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ORIGINAL RESEARCH

QT Interval Dynamics and Cardiovascular Outcomes: A Cohort Study in an Integrated Health Care Delivery System

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BACKGROUND: Long QT has been associated with ventricular dysrhythmias, cardiovascular disease (CVD) mortality, and sudden cardiac death. However, no studies to date have investigated the dynamics of within-person QT change over time in relation to risk of incident CVD and all-cause mortality in a real-world setting.

METHODS AND RESULTS: A cohort study among members of an integrated health care delivery system in Northern California including 61 455 people (mean age, 62 years; 60% women, 42% non-White) with 3 or more ECGs (baseline in 2005–2009; mean±SD follow-up time, 7.6±2.6 years). In fully adjusted models, tertile 3 versus tertile 1 of average QT corrected (using the Fridericia correction) was associated with cardiac arrest (hazard ratio [HR], 1.66), heart failure (HR, 1.62), ventricular dysrhythmias (HR, 1.56), all CVD (HR, 1.31), ischemic heart disease (HR, 1.28), total stroke (HR, 1.18), and all-cause mortality (HR, 1.24). Tertile 3 versus tertile 2 of the QT corrected linear slope was associated with cardiac arrest (HR, 1.22), ventricular dysrhythmias (HR, 1.12), and all-cause mortality (HR, 1.09). Tertile 3 versus tertile 1 of the QT corrected root mean squared error was associated with ventricular dysrhythmias (HR, 1.34), heart failure (HR, 1.28), all-cause mortality (HR, 1.20), all CVD (HR, 1.14), total stroke (HR, 1.08), and ischemic heart disease (HR, 1.07).

CONCLUSIONS: Our results demonstrate improved predictive ability for CVD outcomes using longitudinal information from serial ECGs. Long-term average QT corrected was more strongly associated with CVD outcomes than the linear slope or the root mean squared error. This new evidence is clinically relevant because ECGs are frequently used, noninvasive, and inexpensive.

Key Words: epidemiology ■ long QT ■ QT interval ■ short QT syndrome

The QT interval is the time from the beginning of the Q wave until the end of the T wave in the ECG and is a noninvasive biomarker of ventricular repolarization. An abnormally prolonged QT interval (>450 ms in men and >460 ms in women) can lead to early afterdepolarizations and premature action potentials, which can in turn result in ventricular arrhythmias and sudden cardiac death.[1–6] Congenital but rare forms of long-QT syndrome are well described.[7] Acquired forms of long-QT syndrome are more common and typically induced by cardiac and noncardiac medications.

The association of the QT interval with cardiovascular disease (CVD) outcomes, including sudden cardiac death, is well established.[8] However, limitations of the prior literature on the prognostic value of the QT interval include reliance on selected clinical populations including patients with myocardial infarction,[6,9,10] chronic ischemic heart disease (IHD),[4] heart failure,[11–13] end-stage renal disease,[14] type 2 diabetes,[15] hypertension,[16] rheumatoid arthritis,[17] hypertrophic cardiomyopathy,[18] atrial fibrillation,[19] and chronic obstructive pulmonary disease,[20] and the fact that studies relied on a QT interval measure at a single point in time.[21–29] Thus, the relevance of

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CLINICAL PERSPECTIVE

What Is New?

- Our results demonstrate that within-person QT corrected (QTc) dynamic measures (long-term average, linear change, and fluctuation over time) are independently associated with cardiovascular outcomes.
- Long-term average QTc was the strongest predictor of ischemic heart disease, cardiac arrest, ventricular dysrhythmias, and the combined cardiovascular disease outcome, whereas the average QTc and the last QTc measure were equally predictive of heart failure, total stroke, and all-cause mortality.

What Are the Clinical Implications?

- Valuable information can be obtained from serial QTc measures that outperform a QTc measure at a single point in time.
- Given that ECG testing is ubiquitous, routine, inexpensive, and frequently performed serially, an improved understanding of the predictive ability of QTc change and variability over time may help clinicians to risk stratify patients.

Nonstandard Abbreviations and Acronyms

IHD	ischemic heart disease
KPNC	Kaiser Permanente of Northern California
QTc	QT corrected
RMSE	root mean squared error

within-person QT dynamics (long-term average, linear change, and fluctuation over time) for CVD risk prediction in a real-world ambulatory population is unknown.

The purpose of the present study was therefore to examine the association of QT interval dynamics with incident CVD outcomes and all-cause mortality in a large and ethnically diverse population-based sample. The strengths of our study include not only assessment of a nonselected population, but also ascertainment of multiple QT corrected (QTc) measurements and covariates over time.

METHODS

Data are available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Population and Study Design

Kaiser Permanente of Northern California (KPNC) is an integrated health care delivery system serving ≈4.5 million members. The membership is stable, with <10% turnover annually overall and <3% to 5% among members aged 65 years and older and/or who have a chronic illness. The program delivers comprehensive inpatient and outpatient care to its members and captures many aspects of its care in multiple comprehensive clinical and administrative databases. KPNC's population is ethnically and socioeconomically diverse, and is broadly representative of the Northern California population.[30]

We retrospectively identified all of the 12-lead surface ECGs that were performed on KPNC members as part of routine outpatient or inpatient medical care in the period spanning between January 1, 2005 and December 31, 2009. A total of 3 149 872 ECG tracings were identified among 1 145 665 subjects. ECG tracings with evidence of pacemakers (n=71 947), with QTc (n=8677) or heart rate (n=13 214) out of physiological range (ie, QTc <200 or >800 ms and heart rate <40 or >180 bpm), and those not linked to a KPNC facility (n=153 388) were sequentially excluded, resulting in a total of 2 902 646 ECG tracings in 1 067 749 people. We then selected subjects who were men or women aged over 35 years on January 1, 2005 (n=863 382 subjects). Of those, we selected a subset of 171 141 with 3 or more ECGs, requiring a spacing of ≥3 months between ECGs. An additional 58 507 subjects (yielding a cohort of 112 634) were excluded for not having ≥3 measures of covariate of interest including body mass index, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, diastolic blood pressure, and estimated glomerular filtration rate (eGFR) in the ascertainment period (2005–2009), ensuring that the repeated measures of covariates were also at least 3 months apart. Further exclusions were being unknown smoking status (n=187), continuous health-plan disenrollment for >180 days (n=3623), and history of prior CVD, including IHD, cardiac arrest, total stroke, heart failure, ventricular dysrhythmias (n=45 791), and left or right bundle branch block (n=1578). The final study cohort was 61 455 people with an average (SD) number of ECGs of 3.7 (1.1).

