Hypertension Research (2010) 33, 916–921

www.nature.com/hr

ORIGINAL ARTICLE

QT interval prolongation and the risks of stroke and coronary heart disease in a general Japanese population: the Hisayama study

Daisuke Maebuchi[1], Hisatomi Arima[1], Yasufumi Doi[2], Toshiharu Ninomiya[1], Koji Yonemoto[1], Yumihiro Tanizaki[1], Michiaki Kubo[1], Jun Hata[1], Kiyoshi Matsumura[2], Mitsuo Iida[2] and Yutaka Kiyohara[1]

Uncertainty remains regarding the value of heart-rate-corrected QT interval (QTc) prolongation on electrocardiogram for predicting cardiovascular disease (CVD), particularly among Asian populations. The objective of the present analysis was to analyze the association of QTc prolongation with the development of CVD in a general Japanese population. During the follow-up period, 303 CVD events were observed. Among men, the age-adjusted incidence rates of CVD rose with prolonged QTc levels: 10.9, 12.1, 14.1 and 37.8 per 1000 person-years for subgroups defined by QTc levels of $<$400, 400–419, 420–439 and $\geqslant$440 ms, respectively (P=0.0007 for trend). The risk of CVD in the highest group was 3.09-fold (95% confidence interval, 1.82–5.25) higher than that in the lowest group even after controlling for other confounding factors: age, hypertension, heart rate, electrocardiogram abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterols, alcohol intake, smoking habit and regular exercise. Similar associations were observed for the outcomes of stroke and coronary heart disease. Among women, in contrast, no clear associations were found between QTc levels and the risk of CVD events. In conclusion, prolonged QTc levels were associated with the development of CVD among general Japanese men. Measurement of QTc intervals is likely to provide additional information for the detection of individuals at high risk of future CVD events.
Hypertension Research (2010) **33,** 916–921; doi:10.1038/hr.2010.88; published online 10 June 2010

Keywords: coronary artery disease; epidemiology; QT interval; stroke

INTRODUCTION

Heart-rate-corrected QT interval (QTc) prolongation on the resting 12-lead electrocardiogram (ECG) has been associated with an increased risk for ventricular arrhythmia or sudden cardiac death.[1,2] Recently, several epidemiological studies have also shown that QTc prolongation predicts the likelihood of cardiovascular disease (CVD), suggesting a possible link between QTc prolongation and atherosclerosis.[3–7] However, other epidemiological studies found no clear associations between QTc prolongation and the risk of CVD,[7–10] and there is significant uncertainty surrounding the association between QTc prolongation and CVD. Furthermore, current knowledge of the effects of QTc prolongation on CVD was derived mainly from studies conducted in Western populations; it is unclear to what extent these findings apply to Asian populations. The objective of the present analysis was to analyze the longitudinal relationship between QTc prolongation and the future development of stroke and coronary heart disease in a long-term prospective study of a general Japanese population.

METHODS

Study population

Since 1961, we have been conducting a long-term prospective cohort study of CVD in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[11,12] In 1988, a screening survey for this study was performed in the town. Detailed descriptions of this survey have been published previously.[13–16] Briefly, a total of 2736 residents aged 40 years or older (80.7% of the total population of this age group) consented to participate in the examination. Among those, 102 subjects with a history of stroke or coronary heart disease were excluded from the present analysis based on the results of a questionnaire, face-to-face interviews, physical and neurological examinations, 12-lead ECG and, if necessary, other ancillary laboratory examinations. After further exclusion of 165 subjects who had had atrial fibrillation or ventricular conduction defects (QRS interval of 120 ms or longer), 22 subjects with high heart rates ($\geqslant$100 beats per minute) and 8 subjects whose ECG recordings were not available, we enrolled the remaining 2439 individuals in this study.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Correspondence: Dr H Arima, Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi Higashi-ku, Fukuoka, Japan.
E-mail: harima@envmed.med.kyushu-u.ac.jp
Received 23 November 2009; revised 22 March 2010; accepted 16 April 2010; published online 10 June 2010

Follow-up survey

This population was followed up for 14 years, from December 1988 through November 2002, by repeated health examinations or by a daily monitoring system established by the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 479 subjects died, of whom 362 (75.6%) underwent autopsy. Morphologic examinations by autopsy or brain imaging were performed on all stroke patients.[17] Only one subject was lost to follow-up.

