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Markers of ventricular repolarization and overall mortality in sleep disordered breathing

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Abstract

Introduction: Variability and prolongation of ventricular repolarization – measured by changes in QT interval and QT variability are independently associated with ventricular arrhythmias, sudden death, and mortality but such studies did not examine the role of sleep-disordered

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Declaration of competing interest

There are no conflicts of interest to report.

breathing. We aimed to determine whether sleep-disordered breathing moderated the association between measures of ventricular repolarization and overall mortality.

Methods: Eight hundred participants were randomly selected from each of the following four groups in the Sleep Heart Health Study: mild, moderate, severe or no sleep disordered breathing (n = 200 each). Overnight electrocardiograms were analyzed for QTc duration and QT variability (standard deviation of QT intervals, normalized QT interval variance and the short-term interval beat-to-beat QT variability). Cox proportional hazards penalized regression modeling was used to identify predictors of mortality.

Results: Eight hundred of 5600 participants were randomly selected. The participants (68 ± 10 years; 56.8% male) were followed for an average of 8.2 years during which time 222 (28.4%) died. QTc, SDQT, and QTVN were associated with the presence of SDB ($p = 0.002$, $p = 0.014$, and $p = 0.024$, respectively). After adjusting for covariates, the presence of sleep-disordered breathing did not moderate the association between QTc length, QT variability and mortality ($p > 0.05$).

Conclusion: Sleep-disordered breathing was associated with some measures of ventricular repolarization. However, sleep-disordered breathing was not an effect modifier for the relationship between QTc and QT variability and mortality.

Keywords

Ventricular repolarization; QT interval; QT variability; Sleep disordered breathing; Sleep apnea; Mortality

1. Introduction

Sleep Disordered Breathing (SDB) is a prevalent condition affecting approximately 15–30% of males and 10–15% of females [1,2]. It consists primarily of obstructive sleep apnea (OSA), a chronic medical condition that is widely recognized as an independent risk factor for several clinical consequences including cardiac disease, stroke, hypertension, type 2 diabetes, motor vehicle accidents, arrhythmias, and sudden death [3–6]. Patients with untreated moderate to severe SDB have a two-to three-fold increased risk of all-cause mortality compared with individuals without SDB, independent of other risk factors such as obesity and cardiovascular disease [7–11].

Delayed ventricular repolarization as measured by QTc intervals in electrocardiograms (ECG) is associated with cardiac arrhythmias and sudden cardiac death [12]. The QTc interval has been shown to be prolonged at the onset of apnea compared to the active awake state [13]. There is further prolongation of the QTc interval during the apneic phase and abrupt shortening of the QTc interval during the post-apnea hyperventilation period [13,14]. This marker of ventricular repolarization has been shown to be abnormally prolonged in patients with SDB independent of known risk factors for cardiac arrhythmias [14–16].

Variability in QT interval has also been shown to be greater in patients with SDB than those without SDB [17]. Previous studies have demonstrated that QT variability is independently associated with ventricular arrhythmias, sudden cardiac death, and total mortality, but such

studies did not examine the role of SDB [18]. In patients with SDB, prolonged QTc intervals and increased QT variability may be associated with ventricular arrhythmias, sudden cardiac death and overall mortality. The goal of this study to determine whether sleep-disordered breathing moderated the association between measures of ventricular repolarization and mortality.

2. Methods

2.1. Participants/study design

The study was granted an exemption from the University of Arizona Institutional Review Board. All participants were from the Sleep Heart Health Study (SHHS), details of which have been previously reported [19]. In summary, the SHHS is a prospective multicenter study cohort funded by the National Heart Lung and Blood Institute focusing on consequences of sleep disordered breathing. The SHHS consists of 6441 men and women over the age of 40 years evaluated between 1995 and 1998 (SHHS 1) and then again between 2001 and 2003 (SHHS 2) [20].