QT Measurement and Adjustment for Heart Rate and Secular Trend

All ECGs in the KPNC system were obtained using cardiographs manufactured by Philips Medical Systems (Andover, MA). For this study, we extracted the raw QT and RR measurements that were generated from each 12-lead waveform by the proprietary Philips algorithms (software versions PH07 and PH08), which are described elsewhere.[31] To correct for heart rate, we used the Fridericia correction formula, which significantly improves prediction of 30-day and 1-year mortality compared with the Bazett correction.[32] We

observed a gradual upward trend in mean QTc between 2005 and 2012, which was driven by a change in the algorithm used to measure QT (from PH7 to PH8), and this happened at different time points across KPNC facilities. We generated plots of annual mean QTc for each separate facility and determined the year of transition for each facility. Using data for the entire membership (over 1.1 million subjects), we detrended the QTc values during the transition years by fitting a linear time trend, then subtracting off the mean QTc in each year predicted by the linear model and translating the detrended data to the posttransition QTc values by adding the mean QTc of all data in the posttransition years. We also noticed a slight upward trend of mean QTc in the years preceding the transition. We therefore detrended the QTc values during this period using a spline model (restricted cubic splines with 3 internal knots based on percentiles) to allow for nonlinearity.

Study Covariates and CVD Outcomes

Demographics, smoking status, body mass index, and systolic and diastolic blood pressure were ascertained from inpatient and outpatient electronic records. Use of antihypertensives and cholesterol-lowering agents were obtained from the health-plan outpatient pharmacy database. Diabetes was determined by linkage with the Kaiser Permanente Division of Research Diabetes Registry.[33] Total cholesterol, HDL cholesterol, and serum creatinine were obtained from the Kaiser Permanente Regional Laboratory Utilization Results System. Non-HDL cholesterol was total cholesterol minus HDL cholesterol. eGFR was measured using the Chronic Kidney Disease Epi formula.[34] CVD outcomes were based on primary discharge diagnosis or underlying cause of death that occurred between January 1, 2010 and December 31, 2019 (see Table S1 containing the *International Classification of Diseases, Ninth and Tenth Revision* [*ICD-9* and *ICD-10*] and procedure codes). The CVD outcomes included IHD, cardiac arrest, total stroke, heart failure, ventricular dysrhythmias, all CVD, and total mortality. The study was approved by the Kaiser Foundation Research Institute Institutional Review Board, and the informed consent requirement was waived.

Statistical Analysis

For all continuous variables (QTc, body mass index, non-HDL cholesterol, systolic blood pressure, diastolic blood pressure, and eGFR), we generated 3 variables capturing the dynamics over a 5-year period: long-term average, linear change, and fluctuation.[35] Linear change was the slope against time derived from the longitudinal measurements available per subject. Fluctuation was the root mean squared error (RMSE), which represents the residual variability around the overall time trend. To assess bivariate associations among covariates, we computed Pearson correlation coefficients for continuous variables (all were normally distributed) and point biserial correlations between the 3 QTc dynamic variables and categorical variables. We estimated the age-adjusted risk of each CVD outcome per 10 000 person-years in sex-specific tertiles of QTc average, slope, and RMSE using Poisson regression. Time-to-event survival analysis was performed with Cox proportional hazards models. For each person, follow-up was defined as time from the last ECG in the covariate ascertainment period (2005–2009) to incident outcome of interest or censoring at death from any cause, termination of health-plan membership (defined as a consecutive 6-month gap in membership), or end of follow-up in December 31, 2018, whichever occurred first (see Figure 1 for a schematic of study design). The mean (SD) follow-up time was 7.6 (2.6) years, and the maximum was 9.0 years. We fitted minimally adjusted Cox models controlling for age, sex, and race/ethnicity, and then fully adjusted models with additional control for smoking status, diabetes, hypertension, cholesterol-lowering medication, plus average, linear slope, and fluctuation of body mass index, non-HDL cholesterol, systolic blood pressure, diastolic blood pressure, and eGFR, respectively. We estimated the hazard ratio (HR) and 95% CI for each CVD outcome and total mortality for tertiles 2 and 3 relative to tertile 1 in the case of average and RMSE QTc, and for tertile 1 and 3 relative to tertile 2 in the case of QTc linear slope. To assess linear trends, we fitted another set of models where the main exposures were standardized effects (ie, per 1-SD increment) of continuous QTc average, QTc linear slope, and QTc RMSE, respectively. To evaluate the risks associated with clinically accepted sex-specific thresholds for long QTc (>450 ms in men and >460 ms in women),[36] we fitted 2 supplemental models, one considering any (ie, 1 or more) ECG with long QTc versus no ECG with long QTc and another considering average QTc in the long-QTc range versus average QTc not in the long-QTc range. To allow comparison of strength of independent association with CVD outcomes across static and dynamic QTc measures, we ran 3 separate fully adjusted Cox models series entering the first QTc, the last QTc, and then QTc average. Each of these series of models were adjusted for the same vector of covariates listed above. Because the Bazett correction for QT is more commonly used clinically, we performed a sensitivity analyses of CVD outcomes using the Bazett correction. A 2-tailed *P* value of 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS release 9.13 (SAS Institute, Cary, NC).

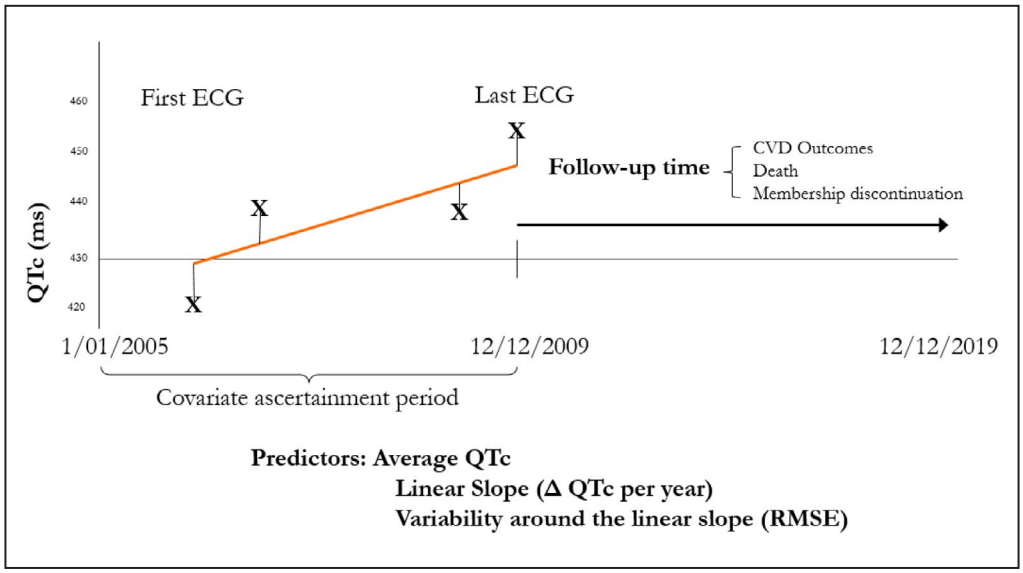

Figure 1. Schematic of the study design.
CVD indicates cardiovascular disease; QTC, QT corrected; and RMSE, root mean squared error.

