Sleep Blood Pressure Self-Measured at Home as a Novel Determinant of Organ Damage: Japan Morning Surge Home Blood Pressure (J-HOP) Study

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To study whether sleep blood pressure (BP) self-measured at home is associated with organ damage, the authors analyzed the data of 2562 participants in the J-HOP study who self-measured sleep BP using a home BP monitoring (HBPM) device, three times during sleep (2 AM, 3 AM, 4 AM), as well as the home morning and evening BPs. The mean sleep home systolic BPs (SBPs) were all correlated with urinary albumin/creatinine ratio (UACR), left ventricular mass index (LVMI), brachial-ankle pulse wave velocity (baPWV), maximum carotid intima-media thickness, and plasma N-terminal pro-hormone pro–brain-type natriuretic peptide (NTproBNP) (all $P<.001$). After controlling for clinic SBP and home morning and evening SBPs, associations of home sleep SBP with UACR, LVMI, and baPWV remained significant (all $P<.008$). Even in patients with home morning BP <135/85 mm Hg, 27% exhibited masked nocturnal hypertension with home sleep SBP ≥120 mm Hg and had higher UACR and NTproBNP. Masked nocturnal hypertension, which is associated with advanced organ damage, remains unrecognized by conventional HBPM. *J Clin Hypertens (Greenwich)*. 2015; 17:340–348. © 2015 Wiley Periodicals, Inc.

Recent population-based and clinical studies using ambulatory blood pressure (BP) monitoring (ABPM) demonstrate that sleep BP is a better predictor of cardiovascular disease than awake BP.[1–3] Nocturnal hypertension with higher sleep BP, and a nondipper/riser pattern with higher sleep BP than awake BP (even they are normotensive), are reported to constitute risks for hypertensive target organ damage and subsequent cardiovascular events.[4–8]

ABPM has historically been the gold standard for measuring sleep BP. Recently, however, self-measured home BP monitoring (HBPM) was introduced to measure sleep BP at home.[9] In the first-ever study of sleep BP using HBPM, BP was measured once at 2 AM automatically.[10] We recently developed an HBPM device that automatically measures sleep home BP (HBP) 20 times with data memory (Medinote; Omron Healthcare Inc., Kyoto, Japan). We showed that the sleep HBP level measured using the Medinote device was almost identical to the sleep BP level measured by ABPM, and both sleep BPs measured by HBPM and ABPM were similarly correlated with hypertensive target organ damage.[11] Another study also demonstrated that HBPM was well accepted for the assessment of nocturnal BP and the detection of nondipping status.[12]

To verify the hypothesis that sleep HBP is worth monitoring in addition to conventional HBPM in the morning (morning HBP) and in the evening (evening HBP), we studied the associations of sleep HBP and target organ damage. For this purpose, we obtained data for 2562 participants of the Japan Morning Surge Home Blood Pressure (J-HOP) study. The J-HOP study is the largest nationwide HBP cohort and employs the same HBP monitoring device and method as used in the present study: self-measurement of sleep HBP using the Medinote three times during sleep (2 AM, 3 AM, 4 AM), as well as three times in the morning and three times in the evening for 14 days.

METHODS

The recruitment of the study patients of the J-HOP study was consecutively conducted from January 2005 to May 2012 by 75 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and four specialized university hospitals) throughout Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. The study protocol was registered on a clinical trials registration site (University Hospital Medical Information Network

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Manuscript received: October 20, 2014; **revised:** December 1, 2014; **accepted:** December 2, 2014
DOI: 10.1111/jch.12500

Clinical Trials Registry: #UMIN000000894). Written informed consent was obtained from all patients who enrolled in the study.

Study Subjects

Between January 2005 and May 2012, we enrolled 4310 ambulatory outpatients with one or more of the following cardiovascular risks: hypertension, hyperlipidemia, diabetes (fasting blood sugar ≥126 mg/dL, receiving an antidiabetic drug), glucose intolerance, metabolic syndrome, chronic kidney disease (estimated glomerular filtration rate <60 mL), history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, congestive heart failure), atrial fibrillation, current smoking, chronic obstructive pulmonary disease, and sleep apnea syndrome. We excluded patients who had malignancy or chronic inflammatory disease. The time interval of HBPM and the assessment of organ damage was <3 months.

BP Measurements

HBP measurement was performed using a validated cuff oscillometric device (HEM-5001; Medinote; Omron Healthcare Co., Ltd)[11] according to hypertension guidelines for the management of hypertension.[13–15] This self-measured HBPM automatically makes three measurements at 15-second intervals on each occasion. The device can be set at bedtime to measure BP during sleep, and all recorded BP parameters are stored in its memory. This new computerized HBPM device automatically stores BP data separately measured in the morning, the evening, and during sleep.

We asked study patients to measure their morning HBP (measured after awakening and before breakfast and taking antihypertensive medication) and evening HBP (measured before taking antihypertensive medication and going to bed) in a sitting position for a 2-week period. All HBP data of the HBPM device were downloaded into a computer and sent to the study control center (Jichi Medical University, Tochigi, Japan). After exclusion of the data from the first day, the averages of all HBPs measured three times in the morning (morning HBP) and three times in the evening (evening HBP) for 13 days (78 readings in total) were separately calculated by the study coordinator, who was blinded to the clinical characteristics of the study participants.

In addition, those participants who agreed to do so (n=2562, or 59% of the total sample) also measured their sleep HBP on at least 1 day within the 2 weeks. Sleep HBP measurements were made only once at each of three preset times (2 AM, 3 AM, and 4 AM), and sleep HBPs were defined as the average of all sleep BPs measured.

Clinic BP was measured at local medical centers using the same HBP device and cuff used for HBP measurement after the patients had been seated for 2 minutes and was calculated as the mean of three consecutive measurements. We generally used cuffs with rubber bags 13 cm wide and 22- to 32-cm long, or 32- to 42-cm long in the case of patients with a large upper arm; this choice was left to the physicians who measured the clinic BP.

Echocardiographic and Ultrasonographic Measurements of the Carotid Artery and Pulse Wave Velocity

Echocardiography was performed at each participating institute. Two-dimensional M-mode or B-mode images were obtained using an ultrasound machine according to the guidelines of the American Society of Echocardiology. Left ventricular (LV) mass (LVM) was obtained using the formula validated by the American Society of Echocardiology: LVM=0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3−[LVIDD]^3))+0.6 g, where IVSTD is the diastolic interventricular septal diameter, LVIDD is the diastolic LV dimension, and PWTD is the diastolic posterior wall diameter. The LVM index (LVMI) was calculated as LVM/body surface area, where IVSd is the interventricular septum thickness at the end of diastole, PWd is the posterior wall thickness at the end of diastole, and LVDd is the LV internal dimension at the end of diastole. Carotid intima-media thickness (IMT) was assessed for the right and left common carotid artery using a B-mode ultrasound scanner at each participating institute. Carotid IMT was measured at three points proximal to the bilateral carotid bulbus (far wall) in 10-mm segments at end-diastole and always in plaque-free segments. If plaque existed at the IMT measuring point, an appropriate adjacent portion was chosen. The mean of the right and left maximum carotid IMT (six points in total) was used in the analysis (MaxIMT). The brachial-ankle PWV (baPWV) was measured by using the volume plethysmographic method with previously validated equipment (form PWV/ABI; Omron Healthcare Co., Ltd). We used the mean of right and left baPWV values for the analysis.

Biomarker Assays

Blood and spot urine samples were collected in the morning in a fasting state at enrollment and at the end of the study. The blood samples were centrifuged at 3000 ×*g* for 15 minutes at room temperature. Plasma/serum samples after separation and urine samples were stored at 4°C in refrigerated containers and sent to a commercial laboratory (SRL Inc., Tokyo, Japan) within 24 hours. Serum samples after separation were also stored at −80°C in a refrigerator. All assays were performed within 24 hours of sample collection at this single laboratory center.

The urinary albumin level was measured using a turbidimetric immunoassay (SRL Inc.) and expressed as UACR (mg/gCr). Both serum and urine creatinine were measured by enzymatic assay. Using the stored serum samples, N-terminal pro–brain-type natriuretic peptide (NTproBNP) was measured as previously described, and high-sensitivity cardiac troponin T (hs-cTnT) levels were measured using a highly sensitive assay on an automated platform (Elecsys-2010 Troponin T hs

STAT; Roche Diagnostics, Mannheim, Germany K.K.), with a lower detection limit of 0.003 ng/mL and a reported 99th percentile value in apparently healthy individuals of 0.014 ng/mL.

The intracoefficients/intercoefficients of variation were 1.93%/3.13% for NTproBNP, 2.02%/3.02% for hs-cTnT, and 1.30%/1.85% for urinary albumin assay.

Statistical Analysis

All analyses were performed in the 2562 patients. We included patients with atrial fibrillation, and data were expressed as means (±standard deviation [SD]) or percentages. When we excluded patients with atrial fibrillation (4.1%), all the results were essentially the same. Because the distributions of UACR, hs-cTnT, and NTproBNP were highly skewed, they were log-transformed before statistical analysis and expressed as the geometric mean (±SD). Values of hs-cTnT <0.003 ng/mL (detection limit) were assigned as 0.0015 ng/mL. The chi-square test was used to evaluate differences in prevalence rates. Unpaired *t* tests were used for comparison of the mean values between two groups. Correlations among variables were analyzed using Pearson's correlation coefficient. To investigate whether lowest or highest sleep BP provides a better index of organ damages, linear regression analysis was performed, and the correlation coefficients were compared after Fisher's *z* transformation. Multiple regression analysis of biomarkers (dependent variables) was performed using BP parameters as independent variables after controlling for age, sex, body mass index, antihypertensive drug use, evening or bedtime dosing of antihypertensive drug, sleep duration, and clinic, morning, evening home SBPs. Variance inflation factors were calculated to examine the possible existence of substantial multicollinearity among the BP measurements, and values >3.0 were considered to indicate collinearity. Associations/differences with a *P* value <.05 (two-tailed) were considered to be statistically significant. All statistical analyses were performed with SPSS version 11 software (IBM, Armonk, NY).