Measurements of QTc

Standard, resting 12-lead ECG was recorded on an FCP-270 device (Fukuda Denshi, Tokyo, Japan) in the supine position on the morning of the screening surveys conducted in 1988. Heart rate (beats per minute) and QT interval duration (ms) were determined using ECG analysis software (PI-01, Fukuda Denshi) as described previously.[18] The program calculated the mean values of QT interval duration from the beginning of QRS to the end of the T wave in 12-lead ECG. The average QT interval duration was then corrected for heart rate by calculating QTc according to Bazett's equation (QTc=QT interval duration/(60/heart rate)$^{1/2}$).[19] Groups of participants defined by four QTc ranges ($<$400, 400–419, 420–439 and $\geqslant$440 ms) were used for the analysis.

Risk factors

A self-administered questionnaire covering medical history, alcohol consumption, smoking habit and regular exercise was completed in advance by each participant and was verified by trained interviewers at the baseline screening examination. Alcohol consumption and smoking habit were classified as either habitual or not. Subjects engaging in sports or other forms of exertion $\geqslant$3 times a week during their leisure time were assigned to the regular exercise group. Blood pressure was measured three times with the subject in a recumbent position, after having rested for at least 5 min before the first measurement and again for at least 5 min between measurements, by means of a standard sphygmomanometer with a standard cuff.[12,20] Korotkoff phase 5 was taken as the diastolic BP unless the sounds persisted at 0, in which case Korotkoff phase 4 was recorded. The mean of the three measurements was used in the present analysis. Hypertension was defined as blood pressure of $\geqslant$140/90 mm Hg or current use of antihypertensive agents. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI $\geqslant$25.0 kg m^{-2}. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code: 3–1) and/or ST depression (Minnesota codes: 4–1, 4–2 or 4–3). To determine serum lipid levels, blood samples were collected from an antecubital vein after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined enzymatically. Dyslipidemia was defined as total cholesterol $\geqslant$5.68 mmol l^{-1}, HDL-cholesterol $\leqslant$1.03 mmol l^{-1} or triglycerides $\geqslant$1.69 mmol l^{-1}. Non-HDL cholesterol was defined as total cholesterol excluding HDL cholesterol. At the baseline examination, we also performed the 75 g glucose tolerance test. Plasma glucose levels were determined by the glucose-oxidase method. Glucose tolerance status was also defined by the 1998 World Health Organization criteria;[21] namely, for impaired fasting glycemia, FPG 6.1–6.9 mmol l^{-1} and 2-h PG $<$7.8 mmol l^{-1}; for impaired glucose tolerance, FPG $<$7.0 mmol l^{-1} and 2-h PG 7.8–11.0 mmol l^{-1}; and for diabetes mellitus, FPG $\geqslant$7.0 mmol l^{-1} and/or 2-h PG $\geqslant$11.1 mmol l^{-1}.

Definition of cardiovascular events

The outcomes of the present analysis were stroke, coronary heart disease and total CVD events (stroke and coronary heart disease). Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for more than 24 h. Rare causes of cerebrovascular disease, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma or Moyamoya disease, were not considered among the stroke cases. The diagnosis and classification of stroke were based on clinical information, ancillary laboratory examinations (that is, neuroimaging, cerebral angiography, echocardiography or carotid duplex imaging) and autopsy findings.

The criteria for a diagnosis of coronary heart disease included first-ever fatal or non-fatal myocardial infarction, sudden cardiac death within 1 h of the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. Myocardial infarction was diagnosed when a subject met at least two of following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic ECG changes; or (4) morphologic changes of the heart, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy or myocardial necrosis or scars $>$1 cm long accompanied by coronary atherosclerosis at autopsy. Sudden cardiac death was defined as natural death attributable to cardiac causes, heralded by an abrupt loss of consciousness, within 1 h after onset of acute symptoms.