RESULTS

The mean (SD) age of the cohort at the last ECG was 63 (12) years (Table 1). The study sample was 60% women and racially/ethnically diverse: 57% White, 9% Black, 12% Asian/Pacific Islander, 14% Hispanic/Latino, and 7% mixed race. For QTc, the mean of the average (SD) was 427 (22) ms, the mean (SD) of the slope was 0.6 (13) ms/y, and the mean (SD) of the RMSE was 15 (12) ms. About 28% of the cohort had at least 1 ECG with long QTc, and 9% had an average QTc in the long-QTc range. By contrast, none had an average QTc in the short-QTc range (≤300 ms), and 20 unique individuals had 1 ECG with short QTc (≤300 ms, ranging from 251 to 297 ms). Five percent were current smokers, 32% had a diagnosis of diabetes, 83% were on antihypertensive medication, and 67% on cholesterol-lowering drugs.

Table 2 summarizes the intercorrelations among QT variables themselves and with the covariates. The first QTc measure correlated 0.19 with age, 0.14 with sex, 0.46 with the last QTc measure, 0.78 with the average QTc, −0.40 with the QTc linear slope and 0.12 with the QTc RMSE, and −0.14 with the eGFR average. The last QTc measure correlated 0.18 with age, 0.10 with sex, 0.80 with average QTc, 0.12 with QTc RMSE, and −0.15 with the eGFR average. QTc average correlated 0.23 with age, 0.15 with sex, 0.11 with hypertensive medication, 0.19 with QTc RMSE, 0.11 with systolic blood pressure average, 0.10 with systolic blood pressure RMSE, and −0.19 with the eGFR average. QT RMSE correlated 0.10 with age and 0.12 with the first and last QTc, respectively.

The associations of average QTc with CVD outcomes are summarized in Table 3. In minimally adjusted models, positive significant linear trends were observed for all CVD outcomes and all-cause mortality (all $P<0.0001$). In the fully adjusted models, tertile 3 (relative to tertile 1) of the average QTc was associated, in order of strength, with cardiac arrest (HR, 1.66), heart failure (HR, 1.62), ventricular dysrhythmias (HR, 1.56), all CVD (HR, 1.31), IHD (HR, 1.28), all-cause mortality (HR, 1.24), and total stroke (HR, 1.18).

The associations of QTc linear slope with CVD outcomes are summarized in Table 4. In minimally adjusted models, significant linear trends were observed for total stroke, heart failure, ventricular dysrhythmias, and all CVD (all $P\leq0.03$). In the fully adjusted models, tertile 3 (relative to tertile 2) of the QTc linear slope was associated, in order of strength, with cardiac arrest (HR, 1.22), ventricular dysrhythmias (HR, 1.12), and total mortality (HR, 1.09), and was not significantly associated with IHD, total stroke, heart failure, or all CVD.

The associations of QTc RMSE with CVD outcomes are summarized in Table 5. In minimally adjusted models, positive significant linear trends were noted for IHD, total stroke, heart failure, ventricular dysrhythmias, all CVD, and all-cause mortality (all $P\leq0.002$). In the fully adjusted models, tertile 3 (relative to tertile 1) of the QTc RMSE was associated, in order of strength, with ventricular dysrhythmias (HR, 1.34), heart failure (HR, 1.28), total mortality (HR, 1.20), all CVD (HR, 1.14), total stroke (HR, 1.08), and IHD (HR, 1.07).

Table S2 details the risks associated with having at least 1 ECG with long QTc. The multivariate-adjusted hazard ratios varied from 1.22 for total stroke to 1.84

Table 1. Characteristics of the Study Cohort

Characteristics	Mean ± SD or n (%)
No.	61 455
Age, y, mean±SD	62.6±12.0
Age categories, y, n (%)	
35–54	16 676 (27.1)
55–64	16 928 (27.5)
65–84	26 615 (43.3)
≥85	1236 (2.0)
Sex, n (%)	
Men	24 759 (40.3)
Women	36 696 (59.7)
Race/ethnicity, n (%)	
White	35 344 (57.5)
Black	5391 (8.8)
Asian and Pacific Islander	7118 (11.6)
Latino	8705 (14.2)
Native American	257 (0.4)
Mixed	4473 (7.3)
Missing	167 (0.3)
Smoking status, n (%)	
Never	29 253 (47.6)
Former	29 130 (47.4)
Current	3072 (5.0)
Diabetes, n (%)	19 402 (31.6)
Hypertension medication, n (%)	51 152 (83.2)
Cholesterol-lowering medication, n (%)	40 960 (66.7)
QTc, ms, mean±SD	
Average	427.3±22.1
Linear slope	0.6±13.1
RMSE	15.2±12.0
First QTc, ms, mean±SD	426.0±27.1
Last QTc, ms, mean±SD	427.8±28.5
BMI, kg/m^2, mean±SD	
Average	29.6±6.0
Linear slope	−0.2±0.9
RMSE	1.3±0.9
Non-HDL cholesterol, mg/dL, mean±SD	
Average	138.6±32.0
Linear slope	−5.0±12.8
RMSE	19.5±13.5
Systolic blood pressure, mm Hg, mean±SD	
Average	130.7±12.1
Linear slope	−1.2±12.7
RMSE	12.5±6.9
Diastolic blood pressure, mm Hg, mean±SD	
Average	74.2±7.6
Linear slope	−1.0±7.2
RMSE	7.2±3.6
eGFR, mL/min per 1.73 m^2, mean±SD	
Average	73.9±19.9
Linear slope	−0.0±3.8
RMSE	7.0±4.0

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; QTc, corrected QT; and RMSE, root mean squared error.

for heart failure. Similar association were seen for having an average QTc in the long-QTc range (Table S3).

Figure 2 displays the HR (95% CI) for CVD conditions associated with the upper tertile of the first and the last static-QT measures along with the 3 longitudinal measures (average, linear slope, and RMSE). For IHD, cardiac arrest, all CVD, and ventricular dysrhythmias, the strongest predictor was the average QTc. For heart failure, total stroke, and all-cause mortality, average QTc and the last QTc had similar strengths of association. We also performed a sensitivity analysis using the more commonly used Bazett QT correction for heart rate instead of the Fridericia correction. Results are depicted in Figure S1. For IHD, all CVD, heart failure, and ventricular dysrhythmias, the strongest predictor was the average QTc. For stroke, cardiac arrest, and all-cause mortality, the strongest predictor was the last QTc measure.

