Original Article

Arterial Stiffness and QT Interval Prolongation in a General Population: The Hisayama Study

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Few population studies have addressed the association of QT interval prolongation with clinical or subclinical arterial disease. The primary objective here was to examine the relationship between the pulse wave velocity (PWV) and the heart rate–corrected QT interval duration (QTc). This is a cross-sectional study, based on a survey of a general population of Japanese. We examined 2,666 community-dwelling individuals without history of cardiovascular disease, aged 40 or over. The PWV was measured between the brachial and ankle regions (baPWV). QTc was estimated using Bazett's equation. The age-adjusted mean values of QTc increased progressively with rising baPWV levels for either sex: for men, 397, 401, 403, and 406 ms for quartile groups defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s, respectively ($p<0.0001$ for trend); for women, 406, 410, 414, and 417 ms for quartile groups defined by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s, respectively ($p<0.0001$ for trend). When male and female subjects were combined, this positive relationship between baPWV and QTc remained significant, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium, alcohol intake, and smoking habits ($p<0.0001$ for trend). In conclusion, baPWV is independently associated with QT interval prolongation. (*Hypertens Res* 2008; 31: 1339–1345)

Key Words: **pulse wave velocity, QT interval duration, epidemiology**

Introduction

The QT interval duration on an ECG represents the duration of ventricular depolarization and repolarization (*1*, *2*). It has been suggested that disturbance of cardiac ion channels (*1*, *2*), decreased autonomic tone (*3*), and myocardial ischemia/infarction (*4*) extend the QT interval duration, but the etiology of the acquired form of QT interval prolongation has not been clearly defined. Recently, several epidemiological studies have shown that QT interval prolongation predicts the risks of clinical arterial disease (*5–9*) as well as sudden cardiac death (*5*). Likewise, a few cross-sectional studies have suggested a positive association between QT interval prolongation and subclinical arterial disease, such as carotid intima media thickness (*10–12*). However, there is significant uncertainty about the association between QT interval prolongation and other forms of subclinical arterial disease.

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Table 1. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,089 Men

Variables	Brachial-ankle pulse wave velocity (cm/s)				*p* for trend
	963–1,369 (*n*=270)	1,370–1,560 (*n*=273)	1,561–1,840 (*n*=276)	1,841–3,690 (*n*=270)	
Age (years)	51.4±8.4	55.6±9.6	60.2±9.7	68.9±8.9	<0.0001
Heart rate (bpm)	60.1±9.9	63.4±9.9	65.2±10.0	70.4±9.9	<0.0001
Systolic blood pressure (mmHg)	116.4±16.4	126.9±14.9	138.9±15.0	151.2±16.4	<0.0001
Diastolic blood pressure (mmHg)	71.1±9.9	78.6±9.9	84.6±10.0	91.2±9.9	<0.0001
Hypertension (%)	11.8	29.4	60.8	89.5	<0.0001
Antihypertensive drugs (%)	5.1	13.6	22.2	21.2	<0.0001
β-Blocker (%)	2.3	2.8	5.7	3.5	0.15
Calcium channel blocker (%)	4.3	9.3	20.7	16.5	<0.0001
ACE inhibitor (%)	0.9	2.8	5.0	5.1	0.0014
ARB (%)	1.8	5.6	3.0	4.1	0.65
ECG abnormalities (%)	11.5	14.5	17.4	18.9	0.001
Total cholesterol (mmol/L)	5.0±0.9	5.0±0.9	5.1±0.9	5.1±0.9	0.23
HDL cholesterol (mmol/L)	1.5±0.4	1.5±0.4	1.4±0.4	1.5±0.4	0.46
LDL cholesterol (mmol/L)	3.1±0.9	3.1±0.8	3.0±0.8	3.0±0.9	0.25
Triglyceride (mmol/L)	1.3±1.4	1.5±1.3	1.9±1.3	1.9±1.5	<0.0001
Dyslipidemia (%)	46.6	50.5	55.4	59.8	0.002
Fasting plasma glucose (mmol/L)	5.8±1.5	6.1±1.4	6.3±1.3	6.7±1.5	<0.0001
HbA1c (%)	4.9±0.8	5.0±0.8	5.1±0.8	5.3±1.0	<0.0001
Diabetes (%)	12.6	15.0	20.5	43.7	<0.0001
BMI	23.0±3.3	23.4±3.3	23.8±3.3	23.8±3.3	0.01
Obesity (%)	30.2	29.5	32.0	53.2	0.09
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.10
Serum potassium (mmol/L)	4.4±0.3	4.4±0.3	4.3±0.3	4.3±0.3	0.08
Alcohol intake (%)	65.7	65.1	74.2	75.5	0.0006
Habitual smoking (%)	55.7	45.1	45.1	37.3	0.04

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Aortic pulse wave velocity (PWV) is an established marker for subclinical arterial disease (*13, 14*) as well as for arterial stiffness (*15*). Brachial-ankle PWV (baPWV) has also been shown to be closely associated with aortic PWV and to be an excellent functional marker for subclinical arterial disease (*16*).

The present cross-sectional study evaluates the association of baPWV with heart rate–corrected QT interval duration (QTc) in a general population of Japanese.

Methods

Study Population

The Hisayama Study is an ongoing population-based epidemiological study designed to investigate the morbidity and mortality of cardiovascular disease and its risk factors in the town of Hisayama, Japan. The design of the Hisayama Study has been described in detail elsewhere (*17*). The present cross-sectional study was based on a screening survey conducted in 2002 and 2003. A total of 3,328 residents aged 40 years or over (77.6 % of the total population of this age group) participated in the examination and underwent a comprehensive assessment including baPWV and ECG. Of these, 242 subjects for whom there was no information on baPWV or ECG, 54 subjects who were likely to have peripheral arterial disease (ankle-brachial index <0.9), 189 subjects with atrial fibrillation or intraventricular conduction disturbance (QRS interval >120 ms), 30 subjects with elevated heart rate (>100 beats/min), 22 subjects who did not take a fasting blood test, 16 subjects taking medication affecting the QT interval duration (*i.e.*, antiarrhythmic drugs, antibiotics, antipsychotic agents or antihistamines) (*2*), 111 subjects with a history of cardiovascular disease (myocardial infarction, coronary revascularization or stroke), and 30 subjects who refused to participate in the present study were excluded from the analyses. The final study group comprised 2,666 subjects (1,089 men and 1,577 women).

