Risk of sudden cardiac death associated with QRS, QTc, and JTc intervals in the general population

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BACKGROUND QRS duration and corrected QT (QTc) interval have been associated with sudden cardiac death (SCD), but no data are available on the significance of repolarization component (JTc interval) of the QTc interval as an independent risk marker in the general population.

OBJECTIVE In this study, we sought to quantify the risk of SCD associated with QRS, QTc, and JTc intervals.

METHODS This study was conducted using data from 3 population cohorts from different eras, comprising a total of 20,058 individuals. The follow-up period was limited to 10 years and age at baseline to 30–61 years. QRS duration and QT interval (Bazett's) were measured from standard 12-lead electrocardiograms at baseline. *JTc interval* was defined as QTc interval – QRS duration. Cox proportional hazards models that controlled for confounding clinical factors identified at baseline were used to estimate the relative risk of SCD.

RESULTS During a mean period of 9.7 years, 207 SCDs occurred (1.1 per 1000 person-years). QRS duration was associated with a significantly increased risk of SCD in each cohort (pooled hazard ratio [HR] 1.030 per 1-ms increase; 95% confidence interval [CI] 1.017–1.043). The QTc interval had borderline to significant associations with SCD and varied among cohorts (pooled HR 1.007; 95% CI 1.001–1.012). JTc interval as a continuous variable was not associated with SCD (pooled HR 1.001; 95% CI 0.996–1.007).

CONCLUSION Prolonged QRS durations and QTc intervals are associated with an increased risk of SCD. However, when the QTc interval is deconstructed into QRS and JTc intervals, the repolarization component (JTc) appears to have no independent prognostic value.

KEYWORDS Electrocardiography; Epidemiology; Sudden cardiac death; Depolarization; Repolarization

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Introduction

Sudden cardiac death (SCD) remains a frequent cause of premature death in Western countries, with an annual incidence estimated in the range of 50–100 SCDs per 100,000 persons.[1,2] Despite the improvements in heart disease prevention and treatment, the prediction and prevention of SCD remains a clinical and public health challenge. The majority of SCDs occur in the general population, and up to 50% are the first manifestation of previously unrecognized heart disease.[3] Thus, improved risk stratification is urgently required and as SCD is primarily a result of electrical disturbance of the normal cardiac rhythm, the standard 12-lead electrocardiogram (ECG) remains an attractive, inexpensive, and easily applied noninvasive tool beyond clinical risk factors for potential risk prediction.

Abnormalities in depolarization and repolarization of the myocardium are reflected in the ECG. Changes could be related to structural abnormalities in the heart affecting electrical activity or functional electrophysiological abnormalities. The duration of the QRS complex reflect impulse propagation and myocardial activation properties and its possible pathological processes, whereas the QT interval is affected by multiple factors but predominantly used as a measure of repolarization. Both the QRS duration and the QT interval have previously been associated with an increased risk of SCD, but the data are somewhat limited or conflicting.[4–10] This study was designed to estimate the risk of SCD associated with these easily obtained ECG measures in the population by analysis of data from 3 large cohorts from different eras.

Methods

Study populations and data collection

This study included data from 3 population samples gathered in Finland: the Finnish Mobile Clinic study (FMC-study), the Mini-Finland Health Survey, and the Health 2000 Survey. Of these, the Mini-Finland Health Survey and the Health 2000 Survey are representative samples of the adult Finnish population. The FMC-study and the Mini-Finland Health Survey were conducted by the Social Insurance Institution of Finland, and the Health 2000 Survey was conducted by the National Public Health Institute. All the data of these cohorts are now controlled by the National Institute for Health and Welfare. The methodology and procedures used at the baseline examinations for each cohort have been described in detail elsewhere.[11–13] Briefly, in addition to undergoing standard 12-lead ECG, all subjects underwent a thorough clinical examination at baseline, including blood pressure, body mass index (BMI), and serum cholesterol. Known diseases, health behavior, and medications were also recorded, and all participants were followed in national registries.