RESULTS

Patient Characteristics

The age, BP level, and degree of target organ damage were only slightly lower in the sleep BP analysis group (n=2562) than in the group of all J-HOP study patients (n=4310) (Table I). The average number of BP readings was 73±15 for morning and evening HBP and 18±13 for sleep HBP. The average of the number of home sleep BP readings was the same (6.14±4.50 for 2 AM, 6.11±4.50 for 3 AM, and 6.03±4.50 for 4 AM; not significant). In the sleep BP analysis group, the mean clinic SBP, morning home SBP, and home sleep SBP levels were 140 mm Hg, 136 mm Hg, and 121 mm Hg, respectively. These are near the threshold of each SBP for defining uncontrolled hypertension (140 mm Hg, 135 mm Hg, and 120 mm Hg), suggesting that almost

TABLE I. Baseline Characteristics of Study Patients

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
Age, y	64.8±10.9	63.3±10.3[a]
Male, %	47.0	49.1[a]
Body mass index, kg/m^2	24.3±3.5	24.4±3.5
Waist/hip ratio	0.90±0.07	0.89±0.07
Alcohol, %	28.0	28.5[b]
Smoking, %	12.0	11.8
Dyslipidemia, %	40.7	43.2[a]
Diabetes, %	23.5	24.1
History, %		
Angina	7.2	7.3
Myocardial infarction	3.9	4.4[b]
Aortic dissection	0.7	0.8
Stroke	4.1	3.9
Congestive heart failure	1.7	1.8
Peripheral artery disease	1.0	0.8
Atrial fibrillation	3.7	4.1
Sleep apnea syndrome	3.3	4.2
Sleep duration, h	7.1±1.2	7.0±1.1[a]
eGFR<60 mL/min/1.73 m^2, %	20.4	20.6
Antihypertensive drug, %	79.1	82.5[a]
Calcium antagonist	50.8	51.3
ACE inhibitor	6.6	6.4
ARBs	51.8	51.9
β-Blocker	13.7	15.4
α-Blocker	5.0	5.1
Diuretics	26.1	28.7[a]
Aldosterone blocker	2.2	2.4
Evening or bedtime dosing of antihypertensive drug, %	27.7	29.0[b]
Statin, %	23.6	23.7
Aspirin, %	15.1	17.4[a]
Clinic SBP, mm Hg	141.3±16.5	140.0±15.3[a]
Clinic DBP, mm Hg	81.2±10.6	81.8±10.2[a]
Home morning SBP, mm Hg	138.4±15.9	136.4±14.7[a]
Home morning DBP, mm Hg	79.1±10.0	79.3±9.6
Home evening SBP, mm Hg	130.1±15.0	128.9±14.3[a]
Home evening DBP, mm Hg	72.7±9.7	72.9±9.3
UACR, mg/gCr	13.2 (7.2, 30.8)	12.1 (6.9, 27.5)[a]
LVMI, g/m^2	100±27.9	97.8±26.3[a]
baPWV, cm/s	1675±352	1630±320[a]

TABLE I. Baseline Characteristics of Study Patients (Continued)

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
MaxIMT, mm	1.05±0.45	1.08±0.48[a]
NTproBNP, pg/mL	50.6 (25.6, 97.8)	45.9 (22.9, 88.2)[a]
hs-cTnT, ng/mL	0.003 (0.003, 0.007)	0.003 (0.003, 0.006)[a]

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity (n=1489); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T (n=2289); LVMI, left ventricular mass index (n=1092); MaxIMT, maximum carotid intima-media thickness (n=828); NTproBNP, N-terminal pro–brain-type natriuretic peptide (number of patients included in the sleep blood prssure analysis: n=2292); SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio (n=2554). Data are presented as mean±standard deviation, median (25%, 75%), or percentage. [a]*P*<.001 vs the patients excluded from the sleep blood pressure analysis. [b]*P*<.05.

half of the study patients were uncontrolled above these thresholds.

Clinic BP and HBP Levels

There was no difference between the sleep home SBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg (*P*<.001) (Figure 1). Sleep diastolic BP (DBP) was also slightly increased by 1.6 mm Hg between the 2 AM and 4 AM measurements.

Distributions of Sleep HBPs

Figure 2A and 2B show the distribution of sleep HSBP (average of the sleep SBPs at 2 AM, 3 AM, and 4 AM) of the sleep BP analysis group. Among these patients, 49% and 47% exhibited uncontrolled hypertension above the threshold for sleep home SBP and DBP (120/70 mm Hg), respectively.

Association with Covariates

Home sleep SBP was positively correlated with age, use of diuretics, and clinic and home morning and evening SBPs even in the subgroup with well-controlled morning BP (all, *P*<.001) (Table S1).

Association with Target Organ Damage

The average (Figure 3), the highest, and the lowest sleep home SBPs were significantly correlated with all six measures of target organ damage (UACR, LVMI, baPWV, MaxIMT, plasma NTproBNP, hs-cTnT), while sleep home DBP was correlated only with UACR (Table II). There was no significant difference between lowest and highest sleep SBP in a comparison of the correlation coefficients from these relationship.

We subclassified the study participants into three groups (few reading, moderate reading, frequent reading) according to the number of home sleep BP readings. The correlation coefficients of home sleep SBP with measures of organ damage were higher the higher tertile than the lower tertile (Table S2).

After controlling for clinic SBP and morning and evening home SBPs, the associations of sleep home SBP with UACR, LVMI, baPWV, NTproBNP, and hs-cTnT remained significant (Table III).

Masked Home Nocturnal Hypertension

In the subanalysis of hypertensive patients with well-controlled morning HBP <135/85 mm Hg (n=1179), 27% exhibited masked home nocturnal hypertension, defined by sleep home SBP ≥120 mm Hg, and 31%

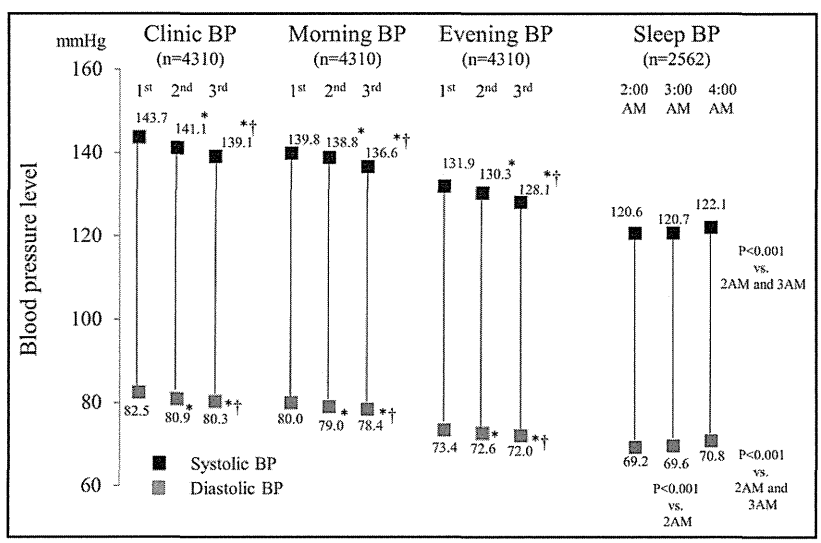

FIGURE 1. Clinic and home blood pressure (BP) level (mean) in the Japan Morning Surge Home Blood Pressure study patients. **P*<.001 vs first measurement. †*P*<.001 vs second measurement by paired *t* test. Home BPs were self-measured three times during sleep, three times in the morning, and three times in the evening, and the average for each time point is shown.

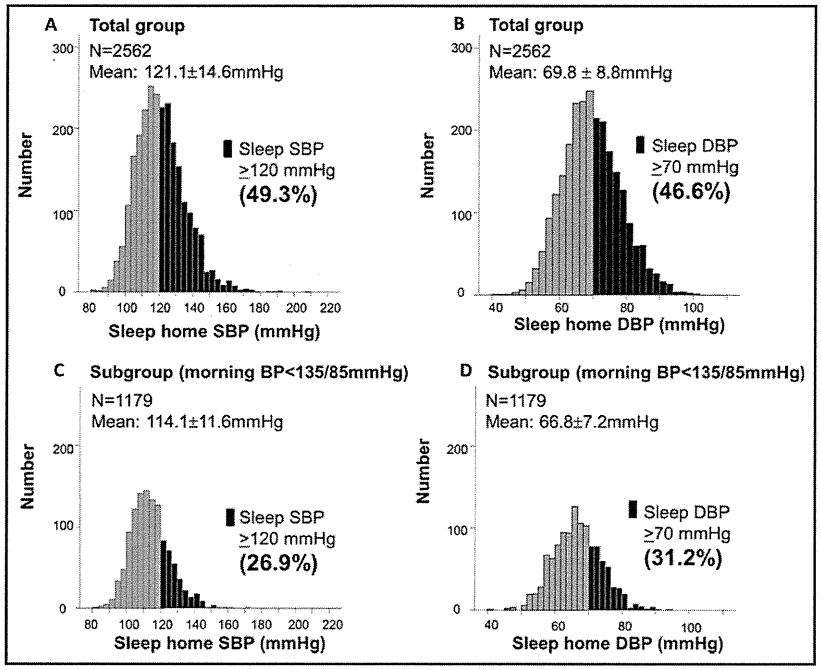

FIGURE 2. Distribution of sleep home blood pressure (BP). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

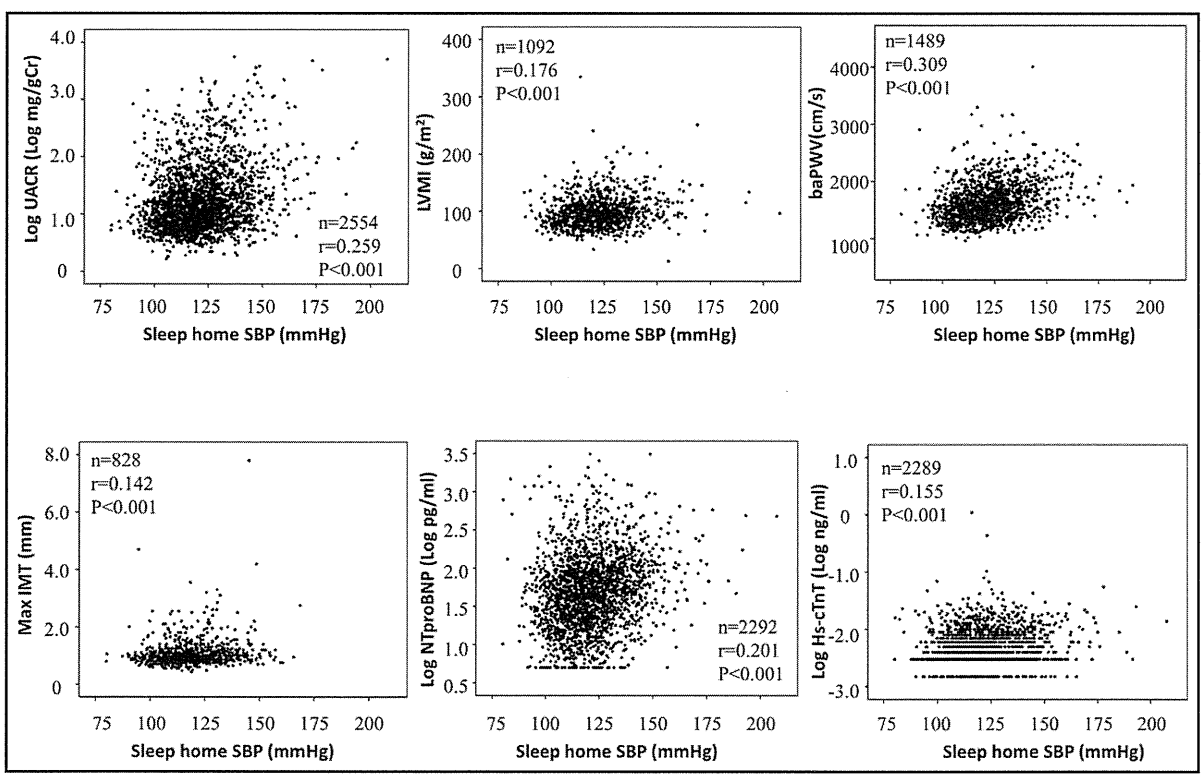

FIGURE 3. Associations of sleep home systolic blood pressure (SBP) with measures of target organ damage. UACR indicates urinary albumin/creatinine ratio; LVMI, left ventricular mass index; baPWV, brachial-ankle pulse wave velocity; MaxIMT, maximum carotid intima-media thickness; NT-proBNP, N-terminal pro–brain-type natriuretic peptide level; hs-cTnT, high-sensitivity cardiac troponin T. Sleep home SBP is calculated as the average of three sleep home blood pressures measured at 2 AM, 3 AM, and 4 AM.