Table 2. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,577 Women

Variables	Brachial-ankle pulse wave velocity (cm/s)				*p* for trend
	900–1,269 (*n*=395)	1,270–1,493 (*n*=392)	1,494–1,821 (*n*=396)	1,822–4,128 (*n*=394)	
Age (years)	49.7±6.8	56.0±8.4	62.7±9.2	71.5±8.4	<0.0001
Heart rate (bpm)	62.9±11.9	64.9±9.9	68.6±10.0	72.8±11.9	<0.0001
Systolic blood pressure (mmHg)	107.5±17.9	121.7±15.8	135.2±15.9	150.5±19.9	<0.0001
Diastolic blood pressure (mmHg)	63.9±11.9	73.5±9.9	80.2±10.0	87.4±11.9	<0.0001
Hypertension (%)	3.2	16.9	50.2	85.5	<0.0001
Antihypertensive drugs (%)	2.5	7.4	25.7	47.5	<0.0001
β-Blocker (%)	0.2	1.4	2.6	6.0	0.0001
Calcium channel blocker (%)	1.9	6.1	20.5	38.1	<0.0001
ACE inhibitor (%)	0.0	0.5	7.3	6.9	<0.0001
ARB (%)	0.2	0.9	5.1	9.8	<0.0001
ECG abnormalities (%)	3.0	8.4	10.3	30.9	<0.0001
Total cholesterol (mmol/L)	5.2±1.0	5.5±0.9	5.6±0.9	5.4±1.0	0.01
HDL cholesterol (mmol/L)	1.8±0.5	1.8±0.4	1.7±0.4	1.6±0.5	0.0002
LDL cholesterol (mmol/L)	3.2±0.9	3.4±0.8	3.4±0.8	3.3±1.0	0.15
Triglyceride (mmol/L)	0.9±0.8	1.1±0.7	1.3±0.7	1.4±0.9	<0.0001
Dyslipidemia (%)	49.2	53.5	58.8	68.4	0.0001
Fasting plasma glucose (mmol/L)	5.4±1.2	5.8±1.1	6.0±1.1	6.4±1.3	<0.0001
HbA1c (%)	4.8±0.8	5.0±0.6	5.1±0.6	5.3±0.8	<0.0001
Diabetes (%)	3.1	8.6	12.4	34.3	<0.0001
BMI	21.7±4.0	22.8±4.0	23.6±4.0	24.0±4.0	<0.0001
Obesity (%)	28.4	24.6	30.5	39.6	0.0004
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.01
Serum potassium (mmol/L)	4.3±0.4	4.3±0.4	4.3±0.4	4.2±0.4	0.003
Alcohol intake (%)	22.5	29.3	31.1	29.3	0.69
Habitual smoking (%)	21.0	6.3	9.4	4.7	0.49

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Measurements of QTc and baPWV

Standard, resting 12-lead ECG was performed using an ECG device (FCP-4266; Fukuda Denshi, Tokyo, Japan) in the supine position in the morning. Heart rate (bpm) and QT interval duration (ms) were determined automatically using the PI-10 ECG Analysis Program (Fukuda Denshi). The program calculated the QT interval duration from the beginning of QRS to the end of the T wave. The QT interval duration was corrected for heart rate by calculating QTc according to Bazett's equation (*18*).

$$QTc = QT \text{ interval duration [ms]}/(60/\text{heart rate})^{1/2}$$

The baPWV was measured in the supine position after at least 5 min of rest using a volume-plethysmographic apparatus (Form PWV/ABI; Colin, Komaki, Japan), as described previously (*19*). Briefly, cuffs to measure baPWV were wrapped on both brachia and ankles. PWV at the brachia and ankles were recorded using a semiconductor pressure sensor. Volume waveforms were stored with automatic gain analysis and quality adjustment. BaPWV was automatically calculated according to the following equation: $baPWV = (L_a - L_b)/T$, with L_a being the distance from the heart to each ankle, L_b the distance from the heart to the right upper arm, and T the time delay from the right brachial waveform to each ankle waveform.

All clinical examinations including 12-lead ECG, measurement of baPWV and blood test were conducted on the same day.

Relevant Factors

At baseline examination, a self-administrated questionnaire concerning current drug use including antihypertensive agents (*e.g.*, β-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker), smoking, and alcohol intake was completed in advance by each participant and was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. Blood pressure was measured three times

after the subject had rested for at least 5 min using a semiautomatic device (BP203RVIII; Colin) based on the cuff-oscillometric principle with the subject in the sitting position. The mean of the three measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or current use of antihypertensive agents. ECG abnormalities were defined as Q wave (Minnesota codes, 1–1, 2, 3), left ventricular hypertrophy (3–1) or ST depression (4–1, 2, 3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kg divided by height in m squared. Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids, plasma glucose levels, serum calcium, and potassium. Serum total cholesterol, triglycerides, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Hemoglobin A1c levels were measured by high-performance liquid chromatography. Dyslipidemia was defined as total cholesterol ≥5.68 mmol/L, LDL-cholesterol ≥4.13 mmol/L, HDL-cholesterol <1.03 mmol/L, triglycerides ≥1.69 mmol/L, or current use of lipid-lowering agents. Diabetes was defined according to the criteria recommended by the American Diabetes Association (*20*), in addition to a medical history of diabetes. Obesity was defined as BMI ≥25.0 kg/m^2.

Statistical Analysis

The age-adjusted frequencies of relevant factors in quartile groups defined by baPWV were calculated by means of the direct method using the total study population as a standard and were compared using age-adjusted logistic regression models. The age-adjusted mean values of QTc and relevant factors in quartile groups defined by baPWV were calculated using covariance analysis and compared using multiple regression models. Multivariate-adjusted mean values of QTc in the four baPWV groups were estimated using multiple regression models including age, gender, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium levels, alcohol intake, and habitual smoking. Comparisons of the relationships of baPWV with QTc among subgroups were carried out by adding an interaction term to the statistical models. p values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS program package (SAS Institute, Cary, USA).