Statistical analysis

The incidence rates were calculated using the person-year method and adjusted for age by the direct method using 10-year age groupings. Differences in incidence rates between subgroups defined by QTc levels were tested using the Cox proportional hazards model including age. The multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) were also estimated using the Cox proportional hazards model. A P-value of $<$0.05 was considered statistically significant in all analyses. The SAS program (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses.

RESULTS

Mean QTc levels were 403 ms for men and 417 ms for women. The baseline characteristics according to QTc prolongation ($>$440 ms) are shown separately for men and women in Table 1. In both sexes, the subjects with QTc prolongation were older, were more likely to have had hypertension, ECG abnormalities, dyslipidemia and smoking habit, and had higher systolic blood pressure, heart rate, plasma fasting glucose and serum triglycerides than those without QTc prolongation.

During the 14-year follow-up period, 145 CVD events (stroke, 85 events; coronary heart disease, 73 events) were observed in men and 158 CVD events (stroke, 121 events; coronary heart disease, 51 events) in women. Table 2 shows the age-adjusted incidence rates and multivariate-adjusted HRs for the development of stroke, coronary heart disease and total CVD according to QTc levels among men. The incidence rates of stroke rose progressively with increasing QTc levels, and the highest risk of stroke was observed in the subgroup with QTc levels of $\geqslant$440 ms. These relationships remained significant even after controlling for age, hypertension, heart rate, ECG abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, BMI, total and HDL cholesterol, alcohol consumption, smoking habit and regular exercise (P=0.02 for trend). Comparable associations were also observed for coronary heart disease (P=0.001 for trend) and total CVD (P=0.0004 for trend). When non-HDL cholesterol was included in the multivariate model as a covariate instead of total cholesterol, similar results were obtained (P trend=0.02 for stroke, 0.001 for coronary heart disease and 0.0004 for total CVD).

In contrast to men, women showed no clear associations between QTc levels and incidence rates of total and cause-specific CVD (Table 3, P trend=0.23 for stroke, 0.76 for coronary heart disease and 0.58 for total CVD). These associations remained insignificant even after adding non-HDL cholesterol into the multivariate model instead of total cholesterol (P trend$>$0.2 for all outcomes). Multivariate-adjusted HRs of QT interval prolongation declined as QTc $\geqslant$450 ms and $\geqslant$460 ms compared with the reference group with QTc $<$ 400 ms were 1.56 (95% CI, 0.76–3.21) and 1.55 (95% CI, 0.68–3.57) for stroke, 1.00 (95% CI, 0.32–3.17) and 1.17 (95% CI, 0.30–4.58) for coronary heart disease, and 1.21 (95% CI, 0.65–2.25) and 1.37 (95% CI, 0.67–2.78) for total CVD. Multivariate-adjusted HRs

Table 1 Baseline characteristics according to QT interval prolongation among men and women

	Men		*Women*	
	QTc <440 ms (n=*913*)	*QTc ⩾440 ms* (n=*74*)	*QTc <440 ms* (n=*1212*)	*QTc ⩾440 ms* (n=*240*)
Age (years)	56 (11)	68 (13)	57 (11)	65 (13)
Systolic blood pressure (mm Hg)	133 (19)	144 (25)	130 (21)	143 (24)
Diastolic blood pressure (mm Hg)	81 (11)	80 (13)	75 (11)	78 (11)
Hypertension (%)[a]	42	66	34	58
Heart rate (b.p.m.)	64 (10)	67 (13)	6 (9)	72 (11)
ECG abnormalities (%)[b]	18	32	12	19
Plasma fasting glucose (mmol l^{-1})	5.88 (1.21)	6.21 (2.31)	5.66 (1.22)	5.97 (1.68)
Diabetes (%)[c]	14	11	9	13
Impaired glucose tolerance (%)[d]	18	15	17	23
Impaired fasting glycemia (%)[e]	7	13	5	5
Body mass index (kg m^{-2})	22.9 (2.9)	21.2 (3.2)	22.9 (3.2)	22.8 (3.6)
Obesity (%)[f]	24	11	23	25
Total cholesterol (mmol l^{-1})	5.14 (1.05)	4.82 (1.05)	5.56 (1.05)	5.37 (1.11)
HDL cholesterol (mmol l^{-1})	1.26 (0.31)	1.18 (0.30)	1.35 (0.30)	1.25 (0.29)
Triglycerides (mmol l^{-1})	1.63 (1.37)	1.80 (2.15)	1.17(0.64)	1.41 (1.15)
Dyslipidemia (%)[g]	56	61	55	58
Alcohol intake (%)	63	38	9	10
Smoking habit (%)	50	54	6	10
Regular exercise (%)	11	19	9	8