Our study focused on participants in SHHS 1 who had undergone unattended polysomnography with the CompuMedics P Series System monitor (Abbotsford, Australia) [21]. Signals available for review included oxyhemoglobin saturation, electroencephalogram (C3/A1 and C4/A2), bipolar electrocardiogram, bipolar electromyogram, bilateral electrooculogram, abdominal and thoracic inductance plethysmography, body position, ambient light, and oronasal thermocouple [22]. Additional details regarding the sleep study set-up and data quality are published [21].

Data was obtained from the National Sleep Research Resource (NSRR) which has 5600 polysomnograms in the database, but does not include participants from the Strong Heart Study cohort of the SHHS, and thus has few American Indians [23]. Participants with an apnea/hypopnea index (AHI) less or equal to 5/hour were considered not to have SDB and those with an AHI greater or equal to 5 per hour were considered to have SDB. Severity of SDB was classified as mild (AHI 5–14.99/hour), moderate (AHI 15–29.99/hour), and severe (AHI ≥30/hour) based on AHI [24]. We randomly selected two hundred participants from each of the mild, moderate, severe and no SDB groups in order to prevent selecting a cohort with predominantly no SDB and mild SDB participants given that approximately 83% of the SHHS participants were found to have no SDB or mild SDB [25]. We also chose to analyze a random sample of participants instead of all the participants in the SHHS 1 database given the rigor required for detailed ECG analysis as manual adjudication was performed for the signals to ensure validity and accuracy of the data. Sleep disordered breathing events were identified as apneas or hypopneas, the latter requiring a minimum 3% oxygen desaturation from baseline. Demographic, mortality, and co-morbid health conditions information were also obtained from the NSRR.

2.2. Electrocardiogram signal analysis

All electrocardiographic signals were evaluated using the Comprehensive Analysis of Repolarization Signal (COMPAS) software developed at the University of Rochester

Medical Center Rochester (NY). The software was applied to polysomnographic ECG signals for all available leads, providing the measurements of the RR and QT intervals measured from 10-beat median signals for the entire duration of each sleep study (mean total sleep duration/subject = 360 ± 65 min). Electrocardiograms were also manually adjudicated to ensure adequacy for automated analysis [26]. Furthermore, it was verified that all the participants were in a normal sinus rhythm. Bazett's heart rate($QTc = QT/RR^{1/2}$) [27] correction was used to calculate QTc [27]. RR values used for QT interval correction for heart rate were the average heart rate across the 10 beats used to compute the median beat.

QT variability was measured based on guidelines established by the European Heart Rhythm Association and the European Society of Cardiology Working Group on Cardiac Cellular Electrophysiology [28]. The different QT variability measurements obtained included the standard deviation of QT intervals [28] (SDQT; $\sqrt{\frac{\Sigma(QTn - QTmean)^2}{N-1}}$), normalized QT interval variance [28] (QTVN; SDQT2 $\frac{SDQT^2}{QTmean^2}$) at = 5-min intervals and the short-term interval beat-to-beat QT variability [28] (STVQT; $\Sigma\frac{|QTn+1-QTn|}{N\sqrt{2}}$ at 5-min intervals. In these equations N = number of beats evaluated, and n varies from 1 to N.

2.3. Statistical analysis

Univariate summary statistics for overall mortality as a binary (alive/dead) outcome include chi square statistics for categorical explanatory variables, and *t*-test statistics for continuous explanatory variables (Table 1). The primary analysis was a Cox proportional hazards model under the hypothesis of whether SDB moderates the relationship between mortality and QTc and QT variability, individually. This evaluation was performed for QTc and the QT variability through examination of the interaction between SDB and the QT variables. Selection for the optimal QT variability variable was chosen by a variable selection method, using regularized regression that optimally selects variables using a shrinkage estimate, between the QTVN, STVQT and SDQT as measures of QT variability (Table 3). Collinearity for all explanatory variables was evaluated using the variance inflation factor (VIF). The primary hypothesis has 0.80 power to detect a significant interaction between QTc and QT variability and SDB with a minimum of 128 deaths. The study was not powered to look at differences in QT variables based on SDB severity.