TABLE II. Simple Correlations of Home Sleep Blood Pressure Parameters With Measures of Target Organ Damage

mean±SD, mm Hg		Log UACR	LVMI	baPWV	MaxIMT	Log NTproBNP	Log hs-cTnT
		R	*R*	*R*	*R*	*R*	*R*
Sleep SBP							
Average	121.1±14.6	0.26[a]	0.18[a]	0.31[a]	0.14[a]	0.20[a]	0.16[a]
2 AM	120.6±15.4	0.25[a]	0.17[a]	0.28[a]	0.13[a]	0.18[a]	0.14[a]
3 AM	120.7±15.5	0.24[a]	0.17[a]	0.29[a]	0.13[a]	0.19[a]	0.13[a]
4 AM	122.1±15.7	0.24[a]	0.16[a]	0.32[a]	0.14[a]	0.20[a]	0.15[a]
Highest	126.2±15.6	0.26[a]	0.20[a]	0.32[a]	0.12[a]	0.19[a]	0.15[a]
Lowest	116.2±14.6	0.24[a]	0.15[a]	0.27[a]	0.16[a]	0.20[a]	0.15[a]
Sleep DBP							
Average	69.8±8.8	0.12[a]	0.02	−0.01	−0.02	−0.03	−0.04[b]
2 AM	69.2±9.5	0.11[a]	0.03	−0.007	0.003	−0.04[b]	−0.05[b]
3 AM	69.6±9.3	0.10[a]	0.02	−0.02	−0.02	−0.04	−0.05[b]
4 AM	70.9±9.7	0.10[a]	0.002	0.01	−0.03	−0.03	−0.02
Highest	73.4±9.5	0.12[a]	0.04	0.01	−0.05	−0.04[b]	−0.03
Lowest	66.3±9.1	0.10[a]	−0.01	−0.03	0.01	−0.02	−0.04[b]

Abbreviations: baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness; NTproBNP, N-terminal pro–brain-type natriuretic peptide; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin/creatinine ratio. Values are presented as Pearson's correlation coefficients (*R*). [a]$P<.001$. [b]$P<.05$.

exhibited masked home nocturnal hypertension defined by sleep home DBP ≥70 mm Hg (Figure 2C and 2D). The masked home nocturnal hypertension group (n=318) with sleep systolic HBP ≥120 mm Hg had higher UACR (11.5 [7.0–23.1 vs 8.9 [5.9–17.4] mg/gCr, *P*<.001]) and NTproBNP (49.1 [23.7–88.8] vs 36.3 [18.5–70.0] pg/mL, *P*=.003) than those with sleep systolic HBP <120 mm Hg (n=861).

Even in those with both well-controlled clinic BP <140/90 mm Hg and well-controlled morning HBP <135/85 mm Hg (n=787; average clinic, morning, and sleep HBP: 126.8±8.8/76.7±7.5 mm Hg, 123.6±7.7/74.0±6.6 mm Hg, 112.6±11.1/66.2±6.7 mm Hg, respectively), 22% exhibited masked home nocturnal hypertension defined by sleep home SBP >120 mm Hg, and 27% exhibited masked home nocturnal hypertension defined by sleep home DBP >70 mm Hg (Figure S1). The masked nocturnal hypertension group (n=173) with sleep systolic HBP >120 mm Hg had higher UACR (11.4 [7.1–21.2 vs 8.3 [5.6–16.2] mg/gCr, *P*=.002]) and NTproBNP (49.2 [26.1–88.4] vs 35.1 [17.6–69.5] pg/mL, *P*=.002) than those with sleep systolic HBP <120 mm Hg (n=614).

DISCUSSION

This study was the first to demonstrate that sleep BP measured by HBPM was associated with almost all the measures of hypertensive target organ damage independently of clinic BP and HBPs measured in the morning and in the evening, and that the prevalence of masked nocturnal hypertension with sleep SBP ≥120 mm Hg was 27% among those with well-controlled morning HBP <135/85 mm Hg in the baseline data of the largest of the nationwide HBPM cohorts that used a single high-quality automatic HBPM device with data memory and three automatic measurements of BP during the sleep period.

Sleep BP Parameters and Target Organ Damage

There was no difference between the three sleep HBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg systolic and 1.6 mm Hg diastolic. However, these differences were not clinically significant. In addition, the sleep BP of ABPM was calculated as the average of the BPs during the sleep period; we also used the average of three sleep HBPs.

The average of all the sleep systolic HBPs and also the individual sleep systolic HBPs at 2 AM, 3 AM, and 4 AM were significantly correlated with all the measures of hypertensive target organ damage, such as UACR, LVMI, baPWV, MaxIMT, and the plasma levels of cardiac biomarkers (NTproBNP and hs-cTnT), while the association of sleep diastolic HBP was only found with UACR. These measures of target organ damage are the surrogate markers for predicting cardiovascular events.[16–20] Thus, a higher sleep BP level would constitute a risk for cardiovascular events independently of morning and evening BPs measured by conventional HBP measurement.

TABLE III. Multiple Linear Regression Analysis Between Sleep SBP and Target Organ Damage Additionally Adjusted for Another Blood Pressure Parameter

	Log UACR, Log mg/gCr		LVMI, g/m^2	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.007 (0.006–0.009)	<.001	0.215 (0.096–0.335)	<.001
+Morning SBP	0.005 (0.004–0.007)	<.001	0.143 (0.007–0.280)	.040
+Evening SBP	0.006 (0.004–0.008)	<.001	0.172 (0.034–0.310)	.034
+Clinic SBP, morning and evening SBP	0.005 (0.003–0.007)	<.001	0.137 (−0.006 to 0.280)	.061
	baPWV, cm/s		MaxIMT, mm	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	3.006 (2.026–3.985)	<.001	0.003 (0.001–0.006)	.011
+Morning SBP	2.394 (1.249–3.540)	<.001	0.002 (−0.001 to 0.005)	.167
+Evening SBP	1.954 (0.810–3.098)	.001	0.002 (0.000–0.005)	.105
+Clinic SBP, morning and evening SBP	1.905 (0.713–3.097)	.002	0.002 (−0.001 to 0.004)	.240
	Log NTproBNP, Log pg/mL		Log Hs-cTnT, Log ng/mL	
	Sleep SBP, mm Hg			
	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.005 (0.003–0.006)	<.001	0.002 (0.001–0.003)	<.001
+Morning SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.017
+Evening SBP	0.004 (0.003–0.006)	<.001	0.002 (0.001–0.002)	.001
+Clinic SBP, morning and evening SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.022

Abbreviations: baPWV, brachial-ankle pulse wave velocity; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness of carotid artery; NTproBNP, N-terminal pro–brain-type natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio. Each blood pressure parameter was added separately to the baseline regression models, which included age, sex, body mass index, use of antihypertensive drug, evening or bedtime dosing of antihypertensive drug, and sleep duration.

In addition, we also used the highest and lowest sleep HBP among the three sleep HBPs at 2 AM, 3 AM, and 4 AM as another sleep HBP parameter. The lowest sleep SBP, under the condition of the lowest sympathetic tone, may be a closer index of basal sleep BP, which is predominantly determined by the circulating volume or the structural remodeling of small resistance arteries.[9] The highest sleep BP may be a closer index of increased sympathetic tone–related sleep BP, which may be prominent in those with sleep apnea syndrome.[9,21,22] In this study, there were no significant differences in the impact of the average, the highest, and the lowest sleep BPs on target organ damage. A future study on hypertensive patients under various conditions could clarify the different impact of these sleep HBP parameters.

Association Independently of Morning BP

The association of sleep systolic HBP with measures of target organ damage (except MaxIMT) remained significant, independently not only of clinic SBP, but also of morning systolic HBP and evening systolic HBP, although morning HBP measured within 1 hour after awakening may partly be influenced by the preceding sleep BP.[23] Considering that approximately 25% of hypertensives with well-controlled morning HBP <135/85 mm Hg exhibit masked nocturnal hypertension with sleep systolic HBP >120 mm Hg, and significantly higher UACR and NTproBNP, sleep BP is worth monitoring in order to identify hypertensive patients with remaining risk during sleep, even if they are normotensive with respect to both clinic BP and morning HBP.

Recommendation of Sleep HBP-Guided Antihypertensive Medication

Sleep BP is more important in medicated than in nonmedicated hypertensive patients. The international ABPM database demonstrated that sleep BP was independently and more closely associated with cardiovascular events than awake BP in medicated hypertensives.[3] In our recent study of HBP-guided antihypertensive treatment in hypertensive patients,[24] sleep BP measured by ABPM was more closely associated with the plasma BNP level than was awake BP.[25] Even in those patients with well-controlled HBP <135/85 mm Hg, those whose sleep BP by ABPM was uncontrolled exhibited markedly higher UACR and higher plasma BNP levels.[26] These results suggest that sleep BP is a "blind spot" in current antihypertensive medication. To reduce cardiovascular events more effectively, strict 24-hour

BP, including sleep BP, is important in the management of hypertension. As a first step, recent guidelines have recommended using HBPM widely in clinical practice.[13–15] These guidelines generally recommend that HBP be measured on two occasions (in the morning and in the evening).[13–15] The measurement of sleep BP by HBPM is referred to in the guidelines, but is not conventionally recommended.[15] In this study, home sleep BP was significantly correlated with morning and evening BPs; however, home sleep BP is worth measuring, particularly in patients with diabetes mellitus, chronic kidney disease, sleep apnea syndrome, or target organ damage (those who are likely to have masked nocturnal hypertension). In this study, HBP was positively associated with age and diabetes, and "masked home nocturnal hypertension" was associated with higher UACR and NTproBNP levels. Although ABPM is the gold standard for assessing sleep BP, ABPM is inconvenient for frequent use in clinical practice. In the future, after the available data on HBPM-measured sleep BP has been expanded, HBPM could be used as an alternative device for sleep BP–guided antihypertensive medication.

