*</td>
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<tr>
<td>Diabetes duration (years)</td>
<td>-</td>
<td>8.11±7.01</td>
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*p<0.05; +p=0.072
TABLE 2. Relative Risk (RR) and 95% confidence intervals (CI) for the associations of (A) reduced heart rate variability (Max-Min), (B) prolonged QTc interval (QTc), (C) QT dispersion, cardiovascular risk factors, and demographic variables with 9-year all-cause mortality in the non-diabetic and diabetic individuals. MONICA Augsburg survey 1989/90, age 55-74 years

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<th>A: Heart Rate Variability</th>
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<tr>
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<td>RR</td>
<td>95% CI</td>
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<tr>
<td>Max-Min (1st Quartile)</td>
<td>0.93</td>
<td>(0.65-1.34)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.59</td>
<td>(1.77-3.78)</td>
</tr>
<tr>
<td>Age</td>
<td>1.11</td>
<td>(1.08-1.15)</td>
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<tr>
<td>CVD</td>
<td>1.64</td>
<td>(0.98-2.74)</td>
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<tr>
<td>High alcohol intake</td>
<td>1.33</td>
<td>(0.93-1.89)</td>
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<tr>
<td>Use of β-Blockers</td>
<td>1.01</td>
<td>(0.63-1.63)</td>
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<tr>
<td>Regular smokers</td>
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<td>(1.40-2.91)</td>
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<tr>
<td>Obesity</td>
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<td>(0.92-1.01)</td>
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<tr>
<td>Dyslipidemia</td>
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<td>Male sex</td>
<td>2.60</td>
<td>(1.76-3.80)</td>
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<tr>
<td>Age</td>
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<td>CVD</td>
<td>1.59</td>
<td>(0.95-2.66)</td>
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<td>High alcohol intake</td>
<td>1.35</td>
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<td>Use of β-Blockers</td>
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<td>Physically active</td>
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<td>Hypertension</td>
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<td>Obesity</td>
<td>0.96</td>
<td>(0.92-1.01)</td>
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<td>Dyslipidemia</td>
<td>0.97</td>
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<tr>
<td>QTD (&gt;60 ms)</td>
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<td>Male sex</td>
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<td>Age</td>
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<td>CVD</td>
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<td>High alcohol intake</td>
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<td>Use of β-Blockers</td>
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<td>Regular smokers</td>
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<td>1.46-3.11</td>
</tr>
<tr>
<td>Physically active</td>
<td>0.64</td>
<td>0.43-0.97</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.58</td>
<td>1.10-2.26</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.97</td>
<td>0.92-1.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.02</td>
<td>0.93-1.12</td>
</tr>
</tbody>
</table>
FIGURE 1. Kaplan-Meier survival probability for the max-min R-R interval difference (1st quartile [broken line] vs 2nd to 4th quartile [continuous line]) in the diabetic (A) and nondiabetic (C) cohort and QTc interval (>440 ms [broken line] vs ≤440 ms [continuous line]) in the diabetic (B) and nondiabetic (D) cohort.

A: p=0.0447 for max-min difference in 1st quartile vs 2nd-4th quartile (diabetic)
C: p=0.4227 for max-min difference in 1st quartile vs 2nd-4th quartile (nondiabetic)
B: p<0.0001 for QTc interval >440 vs ≤440 ms (diabetic)
D: p=0.0026 for QTc interval >440 vs ≤440 ms (nondiabetic)