Additional statistical analyses included univariate data analyses, multivariable modeling, and the development of a prognostic classifier for mortality that included variable selection, and assessment of model performance evaluation (AUC) to predict mortality. Creation of the prognostic classifier was based on Cox proportional hazards modeling generalized from methods advocated by Harrell [29], and Moons [30] and implemented using a regularized regression approach described by Tibshirani [31] and Zou and Hastie. [32] Regularized regression methods are used to both select important predictors as well as develop a weighted linear "score". The score is adjusted by a shrinkage factor that ameliorates the over-estimation of predictive performance that can occur with prediction and small effective sample sizes.

Lasso methods are a special case of these model-based approaches although we used an algorithm called the ‘elastic net’ as it is more robust to collinearity. There is no need for multiple testing adjustments, as these models are not selected based on hypothesis testing (e.g., p-values) and the adjustment for over-performance is already incorporated into the model selection process.

Coefficients of explanatory (or predictor) variables were multiplied by the values of the variables (Table 3) at the participant level and the sum of this product was the “linear predictor” or linear score. This linear predictor was therefore a weighted sum, with the coefficients describing the direction of the association (those that are associated with higher or lower risk of mortality) as well as relative strength (e.g., largely positive or negative contribute more to the score than lower ones). This linear predictor served as an individual score that was then evaluated using the area under the receiver operating characteristic (ROC) curve (AUC); typically, AUCs greater than 0.70 have “moderate” predictive ability. Since the response was mortality, the ROC curves, and subsequent AUC values, were evaluated over time periods to visually note any time dependencies (i.e., difference in performance was dependent on the length of follow-up time to CVD event). We used censored models for time-dependent covariates using the Nearest Neighbor Estimate (NNE) method as described by Heagerty, et. A1 [33].

3. Results

Complete data was available for seven hundred and eighty-one SHHS 1 participants. Age, male gender, body mass index (BMI), waist circumference, neck circumference, hypertension, sleep disordered breathing, QTc, SDQT and QTVN were associated with higher mortality (Table 1). Male gender, BMI, waist circumference, neck circumference, hypertension, mortality, QTc, SDQT, and QTVN were associated with the presence of SDB (Table 2). The primary hypothesis of whether SDB was an effect modifier for the relationship between QTc and QT variability and mortality was rejected for both QTc and SDQT, as the interaction terms were not statistically significant ($p = 0.99$ and $p = 0.86$, respectively). Both QTc and SDQT were statistically significantly associated with mortality after adjusting for SDB ($p = 0.0011$ and $p < 0.0001$, respectively); and SDB was statistically associated with mortality after adjusting for QTc and SDQT ($p = 0.0020$ and $p = 0.0001$, respectively).

Table 3 shows the estimated coefficients, after application of the shrinkage parameter, for explanatory variables selected by the regularized regression to predict mortality. The coefficients under typical Cox proportional hazards modeling are also shown, along with the hazard ratio’s and 95% confidence intervals. It is important to note some variables that were predictive were not statistically significant as the selection criteria for regularized regression method is based on change in model fit and not p-values. Age, BMI, waist circumference, presence of hypertension, diabetes, cardiovascular disease, prolonged QTc and increased SDQT were all significant contributors to mortality after adjusting for the other variables. Since QTVN is a function of SDQT, only one out of the two measures were chosen for the linear score.

Fig. 1 used the selected predictors shown in Table 3 to create a score describing predictive capacity of mortality for those with SDB. While the linear predictor has slightly better predictive capacity in year 2, there is little difference over time. This is likely due to the small number of deaths (n = 26 respectively) during the first two years, with an increasing number over time (16,15, and 158 in years 3,4 and 5, respectively). The results show that the linear score that is formed using the variables from Table 3 is moderately able to predict mortality in participants with SDB, and while we don't see obvious time-dependency in this relationship, it is strongest at year 2 (AUC = 0.83).