DISCUSSION

The association of a static measure of the QT interval with CVD outcomes (including sudden cardiac death) is well established in the literature. However, there are limited data on the relationship of multiple QTc measures with subsequent adverse cardiovascular events. In a recent meta-analysis by Zhang et al with 23 observational studies included, the investigators found consistent associations between prolonged QT interval and increased risk of IHD, cardiovascular and total mortality, as well as sudden cardiac death. The pooled relative risk comparing the highest and lowest categories of QT interval was 1.71 (95% CI, 1.36–2.15) for coronary heart disease, 1.51 (95% CI, 1.29–1.78) for cardiovascular mortality, 1.35 (95% CI, 1.26–1.46) for total mortality, and 1.44 (95% CI, 1.01–2.04) for sudden cardiac death.[37] Our results (even the analysis of a single static measure) are not directly comparable with the findings of Zhang et al, because of methodological differences, including consideration of nonfatal as well as fatal events, adjustment for a more complete set of longitudinal covariates, and the fact that some of the studies included in the meta-analysis employed higher cutoff points for the highest category of QT length.

Table 2. Correlation of QTc Average, Linear Slope, and RMSE With Other Study Variables

	First QTc		Last QTc		QTc average		QTc linear slope		QTc RMSE	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Age	0.19	0.0000	0.18	0.0000	0.23	0.00	0.00	0.80	0.10	<0.0001
Sex	0.14	<0.0001	0.10	<0.0001	0.15	<0.0001	−0.03	<0.0001	−0.02	<0.0001
Race/ethnicity										
White	0.06	<0.0001	0.04	<0.0001	0.07	<0.0001	−0.01	0.01	0.01	0.02
Black	−0.05	<0.0001	−0.02	<0.0001	−0.04	<0.0001	0.02	<0.0001	0.02	<0.0001
Asian and Pacific Islander	−0.02	<0.0001	−0.02	<0.0001	−0.03	<0.0001	−0.0002	0.66	−0.01	0.01
Latino	−0.03	<0.0001	−0.02	<0.0001	−0.03	<0.0001	−0.003	0.95	−0.02	0.00
Native American	−0.01	0.06	−0.01	0.007	−0.01	0.003	−0.002	0.40	0.003	0.49
Mixed	0.002	0.71	0.003	0.45	0.002	0.68	0.002	0.70	−0.0006	0.88
Never smoking	0.0006	0.88	−0.0007	0.86	0.002	0.71	−0.0008	0.70	−0.02	<0.0001
Former smoking	0.01	0.12	0.01	0.07	0.01	0.07	−0.002	0.85	0.02	<0.0001
Current smoking	−0.02	<0.0001	−0.01	0.0002	−0.02	<0.0001	−0.0002	0.66	−0.01	0.00
Diabetes	−0.04	<0.0001	−0.01	0.18	−0.02	<0.0001	0.03	<0.0001	0.02	<0.0001
Hypertension medication	0.08	<0.0001	0.09	<0.0001	0.11	<0.0001	0.01	0.07	0.06	<0.0001
Cholesterol-lowering drugs	0.04	<0.0001	0.05	<0.0001	0.05	<0.0001	0.01	0.02	0.03	<0.0001
First QTc	NA	NA	0.46	<0.0001	0.78	<0.0001	−0.40	0.00	0.12	<0.0001
Last QTc	0.46	<0.0001	NA	NA	0.80	<0.0001	0.46	0.00	0.12	<0.0001
QTc average	0.78	<0.0001	0.80	<0.0001	…	…	0.04	<0.0001	0.19	0.00
QTc linear slope	−0.40	<0.0001	0.46	<0.0001	0.04	<0.0001	NA	NA	0.01	0.01
QTc RMSE	0.12	<0.0001	0.12	<0.0001	0.19	<0.0001	0.01	0.01	NA	NA
BMI average	−0.03	<0.0001	−0.02	<0.0001	−0.03	<0.0001	0.01	0.00	−0.04	<0.0001
BMI linear slope	−0.03	<0.0001	−0.01	0.001	−0.02	<0.0001	0.01	0.02	−0.03	<0.0001
BMI RMSE	0.01	0.0007	0.02	<0.0001	0.02	<0.0001	0.01	0.01	0.02	<0.0001
Non-HDL cholesterol average	−0.05	<0.0001	−0.05	<0.0001	−0.06	<0.0001	−0.01	0.01	−0.04	<0.0001
Non-HDL cholesterol linear slope	−0.02	0.0002	−0.01	0.04	−0.01	0.0006	0.01	0.20	−0.003	0.50
Non-HDL cholesterol RMSE	−0.01	0.0007	−0.01	0.04	−0.01	0.01	0.01	0.06	0.01	0.00
SBP average	0.08	<0.0001	0.09	<0.0001	0.11	<0.0001	0.01	0.00	0.03	<0.0001
SBP linear slope	−0.004	0.27	0.004	0.34	−0.002	0.57	0.01	0.13	−0.01	0.07
SBP RMSE	0.07	<0.0001	0.09	<0.0001	0.10	<0.0001	0.02	<0.0001	0.06	<0.0001
DBP average	−0.08	<0.0001	−0.07	<0.0001	−0.09	<0.0001	0.01	0.10	−0.03	<0.0001
DBP linear slope	0.005	0.22	0.0008	0.84	0.002	0.63	−0.002	0.63	0.0008	0.84
DBP RMSE	0.02	<0.0001	0.03	<0.0001	0.03	<0.0001	0.01	0.0004	0.04	<0.0001
eGFR average	−0.14	<0.0001	−0.15	0.0000	−0.19	0.00	−0.02	<0.0001	−0.09	<0.0001
eGFR linear slope	−0.0002	0.96	−0.03	<0.0001	−0.02	<0.0001	−0.03	<0.0001	−0.01	0.01
eGFR RMSE	−0.01	0.11	−0.003	0.49	−0.005	0.24	0.004	0.32	0.04	<0.0001

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; QTc, corrected QT; RMSE, root mean squared error; and SBP, systolic blood pressure.

The average QTc over a 5-year period was positively correlated with age, female sex, White race, antihypertension medication, and systolic blood pressure average and fluctuation; the average QTc was negatively correlated with long-term average eGFR. Longer QTc intervals with increasing age and in women compared with men is a well-known phenomenon.[38–40] The relationship of QTc with impaired kidney function has also been described.[41] Park et al reported an association between metabolic syndrome and its components, including blood pressure, with prolonged corrected QTc interval in healthy Korean men and women.[42] Several clinical pathologies have been shown to prolong or shorten the QTc interval. In patients with heart failure, an increased brain natriuretic peptide was found to be associated with an increased risk of sudden cardiac death, primarily in patients with a prolonged QTc interval.[42] Similarly, QTc has been found to be positively correlated with high-sensitivity C-reactive protein levels and an increased inflammatory burden. Panoulas et al found that patients with rheumatoid arthritis and a higher inflammatory burden had a prolonged QTc