Study Limitations

Various types of cardiovascular disease were included in the J-HOP study. The cause and effect relationship between sleep BP and cardiovascular disease may have varied by the nature of cardiovascular disease. Thus, by the association study using baseline data of the prospective J-HOP study, we could not refer to the cause and effect relationship between sleep HBP and measures of organ damage. Finally, the causal implication of self-measured sleep HBP will be clarified in the prospective follow-up results of the J-HOP study after adjustment for baseline cardiovascular profiles.

In addition, sleep duration and quality may modulate the association between sleep BP and organ damage. We collected the baseline data of duration and quality of sleep (presence or absence of insomnia and frequency of awakening and nocturia in each of the 14 days) in the J-HOP study, and the association between this sleep information and BPs will be studied more extensively in the future.

Finally, we should note that we did not specify the timing of the clinic BP measurement, leaving this decision to the discretion of the individual medical centers. Therefore, it might be possible that the clinic BP was underestimated because of the peak effect of the drug treatment.

CONCLUSIONS

This study first demonstrated that self-measurement of sleep HBP is feasible in a large cohort, and sleep HBP is significantly correlated with target organ damage independently of clinic BP and morning and evening HBPs. Masked nocturnal hypertension, one fourth of well-controlled morning hypertensives, remains unrecognized by conventional HBPM without sleep BP monitoring, and it was associated with advanced organ damage. Thus, sleep HBP in addition to morning HBP is worth monitoring, particularly in high-risk hypertensive patients with target organ damage. However, there are no prospective studies demonstrating that a strategy of lowering nighttime BP reduces the risk of target organ injury from hypertension. In the future, it needs to be emphasized that clinical significance of self-measured sleep BP at home should prospectively be demonstrated in the J-HOP study.

Acknowledgments: We gratefully acknowledge Ms Kimiyo Saito and Mrs Mayumi Yahata for the coordination and data management of this study, and Mrs Ayako Okura for editorial assistance.

Disclosures: This study was financially supported in part by a grant from the 21st Century Center of Excellence Project run by Japan's Ministry of Education, Culture, Sports, Science and Technology; a grant from the Foundation for Development of the Community (Tochigi); a grant from Omron Healthcare Co., Ltd, a Grant-in-Aid for Scientific Research (B) (21390247) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, 2009–2013; and funds from the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2011–2015 Cooperative Basic and Clinical Research on Circadian Medicine (S1101022). (to K.K.). The authors have no conflicts of interest to declare.

Contributors: Kazuomi Kario is the principle investigator of the J-HOP study, supervised its conduct and data analysis, and had primary responsibility for the writing of this paper. Satoshi Hoshide, the secretary in general of the J-HOP, conducted all statistical analyses.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of sleep home blood pressure (BP) at subgroup (morning BP <135/85 mm Hg and clinic BP <140/90 mm Hg). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

Table S1. Simple correlations of home sleep blood pressure with covariates in the total sleep blood pressure analysis group and in subgroup well-controlled in home morning blood pressure <135/85 mm Hg.

Table S2. Simple correlations of home sleep blood pressure with measures of target organ damage in tertile of number of sleep blood pressure readings.

Journal of Cardiology 65 (2015) 237–242

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Relationships between the QTc interval and cardiovascular, stroke, or sudden cardiac mortality in the general Japanese population

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ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 30 April 2014
Accepted 22 May 2014
Available online 24 July 2014

Keywords:
QTc interval
Cardiovascular death
Sudden cardiac death
Stroke
Myocardial infarction

ABSTRACT

Background: We attempted to evaluate whether the relationship between the QTc interval and mortality (including sudden cardiac death) is linear or J-shaped in the general Japanese population, who tend to be at greater risk of strokes than cardiac events.
Methods: We classified 10,804 subjects according to their Bazett QTc interval quartiles (determined by electrocardiography) at the baseline and followed them up for a mean period of 141.9 ± 28.3 months (127,712 person-years).
Results: In total, 878 subjects died during the study period, including 104 from cardiovascular events, 100 from stroke, and 46 from sudden cardiac death. In a Cox proportional hazards regression model adjusted for conventional cardiovascular risk factors, the risk of cardiovascular mortality increased progressively with the QTc interval quartile [Q2, hazard ratio (HR) = 0.94 (0.43–2.03); Q3, HR = 1.11 (0.53–2.34); Q4, HR = 2.21 (1.12–4.36); HR are vs. Q1]. A parallel analysis found that the risk of stroke mortality was marginally increased in the highest Bazett QTc interval quartile [HR = 1.93 (0.97–3.85)]. On the other hand, the risk of sudden cardiac death exhibited a J-shaped relationship with the Bazett QTc interval quartile [Q1, HR = 8.58 (1.07–69.05); Q3, HR = 7.17 (0.88–58.73); Q4, HR = 13.18 (1.72–101.03); HR are vs. Q2].
Conclusion: In the general Japanese population, cardiovascular and stroke mortality increase progressively with the Bazett QTc interval quartile, while the risk of sudden cardiac death exhibits a J-shaped relationship with the latter variable.

Introduction

A long QTc interval on an electrocardiogram (ECG) is associated with an increased risk of cardiovascular death [1–4] or sudden cardiac death [5,6]. Ventricular arrhythmia is one of the underlying factors responsible for these associations; however, the association between long QTc intervals and an increased risk of cardiovascular death might also be attributable to the fact that long QTc intervals are associated with cardiovascular risk factors [7] such as high blood pressure and left ventricular hypertrophy [8]. Among the general Japanese population, individuals are more likely to suffer a stroke than a cardiovascular event [9], and the relationships between QTc intervals and the risk of cardiovascular, stroke mortality, or sudden cardiac death could differ from those seen in Western countries. In addition, subjects with extremely short QTc intervals have also been demonstrated to be at increased risk of sudden cardiac death [10,11]; however, previous studies have obtained inconsistent findings regarding whether the associations between the QTc interval and the risk of cardiovascular or sudden cardiac death are J-shaped or linear [2,7,12–14].

The purpose of this study was to clarify whether individuals from the general Japanese population with long or short QTc intervals are at increased risk of cardiovascular, stroke, or sudden cardiac death.

Methods

Subjects

The Jichi Medical School (JMS) Cohort Study began in 1992 and aimed to clarify the risk factors for cardiovascular and cerebrovascular disease in the general Japanese population. The details of the

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http://dx.doi.org/10.1016/j.jjcc.2014.05.008
0914-5087/

protocol of the JMS Cohort Study have been reported elsewhere [15]. Baseline data were collected between April 1992 and July 1995 in 12 rural districts of Japan using a government-sponsored mass screening system. In each community, a local government office sent personal invitations to all of the eligible subjects by mail in accordance with the Health and Medical Service Law for the Aged. The individuals that participated in the mass screening examinations were aged 40–69 years in eight regions (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshima, and Akaike), aged ≥30 years in one area (Wara), and belonged to other age groups in three regions (Hokudan, Yamato, and Takasu). At the baseline, there were a total of 12,490 subjects (4911 males and 7579 females) in the JMS Cohort Study. The selection criteria applied to the subjects in the present study are shown in Fig. 1.

ECG measurements and interpretation

ECG was performed at a paper speed of 25 mm/s and a gain of 10 mm/mV (or 5 mm/mV) using the ECG devices at the participating institutions. Initially, a trained individual who was unaware of the subjects' background data manually measured the QT interval in lead II (or lead I or III if the QT interval could not be measured in lead II), which is the best lead for depicting T waves in 12-lead ECG, according to the reported protocol for the measurement of QTc intervals [16]. The ECG measurements were performed using a ruler with 0.01-mm graduations. The QTc interval for a single beat was measured from the beginning of the QRS complex to the end of the T wave. The end of the QT interval was taken as the last point of the T wave, i.e. where the downsloping limb joined the baseline, while we excluded U waves [17,18]. RR intervals were also measured, and the mean of three RR intervals was calculated. Heart rate-adjusted QT intervals (QTc) were calculated using the Bazett formula [19]: [$QTc = QT/(RR^{1/2})$]. The intraobserver reproducibility of the Bazett QTc interval measurements was confirmed by comparing the pairs of measurements obtained for 98 ECGs. The mean relative error of the QTc interval measurements was 0.5%, and their mean absolute intraobserver error was 2.0 ms (SD: 17.0 ms).

Short QTc intervals were defined as Bazett QTc intervals of <330 ms according to the expert consensus statement on the

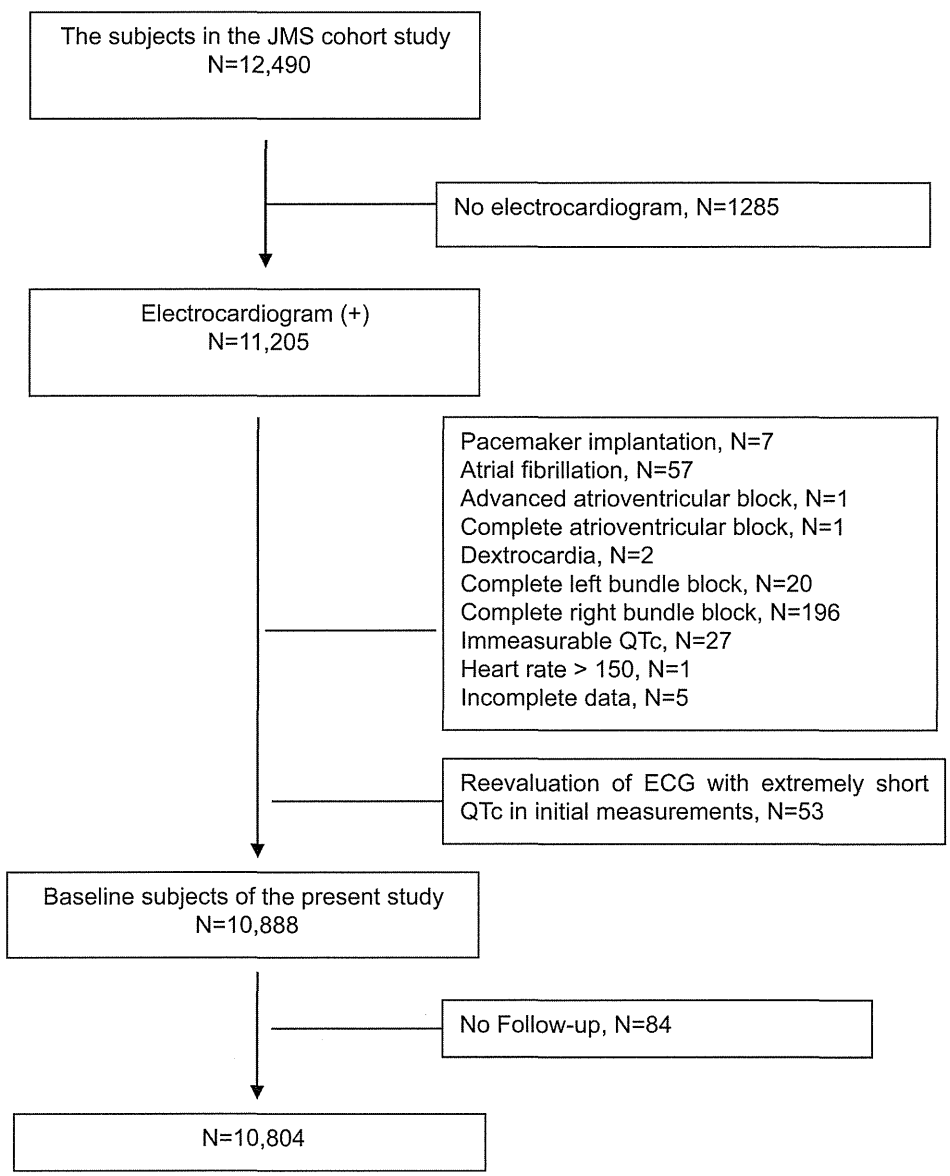

Fig. 1. Selection of subjects. ECG, electrocardiogram.

diagnosis and management of patients with inherited primary arrhythmia syndromes [20]. Prolonged QTc intervals were defined as Bazett QTc intervals of ≥440 ms in men and ≥460 ms in women.