Fig. 1. The predictive capacity of mortality for those with sleep disordered breathing utilizing the selected predictors in Table 3 is shown.

4. Discussion

Changes in QTc, SDQT, and QTVN were associated with the presence of SDB when compared to the absence of SDB. However, SDB was not found to be an effect modifier for the relationship between QTc, QT variability and overall mortality. Several variables including age, BMI, waist circumference, hypertension, diabetes, cardiovascular disease, QTc and SDQT were predictive of mortality in patients with OSA.

The association of demographic-related variables such as BMI, waist circumference and gender with mortality and the presence of SDB are consistent with existing literature [34–37] which shows a clear association between mortality and SDB with these variables. Similarly, the association of hypertension with mortality and SDB is consistent with the literature [38]. Contrary to existing literature [39,40], our study did not find an association between mortality and SDB among those with diabetes or cardiovascular disease likely due to the small number of participants with these conditions in our limited SHHS-1 cohort.

While we had hypothesized that QTc would be increased in participants with SDB when compared to participants without SDB, this was not the case. The QTc of participants without SDB group was 422(±29.3) mm while the QTC of participants with SDB was 415 (±31.7) mm, p = 0.002. This finding is not inconsistent with existing literature as both an increase in QTc with SDB [16,41–51] and a decrease in QTc with SDB [52–54] when compared to controls have been reported, with a majority of the studies showing an increase in QTc with SDB. Additional studies closely evaluating the relationship between QTc and SDB are needed to further clarify the relationship.

Also consistent with existing literature, is the association of QT variability with SDB [17,48,50,55,56]. The measures of QT variability we examined included SDQT, QTVN and STVQT, as recommended by the European Heart Rhythm Association and the European Society of Cardiology Working Group on Cardiac Cellular Electrophysiology [28]. In our sample SDQT and QTVN were associated with mortality and SDB however, STVQT was not. This may be due to the differences in computing QT variability using SDQT and QTVN. The latter incorporates the SDQT in its calculation whereas the STVQT does not. Due to subtle differences in these QT variability parameters, it is usually helpful to use more than one measurement of QT variability [28].

The predictive model for mortality included age, BMI, waist circumference, hypertension, diabetes, cardiovascular disease, and SDQT as significant predictors. This information while not surprising, is novel and can be further validated and strengthened for use in future clinical-decision support tools.

There are multiple strengths to the study, including a well identified SDB cohort based on current American Academy of Sleep Medicine (AASM) guidelines, detailed evaluations of QT-related parameters, and likely generalizability of the results to patients with SDB. Despite these strengths, there are some limitations to this study including the small sample size as well as the retrospective nature of the analysis. An additional possible limitation is the use of 10-beat median measurements for RR and QT intervals instead of beat-to-beat analysis. We do not believe this materially alters our findings because of evidence demonstrating that use of the 10-beat median approach does not lead to significant differences when compared to beat-to-beat analysis [57]. Finally, QTc and QT variability were averaged for the entire night and were not analyzed per specific apnea/hypopnea event due to the nature of how the sleep studies were tagged for respiratory events in the SHHS. Therefore, any QT effect that was apnea/hypopnea specific as has been previously reported [13,14] may have been diluted. Nevertheless, to our knowledge, most of the studies associating the changes in markers of ventricular repolarization with sleep apnea are small and none to our knowledge have also included clinically relevant outcomes such as mortality. Additional research is needed to evaluate the changes in QTc and QT variability with every apnea/hypopnea event in real-time and to clarify the relationship between the QT-related parameters, SDB and patient outcomes including arrhythmias and mortality.