Table 3. Association of QTc Average With CVD Outcomes

Outcomes	Tertile 1, n=20 485			Tertile 2, n=20 485			Tertile 3, n=20 485			1-SD increment	*P* value trend
	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	MaHR (95% CI) FaHR (95% CI)	
IHD	3629	237.6	1	3862	236.7	1.10 (1.05–1.15)	4866	288.9	1.40 (1.34–1.46)	1.16 (1.14–1.18)	<0.0001
			1			1.08 (1.03–1.13)			1.28 (1.22–1.34)	1.10 (1.08–1.12)	<0.0001
Cardiac arrest	333	20.2	1	414	23.6	1.31 (1.14–1.52)	593	32.6	1.81 (1.57–2.08)	1.28 (1.21–1.34)	<0.0001
			1			1.31 (1.14–1.52)			1.66 (1.44–1.91)	1.20 (1.14–1.27)	<0.0001
Total stroke	3067	196.4	1	3486	208.4	1.10 (1.05–1.16)	4039	228.1	1.24 (1.18–1.30)	1.09 (1.07–1.11)	<0.0001
			1			1.10 (1.04–1.15)			1.18 (1.13–1.24)	1.06 (1.04–1.08)	<0.0001
Heart failure	3203	194.6	1	3850	213.9	1.18 (1.13–1.24)	5909	305.0	1.77 (1.70–1.86)	1.31 (1.29–1.33)	<0.0001
			1			1.17 (1.11–1.22)			1.62 (1.55–1.69)	1.23 (1.21–1.25)	<0.0001
Ventricular dysrhythmias	712	43.6	1	810	47.3	1.21 (1.09–1.34)	1130	64.5	1.68 (1.52–1.85)	1.28 (1.23–1.32)	<0.0001
			1			1.19 (1.07–1.31)			1.56 (1.41–1.72)	1.22 (1.18–1.27)	<0.0001
All CVD	7465	531.1	1	8206	549.7	1.11 (1.08–1.15)	10 290	672.6	1.41 (1.27–1.35)	1.17 (1.15–1.18)	<0.0001
			1			1.09 (1.06–1.13)			1.31 (1.27–1.35)	1.12 (1.11–1.13)	<0.0001
All-cause mortality	4917	263.6	1	5671	263.4	1.07 (1.03–1.11)	7776	311.9	1.30 (1.26–1.35)	1.12 (1.11–1.14)	<0.0001
			1			1.08 (1.04–1.12)			1.24 (1.19–1.28)	1.08 (1.07–1.10)	<0.0001

MaHRs are adjusted for age, sex, race/ethnicity, QTc linear slope, and QTc RMSE. FaHRs are adjusted for age, sex, race/ethnicity, QTc linear slope, and QTc RMSE, smoking status, diabetes, hypertension medication, cholesterol-lowering drugs, BMI (average, linear slope, RMSE), non-HDL cholesterol (average, linear slope, RMSE), SBP (average, linear slope, RMSE), DBP (average, linear slope, RMSE), and eGFR (average, linear slope, RMSE). AAR indicates age-adjusted rate; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FaHR, fully adjusted hazard ratio; HDL, high-density lipoprotein; IHD, ischemic heart disease; MaHR, minimally adjusted hazard ratio; QTc, corrected QT; RMSE, root mean squared error; and SBP, systolic blood pressure.

Table 4. Association of QTc Linear Slope With CVD Outcomes

Outcomes	Tertile 1, n=20 485			Tertile 2, n=20 485			Tertile 3, n=20 485			1-SD increment	*P* value trend
	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	MaHR (95% CI) FaHR (95% CI)	
IHD	4059	249.2	0.97 (0.93–1.01)	4084	253.3	1	4214	259.5	0.97 (0.93–1.02)	1.01 (0.99–1.02)	0.37
			0.95 (0.91–1.00)			1			0.94 (0.90–0.99)	1.00 (0.98–1.02)	0.95
Cardiac arrest	449	25.5	1.20 (1.04–1.37)	369	21.1	1	522	29.7	1.31 (1.15–1.50)	1.04 (0.99–1.09)	0.12
			1.16 (1.01–1.33)			1			1.22 (1.07–1.39)	1.02 (0.97–1.07)	0.45
Total stroke	3492	207.3	0.99 (0.95–1.04)	3442	207.1	1	3658	218.2	1.03 (0.99–1.08)	1.02 (1.00–1.04)	0.03
			0.98 (0.94–1.03)			1			1.00 (0.96–1.05)	1.02 (1.00–1.03)	0.10
Heart failure	4210	229.3	0.99 (0.95–1.04)	3939	218.6	1	4813	263.3	1.10 (1.05–1.14)	1.03 (1.02–1.05)	<0.0001
			0.96 (0.92–1.00)			1			1.04 (1.00–1.09)	1.02 (1.01–1.04)	0.002
Ventricular dysrhythmias	854	49.7	1.03 (0.94–1.14)	795	46.6	1	1003	58.9	1.15 (1.05–1.27)	1.04 (1.01–1.07)	0.02
			1.01 (0.92–1.12)			1			1.12 (1.02–1.23)	1.03 (1.00–1.07)	0.06
All CVD	8561	574.4	1.00 (0.97–1.03)	8340	563.4	1	9060	611.7	1.03 (1.00–1.06)	1.02 (1.01–1.03)	0.003
			0.98 (0.95–1.01)			1			1.00 (0.97–1.03)	1.01 (1.00–1.02)	0.06
All-cause mortality	6246	282.6	1.10 (1.06–1.14)	5431	254.1	1	6687	301.7	1.15 (1.11–1.19)	1.01 (1.00–1.03)	0.08
			1.06 (1.02–1.10)			1			1.09 (1.05–1.13)	1.01 (0.99–1.02)	0.39

MaHRs are adjusted for age, sex, race/ethnicity, QTc average, and QTc RMSE. FaHRs are adjusted for age, sex, race/ethnicity, QTc average and QTc RMSE, smoking status, diabetes, hypertension medication, cholesterol-lowering drugs, BMI (average, linear slope, RMSE), non-HDL cholesterol (average, linear slope, RMSE), SBP (average, linear slope, RMSE), DBP (average, linear slope, RMSE), and eGFR (average, linear slope, RMSE). AAR indicates age-adjusted rate; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FaHR, fully adjusted hazard ratio; HDL, high-density lipoprotein; IHD, ischemic heart disease; MaHR, minimally adjusted hazard ratio; QTc, corrected QT; RMSE, root mean squared error; and SBP, systolic blood pressure.