Ethical Considerations

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

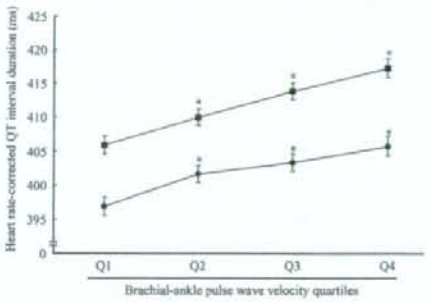

Fig. 1. *Age-adjusted mean values of heart rate–corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels for men (solid circles) and women (solid boxes). For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater. The centers of the circles or boxes are placed at the estimates of mean values. Vertical lines represent SEM for mean values. *$p<0.01$ vs. the lowest quartile group. $p<0.0001$ for trend in both men and women.*

Results

The mean value of QTc was 401.7 ms (SD, 21.5; range, 328.0–494.0) for men and 411.7 ms for women (SD, 23.3; range, 295.0–554.0). Baseline characteristics of male and female participants according to quartile groups defined by baPWV are shown in Tables 1 and 2, respectively. For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s. The subjects with higher baPWV levels were significantly older. The frequencies of hypertension, dyslipidemia, diabetes, obesity, and alcohol intake increased with rising baPWV levels, while an inverse association was observed for the frequency of habitual smoking.

Figure 1 shows the age-adjusted mean values of QTc according to quartiles of the baPWV levels by sex. The age-adjusted mean values of QTc linearly increased with rising baPWV levels for men and women: for men, 396.7, 401.4, 403.2, and 405.6 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend); for women, 405.7, 409.9, 413.8, and 417.4 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend). When the Friedrich formula was used for estimation of QTc, similar associations were observed between baPWV and QTc in both men and women

Table 3. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and Relevant Factors

	Quartiles of brachial-ankle pulse wave velocity				*p* for trend	*p* for homogeneity
	Q1	Q2	Q3	Q4		
Hypertension						
No (n=1,618)	402.4±0.9	405.8±0.9	408.8±1.3	410.8±1.9	<0.0001	0.43
Yes (n=1,048)	402.8±3.9	408.8±2.0	409.7±1.3	412.8±1.2	0.01	
Dyslipidemia						
No (n=1,202)	403.1±1.4	405.9±1.3	410.0±1.4	408.6±1.8	0.03	0.14
Yes (n=1,464)	401.3±1.4	407.0±1.2	408.8±1.1	414.5±1.2	<0.0001	
Diabetes						
No (n=2,243)	402.4±1.0	406.4±0.9	408.7±0.9	411.9±1.2	<0.0001	0.39
Yes (n=423)	404.1±3.8	407.6±2.7	411.7±2.2	412.9±1.9	0.06	
Obesity						
No (n=1,938)	402.7±1.1	406.4±1.0	408.7±1.0	411.2±1.2	<0.0001	0.19
Yes (n=728)	401.7±2.0	406.9±1.7	410.5±1.6	414.8±1.8	<0.0001	
ECG abnormalities						
No (n=2,196)	402.2±1.0	405.8±0.9	409.1±0.9	411.8±1.2	<0.0001	0.43
Yes (n=470)	402.3±3.7	411.1±2.9	410.6±2.3	413.7±2.1	0.04	
Alcohol intake						
No (n=1,504)	404.3±1.4	408.1±1.2	410.6±1.2	413.6±1.3	<0.0001	0.34
Yes (n=1,162)	399.8±1.4	404.4±1.3	407.6±1.3	410.9±1.6	<0.0001	
Habitual smoking						
No (n=2,068)	403.9±1.2	407.2±1.0	409.7±1.0	413.7±1.1	<0.0001	0.21
Yes (n=598)	397.2±1.6	404.1±1.7	408.1±1.8	407.5±2.3	0.0003	

Values are age- and sex-adjusted means±SEM.

Table 4. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and the Number of Relevant Factors

Number of relevant factors	Quartiles of brachial-ankle pulse wave velocity				*p* for trend
	Q1	Q2	Q3	Q4	
0–1 (n=903)	406.0±1.6	404.0±1.4	408.1±1.4	411.6±1.7	0.001
2–3 (n=1,313)	402.5±1.4	404.8±1.3	409.4±1.3	410.4±1.5	0.003
4–7 (n=450)	407.4±2.3	407.7±2.2	413.9±2.2	413.5±2.4	0.02

Values are age- and sex-adjusted means±SEM. Relevant factors: hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, and habitual smoking.

(p<0.0001 for trend in both sexes). In the following analyses, male and female subjects were combined because the relationships of baPWV to QTc were comparable between men and women.

Table 3 shows the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels for subgroups of participants defined on the basis of the presence or absence of hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, or smoking habits. There were comparable relationships between baPWV and QTc for participants who were and were not hypertensive. Likewise, there were no interactions in the relationships of baPWV with QTc between subgroups defined by every other relevant factor (all p values for interaction >0.05). There were also comparable relationships of baPWV with QTc between participants who were and were not taking antihypertensive agents or lipid-lowering agents (p for interaction >0.5). We also estimated the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels by the number of relevant factors (Table 4). There was a significantly positive relationship between baPWV and QTc in each of the groups defined by a number of cardiovascular risk factors of 0–1, 2–3, and 4–7.

Figure 2 shows the multivariate-adjusted mean values of QTc according to quartiles of the baPWV levels. The multivariate-adjusted mean values of QTc significantly increased with rising baPWV levels, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes,

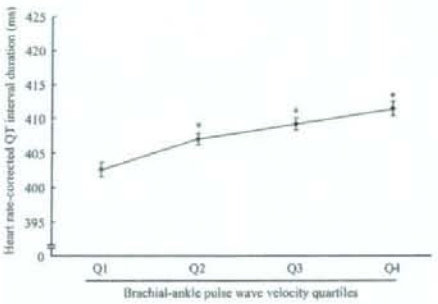

Fig. 2. *Multivariate-adjusted mean values of heart rate–corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels. The centers of the boxes are placed at the estimates of mean values. Other conventions are the same as in Fig. 1. Mean values and p values are adjusted for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes mellitus, obesity, serum calcium and potassium, alcohol intake, and smoking habits.* $*p<0.01$ *vs. the lowest quartile group.* $p<0.0001$ *for trend.*

obesity, serum calcium, serum potassium, alcohol intake, and smoking habits ($p<0.0001$ for trend).