5. Conclusions

Although QTc and markers of QT variability (SDQT and QTVN) were associated with the presence of SDB, SDB was not found to be moderating the relationship between these parameters and mortality. Risk prediction (using regularized regression) selected age, BMI, waist circumference, presence of hypertension, diabetes, cardiovascular disease, prolonged QTc and increased SDQT as significant contributors to mortality after adjusting for the other variables as optimal predictors of future mortality. Time-dependent ROC analysis showed that these predictors were optimal for classifying those with a death within 2 years of the study (AUC = 0.832) though all AUC were greater than 0.75. Additional research is needed to clarify the relationship between QTc, QT variability, and outcomes including arrhythmias and mortality in patients with SDB.

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea/Hypopnea index
AUC	Area Under the receiver operating characteristic Curve
COMPAS	Comprehensive Analysis of Repolarization Signal
ECG	Electrocardiograms
NSRR	National Sleep Research Resource
OSA	Obstructive Sleep Apnea
QTVN	Normalized QT Interval Variance
ROC	Receiver Operating Characteristic
SDB	Sleep Disordered Breathing
SDQT	Standard Deviation of QT Intervals
SHHS	Sleep Heart Health Study
STVQT	Short-term Interval Beat-to-Beat QT Variability
VIF	Variance Inflation Factor

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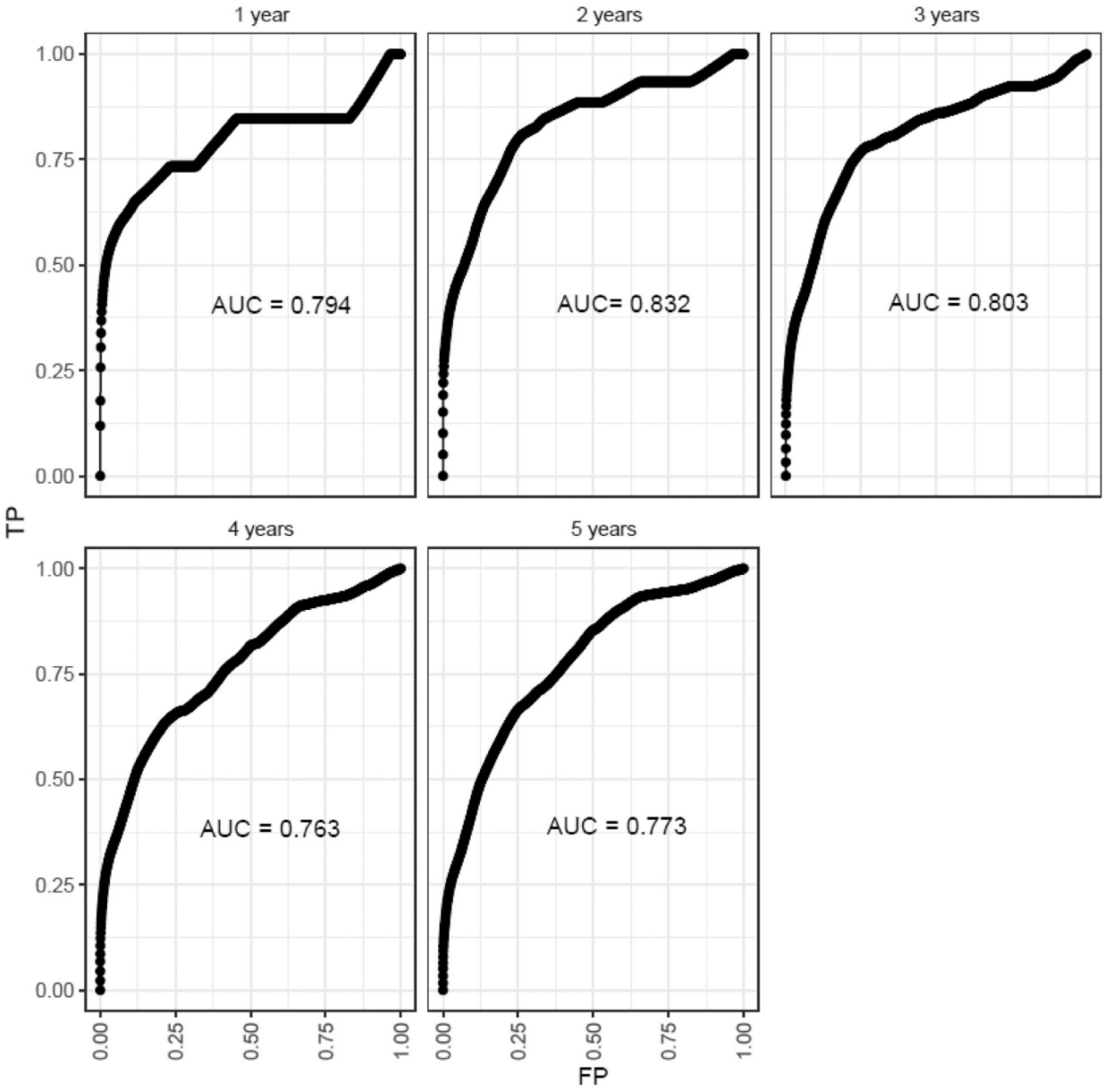