Questionnaire and other measurements

Information about each subject's medical history and lifestyle was obtained at the baseline using a questionnaire. The questionnaire included questions about past or present illnesses, as well as any heart conditions suffered by the subjects' parents. Age was recorded at the baseline. Smoking status was classified as smoker, ex-smoker, or never smoked. Alcohol drinkers were defined as subjects who drank at least 20 g/alcohol per day. Systolic and diastolic blood pressure were measured at the baseline using a fully automated sphygmomanometer (BP203RV-II, Nippon Colin, Komaki, Japan). Blood pressure was measured once after the subjects had rested for at least 5 min in a sitting position. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or hypertension because of the presence of medication. Diabetes mellitus was defined as a fasting glucose level of >7.0 mmol/L (126 mg/dl), a random nonfasting glucose level of >11.1 mmol/L (200 mg/dl), or because of the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined as a total cholesterol level of >5.7 mmol/L (220 mg/dl), a triglyceride level of >1.7 mmol/L (150 mg/dl), or because of the use of an oral lipid-lowering agent according to the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Disease.

Informed consent

The internal review board at Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained from each individual who participated in the mass screening health check-up examinations at the baseline.

Follow-up

We used the mass screening examination system to check the subjects every year for 10 years. During these examinations, we asked the subjects directly whether they had suffered a stroke or cardiovascular disease after enrollment. If a subject did not undergo a scheduled annual screening examination, we contacted them or their family members by mail or telephone to confirm whether they had suffered any cardiovascular events or had died. In cases in which the subject had visited a medical institution due to a cardiovascular event or had died at a medical institution, doctors or health nurses associated with the JMS Cohort Study visited the institution and checked the subject's medical records. When an incident case was suspected, we filled out the relevant forms and obtained copies of brain computed tomography or magnetic resonance imaging scans (when a cerebrovascular event was suspected) and/or electrocardiograms (when myocardial infarction was suspected). In cases in which a subject died and their family could not be contacted during the follow-up period, death certificates were collected at the public health centers with the permission of the Agency of General Affairs and the Ministry of Health, Labour and Welfare. Data regarding residence changes during the study were obtained from each municipal government annually.

Diagnostic criteria

All diagnoses were determined independently by a diagnostic committee composed of radiologists, neurologists, and cardiologists. Questionnaire responses and copies of the subjects' medical records were used to assess whether myocardial infarction or stroke events had occurred. Detailed definitions of stroke and myocardial infarction events have been reported previously [9]. Sudden cardiac death was defined as a death that occurred within 24 h of symptom onset that did not have an identifiable cause. We could not confirm whether fatal arrhythmia had been responsible for any of the cases of sudden cardiac death. Causes of death were identified using death certificates, which were collected at the respective local public health centers with the permission of the Ministry of General Affairs and the Ministry of Health, Labour and Welfare. Death and events were diagnosed based on the consensus of all members of the diagnostic committee.

Statistical analysis

This study was a retrospective analysis of the ECG data obtained during the JMS Cohort Study. Data are shown as mean ± SD or percentage values. One-way analysis of variance was performed to evaluate the overall differences among the groups, and Tukey's honestly significant difference test was used for inter-group comparisons of mean values. The chi-square test was used to detect differences in percentage values among the groups. Mortality rates are shown as the number of deaths per 10,000 person-years. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality were calculated according to the QTc interval quartiles using Cox proportional hazards regression analysis. In the latter models, we adjusted for the following conventional cardiovascular risk factors: age, gender, body mass index, history of myocardial infarction, history of stroke, smoking status, alcohol intake of >20 g/day, systolic blood pressure, antihypertensive drug use, heart rate, the presence of hyperlipidemia, and the presence of diabetes. A probability <0.05 was considered statistically significant. The software SPSS (version 18.0, Chicago, IL, USA) was used for all analyses.

Results

Subjects

At the baseline, the mean age of the subjects was 55.5 ± 11.2 years, and 37.9% of the subjects were men. The subjects' Bazett QTc intervals ranged from 303 to 563 ms (mean QTc interval: 388 ± 27 ms). In the lowest, second, third, and highest Bazett QTc interval quartiles, the Bazett QTc interval was 303–370 (358) ms, 371–387 (median: 379) ms, 388–405 (395) ms, and 406–563 (418) ms, respectively. In addition, 3.6% of the subjects had Bazett QTc intervals of >440 ms.

Among the 6713 female subjects, 28 (0.4%) had Bazett QTc intervals of <330 ms and 78 (1.2%) had Bazett QTc intervals of ≥460 ms. Among the 4091 male subjects, 64 (1.6%) had Bazett QTc intervals of <330 ms, and 97 (2.4%) had Bazett QTc intervals of ≥440 ms.

Subjects' characteristics classified according to their Bazett QTc interval quartiles

The subjects' baseline characteristics have been classified according to their Bazett QTc interval quartiles in Table 1. Age, body mass index, and the prevalences of hypertension and hyperlipidemia increased progressively with the Bazett QTc interval quartile, while the frequency of male subjects and smokers decreased with the Bazett QTc interval quartile.

The risk of mortality according to the Bazett QTc interval quartile

During the mean follow-up period of 141.9 ± 28.3 months (127,712 person-years), there were a total of 878 deaths, including 92

Table 1
Subjects' characteristics according to the Bazett QTc interval quartile at the baseline (N = 10,804).

	Q1	Q2	Q3	Q4	p
Range of QTc interval, ms	≤370	371–378	388–405	≥406	
Number of subjects	2701	2702	2700	2701	
Age, years	53.1 ± 12.2	55.3 ± 11.0	56.3 ± 10.6	57.4 ± 10.4	<0.001
Male, %	53.4	40.6	30.8	26.8	<0.001
Body mass index, kg/m^2	22.9 ± 2.9	23.0 ± 3.0	23.2 ± 3.2	23.3 ± 3.3	<0.001
History of stroke, %	0.9	0.8	0.7	1.6	0.012
History of myocardial infarction, %	0.7	0.3	0.5	0.7	0.116
Smoking status					<0.001
Former, %	16.5	13.3	10.8	10.2	
Current, %	29.4	23.9	18.8	17.9	
Alcohol consumption >20 g/day, %	33.3	31.8	30.4	32.1	0.215
Hypertension, %	28.4	31.7	36.1	40.8	<0.001
SBP, mmHg	126.4 ± 20.3	128.2 ± 20.5	130.6 ± 21.1	132.7 ± 21.5	<0.001
DBP, mmHg	75.9 ± 12.2	76.6 ± 12.0	78.2 ± 12.2	79.2 ± 12.5	<0.001
Hyperlipidemia, %	33.4	34.2	37.6	38.1	<0.001
Total cholesterol, mg/dl	189 ± 34	192 ± 35	194 ± 35	195 ± 35	<0.001
Triglycerides, mg/dl	114 ± 76	116 ± 75	117 ± 71	123 ± 83	<0.001
Diabetes, %	3.3	3.9	3.9	4.4	0.227
Blood glucose, mg/dl	100 ± 23	103 ± 27	104 ± 27	105 ± 28	<0.001
Heart rate, beats/min	62 ± 9	65 ± 10	68 ± 10	72 ± 12	<0.001

Data are shown as mean ± SD or percentage values. QTc data are shown as ranges. Overall p values were calculated using an analysis of covariance test. Probability values of <0.05 were considered significant. SBP, systolic blood pressure; DBP, diastolic blood pressure.

due to cardiac events (including 46 sudden cardiac deaths), 12 due to vascular events, and 100 due to stroke. In addition, there were 674 deaths from other causes (i.e., cancer, infection, trauma, suicide, etc.). The total number of cardiovascular and stroke deaths increased according to the Bazett QTc interval quartile (Fig. 2). On the other hand, the relationship between the Bazett QTc interval quartile and the frequency of sudden cardiac death was J-shaped.

Even in the Cox proportional hazards regression model adjusted for conventional cardiovascular risk factors (Table 2), the risk of cardiovascular mortality increased progressively with the QTc interval quartile [Q2, HR = 0.94 (0.43–2.03); Q3, HR = 1.11 (0.53–2.34); Q4, HR = 2.21 (1.12–4.36); HR are vs. Q1]. In a parallel analysis, the risk of stroke mortality was found to be increased in the highest Bazett QTc interval quartile [HR = 1.93 (0.97–3.85)], but the increase was not statistically significant. The risk of sudden cardiac death exhibited a J-shaped relationship with the Bazett QTc interval [Q1, HR = 8.58 (1.07–69.05); Q3, HR = 7.17 (0.88–58.73); Q4, HR = 13.18 (1.72–101.03); HR are vs. Q2].

Even when we entered the presence of the ST–T strain pattern into the model, the results were not changed.