The FMC-study included 10,962 individuals (52% men) aged 30–61 years drawn from 12 community populations, and participants were enrolled between 1966 and 1972. The Mini-Finland Health Survey included 7217 individuals (51% men) aged over 30 years, with enrollment done between 1978 and 1980 in 40 study areas around the country. Similarly, the Health 2000 Survey included 6354 individuals (51% men) aged over 30 years and enrollment was done between 2000 and 2001 in 80 regions in Finland.

In order to standardize the analyses and minimize the influence of changing risks of death, we limited the follow-up period to 10 years. Individuals aged over 61 years were excluded from the Mini-Finland Health Survey and the Health 2000 cohorts, as the inclusion age for the FMC-study had been 30–61 years. After other exclusions for missing or uninterpretable data, left or right bundle branch block, and atrial fibrillation on the ECG, the FMC-study cohort included 10,770 subjects, the Mini-Finland Health Survey 5030 subjects, and the Health 2000 cohort 4258 individuals. Thus, the pooled study cohort consisted of 20,058 individuals (49.9% men; mean age 44 $\pm$ 12 years). Our study was approved by the institutional review board.

Outcome assessment

Participants in each of the study cohorts were continuously monitored for major events through extensive national registers. Monitored events included myocardial infarction and all other hospitalizations and death. Causes of death were determined by examining detailed death certificates from Statistics Finland. Every death in the country is recorded, and the quality as well as the reliability of these registers has been validated previously.[14,15]

To identify the cases of sudden death due to presumed arrhythmia, all deaths due to cardiac causes have been evaluated and adjudicated by an independent committee of experienced clinicians. The primary end point of this study was sudden death due to arrhythmia, with definite and probable deaths due to arrhythmia included in the SCD end point. In FMC-study and Mini-Finland Health Survey, SCDs were classified according to the definitions described in the Cardiac Arrhythmia Pilot Study.[16] In this definition, a spontaneous cessation of respiration and circulation with loss of consciousness is considered as death from arrhythmia in one of the following situations: witnessed and instantaneous, without new or accelerating symptoms; witnessed and preceded or accompanied by symptoms attributable to myocardial ischemia in the absence of heart failure; witnessed and preceded by symptoms attributable to cardiac arrhythmia (syncope); and unwitnessed but without evidence of another cause. Cardiac arrests during hospitalizations for severe congestive heart failure were not classified as SCDs. In Health 2000 Survey, SCDs were classified similarly, as described elsewhere in more detail.[17]

ECG measurements

At baseline, standard resting 12-lead ECGs were recorded at a paper speed of 50 mm/s and stored for possible further analyses. In the FMC-study, the ECG intervals were measured from paper ink tracings; in the Mini-Finland Health Survey, the intervals were measured digitally (paper tracings were transformed into digital format).[18] In the Health 2000 Survey, the ECG intervals were measured digitally from native digital

tracings and a custom-made software was used to measure QT intervals.[19] The measurements were reviewed on-screen in a blinded fashion. All ECGs were analyzed blinded to both the clinical and the outcome data.

QRS duration was defined as the maximum duration in leads II and V_5 in the FMC-study and the Mini-Finland Health Survey and as the mean of all leads in the Health 2000 Survey. The QT interval was measured by tangent in leads II and V_5, and the maximum value was used for analyses and corrected for heart rate using the Bazett formula (corrected QT [QTc] = QT/$\sqrt{}$R-R). *JTc interval* was defined as QTc interval – QRS duration.

Statistical analyses

Continuous variables are presented as mean ± SD, and categorical variables are presented as percentage in each group. Linear regression was used to compare the mean values for continuous variables and the prevalence of categorical variables between the no SCD and SCD groups in the 3 different cohorts. The reported *P* values are 2-sided. The hazard ratios (HRs) and 95% confidence intervals (CIs) for death were calculated with Cox proportional hazards models, and multivariable models were adjusted for confounding factors, including age, gender, BMI, smoking status, history of hypertension, history of myocardial infarction, history of diabetes mellitus, serum total cholesterol, heart rate, and left ventricular hypertrophy by Sokolow-Lyon ECG criteria. These confounding factors were selected a priori as the most common and significant clinical risk factors for SCD. Model discrimination was further assessed with C-statistics and integrated discrimination increment (IDI).