Fig. 1.

Auc estimates and ROC curves over Yearly time intervals from initial evaluation using nearest neighbor estimation.

Table 1

Demographic and QT variables stratified by mortality.

	Dead (n = 222)	Alive (n = 559)	P-value
Age, years, mean (SD)	74.9 (7.97)	64.9 (9.19)	<0.001
Age, 65 years and over, no. %	202 (91.0%)	299 (53.5%)	<0.001
Men, no. %	126 (56.8%)	253 (45.3%)	<0.001
Race, no. (%)			
White	202 (91.0%)	512 (91.6%)	0.976
Black	17 (7.7%)	35 (6.3%)	
Other	3 (1.4%)	12 (2.1%)	
BMI, kg/m^2, mean (SD)	26.3 (4.34)	27.4 (4.34)	<0.001
Waist Circumference, cm, mean (SD)	95.4 (12.6)	95.0 (12.4)	<0.001
Neck Circumference, mean (SD)	37.6 (3.80)	37.4 (3.87)	<0.001
Smoking Status, no. (%)			
Never	94 (42.3%)	282 (50.4%)	0.256
Current	13 (5.9%)	46 (8.2%)	
Former	115 (51.8%)	231 (41.3%)	
Hypertension, no. (%)	135 (60.8%)	216 (38.6%)	<0.001
Diabetes, no. (%)	30 (13.5%)	28 (5.0%)	0.594
Cardiovascular Disease, no. (%)	23 (10.4%)	64 (11.4%)	0.662
Sleep Disordered Breathing, no. (%)			
None	45 (20.3%)	120 (21.5%)	<0.001
Mild	49 (22.1%)	194 (34.7%)	
Moderate	61 (27.5%)	136 (24.3%)	
Severe	67 (30.2%)	109 (19.5%)	
Heart Rate, mean (SD)	65.6 (10.3)	65.2 (8.82)	0.191
QTc interval, mean (SD)[a]	422 (37.4)	415 (28.3)	0.002
Standard deviation of the QT intervals (SDQT), mean (SD)	11.9 (16.8)	7.72 (8.89)	0.014
Normalized QT interval variance (QTVN), mean (SD)	0.002 (0.006)	0.001 (0.003)	0.025
The short-term interval beat-to-beat QT variability (STVQT), mean (SD)	4.59 (4.95)	3.33 (2.78)	0.055

[a]QTc = QT interval with Bazett's heart rate correction.

Table 2

Demographics and QT variables Stratified by Presence of Sleep Disordered Breathing.