Table 5. Association of QTc RMSE With CVD Outcomes

Outcomes	Tertile 1, n=20 485			Tertile 2, n=20 485			Tertile 3, n=20 485			1-SD increment	*P* value trend
	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	No. of events	AAR per 10 000 person-years	MaHR (95% CI) FaHR (95% CI)	MaHR (95% CI) FaHR (95% CI)	
IHD	3864	235.8	1	4170	259.4	1.11 (1.06–1.16)	4323	267.9	1.12 (1.07–1.17)	1.03 (1.01–1.04)	0.002
			1			1.08 (1.03–1.13)			1.07 (1.02–1.11)	1.01 (1.00–1.03)	0.12
Cardiac arrest	393	22.2	1	438	25.1	1.10 (0.96–1.26)	509	29.2	1.18 (1.04–1.35)	1.04 (0.99–1.09)	0.09
			1			1.06 (0.92–1.21)			1.08 (0.95–1.24)	1.02 (0.97–1.07)	0.51
Total stroke	3304	196.1	1	3589	216.3	1.11 (1.06–1.16)	3699	220.9	1.13 (1.08–1.18)	1.03 (1.01–1.05)	0.0009
			1			1.09 (1.04–1.14)			1.08 (1.03–1.13)	1.02 (1.00–1.04)	0.08
Heart failure	3665	202.5	1	4193	232.2	1.17 (1.12–1.22)	5104	279.0	1.37 (1.31–1.43)	1.08 (1.07–1.10)	<0.0001
			1			1.12 (1.07–1.17)			1.28 (1.23–1.34)	1.07 (1.05–1.09)	<0.0001
Ventricular dysrhythmias	743	42.9	1	852	50.0	1.16 (1.06–1.28)	1057	62.8	1.40 (1.27–1.53)	1.11 (1.07–1.14)	<0.0001
			1			1.14 (1.04–1.26)			1.34 (1.22–1.47)	1.09 (1.06–1.13)	<0.0001
All CVD	7944	527.2	1	8652	588.9	1.13 (1.09–1.16)	9365	637.4	1.20 (1.16–1.23)	1.06 (1.05–1.07)	<0.0001
			1			1.10 (1.07–1.13)			1.14 (1.11–1.18)	1.04 (1.03–1.06)	<0.0001
All-cause mortality	5175	243.7	1	5899	274.1	1.13 (1.08–1.17)	7290	322.7	1.31 (1.27–1.36)	1.10 (1.09–1.11)	<0.0001
			1			1.08 (1.04–1.12)			1.20 (1.16–1.25)	1.07 (1.06–1.09)	<0.0001

MaHRs are adjusted for age, sex, race/ethnicity, QTc average and QTc slope. FaHRs are adjusted for age, sex, race/ethnicity, QTc average and QTc slope, smoking status, diabetes, hypertension medication, cholesterol-lowering drugs, BMI (average, linear slope, RMSE), non-HDL cholesterol (average, linear slope, RMSE), SBP (average, linear slope, RMSE), DBP (average, linear slope, RMSE), and eGFR (average, linear slope, RMSE). AAR indicates age-adjusted rate; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FaHR, fully adjusted hazard ratio; HDL, high-density lipoprotein; IHD, ischemic heart disease; MaHR, minimally adjusted hazard ratio; QTc, corrected QT; RMSE, root mean squared error; and SBP, systolic blood pressure.

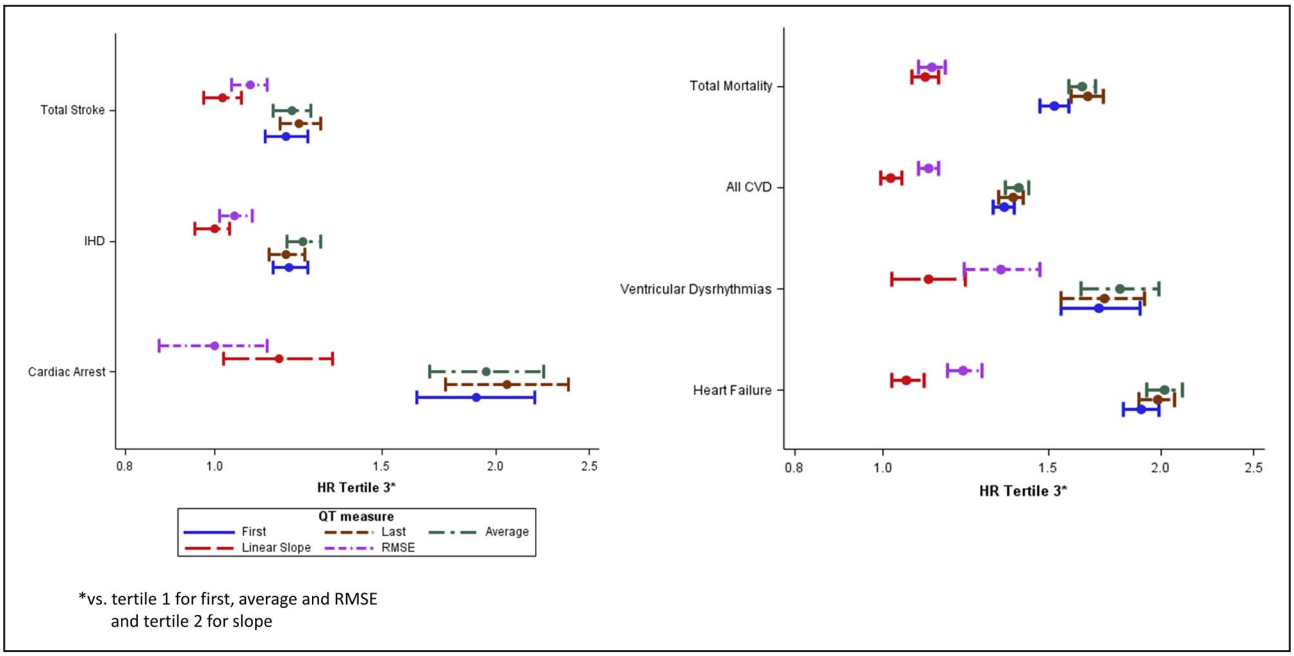

Figure 2. Comparison of strength of association for different QTc measures (n=61 455).
*The hazard ratio displayed is for tertile 3 vs tertile 1 for first QTc, average QTc, last QTc and RMSE, and for tertile 3 vs 2 for QTc slope. CVD indicates cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; and RMSE, root mean squared error.

interval and increased rates of sudden cardiac death; a 50-ms increase in QTc was found to be associated with a doubling of the hazard for all-cause mortality in patients with rheumatoid arthritis.[17]

Our results demonstrate that long-term average QTc was the better predictor of IHD, cardiac arrest, all CVD, and ventricular dysrhythmias, and that average QTc and the last QTc measure were equally predictive in the case of heart failure, total stroke, and all-cause mortality. The QTc linear slope conveyed independent predictive ability for cardiac arrest, ventricular dysrhythmias, and all-cause mortality, whereas the QTc RMSE remained independently associated with IHD, total stroke, heart failure, ventricular dysrhythmias, all CVD, and all-cause mortality.