A 2-step meta-analysis was performed. Analyses were performed separately in each individual study. Heterogeneity across study-specific HRs was tested using the Q statistic. The cohort-specific logs of HRs were weighted by the inverse of their variance, and an overall pooled estimate of the R-R interval was computed using a random effects model.[20] The *P* value for the test of trend was based on a Wald test of the pooled estimates. In addition, Cox models with penalized splines were used to assess and plot the relationships of continuous QRS, QTc, and JTc intervals to SCD risk. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R Statistics version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). All reported *P* values are 2-sided, with a *P* value of less than .05 considered to indicate statistical significance. In addition, we applied the Fine and Gray competing risk model for the assessment of adjusted and unadjusted HRs and their 95% CIs in the competing risk regression model, where all-cause mortality was used as the competing event. Adjustments in the multivariate model included the same confounding factors as the Cox model.

Results

In the pooled cohort of 20,058 participants, a total of 1757 deaths, including 207 SCDs, occurred during a mean follow-up period of 9.7 ± 1.4 years (113 SCDs in the FMC-study, 39 in the Mini-Finland Health Survey, and 55 in the Health 2000 Survey, respectively), yielding an incidence of approximately 1.1 SCDs per 1000 person-years. In all cohorts, when comparing those who suffered SCD with the rest of the cohort, they were more often male and were older. Cohort-specific differences among groups are presented in Table 1.

QRS duration and the risk of SCD

The mean QRS duration was significantly longer in SCD cases than in survivors in each cohort ($P < .001$) (Table 1). When analyzed as a continuous variable, QRS duration was significantly related to the risk of SCD (Table 2 and Figure 1A). The elevation in the relative risk of SCD associated with every millisecond increase in QRS duration varied from 1.2% to 3.6% between the cohorts, averaging to 3.0% (HR 1.030; 95% CI 1.017–1.043) when all cohorts were pooled. When examined according to quintiles in the pooled cohort, participants in the highest vs lowest quintile of QRS duration had a nearly 2-fold adjusted increased risk of SCD (Table 3).

QTc interval and the risk of SCD

The mean QTc interval was significantly longer in SCD cases than others in all cohorts (Table 1). An increase in QTc interval was associated with a significantly higher adjusted risk of SCD in the FMC-study and the Mini-Finland Health Survey cohorts, but not in the Health 2000 Survey cohort (Table 2). When all data were pooled, each millisecond increase in QTc interval predicted a 0.7% higher adjusted risk of SCD (HR 1.007; 95% CI 1.001–1.012) (Table 2 and Figure 1B). The highest vs lowest QTc quintile had a nearly 2-fold adjusted risk of SCD (Table 3).

JTc interval and the risk of SCD

The mean JTc interval did not statistically differ between those with SCD and the rest of the cohorts in the FMC-study and Mini-Finland Health Survey, but was statistically longer in SCD cases than others in the Health 2000 cohort (Table 1). In the pooled cohort, JTc interval did not predict SCD (Tables 2 and 3 and Figure 1C).

Risk prediction value and competing risk

To examine the incremental risk prediction value of QRS, QTc, and JTc intervals, we analyzed C-index and IDI for the pooled cohort. The IDI analysis for QRS duration revealed a minor improvement in risk prediction for SCD (IDI 0.0035; $P = .015$) (Online Supplemental Table 1), whereas QTc and JTc intervals had no improvement compared to the original model (IDI −0.0004; $P = .89$ and IDI −0.0001; $P = .10$, respectively) (Online Supplemental Table 1). Additionally, none of the examined ECG intervals showed a significant improvement in C-index for SCD compared to the original model (Online Supplemental Table 2).