Discussion

To our knowledge, this is the first study to address the associations between baPWV and QTc in a general population without preexisting cardiovascular disease. In the present analysis, the mean values of QTc increased with rising baPWV levels for both men and women. These associations remained strong and continuous, even after controlling for traditional cardiovascular risk factors, suggesting an independent relationship between subclinical arterial disease (atherosclerosis) and QT interval prolongation.

In the present study, there were strong and continuous relationships between QTc and baPWV, which has been shown to be a functional marker for subclinical atherosclerotic disease in central and peripheral arteries (*16*, *21*). Ours is the largest study to have investigated the association between subclinical arterial disease and QT interval prolongation, but there have been a few other cross-sectional studies addressing this question using other structural markers of subclinical arterial disease (*10–12*). The Insulin Resistance Atherosclerosis Study (IRAS) investigated the association between carotid intima media thickness and QTc in 912 nondiabetic subjects without coronary artery disease and found a close association between carotid atherosclerosis and QT interval prolongation (*10*). The Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk also showed a positive correlation between carotid intima media thickness and QT interval duration in 1,199 clinically healthy subjects (*11*). These observational data support our hypothesis that subclinical arterial disease is associated with QT interval prolongation.

It is well known that the QT interval is affected by heart rate (*18*, *22*). In order to control for the confounding effects of heart rate, we used QTc, which was estimated by Bazett's formula, and found significant associations between baPWV and QTc. When the Friedrich formula was used for estimation of QTc instead of Bazett's formula, similar associations were observed. We also investigated the association between baPWV and crude QT interval duration and found significantly positive relationships even after adjustment for heart rate, ECG abnormalities, and other cardiovascular risk factors (data not shown). These results suggest that baPWV is significantly associated with QT interval duration and this association is independent of the effects of heart rate.

The mechanism underlying the association between subclinical arterial disease and the acquired form of QT interval prolongation has not been clearly defined. Subclinical arterial disease and subsequent arterial stiffness may increase ventricular load and, as a consequence, may promote myocardial and electrophysiological remodeling, resulting in QT interval prolongation (*23*, *24*). Another possible mechanism is that microvascular atherosclerosis in the coronary artery, which is strongly related to systemic arterial disease, may lead to subendocardial ischemia and thus extend QT interval duration (*25*).

One limitation of our study is that we have no information on subjects with congenital long QT syndrome. However, the prevalence of the congenital long QT syndrome has been reported to be less than 0.1% (*26*). Furthermore, in our subjects the relationship between baPWV and QTc was strong and continuous, even after excluding participants with QT intervals of 440 ms or more ($p<0.0001$ for trend). Thus, the influence of congenital long QT syndrome would seem to have been negligible. Another limitation is that information on repeated measurements of baPWV and QTc is limited. This fact made it difficult for us to conduct longitudinal analysis.

In conclusion, we found close associations between baPWV and QTc for men and women without histories of cardiovascular disease. These associations were independent of hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, alcohol intake, and smoking habits. Thus, subclinical arterial disease appears to contribute to the pathogenesis of QT interval prolongation. Future longitudinal studies are necessary to clarify the causal relationship between subclinical arterial disease and QT interval prolongation.

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Secular Trends in the Incidence of and Risk Factors for Ischemic Stroke and Its Subtypes in Japanese Population

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Background—The study of long-term trends in the incidence of and risk factors for ischemic stroke subtypes could offer insights into primary and secondary prevention.

Methods and Results—We established 3 cohorts of residents ≥40 years of age in 1961, 1974, and 1988 in the Japanese community of Hisayama. Morphological examinations by autopsy or brain imaging were performed on most of the ischemic stroke cases developed in these cohorts. When 13-year follow-up data were compared, the age-adjusted incidence of ischemic stroke and lacunar infarction declined significantly from the first to the third cohort for both sexes, whereas the incidences of atherothrombotic and cardioembolic infarction did not change during this period. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. A rapid increase in the prevalence of metabolic disorders may have offset the impact of improvements in hypertension control and resulted in a slowdown of the decline in the incidence of ischemic stroke in the cohorts in the present study; however, hypertension still makes a large contribution to the development of ischemic stroke.

Conclusions—These findings suggest that in the Japanese population, the incidence of ischemic stroke has declined significantly over the past 40 years, probably owing to better management of hypertension. There is a need for greater primary prevention efforts in the treatment of hypertension and metabolic disorders. (***Circulation.*** **2008;118:2672-2678.)**

Key Words: cerebral infarction ■ morbidity ■ risk factors ■ hypertension ■ trend

Stroke continues to be a major public health concern worldwide. In Japan, it is the third leading cause of death and a major neurological cause of long-term disability.[1] The increase in the elderly population that accompanies the improvement in life expectancy is expected to further increase stroke prevalence. On the other hand, there have been major advances in the identification and management of stroke risk factors and the treatment of acute stroke. The study of temporal trends in stroke incidence provides insights into the effect of these factors. Several epidemiological studies have reported that the declining or stable incidence of stroke is likely attributable to better treatment of risk factors over time.[2–8] On the basis of their 50 years of follow-up data, the authors of the Framingham Study recently showed that the age-adjusted incidence of stroke decreased significantly in men and women owing to the improved control of hypertension and smoking.[2] In Japan, the incidence of stroke declined by 60% from 1964 to 1983 in a rural population.[7] We also found in a Japanese urban area that the incidence of ischemic stroke declined markedly between the 1960s and 1970s as a result of hypertension control, but this declining trend was slowed in the late 1980s and 1990s, probably because of an increase in metabolic disorders.[8]

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Because the pathogenesis, prognosis, and treatment differ among ischemic stroke subtypes,[9,10] the evaluation of temporal trends in the incidence of and risk factors for ischemic stroke subtypes may contribute to more effective primary and secondary prevention of ischemic stroke. However, morphological features of the brain were not readily available before the widespread use of computed tomography and magnetic resonance imaging, and the definition of ischemic stroke subtypes was not determined until the early 1990s.[11–13] Therefore, there is little information on the effect of the changes in cardiovascular risk factors on secular trends in the incidence of ischemic stroke and its subtypes.