Abbreviations: BMI, body mass index; b.p.m., beats per minute; ECG, electrocardiogram; HDL, high-density lipoprotein; QTc, heart-rate-corrected QT interval.
Values are means (s.d.) or frequencies.
[a]Blood pressure ⩾140/90 mm Hg or current use of antihypertensive agents.
[b]Minnesota codes: 3–1, 4–1, 4–2 or 4–3.
[c]Fasting glucose ⩾7.0 mmol l^{-1}, postprandial blood glucose ⩾11.1 mmol l^{-1} or current use of hypoglycemic agents.
[d]Fasting glucose <7.0 mmol l^{-1}, and 2-h postprandial blood glucose 7.8–11.0 mmol l^{-1}.
[e]Fasting glucose 6.1–6.9 mmol l^{-1}, and 2-h postprandial blood glucose <7.8 mmol l^{-1}.
[f]BMI ⩾25.0 kg m^{-2}.
[g]Total cholesterol ⩾5.68 mmol l^{-1}, HDL cholesterol ⩽1.03 mmol l^{-1} or triglyceride ⩾1.69 mmol l^{-1}.

Table 2 Age-adjusted incidence rate and multivariate-adjusted hazard ratio for development of stroke, coronary heart disease and total cardiovascular disease according to heart-rate-corrected QT interval among men

	QTc (ms)				
	–399 (n=*463*)	*400–419* (n=*303*)	*420–439* (n=*147*)	*440–* (n=*74*)	P *trend*
Stroke					
Number of events/person-years	32/5940	23/3681	17/1565	13/601	
Incidence rate	6.9	7.3	9.4	16.3	0.03
Hazard ratio (95% CI)[a]	1 (reference)	0.97 (0.56–1.69)	1.31 (0.69–2.47)	2.59 (1.25–5.34)	0.02
Coronary heart disease					
Number of events/person-years	27/5961	20/3715	9/1623	17/633	
Incidence rate	5.2	5.8	4.4	26.2	0.0005
Hazard ratio (95% CI)[a]	1 (reference)	0.86 (0.43–1.69)	0.94 (0.41–2.18)	4.50 (2.18–9.27)	0.001
Total cardiovascular disease					
Number of events/person-years	54/5829.5	39/3614	26/1538	26/578	
Incidence rate	10.9	12.1	14.1	39.1	0.0007
Hazard ratio (95% CI)[a]	1 (reference)	0.97 (0.64–1.49)	1.23 (0.75–2.04)	3.09 (1.82–5.25)	0.0004

Abbreviations: QTc, heart-rate-corrected QT interval; 95% CI, 95% confidence interval.
[a]Hazard ratios and *P*-values were adjusted for age, hypertension, heart rate, electrocardiographic abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterol, alcohol consumption, smoking habit and regular exercise.

per 10-ms increase in QTc interval were 1.05 (95% CI, 0.98–1.13) for stroke, 1.03 (95% CI, 0.91–1.17) for coronary heart disease and 1.03 (95% CI, 0.96–1.10) for total CVD among women.