Table 1 Baseline characteristics of the study cohorts

Characteristic	Finnish Mobile Clinic study			Mini-Finland Health Survey			Health 2000 Survey		
	No SCD	SCD	*P*	No SCD	SCD	*P*	No SCD	SCD	*P*
No. of subjects	10,657	113		4991	39		4203	55	
Age (y)	44 ± 8	52 ± 7	<.001	44 ± 9	51 ± 7	<.001	45 ± 8	52 ± 6	<.001
Male gender	51.9	85.9	<.001	48.5	82.1	<.001	47.0	89.1	<.001
BMI (kg/m^2)	26 ± 4	26 ± 4	.59	26 ± 4	27 ± 5	.07	26 ± 5	28 ± 5	.005
Current smoker	33.7	62.9	<.001	27.1	53.9	<.001	26.1	65.5	<.001
Hypertension	4.2	14.2	<.001	9.4	28.3	<.001	35.3	65.5	<.001
History of MI	1.1	2.7	.11	1.8	25.7	<.001	0.6	5.5	<.001
Diabetes mellitus	1.8	5.4	.004	2.7	23.1	<.001	3.6	9.1	.03
Total cholesterol (mmol/l)	6.5 ± 1.3	6.9 ± 1.4	<.001	6.8 ± 1.3	7.2 ± 1.2	.10	5.8 ± 1.1	6.5 ± 1.0	<.001
Heart rate (beats/min)	76 ± 15	76 ± 15	.75	67 ± 13	72 ± 16	.02	63 ± 11	69 ± 13	<.001
QRS duration (ms)	85 ± 11	90 ± 14	<.001	88 ± 11	96 ± 15	<.001	93 ± 9	97 ± 11	.005
QTc interval (ms)	408 ± 27	414 ± 33	.027	412 ± 28	422 ± 37	.03	400 ± 23	410 ± 23	.001
JTc interval (ms)	323 ± 29	323 ± 34	.95	324 ± 30	327 ± 39	.54	306 ± 25	313 ± 21	.04
LVH by SL	31.3	49.6	<.001	11.6	30.8	<.001	8.0	14.6	.08

Values are presented as mean ± SD or percentage.

QRS MAX II/V5 = longest QRS duration in lead II or V5. QTc MAX II/V5, tangent, Bazett's = longest Bazett equation corrected QT interval measured with tangent method in lead II or V5.

BMI = body mass index; JTc = repolarization component of the corrected QT interval (JTc = QTc − QRS); LVH by SL = left ventricular hypertrophy by Sokolow-Lyon ECG criteria; MI = myocardial infarction; QTc = corrected QT; SCD = sudden cardiac death.

In univariate models accounting for the competing risk of non-SCD mortality, QRS and QTc intervals were associated with SCD. In competing risk models further adjusted for clinical risk factors, only QRS duration retained a significant association with SCD (Table 4).

Discussion

In these 3 population cohort studies performed at separate time points over 30 years, QRS duration was found to be consistently and independently associated with SCD in a linear fashion. The QTc interval demonstrated a more modest statistical association with SCD, but when the QTc interval was deconstructed into QRS and JTc intervals, the repolarization component (JTc) was no longer associated with SCD risk. This finding is novel and merits further discussion.

To date, this is the largest study to quantify the association between QTc, QRS, and JTc intervals and SCD risk. We investigated 3 cohorts collected in 3 different eras: late 1960s, late 1970s, and early 2000. Although the diagnostics and treatment of cardiovascular disease have improved over the decades, the clinical risk profiles for SCD have generally remained unchanged.