Because of the accessibility and cost-effective nature of a 12-lead ECG, this is often the initial diagnostic test performed in patients presenting to the inpatient or outpatient setting with chest pain or shortness of breath. By using data over several ECGs, rather than a single data point, and understanding the predictive ability of QTc change and variability over time, clinicians will be better equipped to risk stratify patients for CVD outcomes. This may aid in determination of which patient cohorts would benefit from longer-term rhythm monitoring and aid in primary and secondary CVD prevention recommendations. A simple calculator could be embedded in the electronic health record to estimate the patient's long-term QTc average, slope, and RMSE. Further research is needed to determine the extent to which the associations of QTc change and fluctuation with CVD outcomes are attributable to variations in medication compliance with drugs known to alter the QT interval.

Within-person QTc variability has been described in relation to brief high-intensity intermittent exercise[43] and with postural changes[44]; this is thought to be secondary to the effects of the autonomic nervous system.[45] Thus, autonomic dysregulation may be the substrate of greater QTc variability and enhanced predisposition to ventricular dysrhythmias and heart failure.

The strengths of our study include (1) the large sample size and up to 9 years of cohort follow-up; (2) the racial and ethnic diversity of the sample, thus increasing generalizability; (3) the source of data reflecting a real-world health care setting; and (4) the availability of longitudinal information on QT length and covariates, thus allowing assessment of within-person change and fluctuation in QTc and adjustment for dynamic changes in risk factors. However, the present study also has several limitations. First, KPNC does not currently offer ECGs at annual physicals; therefore, the ECGs were obtained for cause as part of routine medical care. Second, although we adjusted for traditional risk factor level, change, and fluctuation, there may be unmeasured confounding variables that bias the results including electrolyte levels, medication use, structural heart disease, or clinical pathologies that are known to alter the QT interval. Third, we cannot rule out reverse causality, for example, onset of heart failure leading to prolonged QT. Fourth, we did not have data on natriuretic peptides (brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide) or high-sensitivity

C-reactive protein, both important risk markers of heart failure. Fifth, we did not have information on left ventricular ejection fraction, so distinguishing types of heart failure was not possible. Sixth, we did not adjust for other clinical pathologies known to influence the QT interval (hypothyroidism, anorexia nervosa).[46,47] Lastly, we did not attempt to capture sudden cardiac death in our population, because the validity of this outcome is questionable in the absence of informant or next-of-kin interviews.[48] We did not report outcomes of short QT in the current cohort, because there were too few for meaningful analyses. We have reported findings on cardiovascular outcomes of short QT in a prior publication in a larger population.[49]

In summary, our study is the first large-scale investigation of the predictive ability of QTc dynamics (long-term average, change, and fluctuation) for CVD outcomes in a real-world population-based setting. We believe the results of our study will enable clinicians to better interpret the meaning of serial QTc interval measures, help predict long-term CVD risk, and enable proper QTc monitoring in high-risk populations.

In particular, our findings demonstrate the potential usefulness of monitoring within-person change and fluctuation in QTc over time as new markers to predict increased risk of CVD outcomes. These are clinically relevant results because ECG is a routine, widely available, noninvasive, and inexpensive clinical test.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Ascertainment of Cardiovascular Endpoints and Exclusionary Conditions.

Condition	Primary hospital discharge code or underlying cause of death ICD-9 code	Primary hospital discharge code or underlying cause of death ICD-10* code	CPT4 Code(s)	ICD-10 procedure Codes (PCS)
Pacemaker insertion	37.6, 37.7, 37.8, 37.9 (ICD-9 procedure codes)		33217, 33218, 33220, 33221, 33222, 33223, 33224, 33225, 33226, 33227, 33228, 33229, 33230, 33231, 33233, 33234, 33235, 33236, 33236, 33237, 33238, 33240, 33244, 33249, 33262, 33263, 33264, 33270, 33271, 33272, 33273	0JH636Z, 02H63JZ 02HK3JZ, 3E0132A
Acute myocardial infarction (AMI)	410.x	I21.x, I22.x	NA	
Angina pectoris	411.x, 413.x	I20.x, I25.11x, I25.7x	NA	
Coronary atherosclerosis due to calcified coronary lesion	414.4	I25.84	NA	
Other forms of ischemic heart disease	414.x	I25.x	NA	
Coronary artery bypass surgery (CABG)	36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.03	NA	33510, 33511, 33512, 33513, 33514, 33515, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536	02120Z9, 021009W
Percutaneous coronary intervention (PCI) with or without intra-coronary stenting	36.01, 36.02, 36.05, 36.06, 36.07, 36.09	NA	92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977	0270346, 02703ZZ, 02703DZ, 02CO3ZZ
Cardiac arrest	427.5	I46.2		
Hemorrhagic stroke	430.x, 431.x, 432.1, 432.9	I60.x, I61.x, I62.x	NA	
Ischemic stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436.x	I63.x	NA	
Heart failure (HF)	428.x, 402.01, 402.11, 402.91, 398.91, 404.01, 404.03, 404.11, 404.12, 404.13, 404.91, 404.93	I50.x, I09.81, I11.0, I13.0, I13.2, I13.11	NA	
Ventricular dysrhythmias	427.1, 427.2, 427.41, 427.42	I47.2, I47.9, I49.01, I49.02		
Right bundle branch block	426.4	I44.10		
Left bundle branch block	426.3	I44.7		

CABG + PCI = Revascularization Procedures (RP)
AMI + Angina pectoris + other forms of ischemic heart disease + RP = Ischemic Heart Disease (IHD)
Ischemic Stroke + Hemorrhagic Stroke = Total Stroke (TS)
CHD + TS + HF = Total CVD
NA: not applicable

Table S2. Association of one or more QTc in the long QT range (any ECG) with CVD outcomes.

Outcomes	QTc ≤ 450 ms in men or ≤ 460 ms in women (n=43,431)			QTc > 450 ms in men or > 460 ms in women (n=18,024)		
	Num events	AAR per 10,000 person-years	MaHR (95% CI) FaHR (95% CI)	Num events	AAR per 10,000 person-years	MaHR (95% CI) FaHR (95% CI)
IHD	7,811	229.8	1 1	4,546	317.9	1.39 (1.34, 1.45) 1.39 (1.34, 1.45)
Cardiac arrest	750	20.5	1 1	590	38.1	1.76 (1.56, 1.98) 1.76 (1.56, 1.98)
Total Stroke	7,002	201.2	1 1	3,590	235.8	1.22 (1.17, 1.27) 1.22 (1.17, 1.27)
Heart failure	7,262	196.0	1 1	5,700	345.2	1.84 (1.77, 1.91) 1.84 (1.77, 1.91)
Ventricular dysrhythmias	1,509	42.0	1 1	1,143	77.1	1.72 (1.58, 1.87) 1.72 (1.58, 1.87)
All CVD	16,405	525.0	1 1	9,556	739.4	1.43 (1.39, 1.47) 1.43 (1.39, 1.47)
All-cause mortality	10,811	250.8	1 1	7,553	353.2	1.38 (1.34, 1.43) 1.38 (1.34, 1.43)