To examine the combined effect of prolonged QTc and other cardiovascular risk factors on CVD incidence, we estimated the age-adjusted HRs of CVD among four groups of male subjects according to the presence or absence of QTc prolongation (>440 ms) and each of the other risk factors (Table 4). Compared with the reference group without QTc prolongation or hypertension, the risk of developing CVD was significantly higher for the groups with either QTc

Table 3 Age-adjusted incidence rate and multivariate-adjusted hazard ratio for development of stroke, coronary heart disease, and total cardiovascular disease according to heart-rate-corrected QT interval among women

	QTc (ms)				
	–399 (n=*350*)	*400–419* (n=*488*)	*420–439* (n=*374*)	*440–* (n=*240*)	P *trend*
Stroke					
Number of events/person-years	16/4664	35/6268	42/4639	28/2732	
Incidence rate	6.6	6.6	9.6	7.7	0.08
Hazard ratio (95% CI)*	1 (reference)	1.40 (0.77–2.54)	1.86 (1.02–3.41)	1.44 (0.75–2.78)	0.23
Coronary heart disease					
Number of events/person-years	11/4676	16/6381	14/4787	10/2856	
Incidence rate	3.1	2.2	3.1	1.9	0.84
Hazard ratio (95% CI)*	1 (reference)	0.81 (0.33–1.97)	1.29 (0.53–3.12)	0.99 (0.37–2.65)	0.76
Total cardiovascular disease					
Number of events/person-years	25/4605	48/6228	51/4609	34/2729	
Incidence rate	8.5	9.3	11.6	8.3	0.37
Hazard ratio (95% CI)*	1 (reference)	1.25 (0.76–2.06)	1.48 (0.89–2.47)	1.15 (0.66–2.02)	0.58

Abbreviations: QTc, heart-rate-corrected QT interval; 95% CI, 95% confidence interval.
*Hazard ratios and *P*-values were adjusted for age, hypertension, heart rate, electrocardiographic abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterol, alcohol consumption, smoking habit, and regular exercise.

Table 4 Age-adjusted hazard ratio for development of total cardiovascular disease according to heart-rate-corrected QT interval prolongation and other risk factors among men

Risk factor	*QTc prolongation*	*No. of events/person-years*	*Relative risk (95% CI)*	P *interaction*
Hypertension[a]				
Absent	Absent	48/6660	1 (reference)	0.38
Present	Absent	71/4322	1.88 (1.30–2.72)	
Absent	Present	8/230	2.63 (1.22–5.65)	
Present	Present	18/348	4.51 (2.58–7.89)	
Diabetes[b]				
Absent	Absent	94/9534	1 (reference)	0.72
Present	Absent	25/1448	1.60 (1.03–2.49)	
Absent	Present	22/513	2.56 (1.58–4.15)	
Present	Present	4/66	5.74 (2.11–15.64)	
Obesity[c]				
Absent	Absent	90/8279	1 (reference)	0.69
Present	Absent	29/2703	1.27 (0.83–1.94)	
Absent	Present	22/505	2.42 (1.50–3.92)	
Present	Present	4/73	6.13 (2.25–16.73)	
Dyslipidemia[d]				
Absent	Absent	49/4875	1 (reference)	0.27
Present	Absent	70/6107	1.35 (0.93–1.95)	
Absent	Present	7/239	1.75 (0.79–3.88)	
Present	Present	19/339	4.11 (2.39–7.04)	
Current smoking				
Absent	Absent	58/5514	1 (reference)	0.15
Present	Absent	61/5468	1.23 (0.86–1.77)	
Absent	Present	9/298	1.96 (0.97–3.98)	
Present	Present	17/281	3.74 (2.15–6.50)	

Abbreviations: BMI, body mass index; QTc, heart-rate-corrected QT interval; QTc prolongation, QTc $\geqslant$440 ms; 95% CI, 95% confidence interval.
[a]Blood pressure $\geqslant$140/90 mm Hg or current use of antihypertensive agents.
[b]Fasting glucose $\geqslant 7.0\,mmol\,l^{-1}$, postprandial blood glucose $\geqslant 11.1\,mmol\,l^{-1}$ or current use of hypoglycemic agents.
[c]BMI $\geqslant 25.0\,kg\,m^{-2}$.
[d]Total cholesterol $\geqslant 5.68\,mmol\,l^{-1}$, high-density lipoprotein cholesterol $\leqslant 1.03\,mmol\,l^{-1}$ or triglyceride $\geqslant 1.69\,mmol\,l^{-1}$.