In our analysis, QTc interval was significantly associated with SCD, although some discrepancy was observed between cohorts after adjustments for all clinical factors. Further, in our analysis the QTc interval did not improve the original risk prediction model in C-statistics. In older populations, QTc prolongation has been associated with a 3-fold risk of SCD,[6,7] whereas in patients with coronary heart disease, those with a prolonged QTc interval but without diabetes or QT-prolonging drugs had up to a 5-fold risk of SCD.[8] QTc prolongation has also been associated with SCD risk when observed during Holter monitoring.[9] However, no association between QTc interval and SCD was observed in the Framingham study.[10]

The QT interval incorporates both depolarization (QRS complex) and repolarization (JT interval) components. When analyzed separately, the distribution of durations of the QRS complexes generated a linear increase in SCD risk. The independent SCD predictive value of JTc interval, assessed first time in the population study, was borderline

Table 2 HRs of SCD for continuous variables

Model	Continuous, per ms ECG measure	HR (95% CI) FMC	Mini-Finland Health	Health 2000	Pooled	*P* for heterogeneity
Univariable	QRS duration	1.046 (1.029−1.063)	1.056 (1.029–1.082)	1.040 (1.013–1.069)	1.047 (1.034–1.059)	.75
	QTc interval	1.008 (1.001−1.014)	1.010 (1.002–1.019)	1.018 (1.007–1.028)	1.011 (1.005–1.016)	.30
	JTc interval	1.000 (0.994–1.007)	1.003 (0.993–1.013)	1.010 (1.000–1.021)	1.003 (0.998–1.009)	.27
Multivariable	QRS duration	1.034 (1.017−1.051)	1.036 (1.008–1.066)	1.012 (0.984–1.040)	1.030 (1.017–1.043)	.37
	QTc interval	1.006 (0.998−1.014)	1.006 (0.996–1.016)	1.009 (0.998–1.021)	1.007 (1.001–1.012)	.89
	JTc interval	0.999 (0.991–1.007)	1.001 (0.990–1.011)	1.008 (0.995–1.020)	1.001 (0.996–1.007)	.52

Covariates in the multivariate analyses: age, gender, body mass index, current smoker (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), prior acute myocardial infarction (yes/no), heart rate, and left ventricular hypertrophy by Sokolow-Lyon ECG criteria (yes/no).

CI = confidence interval; ECG = electrocardiographic; FMC = Finnish Mobile Clinic; HR = hazard ratio; JTc = repolarization component of the corrected QT interval (JTc = QTc − QRS); QTc = corrected QT; SCD = sudden cardiac death.