The Hisayama Study is a population-based study that has established several cohorts at times that correspond to periods of remarkable lifestyle changes in Japan.[8,14–16] One of the

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characteristics of this study is that most of the deceased study subjects underwent autopsy examination from the beginning of the study, and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort.[8,14] Furthermore, study-team physicians performed physical and neurological examinations on the subjects who developed stroke and collected detailed clinical information throughout the study period. These characteristics of the study design enabled us to examine secular trends in the incidence of and risk factors for ischemic stroke subtypes. We previously reported the steadily declining incidence of lacunar infarction (LAI) using 12-year follow-up data of the first 3 cohorts.[17] In this article, we extend the follow-up period of these cohorts to 13 years and compare the impact of cardiovascular risk factors on the incidence of ischemic stroke subtypes.

Methods

Study Population

The Hisayama Study, an epidemiological study of cerebrovascular-cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town was ~8000 in 2007, and full community surveys of the residents have been repeated since 1961. The study design and characteristics of the subject population have been described in detail elsewhere.[14–16] Briefly, we established 4 study cohorts from Hisayama residents ≥40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. In 1961, a total of 1658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of subjects with a history of stroke or myocardial infarction and subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. Similarly, after excluding subjects with a history of stroke or myocardial infarction, we established a second cohort consisting of 2038 subjects from 2135 participants (participation rate 81.2%) in 1974, a third cohort of 2637 subjects from 2742 participants (participation rate 80.9%) in 1988, and a fourth cohort of 3123 subjects from 3328 participants (participation rate 77.6%) in 2002. The health status of these cohort populations was followed up every year by repeated health examinations or by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up. The development of cardiovascular diseases in the study populations was also checked by a daily monitoring system organized by the study team, local physicians, and members of the local health and welfare office. When the subjects died, autopsy examinations were performed at the Department of Pathology, Kyushu University.

Measurement of Cardiovascular Risk Factors

Details of the measurement of cardiovascular risk factors in each cohort were published previously.[8,14–16] In brief, blood pressures were measured 3 times with subjects in a recumbent position in 1961 and in a sitting position in 1974, 1988, and 2002, and hypertension was defined as a mean systolic blood pressure ≥140 mm Hg, a mean diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988 and 2002, in addition to medical history of diabetes. Serum cholesterol levels were measured by the Zak-Henly method with the modification by Yoshikawa in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988 and 2002. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured with subjects in light clothing without shoes, and obesity was defined as body mass index ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standardized questionnaire and was categorized as current habitual use or not. Current drinking was also categorized as light (1 to 33 g/d) or heavy (≥34 g/d) drinking according to daily ethanol intake.

Definition of Ischemic Stroke Subtypes

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit that persisted for >24 hours and was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.[8] The diagnoses of ischemic stroke subtypes were made on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study[12] and Cerebral Embolism Task Force.[13] We classified ischemic stroke subtypes into 4 categories: LAI, atherothrombotic infarction (ATI), cardioembolic infarction (CEI), and undetermined subtype. Details of the diagnostic criteria of ischemic stroke subtypes have been published previously.[10] Briefly, LAI was diagnosed as the presence of a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subject had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[13] The category of undetermined stroke included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphological information. We considered morphological findings significant and used clinical features as reference information.

During the 13-year follow-up period, first-ever ischemic stroke developed in 134 subjects (83 cases of LAI, 28 of ATI, 17 of CEI, and 6 of undetermined subtype) in the first cohort, in 142 subjects in the second cohort (76 cases of LAI, 29 of ATI, 34 of CEI, and 3 of undetermined subtype), and in 154 subjects in the third cohort (74 cases of LAI, 42 of ATI, 38 of CEI, and 0 of undetermined subtype). Among these, morphological examinations by autopsy or brain imaging were performed on 90.3% (autopsy rate 90.3%) in the first cohort, 97.2% (autopsy rate 87.5%) in the second cohort, and 100.0% (autopsy rate 72.4%) in the third cohort.

Statistical Analysis

The prevalences of possible risk factors were adjusted for age by the direct method and were examined for trends across cohorts by the Cochran-Mantel-Haenszel χ^2 test with 10-year age groupings. Age-adjusted mean values of risk factors were calculated by the covariance method, and their trends were tested by the linear regression model. The incidences of first-ever ischemic stroke and its subtypes were calculated by the person-year method with adjustment for age by the direct method. The world standard population was used as a standard population. The age-adjusted incidences among the first 3 cohorts were compared with the use of the Cox proportional hazards model. Age and sex-adjusted hazard ratios (HRs) and 95% CIs of cardiovascular risk factors for the development of ischemic stroke and its subtypes were estimated by the Cox proportional hazards model in each cohort, and the population attributable risk fraction of each risk factor was calculated.

Ethical Considerations

The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Table 1. Trends in Age-Adjusted Prevalence of Cardiovascular Risk Factors Among 4 Examinations of the Hisayama Study by Sex