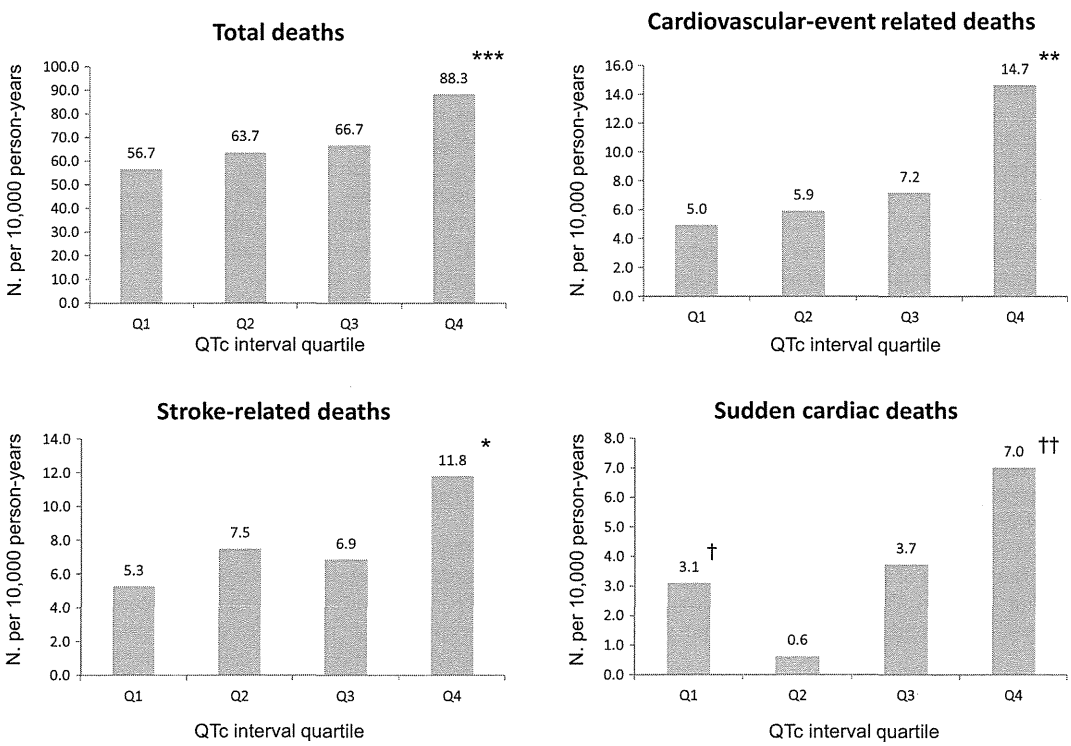

Fig. 2. Total, cardiovascular, stroke, and sudden cardiac deaths according to QTc interval quartile (Q). Data are shown as the number of deaths per 10,000 person-years. The p values were calculated using an unadjusted Cox proportional hazards model. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. the subjects in the lowest QTc interval quartile; †$p < 0.05$; ††$p < 0.01$ vs. the subjects in the second QTc interval quartile.

Table 2
Cox proportional hazards regression analyses of mortality according to the QTc interval quartile.

QTc interval quartile	HR	95% CI		p
Total mortality (N=878)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.05	0.83	1.31	0.694
Q3, 388–405 ms	1.11	0.89	1.40	0.352
Q4, ≥406 ms	1.29	1.02	1.62	0.030
Combined cardiovascular and stroke mortality (N=204)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.18	0.71	1.96	0.533
Q3, 388–405 ms	1.05	0.61	1.78	0.871
Q4, ≥406 ms	2.07	1.28	3.36	0.003
Cardiovascular mortality (N=104)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	0.94	0.43	2.03	0.871
Q3, 388–405 ms	1.11	0.53	2.34	0.782
Q4, ≥406 ms	2.21	1.12	4.36	0.023
Stroke mortality (N=100)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.39	0.70	2.78	0.345
Q3, 388–405 ms	0.97	0.46	2.08	0.947
Q4, ≥406 ms	1.93	0.97	3.85	0.062
Sudden cardiac death (N=46)				
Q1, ≤370 ms	8.58	1.07	69.05	0.043
Q2, 371–387 ms	Reference			
Q3, 388–405 ms	7.17	0.88	58.73	0.066
Q4, ≥406 ms	13.18	1.72	101.03	0.013

Data are shown as hazard ratios (95% confidence intervals). The hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards model adjusted for age, gender, body mass index, history of stroke, history of myocardial infarction, alcohol consumption of >20 g/day, smoking status, systolic blood pressure, antihypertensive drug use, heart rate, diabetic status, and the presence of hyperlipidemia. HR, hazard ratio; CI, confidence interval; Q, quartile.

The risk of mortality in subjects with short or prolonged QTc intervals

Of the subjects with extremely short QTc intervals (<330 ms), none died from cardiovascular, stroke, or sudden cardiac death during the follow-up period. Data regarding the risk of mortality associated with a prolonged QTc interval (≥440 ms in men and ≥460 ms in women) are shown in Table 3. The risk of cardiovascular mortality was increased in both the male and female subjects with prolonged QTc intervals. However, the increase in the risk of sudden cardiac death detected in the subjects with prolonged QTc intervals did not reach statistical significance.

Table 3
The mortality risks of subjects with prolonged QTc interval in male and female subjects.

	Males (QTc interval ≥440 ms)				Females (QTc interval ≥460 ms)			
	HR	LCI	UCI	p	HR	LCI	UCI	p
Total mortality								
Unadjusted	2.05	1.29	3.24	0.002	2.77	1.37	5.59	0.005
Adjusted	1.28	0.79	2.08	0.313	1.58	0.77	3.24	0.214
Cardiovascular and stroke mortality								
Unadjusted	3.86	1.78	8.36	0.001	5.32	1.94	14.59	0.001
Adjusted	2.23	0.98	5.10	0.056	3.35	1.17	9.58	0.024
Cardiovascular mortality								
Unadjusted	5.37	2.12	13.63	<0.001	5.82	1.39	24.27	0.016
Adjusted	2.75	1.02	7.45	0.046	4.65	1.07	20.22	0.041
Stroke-related mortality								
Unadjusted	2.26	0.55	9.38	0.261	4.91	1.18	20.36	0.028
Adjusted	1.62	0.36	7.25	0.525	2.72	0.61	12.16	0.189
Sudden cardiac death								
Unadjusted	3.30	0.71	15.44	0.129	8.49	1.10	65.81	0.041
Adjusted	1.45	0.30	7.01	0.647	7.60	0.90	64.39	0.063

Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated using Cox hazard model. In the adjusted model, we also entered age, gender, body mass index, history of stroke, history of myocardial infarction, alcohol drinking >20 g/day, smoking status, systolic blood pressure, antihypertensive drug use, heart rate, diabetic status, and presence of hyperlipidemia. LCI, lower confidence interval; UCI, upper confidence interval.

Discussion

In this study, the QTc interval was found to be associated with cardiovascular risk factors, and the risk of cardiovascular mortality increased with the Bazett QTc interval quartile. On the other hand, a J-shaped relationship was detected between the Bazett QTc interval quartile and the risk of sudden cardiac death. When we evaluated the risk of mortality using QTc interval cut-off levels, a prolonged QTc interval was found to be associated with cardiovascular mortality; however, none of the subjects with extremely short QTc intervals of <330 ms suffered sudden cardiac death.

The Rotterdam study [2] reported that a J-shaped relationship exists between the Bazett QTc interval quartile and the risk of cardiovascular mortality (regardless of the formula used to calculate the QTc interval). Moreover, the Third National Health and Nutrition Examination Survey found that shortened and prolonged QT intervals, even those within the reference range, are associated with an increased risk of mortality in the general population [14]. However, our data only support the findings of these previous reports regarding the relationship between the QTc interval and the risk of sudden cardiac death.

In the present study, a J-shaped association was detected between the Bazett QTc interval quartile and the risk of sudden cardiac death in the general Japanese population. It is well established that long QT syndrome is associated with sudden cardiac death attributable to ventricular arrhythmia and that a long QTc interval constitutes a risk factor for sudden cardiac death in the general population. For example, Algra et al. [18] reported that a long QTc interval (>440 ms) was associated with an increased risk of sudden cardiac death, and Straus et al. [6] agreed; although they defined long QTc intervals differently (males: >451 ms; females: >471 ms). In the Framingham study [13], a trend toward an increased risk of sudden cardiac death was detected in the subjects with the shortest QTc intervals (<360 ms) in comparison with those in the second QTc interval quartile. However, when we performed an analysis using the lowest Bazett QTc interval quartile, we found that the increase in the risk of sudden cardiac death observed in the highest Bazett QTc interval quartile was insignificant (data not shown).

There have been reports of familial cases of short QTc interval-associated sudden cardiac death (ventricular arrhythmia) [10,21]; however, some epidemiological studies have found that a short QTc interval is not associated with sudden cardiac death in the general population [12,22]. On the other hand, in the Framingham study [13], the subjects with short QTc intervals (<360 ms) were found to be more likely to suffer sudden cardiac death, and the findings we obtained using a QTc interval cut-off value of <370 ms support these results. In the JMS Cohort Study, there were a total of 46 sudden cardiac deaths, but there were only 10 sudden cardiac deaths among the subjects in the lowest QTc interval quartile (≤370 ms) during a mean follow-up period of 141.9 ± 28.3 months (127,712 person-years). Previous reports of familial cases of short QTc intervals [10,21] defined QTc intervals of <300 ms as short QTc intervals, but there were no subjects with QTc intervals of <300 ms in this study. When we used a cut-off level of <330 ms as a definition of short QTc intervals [20], we found that none of the subjects with such short QTc intervals suffered sudden cardiac death during the follow-up period. When we used the Fridericia or Framingham formula to calculate QTc intervals, the increase in the risk of sudden cardiac death observed in the subjects in the shortest QTc interval quartile

became insignificant (data not shown). Moreover, the risk of sudden cardiac death associated with a shorter QTc interval did not significantly increase at any cut-off level in the general population.

A prolonged QTc interval was reported to be associated with increased arterial stiffness [23] and left ventricular hypertrophy [8]. In other reports [24,25], a prolonged QTc interval was found to be associated with an increased risk of stroke events, suggesting that the association between the risk of cardiovascular mortality and the QTc interval can not only be derived from the risk of ventricular arrhythmia, but must also be affected by the associations between the QTc interval and cardiovascular risk factors. In this study, the relationship between the QTc interval and stroke mortality disappeared after we adjusted for conventional cardiovascular risk factors.

The current study had the following limitations: (1) We measured the QT interval manually in lead II (or lead I or III if it was difficult to measure in lead II), and the mean QTc interval was about 20 ms shorter than the value obtained in a previous report involving 12,149 Japanese patients who were referred to a university hospital [26]. Moriya et al. [27] studied 19,153 subjects who were exposed to the atomic bombs dropped on Nagasaki and Hiroshima and found that only two subjects had QTc intervals of <350 ms, while about 6.9% of subjects ($N = 741$) exhibited QTc intervals of <350 ms in the JMS Cohort Study, in which we enrolled subjects from rural districts across Japan. In addition, the incidence of fatal cardiovascular and stroke events in the present study was much lower than those described in previous reports involving other general Japanese populations [9], suggesting that the subjects in the JMS Cohort Study had relatively few cardiovascular risk factors, which might explain why the mean QTc interval of the subjects of the JMS Cohort Study was shorter than those obtained in previous studies involving general Japanese populations. (2) The QTc interval can also be affected by drug use and electrolyte levels; however, these factors were not evaluated in this study. (3) We should have measured the RR interval between the beat for which the QT interval was calculated and the previous beat, whereas we actually calculated the mean of three RR intervals in this study. (4) We were unable to confirm whether fatal arrhythmia had been responsible for any of the cases of sudden cardiac death. (5) We enrolled the subjects during annual health examinations. Therefore, a greater number of female than male subjects participated in this study. In addition, the QTc interval was found to have a more significant effect on mortality risk in women, which was probably attributable to the larger number of female subjects enrolled.