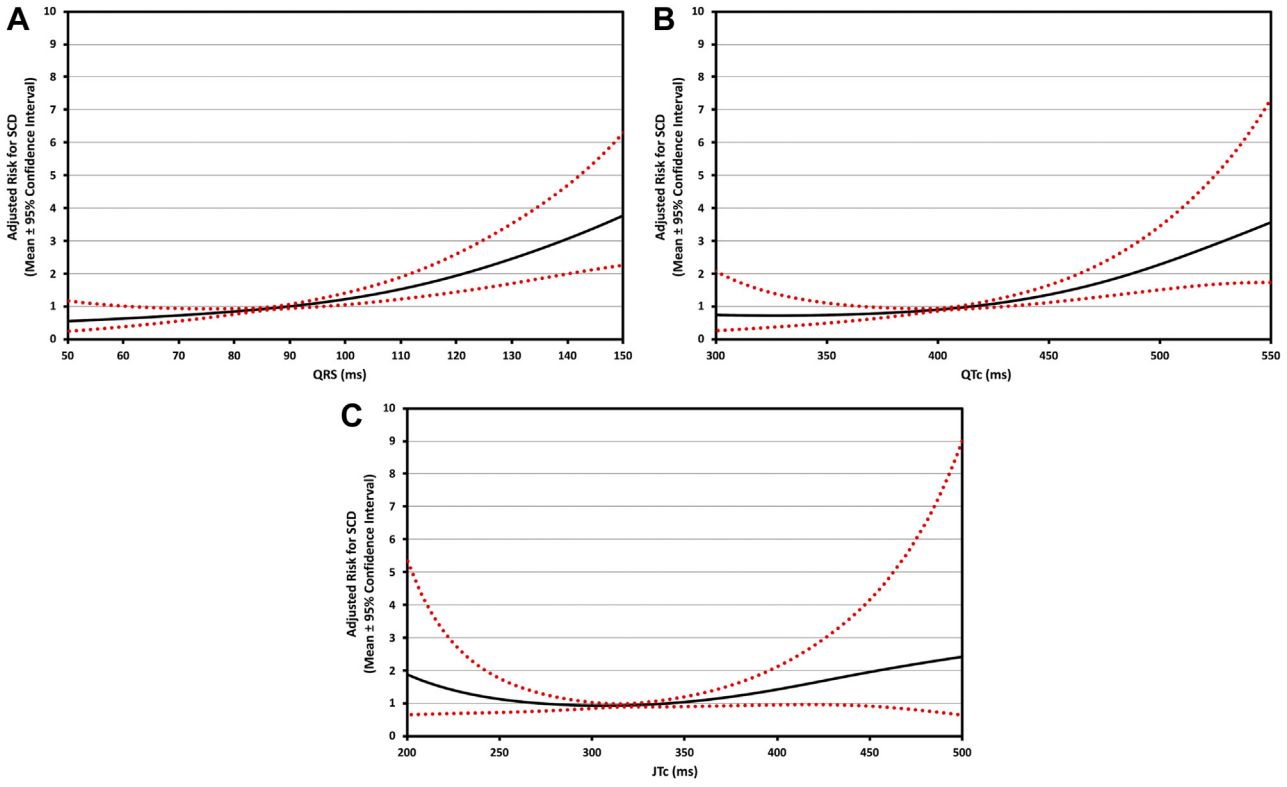

Figure 1 Adjusted hazard ratios for sudden cardiac death for QRS, corrected QT (QTc), and repolarization component of the QTc interval (JTc) intervals. SCD = sudden cardiac death.

or nonsignificant across the studied cohorts. We have earlier reported that prolongation of the QRS complex without bundle branch blocks associates with an increased risk of SCD in one of the cohorts (the FMC-study) of the present study. Additionally, a similar association has been presented in a separate population of middle-aged men.[4,5] When we assessed the incremental risk prediction value of QRS and JTc intervals in the present study, only QRS interval improved the original model with robust clinical risk factors (age, gender, BMI, smoking status, history of hypertension, history of myocardial infarction, history of diabetes mellitus, serum total cholesterol, heart rate, and left ventricular hypertrophy by Sokolow-Lyon ECG criteria). We also now show that those with longer QRS duration were at increased risk of SCD without meaningful elevations of competing deaths.

On the basis of the present results, one can argue that at least in the general population with a low absolute event rate of SCD, prolongation of depolarization is more

Table 3 HRs of SCD for quintiles in the pooled cohort

Model	HR (95% CI)	Q1	Q2	Q3	Q4	Q5	*P* for trend
	QRS interval range (ms)	60–78	80	82–88	90–98	100–144	
	QTc interval range (ms)	304–384.8	384.9–399.6	399.7–412.9	413–428.7	428.8–703	
	JTc interval range (ms)	220–295.1	295.2–312.1	312.2–326.5	326.6–343.8	343.9–631	
Univariable	QRS interval	1	1.132 (0.595–2.154)	0.974 (0.358–2.649)	1.763 (1.006–3.089)	2.910 (1.664–5.087)	<.001
	QTc interval	1	0.967 (0.575–1.626)	1.577 (0.996–2.497)	1.525 (0.959–2.426)	2.033 (1.299–3.183)	<.001
	JTc interval	1	1.564 (0.575–4.254)	1.073 (0.536–2.147)	1.477 (0.791–2.755)	1.129 (0.707–1.802)	.23
Multivariable	QRS interval	1	1.021 (0.535–1.951)	0.862 (0.314–2.364)	1.281 (0.723–2.269)	1.793 (1.011–3.181)	<.001
	QTc interval	1	0.926 (0.546–1.570)	1.575 (0.977–2.539)	1.508 (0.917–2.478)	1.728 (1.034–2.887)	.02
	JTc interval	1	1.396 (0.557–3.501)	1.038 (0.539–2.000)	1.420 (0.794–2.539)	1.091 (0.636–1.872)	.65

Covariates in the multivariate analyses: age, gender, body mass index, current smoker (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), prior acute myocardial infarction (yes/no), heart rate, and left ventricular hypertrophy by Sokolow-Lyon ECG criteria (yes/no).