	Men					Women				
Variables	1961 (n=705)	1974 (n=855)	1988 (n=1110)	2002 (n=1315)	P for Trend	1961 (n=913)	1974 (n=1183)	1988 (n=1527)	2002 (n=1808)	P for Trend
Age, y	55±11	56±11	57±12	60±12	<0.001	57±12	58±12	59±12	62±13	<0.001
Hypertension, %	38.4	43.1	44.1	42.0	0.25	35.9	40.1	35.1	31.3	<0.001
Antihypertensive agents, %	2.0	8.4	13.2	18.2	<0.001	2.1	7.4	13.4	16.6	<0.001
Systolic BP, mm Hg*	162±18	157±18	151±18	148±18	<0.001	163±19	161±19	154±19	149±19	<0.001
Diastolic BP, mm Hg*	91±11	90±11	87±11	89±11	0.011	88±11	87±11	83±11	86±11	<0.001
Glucose intolerance, %	11.6	14.1	39.3	54.5	<0.001	4.8	7.9	30.0	35.5	<0.001
Obesity, %	7.0	11.6	24.1	29.3	<0.001	12.9	21.5	23.8	24.0	<0.001
Body mass index, kg/m^2	21.3±2.8	21.7±2.8	22.8±2.8	23.5±2.8	<0.001	21.7±3.4	22.5±3.3	22.9±3.3	22.9±3.4	<0.001
Hypercholesterolemia, %	2.8	12.2	26.9	25.8	<0.001	6.6	19.9	41.6	41.6	<0.001
Total cholesterol, mmol/L	3.9±0.9	4.7±0.9	5.1±0.9	5.1±0.9	<0.001	4.2±1.0	5.0±1.0	5.5±1.0	5.4±1.0	<0.001
Atrial fibrillation, %	0.7	1.6	1.6	1.1	0.84	0.5	0.4	0.9	0.6	0.55
Current smoking, %	75.0	73.3	50.4	46.9	<0.001	16.6	10.2	6.9	8.5	<0.001
Current drinking, %	69.6	63.8	61.5	71.7	0.043	8.3	5.7	9.5	29.1	<0.001
Light drinking, %	43.4	31.9	29.5	37.7	...	8.2	5.5	8.0	27.1	...
Heavy drinking, %	26.3	31.9	32.0	34.0	...	0.1	0.2	1.5	2.0	...

BP indicates blood pressure. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or current use of antihypertensive agents. Hypercholesterolemia was definec as total cholesterol level ≥5.7 mmol/L (220 mg/dL). Obesity was defined as body mass index ≥25.0 kg/m^2. Current drinking was divided into light (1 to 33 g) and heavy (≥34 g) drinking according to daily ethanol intake.

*Mean systolic and diastolic BPs among hypertensive subjects in each examination.

Results

Trends in Cardiovascular Risk Factors

We compared the age-adjusted prevalence of cardiovascular risk factors at baseline examination among the 4 cohorts by sex (Table 1). During the 40-year period from 1961 to 2002, the populations grew 5 years older in both sexes. The age-adjusted prevalence of hypertension was stable at ≈40% in men (P for trend=0.25) and decreased significantly in women (P for trend <0.001), whereas the proportion of individuals using antihypertensive agents increased consistently with time in both men and women. As a result, age-adjusted mean blood pressures among hypertensive men and women decreased significantly throughout the study period. In contrast, the age-adjusted prevalence of glucose intolerance and obesity increased greatly over the study period for both sexes. More than half of men and one third of women had glucose intolerance in 2002. The age-adjusted prevalence of hypercholesterolemia increased 10-fold in men and 6-fold in women from 1961 to 1988 but was unchanged in 2002. The age-adjusted prevalence of current smoking for men was 4-fold higher than that for women in 1961, and it decreased significantly with time for both sexes. The prevalence of current drinking increased significantly for both sexes in 2002.

Trends in Incidence of Ischemic Stroke Subtypes

We then compared the age-adjusted incidence of ischemic stroke using the results of a 13-year follow-up in the first 3 cohorts (1st, 2nd, and 3rd cohort). The age-adjusted incidence of ischemic stroke declined significantly for both sexes throughout the cohorts: It significantly declined by 56% for men and by 40% for women from the first to the third cohort (P for trend <0.001 for either sex; Table 2). In regard to ischemic stroke subtypes, the age-adjusted incidence of LAI for men declined significantly by 54% from the first to the second cohort, and it continued to decline by 39% from the second to the third cohort (P for trend <0.001). The age-adjusted incidence of LAI for women also declined by 25% from the first to the second cohort, and it continued to decline by 17% from the second to the third cohort (P for trend=0.003). The age-adjusted incidence of ATI and CEI did not change significantly among the cohorts for either sex.

Trends in Proportion of Ischemic Stroke Subtype

The proportions of ischemic stroke subtypes among the cohorts are shown by sex in the Figure. For men, the proportion of subjects with LAI decreased steadily from the first to the third cohort, whereas the proportions with ATI and CEI increased. For women, the proportion of the subjects with CEI increased slightly from the first to the third cohort, but the proportions of those with the other subtypes were constant among the cohorts.

Trends in the Effect of Cardiovascular Risk Factors on Ischemic Stroke

Because both cardiovascular risk factors and the incidence of ischemic stroke changed dramatically, we compared the impact of cardiovascular risk factors on the development of ischemic stroke among the first 3 cohorts (Table 3). In the first cohort, hypertension was a powerful risk factor for ischemic stroke (age- and sex-adjusted HR 3.25, 95% CI 2.17 to 4.86) and largely contributed to its occurrence (population attributable risk fraction 51%). The impact of hypertension gradually declined during the study period; however, hyper-

Table 2. Age-Adjusted Incidence Rate (per 1000 Person-Years) of Ischemic Stroke and Its Subtypes Among 3 Cohorts of the Hisayama Study by Sex, With a 13-Year Follow-Up in Each Cohort

	Men				Women			
	1st Cohort (7456 PY)	2nd Cohort (9655 PY)	3rd Cohort (12 333 PY)	*P* for Trend	1st Cohort (10 294 PY)	2nd Cohort (13 762 PY)	3rd Cohort (17 953 PY)	*P* for Trend
Ischemic stroke								
No. of events	72	70	70		62	72	84	
Incidence rate	8.73	5.44	3.85	<0.001	4.28	3.06	2.57	<0.001
LAI								
No. of events	48	34	30		35	42	44	
Incidence rate	5.68	2.59	1.59	<0.001	2.41	1.81	1.50	0.003
ATI								
No. of events	14	14	22		14	15	20	
Incidence rate	1.88	1.03	1.23	0.27	0.96	0.61	0.54	0.084
CEI								
No. of events	9	21	18		8	13	20	
Incidence rate	1.08	1.74	1.03	0.43	0.58	0.56	0.53	0.86
Undetermined subtype								
No. of events	1	1	0		5	2	0	
Incidence rate	0.09	0.09	0.00	0.20	0.33	0.08	0.00	0.004