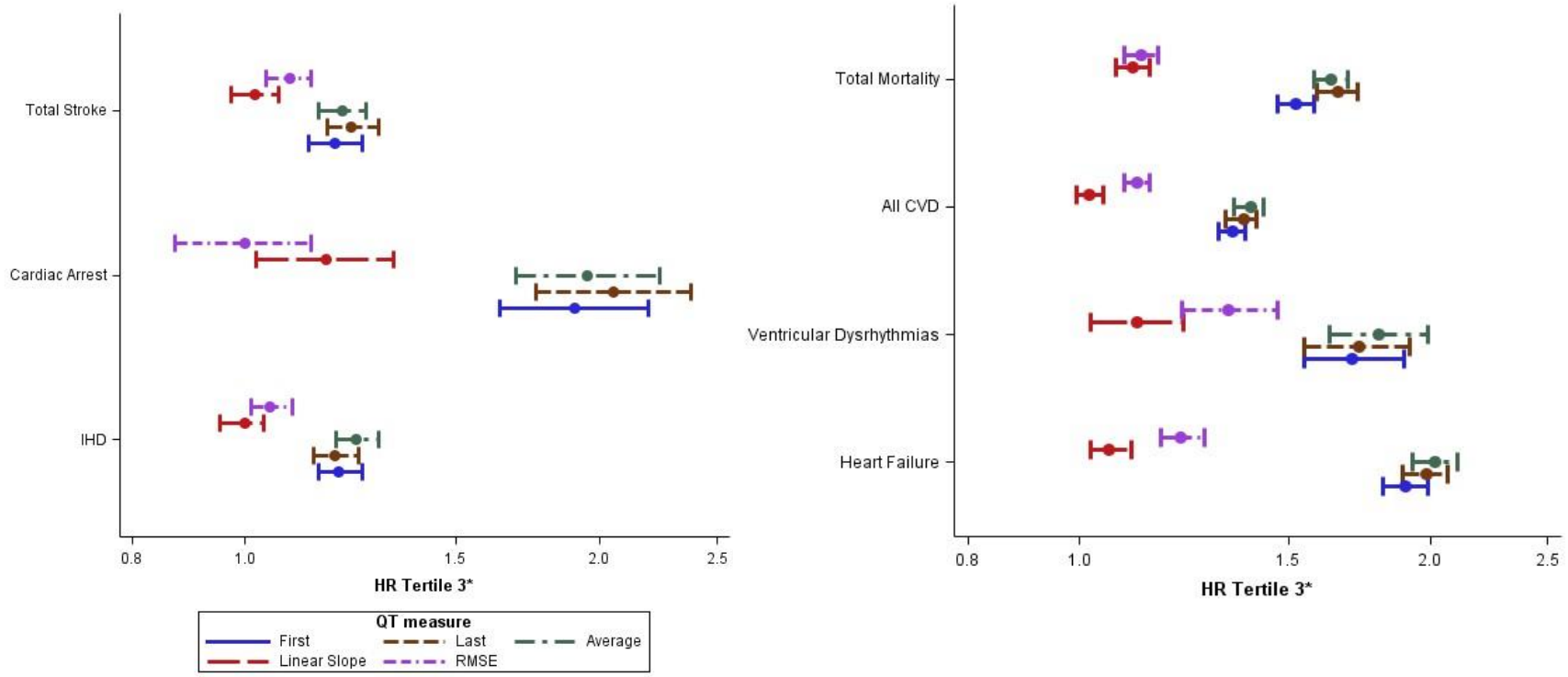
IHD: ischemic heart disease; CVD: cardiovascular disease; AAA: age-adjusted rate; MaHR: minimally-adjusted hazard ratios; FaHR: fully-adjusted-adjusted hazard ratios; RMSE: Root mean square error; BMI: body mass index; HDL: high-density lipoprotein; GFR: glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MaHR are adjusted for age, sex, race/ethnicity, QTc slope and QTc RMSE; FaHR are adjusted for age, sex, race/ethnicity, QTc slope and QTc RMSE, smoking status, diabetes, hypertension medication, cholesterol lowering drugs, BMI (average, linear slope, RMSE), non-HDL cholesterol (average, linear slope, RMSE), SBP (average, linear slope, RMSE), SBP (average, linear slope, RMSE) and e-GFR (average, linear slope, RMSE).

Table S3. Association of average QTc in the long QT range (by average) with CVD outcomes.

Outcomes	QTc ≤ 450 ms in men or ≤ 460 ms in women (n=55,510)			QTc > 450 ms in men or > 460 ms in women (n=5,945)		
	Num events	AAR per 10,000 person-years	MaHR (95% CI) FaHR (95% CI)	Num events	AAR per 10,000 person-years	MaHR (95% CI) FaHR (95% CI)
IHD	10,621	243.7	1 1	1,736	361.0	1.44 (1.37, 1.52) 1.44 (1.37, 1.52)
Cardiac arrest	1,095	23.3	1 1	245	46.5	1.79 (1.55, 2.07) 1.79 (1.55, 2.07)
Total Stroke	9,360	208.5	1 1	1,232	234.7	1.17 (1.10, 1.25) 1.17 (1.10, 1.25)
Heart failure	10,630	220.8	1 1	2,332	405.1	1.87 (1.79, 1.96) 1.87 (1.79, 1.96)
Ventricular dysrhythmias	2,174	47.3	1 1	478	96.1	1.85 (1.67, 2.05) 1.85 (1.67, 2.05)
All CVD	22,408	561.1	1 1	3,553	816.1	1.45 (1.40, 1.50) 1.45 (1.40, 1.50)
All cause mortality	15,501	270.6	1 1	2,863	368.4	1.32 (1.27, 1.38) 1.32 (1.27, 1.38)

IHD: ischemic heart disease; CVD: cardiovascular disease; AAA: age-adjusted rate; MaHR: minimally-adjusted hazard ratios; FaHR: fully-adjusted-adjusted hazard ratios; RMSE: Root mean square error; BMI: body mass index; HDL: high-density lipoprotein; GFR: glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MaHR are adjusted for age, sex, race/ethnicity, QTc slope and QTc RMSE; FaHR are adjusted for age, sex, race/ethnicity, QTc slope and QTc RMSE, smoking status, diabetes, hypertension medication, cholesterol lowering drugs, BMI (average, linear slope, RMSE), non-HDL cholesterol (average, linear slope, RMSE), SBP (average, linear slope, RMSE), SBP (average, linear slope, RMSE) and e-GFR (average, linear slope, RMSE).

Figure S1. Comparison of Strength of Association for Different QTc Measures Using Bazett's heart rate correction (n=59,540).



*vs. tertile 1 for first, average and RMSE
and tertile 2 for slope