CI = confidence interval; HR = hazard ratio; JTc = repolarization component of the corrected QT interval (JTc = QTc − QRS); Q1/Q2/Q3/Q4/Q5 = quintile 1/2/3/4/5; QTc = corrected QT; SCD = sudden cardiac death.

Table 4 Competing risk regression model (pooled cohort)

	Univariate		Multivariate	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
QRS duration	1.03 (1.02–1.04)	<.001	1.015 (1.006–1.025)	.0013
QTc interval	1.01 (1.01–1.02)	<.001	1.003 (0.999–1.008)	.16
JTc interval	1.01 (1.0–1.01)	.0079	1.00 (0.995–1.005)	.92

Covariates in the multivariate analyses: age, gender, body mass index, current smoker (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), prior acute myocardial infarction (yes/no), heart rate, and left ventricular hypertrophy by Sokolow-Lyon ECG criteria (yes/no).

CI = confidence interval; HR = hazard ratio; JTc = repolarization component of the corrected QT interval (JTc = QTc − QRS); QTc = corrected QT.

significant than moderate prolongation of the repolarization component. Thus, although completely speculative, it is somewhat reasonable to speculate that in subjects with a slightly prolonged QT interval due to prolonged QRS duration, strict restrictions on QT-affecting medications might not be required. The QTc interval is not only a measure of depolarization and repolarization but also reflective of the degree of underlying structural heart disease.[21] Whether the risk of SCD associated with QTc prolongation is actually due to an abnormality of cardiac depolarization merits further investigation.

Although this study has strengths in volume and methodology, several limitations require attention. First, there was modest variance in the ECG collection as they were obtained in different eras and errors in measurements due to technical issues cannot be ruled out. In Health 2000 population, ECGs were digitally recorded, which could cause differences in analysis and may explain some of the differences between Health 2000 cohort and the other cohorts in this study. Second, the measurements were performed only at baseline and both QRS and QTc intervals could have changed if recordings were repeated during follow-up. Thus, we limited the follow-up period to 10 years, since it is reasonable to hypothesize that the risk conferred by a single parameter that is subject to change over time may also change. This limitation in follow-up and limited number of SCD events could have negatively affected the statistical power of the study and its results. Third, our study included only middle-aged individuals of Caucasian origin and thus the results cannot be extrapolated to other patient groups. Nevertheless, middle-aged populations might yield the greatest benefit in SCD prevention as compared with older populations because of life expectancy and compared with younger populations because of low event rates. Fourth, the cohorts were obtained in 3 different eras and the diagnostics and treatment of cardiovascular disease have improved significantly over time and pooling the data might have yielded some errors owing to variability in the cohort data. It should also be acknowledged that our analyses included only the most commonly used formula in clinical settings (Bazett's) for the QT interval, while the present guidelines prefer other formulas for heart rate adjustments.[22] Also, the formal test between different ECG indices studied could not be statistically performed because of interactions, although the major conclusion of the study was that QRS interval should be identified as a significant part of the risk related to prolonged QT interval, and in our view this conclusion can be drawn with the analyses chosen for the study. Additionally, no sufficient medication data were available for all cohorts and thus there is a possibility of confounding effects of drugs on the QT interval. Finally, we could not adjust for left ventricular systolic function as no data were available, which might have affected the results.

Conclusion

Our data suggest that depolarization abnormality detected as a prolongation of QRS duration is an important and easily obtained independent predictor of SCD in the general population, but prolonged repolarization measured as JTc interval has no independent prognostic value.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at 10.1016/j.hrthm.2022.04.016.

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