PY indicates person-years.

tension was still a significant risk factor and made the largest contribution to the development of ischemic stroke even in the third cohort (HR 1.83, 95% CI 1.29 to 2.58, population attributable risk fraction 30%). Glucose intolerance was also a significant risk factor for ischemic stroke in the first cohort. The effect of glucose intolerance on the occurrence of ischemic stroke was reduced and was not significant in the second cohort, but it appeared to be a significant risk factor in the third cohort. The population attributable risk fraction for glucose intolerance decreased from 13% in the first cohort to 4% in the second cohort and then increased to 13% in the third cohort. Obesity appeared to be a significant risk factor for ischemic stroke in every cohort, and its population attributable risk fraction was increased gradually from 6% in the first cohort to 9% in the third cohort. Hypercholesterolemia, smoking habits, and alcohol intake were not significant risk factors for ischemic stroke in any of the cohorts. In the multivariate analysis that included all risk factors, hypertension was a significant risk factor for ischemic stroke, and its HR decreased from 2.92 (95% CI 1.93 to 4.41) in the first cohort to 1.71 (95% CI 1.20 to 2.45) in the third cohort. Glucose intolerance was an independent risk factor for ischemic stroke in the first cohort (HR 1.91, 95% CI 1.23 to 2.95) but was not significant in the third cohort (HR 1.28, 95% CI 0.93 to 1.78). Obesity was not a significant risk factor in any of the cohorts after adjustment for other risk factors. We tried to investigate the effect of cardiovascular risk factors on ischemic stroke subtypes, but we could not find reliable evidence of an effect of these risk factors on the development of each subtype, probably because of the small number of events.

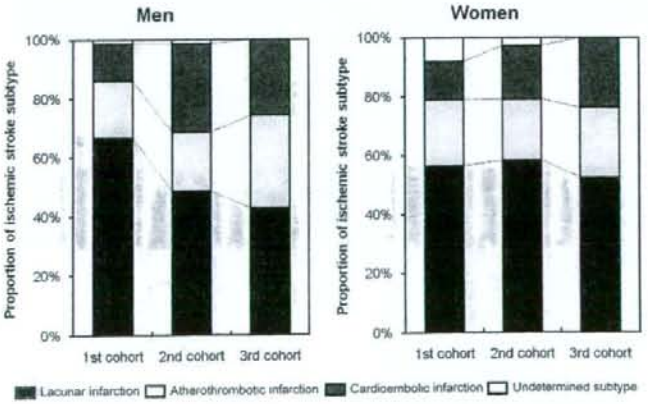

Figure. Proportion of ischemic stroke subtypes among the 3 cohorts of the Hisayama Study by sex.

Table 3. Age- and Sex-Adjusted HRs of Cardiovascular Risk Factors for Ischemic Stroke Among 3 Cohorts of the Hisayama Study

	1st Cohort			2nd Cohort			3rd Cohort		
	HR (95% CI)	*P*	PAF	HR (95% CI)	*P*	PAF	HR (95% CI)	*P*	PAF
Hypertension	3.25 (2.17–4.86)	<0.001	0.51	3.09 (2.05–4.65)	<0.001	0.53	1.83 (1.29–2.58)	<0.001	0.30
Glucose intolerance	2.45 (1.60–3.74)	<0.001	0.13	1.38 (0.87–2.17)	0.17	0.04	1.41 (1.02–1.94)	0.036	0.13
Obesity	1.83 (1.12–3.00)	0.017	0.06	1.63 (1.04–2.57)	0.034	0.07	1.54 (1.07–2.21)	0.021	0.09
Hypercholesterolemia	1.07 (0.50–2.29)	0.87	0.00	1.42 (0.95–2.12)	0.085	0.07	0.96 (0.68–1.35)	0.80	−0.02
Current smoker	1.27 (0.85–1.90)	0.24	0.10	0.83 (0.55–1.24)	0.36	−0.08	1.33 (0.89–1.98)	0.16	0.07
Current drinker	0.99 (0.65–1.51)	0.94	−0.01	1.45 (0.96–2.19)	0.081	0.12	1.09 (0.72–1.64)	0.70	0.02

PAF indicates the population attributable risk fraction.

Discussion

By comparing the incidence of ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the first to the third cohort for both sexes, whereas the incidence of ATI and CEI remained stable. During the study period, blood pressure levels among hypertensive subjects decreased significantly with time as a result of the popularization of antihypertensive medication. The prevalence of smoking habits declined steadily for both sexes. Contrary to these declining trends, the prevalence of metabolic disorders, namely, obesity, glucose intolerance, and hypercholesterolemia, increased steeply with time. These changes in cardiovascular risk factors might affect the incidence of ischemic stroke and its subtypes.

Hypertension is the most powerful risk factor for ischemic stroke.[9] In the first cohort, hypertension contributed to approximately half of the occurrence of ischemic stroke. During the study period, the age-adjusted prevalence of hypertension declined in women, and the proportion of all participants receiving hypertensive treatment increased steeply in both sexes. This improvement of hypertension control resulted in a decrease in age-adjusted mean systolic blood pressure level of 14 mm Hg among hypertensive subjects in both sexes. Because of this improved control of hypertension, the impact of the disease on the development of ischemic stroke was seen to weaken in the third cohort. The Framingham Study also showed a decline in the annual incidence of nonembolic stroke during a follow-up period of 50 years or more.[2] During this period, the mean systolic blood pressure level, prevalence of hypertension, and proportion of all participants receiving treatment for hypertension improved significantly. These reductions in the incidence of ischemic stroke and improvements in treatment for hypertension were similar to the findings of the present study. Our previous study showed that the impact of hypertension was similar for all ischemic stroke subtypes.[10] These results suggest that better management of hypertension might have made the biggest contribution to the declining trend in the incidence of ischemic stroke, especially of LAI; however, hypertension was still a significant risk factor in the third cohort and had a large attributable risk fraction for ischemic stroke. Because half of the hypertensive subjects did not undergo treatment for hypertension in the third cohort, there is a need for greater primary prevention efforts to improve the treatment of hypertension.