Table 5 Age-adjusted hazard ratio for development of total cardiovascular disease according to heart-rate-corrected QT interval prolongation and the number of other risk factors among men

Number of risk factors[a]	*QTc prolongation*	*No. of events/person-years*	*Relative risk (95% CI)*	P *interaction*
0–1	Absent	34/4338	1 (reference)	0.89
⩾2	Absent	85/6644	1.74 (1.17–2.59)	
0–1	Present	7/225	2.33 (1.02–5.30)	
⩾2	Present	19/354	4.70 (2.65–8.32)	

Abbreviations: QTc, heart-rate-corrected QT interval; QTc prolongation, QTc ⩾440 ms; 95% CI, 95% confidence interval.
[a]Hypertension, diabetes, obesity, dyslipidemia and current smoking.

prolongation or hypertension, and the highest risk was observed for the group with both QTc prolongation and hypertension. Similar associations were observed for combinations of QTc prolongation and every other risk factor (diabetes, obesity, dyslipidemia or current smoking). There were no significant interactions between QTc prolongation and these cardiovascular risk factors (all $P>0.1$ for interaction). The findings obtained from these analyses were substantially unchanged even after controlling for other risk factors in the multivariate analyses. Age-adjusted HRs for the development of total CVD according to the presence or absence of QTc prolongation (>440 ms) and number of risk factors (0–1 *vs.* ⩾2) among men are also shown in Table 5. There were no significant interactions between QTc prolongation and the number of risk factors (P=0.89 for interaction).

DISCUSSION

The present prospective analysis of a community-dwelling Japanese population clearly shows that QTc prolongation on ECG is an independent predictor of stroke, coronary heart disease and total CVD events among men. These associations remained strong even after controlling for age, hypertension, heart rate, ECG abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, BMI, total and HDL cholesterol, alcohol consumption, smoking habit and regular exercise. Furthermore, the effects of QTc were comparable for patients with or without other cardiovascular risk factors such as hypertension, diabetes, obesity, dyslipidemia or current smoking. However, similar associations were not observed for women.

To the best of our knowledge, only two hospital-based prospective studies have reported an association between QT interval prolongation and the risk of stroke.[5,7] QT interval prolongation (QTc ⩾470 ms) was associated with 2.2-fold higher incidence rates of stroke among 471 Brazilian subjects with type 2 diabetes,[5] whereas no clear associations between QT interval prolongation (QTc ⩾440 ms for men and QTc ⩾450 ms for women) and the development of stroke were found among 2110 Italian subjects with essential hypertension.[7] This study is the first to examine this issue in a general population and clearly shows that QT interval prolongation can predict the incidence of stroke among Japanese men.

A few large-scale observational studies have investigated the association between QT interval prolongation and the future risk of coronary heart disease.[3,4,6] The Atherosclerosis Risk in Communities study reported that QT interval prolongation (QTc ⩾440 ms for men and QTc ⩾454 ms for women) was associated with 1.5- to 5.0-fold increased risk of incident coronary heart disease among general populations of white Americans or African Americans.[3] Robbins *et al.*[4] reported that elderly subjects in the United States with QTc intervals >450 ms had higher coronary heart disease mortality than those with QTc intervals <410 ms. The Zutphen study showed that Dutch men with prolonged QTc (⩾440 ms) had 3.3- to 4.3-fold higher risk of death from coronary heart disease.[6] An Adult Health Study of the Radiation Effects Research Foundation showed that elderly Japanese with prolonged QTc (> 440 ms) had a 2.49-fold higher risk of coronary death compared with those with QTc intervals ⩽420 ms.[22] The present analysis from the Hisayama study confirms the results of previous cohort studies and provides more detailed information regarding the effects of QTc prolongation on the risk of future coronary events in Japanese men.