Conclusion

The QTc interval is associated with cardiovascular risk factors in the general Japanese population. Among the general Japanese population examined in this study, the risk of cardiovascular and stroke mortality increased progressively with the Bazett QTc interval quartile, while a J-shaped relationship was observed for the effect of the latter parameter on the risk of sudden cardiac death.

Acknowledgments

This study was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan and grants from the Foundation for the Development of the Community, Tochigi, Japan.

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Prolonged Corrected QT Interval Is Predictive of Future Stroke Events Even in Subjects Without ECG-Diagnosed Left Ventricular Hypertrophy

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Abstract—We attempted to evaluate whether subjects who exhibit prolonged corrected QT (QTc) interval (≥440 ms in men and ≥460 ms in women) on ECG, with and without ECG-diagnosed left ventricular hypertrophy (ECG-LVH; Cornell product, ≥244 mV×ms), are at increased risk of stroke. Among the 10643 subjects, there were a total of 375 stroke events during the follow-up period (128.7±28.1 months; 114142 person-years). The subjects with prolonged QTc interval (hazard ratio, 2.13; 95% confidence interval, 1.22–3.73) had an increased risk of stroke even after adjustment for ECG-LVH (hazard ratio, 1.71; 95% confidence interval, 1.22–2.40). When we stratified the subjects into those with neither a prolonged QTc interval nor ECG-LVH, those with a prolonged QTc interval but without ECG-LVH, and those with ECG-LVH, multivariate-adjusted Cox proportional hazards analysis demonstrated that the subjects with prolonged QTc intervals but not ECG-LVH (1.2% of all subjects; incidence, 10.7%; hazard ratio, 2.70, 95% confidence interval, 1.48–4.94) and those with ECG-LVH (incidence, 7.9%; hazard ratio, 1.83; 95% confidence interval, 1.31–2.57) had an increased risk of stroke events, compared with those with neither a prolonged QTc interval nor ECG-LVH. In conclusion, prolonged QTc interval was associated with stroke risk even among patients without ECG-LVH in the general population. **(*Hypertension*. 2015;65:554-560. DOI: 10.1161/HYPERTENSIONAHA.114.04722.) • Online Data Supplement**

Key Words: electrocardiography ■ epidemiology ■ hypertrophy, left ventricular ■ stroke

The detection of a prolonged corrected QT (QTc) interval on an ECG has been reported to be a risk factor for cardiovascular mortality, which could be attributable to an increased risk of fatal arrhythmia. However, subjects with prolonged QTc intervals are often older and commonly exhibit higher blood pressure and left ventricular hypertrophy (LVH); thus, a prolonged QTc interval could be a marker of cardiovascular risk factor accumulation. Therefore, some studies have suggested that prolonged QTc intervals are associated with an increased risk of future stroke events.[1–3]

Individuals with prolonged QTc intervals often have LVH. The detection of LVH on ECG (ECG-LVH) is a strong risk marker for future stroke events, independently of blood pressure.[4] However, it is not known whether the association between prolonged QTc intervals and the risk of stroke is derived from the associations with LVH.

The purpose of this study was to evaluate whether a prolonged QTc interval is a marker of future stroke events among subjects with or without ECG-LVH and to compare the effects of prolonged QTc intervals and ECG-LVH on the risk of such events.

Methods

Subjects

The Jichi Medical School Cohort Study began in 1992 and aimed to clarify the risk factors for cardiovascular and cerebrovascular diseases in the Japanese general population. The details of the protocol of the Jichi Medical School Cohort Study have been reported elsewhere.[5] Baseline data were collected between April 1992 and July 1995 in 12 rural districts using a government-sponsored mass screening system. In each community, a local government office sent personal invitations to all potential subjects by mail in accordance with the Health and Medical Service Law for the Aged. The individuals who participated in the mass screening examinations were aged 40 to 69 years in 8 areas (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshima, and Akaike), were aged ≥30 years in 1 area (Wara), and belonged to other age groups in 3 areas (Hokudan, Yamato, and Takasu). At the baseline, the total number of subjects enrolled in the Jichi Medical School Cohort Study was 12490 (4911 men and 7579 women). We initially excluded potential subjects for the following reasons: no ECG (n=1285), pacemaker implantation (n=7), atrial fibrillation (n=57), advanced atrioventricular block (n=1), complete atrioventricular block (n=1), dextrocardia (n=2), complete left bundle block (n=20), complete right bundle block (n=196), immeasurable QTc (n=27), heart rate of >150 bpm (n=1), incomplete data (n=5), or no follow-up data (n=84).[6] In addition, we excluded subjects without

Received October 8, 2014; first decision October 26, 2014; revision accepted December 1, 2014.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.114.04722/-/DC1.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.114.04722**

data of Cornell product (n=7), with a history of stroke (n=104), or with myocardial infarction (n=50). Therefore, the number of subjects analyzed in this study was 10643.

ECG Measurement and Interpretation

The ECG was performed at a paper speed of 25 mm/s and a gain of 10 mm/mV (or 5 mm/mV), using the ECG devices at each institution. Initially, a trained individual who was unaware of the subjects' background data measured the QT interval manually from lead II (or lead I or III if the QT interval could not be measured from lead II), which is the best lead for depicting the end of the T wave on a 12-lead ECG, according to a previously described method for measuring the QTc interval.[7] The ECG measurements were performed using a ruler with 0.01-mm graduations. The QTc interval for a single beat was measured from the beginning of the QRS complex to the end of the T wave. The end of the QT interval was taken as the last point of the T wave over leads I, II, and III, ie, where the downsloping limb joined the baseline, while we excluded U waves.[8,9] RR intervals were also measured, and the mean of 3 RR intervals was calculated. Heart rate-adjusted QT intervals (QTc) were calculated using the Bazett[10] formula: ($QTc=QT/[RR^{1/2}]$). The intraobserver reproducibility of the Bazett QTc interval data was confirmed by comparing pairs of measurements for 98 ECGs. The mean relative error of the QTc interval data was 0.5%, and the mean intraobserver absolute error of the QTc interval data was 2.0 ms (SD, 17.0 ms).

A Cornell product of ≥244 mV×ms was used to diagnose ECG-LVH according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (2009)[11] and the Losartan Intervention For End point (LIFE) Reduction in Hypertension Study.[12] A prolonged QTc interval was defined as a Bazett QTc interval of ≥440 ms in men and ≥460 ms in women according to the method described in a previous report.[6]

Questionnaire and Other Measurements

Details of Questionnaire and Other Measurements are provided in the online-only Data Supplement.

Informed Consent

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained from each individual who participated in the mass screening health check-up examinations at the baseline.

Follow-Up and Diagnostic Criteria

Details of Follow-Up and Diagnostic Criteria are provided in the online-only Data Supplement.

Statistical Analysis

Data are shown as mean±SD or percentage values. The nonpaired *t* test was performed to evaluate the difference in continuous variables between the subjects with and without prolonged QTc intervals. The χ^2 test was used to detect differences in the frequencies of characteristics between the groups. Improvement of the predictive value of QTc intervals in addition to the traditional cardiovascular risk factors for stroke events was evaluated using net reclassification improvement (NRI) and integrated discrimination improvement.[13] One-way ANOVA was performed to evaluate the overall differences among the subjects with neither prolonged QTc intervals nor ECG-LVH, those with prolonged QTc intervals but not ECG-LVH, and those with ECG-LVH; the Tukey honestly significant difference test was used for comparisons of mean values among the groups. Survival curves among the 3 groups were estimated using the Kaplan–Meier method. Adjusted hazard ratios and 95% confidence intervals for stroke events were calculated using Cox proportional hazards regression analysis adjusted for the following conventional cardiovascular risk factors: age, sex, body mass index, current smoking, alcohol intake of >20 g/d, systolic blood pressure, antihypertensive drug use, heart rate, the presence of hyperlipidemia, and the presence of diabetes mellitus. *P* values of <0.05 were considered to be statistically significant. The statistical software SPSS (version 18.0; Chicago, IL) was used for all analyses.

Table 1. Characteristics of the Subjects With and Without Prolonged QTc Interval Shown Separately in Men and Women

		QTc Interval ≥440 ms in Men			QTc Interval ≥460 ms in Women		
Variables	Total Subjects, n=10643	No, n=3918	Yes, n=89	*P* Value	No, n=6563	Yes, n=73	*P* Value
Age, y	55.4±11.2	55.1±11.6	61.6±8.4	<0.001	55.5±10.9	58.6±9.2	0.006
Men, %	37.6	...	...	...	...	...	...
Body mass index, kg/m^2	23.1±3.1	23.0±2.9	22.7±3.2	0.333	23.2±3.2	23.1±3.0	0.71
Current smokers, %	22.6	50.1	48.9	0.824	5.7	4.2	0.591
Alcohol drinking, >20 g/d, %	31.9	31.6	31.7	0.979	32.2	28.8	0.584
Hypertension, %	33.9	36.2	51.7	0.003	32.1	43.8	0.033
Antihypertensive medication use, %	11.1	9.4	8.1	0.687	12.0	18.6	0.095
Systolic blood pressure, mm Hg	129.4±21.0	131.3±20.4	140.3±26.8	0.003	128.0±21.0	138.2±23.4	<0.001
Diastolic blood pressure, mm Hg	77.5±12.3	79.2±12.2	83.1±13.5	0.004	76.3±12.1	81.7±15.4	0.004
Hyperlipidemia, %	35.6	35.3	34.1	0.822	36.2	34.7	0.789
Total cholesterol, mg/dL	192.6±35.0	185.1±33.8	183.6±38.5	0.687	197.2±34.8	196.4±33.5	0.842
Triglyceride, mg/dL	117.3±76.4	128.7±87.6	135.2±102.9	0.494	110.3±67.7	114.8±59.1	0.537
Diabetes mellitus, %	3.6	5.5	4.8	0.757	2.8	1.4	0.505
Blood glucose, mg/dL	103.1±26.4	106.6±31.5	107.1±31.9	0.878	100.9±22.3	107.4±30.9	0.083
Cornell product, mV×ms	150.7±58.2	137.9±61.3	180.9±90.2	<0.001	157.5±53.7	191.3±85.1	0.001
Sokolow–Lyon voltage, mV	2.7±0.8	2.9±0.9	3.4±1.1	<0.001	2.5±0.8	2.8±1.0	0.012
Bazett QTc, ms	388±27	379±24	462±24	<0.001	391±24	481±23	<0.001
Heart rate, bpm	67.0±10.8	64.7±10.8	79.9±15.6	<0.001	68.0±10.3	79.3±14.6	<0.001

Data are shown as mean±SD or percentage. *P* values were calculated using nonpaired *t* test or χ^2 test. QTc indicates corrected QT.