	No SDB (n = 165)	SDB(n = 616)	P-value
Age, years, mean (SD)	67.1 (9.93)	67.8 (9.9)	0.795
Men, no. %	47 (28.5)	332 (53.9)	<0.001
Race, no. (%)			
White	151 (91.5)	563 (91.4)	0.976
Black	11 (6.7)	41 (6.7)	
Other	3 (1.8)	12 (1.9)	
BM1, kg/m^2, mean (SD)	26.2 (3.57)	27.3 (4.5)	0.013
Waist Circumference, cm, mean (SD)	91.0 (12.8)	96.2 (12.1)	0.014
Neck Circumference, mean (SD)	35.7 (3.39)	37.9 (3.8)	<0.001
Smoking Status, no. (%)			
Never	90 (54.5)	286 (46.4)	0.256
Current	10 (6.1)	49 (8.0)	
Former	65 (39.4)	281 (45.6)	
Hypertension, no. (%)	66 (40.0)	285 (46.3)	<0.001
Diabetes, no. (%)	12 (7.3)	46 (7.5)	0.594
Cardiovascular Disease, no. (%)	20 (12.1)	67 (10.9)	0.662
Dead, no. (%)	45 (27.3)	177 (28.7)	<0.001
QTc interval[a]	422 (29.3)	415 (31.7)	0.002
Standard deviation of QT interval (SDQT), mean (SD)	6.84 (9.31)	9.45 (12.4)	0.014
Normalized QT interval variance (QTVN), mean (SD)	0.0010 (0.004)	0.0014 (0.005)	0.024
The short-term interval beat-to-beat QT variability (STVQT), mean (SD)	3.11 (2.04)	3.84 (3.9)	0.055

[a]QTc = QT interval with Bazett's heart rate correction.

Table 3

Regularized regression (Cox proportional hazards) with coefficients after applying shrinkage parameter and estimates from Cox proportional hazards without shrinkage estimation.

	Regularized Regression (Cox Model w/Shrinkage)	**Cox Proportional Hazards (No Shrinkage)**	
	Coefficient	**Coefficient**	**HR (95% CI)**
Age[a]	0.1183	0.14043	1.1321 (1.1094, 1.1552)
BMI[a]	−0.0720	−0.0908	0.9132 (0.8614, 0.9681)
Waist Circumference (cm)[a]	0.0158	0.0212	1.0214 (1.0030, 1.0401)
Neck Circumference (cm)	0.023	0.0349	1.0355 (0.9749, 1.0999)
Gender (Female)	−0.2953	−0.2483	0.7801 (0.5144, 1.1830)
Race (Black)	−0.0674	−0.1135	0.8927 (0.5282, 1.5086)
Never Smoker (vs Current)	−0.1928	−0.2435	0.8927 (0.5282, 1.5086
Former Smoker (vs Current)	N/A[b]	−0.0257	0.9747 (0.5362, 1.7716)
Hypertension (Yes)[a]	0.3630	0.4131	1.5115 (1.1380, 2.0075)
Diabetes (Yes)[a]	0.4576	0.4903	1.6328 (1.1027, 2.4175
Cardiovascular Disease (Yes)[a]	0.5838	0.6716	1.9573 (1.2363, 3.0990)
QTc[a]	0.0043	0.0049	1.0049 (1.0003, 1.0096)
Log(SDQT)[a]	0.3391	0.4546	1.5755 (1.1851,2.0946)
Log(STVQT)	−0.1398	−0.2936	0.7455 (0.5230, 1.0628)
Heart Rate	0.0103	0.0114	1.0115 (0.9968, 1.0264)
SDB	−0.1943	−0.2720	0.7619 (0.5408, 1.0732)

SDB = Sleep disordered breathing, QTc = QT with Bazett's heart rate correction, SDQT = standard deviation of the QT intervals at 5-min intervals.

[a]Statistically significant using Cox proportional hazards models.

[b]Estimate after shrinkage set to zero for linear predictor calculation.