The mechanism underlying the association between QT interval prolongation and CVD has not been clearly defined, but the QT interval has been shown to be related to ventricular hypertrophy.[23] QT interval has also been shown to be associated with subclinical arterial disease.[24–26] Thus, QT interval prolongation, as a marker of ventricular hypertrophy or subclinical arterial disease, may predict future CVD events.

Another important finding from the present analysis is the lack of clear associations between QTc prolongation and CVD among women. This finding was consistent with previous observational studies. Schouten *et al.* have shown that QTc prolongation (⩾440 ms) was associated with 1.8-fold higher mortality rates from CVD among healthy Dutch men, but not among women. The reason for this finding has not been clearly resolved, but it has been suggested that sex hormones attenuate the association between QT interval prolongation and CVD. Estrogen has been reported to prolong the QT interval through downregulation of HERG-encoded potassium channel expression.[27] At the same time, endogenous estrogen has been shown to protect against the development of atherosclerosis.[18,27,28] Such conflicting effects of sex hormones might weaken the association of QT interval with CVD among women. Another possible reason for the sex difference in the risks of CVD might stem from differences in the atherosclerotic process between men and women. Generally, it is considered that atherosclerosis progresses at a faster rate in men than in women. Thus, it may be easier to detect the association between QT interval prolongation and CVD in men.

Several limitations of our study should be discussed. First, our study lacks information on medication use, which could affect the QT interval duration. It is known that several medications, including antiarrhythmic medications, antibiotics, antipsychotic agents or antihistamines can alter QT interval duration. However, these medications were rarely used in Japan in 1988, when the ECGs in our study were performed. This suggests that such a bias did not invalidate the present findings. Second, we have no information on subjects with congenital long-QT syndrome. However, the prevalence of congenital long-QT syndrome has been reported to be <0.1%.[29] Thus, the influence of congenital long-QT syndrome would seem to be negligible. Third, our findings are based on a 1-day measurement of clinical findings such as ECG, blood pressure levels and blood tests, which may not accurately reflect the status of the study participants. Errors in measuring QTc interval, blood pressure levels or blood test results could have weakened the relationships in the present analysis.

However, this source of variability could not account for the relationship observed in this study, because a random misclassification of such a nature would tend to underestimate the study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study.

In conclusion, our study found that QTc prolongation was an independent predictor of stroke and coronary heart disease in a general population of Japanese male subjects. QTc measurement is a low-cost and noninvasive test to detect high-risk males who should receive special attention. Approaches for the prevention of high-risk CVD using QTc measurement are likely to provide additional protection against the burden of CVD among Japanese male subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported in part by Grants-in-Aid for Scientific Research A (No. 18209024) and Scientific Research C (No. 19590633) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