Results

Subjects

The characteristics of the study subjects are shown in Table 1. At the baseline, the subjects' mean age was 55.4±11.2 years, and 37.6% of the subjects were men. The mean Bazett QTc interval was 388±27 ms.

QTc Interval as a Risk Marker of Stroke Events

During the mean follow-up period of 128.7±28.1 months (114 142 person-years), there were a total of 375 stroke events (85 cerebral hemorrhages, 242 ischemic strokes, 47 subarachnoid hemorrhages, and 1 stroke event of unknown cause).

The Stroke Risk in Subjects With Prolonged QTc Intervals (≥440 ms in Men and ≥460 ms in Women)

Characteristics of subjects with and without prolonged QTc intervals (≥440 ms in men and ≥460 ms in women) are shown separately in men and women (Table 1). The subjects with prolonged QTc interval were older and had higher percentage of hypertension and greater blood pressure level than those without prolonged QTc interval in both men and women.

In the analysis, combining men and women together, there were 354 stroke events (3.4%; 31.5 events per 10 000 person-years) in subjects without prolonged QTc intervals (n=10 481) and there were 16 stoke events (9.9%; 99.6 events per 10 000 person-years) in those with prolonged QTc intervals (n=162). The subjects with prolonged QTc intervals had a 2.13 times higher risk of stroke events than those without prolonged QTc intervals even after adjustment for the traditional risk factors and ECG-LVH (assessed as a Cornell product of >244 mV×ms; Table 2). The interaction between prolonged QTc interval and ECG-LVH was statistically insignificant (P=0.171) in the multivariate-adjusted Cox regression model. The multivariate-adjusted hazard risks stratified by the patients' characteristics are shown in Figure 1. The stroke risk associated with prolonged QTc intervals was significant in subjects of older age and male sex and with hypertension and hyperlipidemia and in those without diabetes mellitus, obesity, or ECG-LVH.

NRI by Adding QTc Interval Into the Traditional Cardiovascular Risk Factors

The NRI for predictive values of stroke events was insignificant when the prolonged QTc interval (as a categorical variable) was included in the model in addition to the traditional risk factors (data not shown). The NRI of predictive values was significant when the QTc interval as a continuous variable was included in the model in addition to the traditional cardiovascular risk factors. The NRI was also significant when ECG-LVH alone was added and also when both the QTc interval and ECG-LVH were added to the traditional cardiovascular risk factors (Tables S1–S3 in the online-only Data Supplement). Moreover, NRI was significantly increased after adding the QTc interval (as a continuous variable) to the traditional cardiovascular risk factors that included ECG-LVH (NRI=0.014; P<0.001; Table 3).

Table 2. The Stroke Event Risk of the Subjects With Prolonged QTc Interval

Models	HR	95% CI		*P* Value
Total stroke events, n=375				
Model 1; unadjusted				
Prolonged QTc interval (≥440 ms in men and ≥460 ms in women)	3.42	2.00	5.86	<0.001
Model 2; adjusted for conventional risk factors				
Prolonged QTc interval	2.31	1.32	4.04	0.003
Model 3; adjusted for ECG-LVH in addition to model 2				
Prolonged QTc interval	2.13	1.22	3.73	0.008
Cornell product ≥ 244 mV×ms	1.71	1.22	2.40	0.002
Cerebral hemorrhage, n=85				
Model 1; unadjusted				
Prolonged QTc interval (≥440 ms in men and ≥460 ms in women)	3.37	1.06	10.75	0.040
Model 2; adjusted for conventional risk factors				
Prolonged QTc interval	2.75	0.83	9.07	0.098
Model 3; adjusted for ECG-LVH in addition to model 2				
Prolonged QTc interval	2.54	0.76	8.44	0.128
Cornell product ≥ 244 mV×ms	1.70	0.82	3.50	0.153
Ischemic stroke, n=242				
Model 1; unadjusted				
Prolonged QTc interval (≥440 ms in men and ≥460 ms in women)	3.85	2.04	7.28	<0.001
Model 2; adjusted for conventional risk factors				
Prolonged QTc interval	2.41	1.24	4.72	0.010
Model 3; adjusted for ECG-LVH in addition to model 2				
Prolonged QTc interval	2.27	1.16	4.44	0.017
Cornell product ≥ 244 mV×ms	1.54	0.99	2.38	0.054
Subarachnoid hemorrhage, n=47				
Model 1; unadjusted				
Prolonged QTc interval (≥440 ms in men and ≥460 ms in women)	1.70	0.23	12.37	0.600
Model 2; adjusted for conventional risk factors				
Prolonged QTc interval	1.29	0.17	9.62	0.806
Model 3; adjusted for ECG-LVH in addition to model 2				
Prolonged QTc interval	1.12	0.15	8.43	0.912
Cornell product ≥ 244 mV×ms	2.33	1.01	5.41	0.049

Data are shown as the values that compared with those in the subjects with below the thresholds of QTc interval or Cornell product in Cox regression analyses. Age, sex, body mass index, current smoking, alcohol drinking habit >20 g/d, systolic blood pressure, antihypertensive medication use, presence of diabetes mellitus, presence of hyperlipidemia, and heart rate were entered as conventional risk factors. For total stroke events, *P* values for interaction between the prolonged QTc interval and Cornell product ≥ 244 mV×ms was 0.171 in the multivariate-adjusted model. CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy; and QTc, corrected QT.

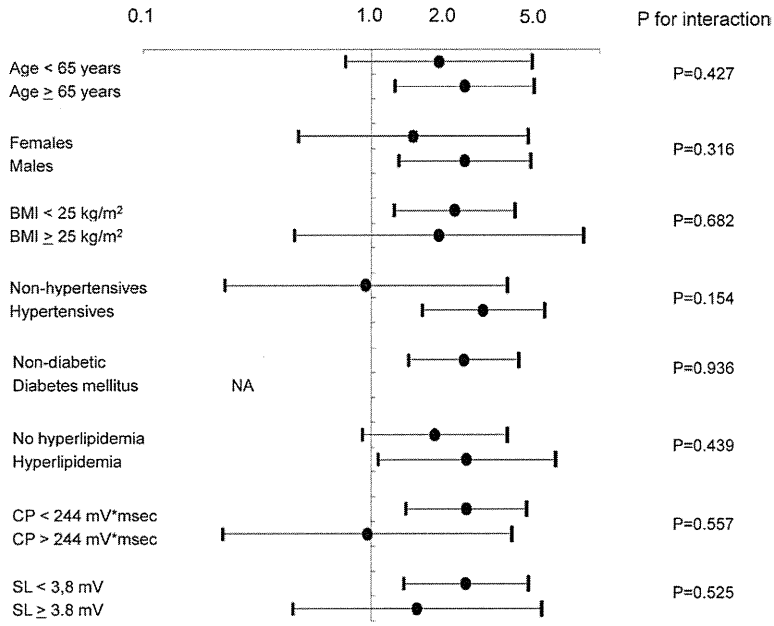

Figure 1. Multivariate-adjusted hazard ratios (HRs) stratified by the characteristics of subjects for stroke events. HRs and 95% confidence intervals were calculated using Cox proportional hazards analysis after adjusting for age, sex, body mass index (BMI), smoking status, alcohol drinking habits, systolic blood pressure, antihypertensive medication use, the presence of diabetes mellitus, the presence of hyperlipidemia, and heart rate. *P* values for interaction between the subgroups and prolonged corrected QT intervals were also computed. CP indicates Cornell product; NA, not applicable; and SL, Sokolow–Lyon voltage.

Characteristics of the Subjects With Prolonged QTc Intervals but Not ECG-LVH

As the number of subjects with both prolonged QTc intervals and ECG-LVH was too small to allow a statistical analysis to be performed, we stratified the subjects into the following 3 groups: (1) those with neither prolonged QTc intervals nor ECG-LVH, (2) those with prolonged QTc intervals but not ECG-LVH, and (3) those with ECG-LVH. The characteristics of the subjects in each group are shown in Table 4. In total, 1.2% of the subjects had prolonged QTc intervals without ECG-LVH. The subjects with prolonged QTc intervals but not ECG-LVH were older, had higher percentage of men among them, and had higher blood pressure and heart rates than those with neither prolonged QTc intervals nor ECG-LVH. There were no significant differences in age and blood pressure level between the subjects with prolonged QTc intervals but not ECG-LVH and those with ECG-LVH. The propensity stroke risk score matched for traditional cardiovascular risk factors was significantly greater in subjects with prolonged QTc intervals but not ECG-LVH and in the subjects with ECG-LVH than that in the subjects with neither prolonged QTc intervals nor ECG-LVH (both $P<0.001$); however, it was insignificant between the subjects with prolonged QTc intervals but not ECG-LVH and the subjects with ECG-LVH ($P=0.089$).

Incidence of Stroke Events in the Subjects With Prolonged QTc Intervals Without ECG-LVH

The cumulative incidence of stroke events during the follow-up period is shown in Figure 2. The subjects with prolonged QTc intervals but not ECG-LVH exhibited a greater incidence of stroke events than those who exhibited ECH-LVH and those who exhibited neither prolonged QTc intervals nor ECG-LVH. Even after adjusting for traditional cardiovascular risk factors, the subjects with prolonged QTc intervals but not ECG-LVH were found to be at increased risk of stroke events in comparison with the subjects who exhibited neither prolonged QTc intervals nor ECG-LVH (Table 5). The hazard risks for stroke events of prolonged QTc interval but not ECG-LVH were greater than the hazard risks of ECG-LVH for cerebral hemorrhage and ischemic stroke but not for subarachnoid hemorrhage.

Discussion

A prolonged QTc interval was found to be associated with an increased risk of future stroke events even among Japanese

Table 3. Net Reclassification Improvement in the Model-Included ECG-LVH With and Without QTc Interval

Model Without QTc Interval	Model With QTc Interval			
Frequency Percentage	<2.5%	2.5–5.0%	>5.0%	Total
Stroke event				
<2.5%	40	3	0	43
	(87.0%)	(5.5%)	(0.0%)	
2.5–5.0%	6	46	11	63
	(13.0%)	(83.6%)	(5.6%)	
>5.0%	0	6	185	191
	(0.0%)	(10.9%)	(94.4%)	
Total	46	55	196	297
No stroke event				
<2.5%	4451	153	1	4605
	(95.8%)	(8.8%)	(0.1%)	
2.5–5.0%	194	1397	165	1756
	(4.2%)	(80.5%)	(9.3%)	
>5.0%	0	185	1610	1795
	(0.0%)	(10.7%)	(90.7%)	
Total	4645	1735	1776	8156

Categorical net reclassification improvement=0.014, $P<0.001$. Integrated discrimination improvement=0.002, $P=0.88$. In the model, we included age, sex, body mass index, current smoking, alcohol intake >20 g/d, systolic blood pressure, antihypertensive medication use, diabetes mellitus, hyperlipidemia, heart rate, and ECG-LVH. LVH, left ventricular hypertrophy; and QTc, corrected QT.