1 Roden DM, Woosley RL. QT prolongation and arrhythmia suppression. *Am Heart J* 1985; **109**: 411–415.
2 Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, Mariani R, Gunson K, Jui J. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation* 2009; **119**: 663–670.
3 Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol* 2004; **43**: 565–571.
4 Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med* 2003; **115**: 689–694.
5 Cardoso CR, Salles GF, Deccache W. QTc interval prolongation is a predictor of future strokes in patients with type 2 diabetes mellitus. *Stroke* 2003; **34**: 2187–2194.
6 Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. *Circulation* 1994; **90**: 779–785.
7 Schillaci G, Pirro M, Ronti T, Gemelli F, Pucci G, Innocente S, Porcellati C, Mannarino E. Prognostic impact of prolonged ventricular repolarization in hypertension. *Arch Intern Med* 2006; **166**: 909–913.
8 Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). *Am J Cardiol* 1991; **67**: 55–58.
9 Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. *Arch Intern Med* 2004; **164**: 943–948.
10 Porthan K, Viitasalo M, Jula A, Reunanen A, Rapola J, Vaananen H, Nieminen MS, Toivonen L, Salomaa V, Oikarinen L. Predictive value of electrocardiographic QT interval and T-wave morphology parameters for all-cause and cardiovascular mortality in a general population sample. *Heart Rhythm* 2009; **6**: 1202–1208.
11 Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 1966; **21**: 64–89.
12 Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, Tanaka K, Ohkubo K, Nakamura H, Abe I, Fujishima M, Iida M. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama Study. *Arch Intern Med* 2003; **163**: 361–366.
13 Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawu A *et al*. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia* 1993; **36**: 1198–1203.
14 Arima H, Kiyohara Y, Kato I, Tanizaki Y, Kubo M, Iwamoto H, Tanaka K, Abe I, Fujishima M. Alcohol reduces insulin-hypertension relationship in a general population: the Hisayama study. *J Clin Epidemiol* 2002; **55**: 863–869.
15 Wakugawa Y, Kiyohara Y, Tanizaki Y, Kubo M, Ninomiya T, Hata J, Doi Y, Okubo K, Oishi Y, Shikata K, Yonemoto K, Maebuchi D, Ibayashi S, Iida M. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. *Stroke* 2006; **37**: 27–32.
16 Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, Hata J, Matsumura K, Iida M, Kiyohara Y. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1385–1391.
17 Kubo M, Kiyohara Y, Ninomiya T, Tanizaki Y, Yonemoto K, Doi Y, Hata J, Oishi Y, Shikata K, Iida M. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. *Neurology* 2006; **66**: 1539–1544.
18 Maebuchi D, Arima H, Ninomiya T, Yonemoto K, Kubo M, Doi Y, Tanizaki Y, Matsumura K, Iida M, Kiyohara Y. Arterial stiffness and QT interval prolongation in a general population: the Hisayama Study. *Hypertens Res* 2008; **31**: 1339–1345.
19 Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. *Am J Cardiol* 1993; **72**: 17B–22B.
20 Arima H, Tanizaki Y, Yonemoto K, Doi Y, Ninomiya T, Hata J, Fukuhara M, Matsumura K, Iida M, Kiyohara Y. Impact of blood pressure levels on different types of stroke: the Hisayama study. *J Hypertens* 2009; **27**: 2437–2443.
21 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
22 Nakanishi S, Yamada M, Hattori N, Suzuki G. Relation between QT duration and mortality in an elderly Japanese population. *Am J Cardiol* 2004; **93**: 1182–1185.
23 Oikarinen L, Nieminen MS, Viitasalo M, Toivonen L, Jern S, Dahlof B, Devereux RB, Okin PM. QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 2004; **43**: 1029–1034.
24 Festa A, D'Agostino Jr R, Rautaharju P, O'Leary DH, Rewers M, Mykkanen L, Haffner SM. Is QT interval a marker of subclinical atherosclerosis in nondiabetic subjects? The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 1999; **30**: 1566–1571.
25 Strohmer B, Pichler M, Iglseder B, Paulweber B. Relationship of QT interval duration with carotid intima media thickness in a clinically healthy population undergoing cardiovascular risk screening. *J Intern Med* 2005; **257**: 238–246.
26 Maule S, Rabbia F, Perni V, Tosello F, Bisbocci D, Mulatero P, Veglio F. Prolonged QT interval and reduced heart rate variability in patients with uncomplicated essential hypertension. *Hypertens Res* 2008; **31**: 2003–2010.
27 Yuill KH, Borg JJ, Ridley JM, Milnes JT, Witchel HJ, Paul AA, Kozlowski RZ, Hancox JC. Potent inhibition of human cardiac potassium (HERG) channels by the anti-estrogen agent clomiphene—without QT interval prolongation. *Biochem Biophys Res Commun* 2004; **318**: 556–561.
28 Hodis HN, Mack WJ. Atherosclerosis imaging methods: assessing cardiovascular disease and evaluating the role of estrogen in the prevention of atherosclerosis. *Am J Cardiol* 2002; **89**: 19E–27E.
29 Skinner JR. Guidelines for the diagnosis and management of familial long QT syndrome. *Heart Lung Circ* 2007; **16**: 22–24.