In subjects in the present study, the age-adjusted prevalence of metabolic disorders, such as obesity, hypercholesterolemia, and glucose intolerance, increased greatly during the past 40 years, probably owing to the westernization of the Japanese lifestyle. When we examined the impact of these metabolic disorders on the development of ischemic stroke, glucose intolerance was a significant risk factor in the first and the third cohort, and the impact of obesity was constant throughout the study period. Both glucose intolerance and body mass index have been shown to be significant risk factors for ischemic stroke and LAI.[10,18] Moreover, obesity is closely related to other cardiovascular risk factors and jointly increases the risk of ischemic stroke.[19] Our previous study also showed that the accumulation of metabolic disorders (that is, metabolic syndrome) was a significant risk factor for the development of ischemic stroke in our third cohort.[20] We speculate that the improved management of hypertension and the worsening of metabolic disorders cancelled each other out and resulted in the slowdown of the declining trend of the incidence of LAI and the sustained incidence of ATI.

Smoking is a widely accepted risk factor for ischemic stroke in Western populations, but this relationship is controversial for Japanese.[10,21,22] In the present study cohorts, the declining prevalence of smoking habits closely mirrored the declining trend in the incidence of ischemic stroke; however, smoking habits had little impact on the incidence of ischemic stroke in the present study cohorts. One possible explanation is that the association between smoking and the risk of ischemic stroke is only evident in populations with moderate to high levels of serum cholesterol.[23] A recent review of cardiovascular mortality trends in Japan[23] showed that the increase in serum cholesterol appeared mainly in young to middle-aged people. In contrast, elderly people, a high-risk group for ischemic stroke, continued to maintain a lower cholesterol level. However, the prevalence of smoking habits is still high in Japanese men, and therefore, the adverse influence of smoking might appear in the current generation of younger men, with a higher cholesterol level to be seen in the future.

LAI is the most common subtype of ischemic stroke in the Japanese population, unlike in Western populations.[1] Among subjects in the present study, because of the decreased incidence of LAI and the sustained incidences of ATI and CEI, the proportion of ischemic stroke subtypes has become closer to that of Western populations in men (Figure).

However, the pattern of ischemic stroke subtypes differed from that of Western populations, with subjects in the present study showing a high proportion of LAI even in recent years (43% for men and 52% for women in the third cohort). A recent hospital-based registration study in an urban area[24] and a study of 16 992 patients with acute ischemic stroke from rural areas in Japan[25] also showed a higher prevalence of LAI than of other subtypes. One possible explanation for this is the racial difference in the genetic susceptibility of LAI. We recently found 2 susceptibility genes for ischemic stroke, *PRKCH* and *AGTRL1*, in a genome-wide association study.[26,27] A single-nucleotide polymorphism in the *PRKCH* gene increased the risk of LAI, but this single-nucleotide polymorphism is specific to Asian populations.[27]

The present study has several limitations. First, the number of events of subtypes other than LAI was relatively small, and therefore, the power to assess trends in the incidence of and risk factors for ischemic stroke subtypes was weak. Second, there were a large number of subjects overlapping among the cohorts. Indeed, 916 of the subjects in the first cohort also accounted for 45% of the population of the second cohort. In addition, a total of 1229 subjects in the second cohort also participated in the third cohort (47% of the third cohort). However, we treated the overlapping subjects as in any life table analysis, establishing every cohort after excluding subjects with prior stroke or myocardial infarction at baseline. Therefore, these overlapping populations were not considered to distort the incidence trends in the present study. Third, the measurement of blood glucose and the criteria for glucose intolerance were different among the cohorts, which suggests an underestimation of the prevalence of glucose intolerance in the former cohorts. Nevertheless, the rapid changes in other risk factors in the present study are in accordance with the results of the National Nutritional Survey and other surveys of Japan.[23] Finally, the methods of case ascertainment and the diagnostic sensitivity of imaging techniques changed dramatically during the study period. The proportion of case subjects with of incident ischemic stroke who received diagnostic imaging tests increased over time. Echocardiography and carotid scanning were rarely performed in the former cohorts (3.0% and 0% in the first cohort, 29.6% and 4.2% in the second cohort, and 61.7% and 27.3% in the third cohort, respectively). Therefore, it is possible that the trends in the incidence of ATI and CEI were less accurate than the trends for LAI. Nonetheless, we believe that the findings of the present study reflect the actual secular trends in the incidence of ischemic stroke subtypes and their risk factors in the Japanese population, because we performed comprehensive surveillance, including autopsy examinations, in most of the cases.

Conclusions

By comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the 1960s to the late 1990s, but LAI remained the most frequent subtype of ischemic stroke in the Japanese. The improvement in hypertension control might have had a major influence on this declining trend. However, hypertension still has a large impact on ischemic stroke, and the increasing prevalence of metabolic disorders might emerge as an additional risk in future cohorts. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

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Disclosure

None.

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CLINICAL PERSPECTIVE

Stroke continues to be a major public health concern worldwide. Several epidemiological studies have reported that the declining or stable incidence of stroke is most often attributed to better treatment of risk factors over time. Here, by comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrate that the age-adjusted incidence of ischemic stroke and of lacunar infarction declined significantly from the 1960s to the late 1990s, but lacunar infarction remains the most frequent subtype of ischemic stroke in the Japanese. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. However, hypertension still has a large impact on ischemic stroke, and the increase in metabolic disorders might emerge as an additional risk in the third cohort. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

Impact of Kidney Disease and Blood Pressure on the Development of Cardiovascular Disease

An Overview From the Japan Arteriosclerosis Longitudinal Study

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Background—Kidney disease is associated with an increased risk of cardiovascular disease (CVD); however, there have been few well-designed prospective studies of this issue in Asian populations. Recent epidemiological studies have suggested that a lower blood pressure level may be associated with an increased risk of CVD in individuals with kidney dysfunction.

Methods and Results—Using data from 10 community-based cohort studies in Japan, we conducted follow-up on a total of 30 657 individuals 40 to 89 years of age without preexisting CVD or kidney failure and examined the relationship between reduced glomerular filtration rate (GFR) and the risk of CVD. During an average 7.4-year follow-up, 727 individuals experienced CVD. The age- and sex-adjusted incidence of CVD increased significantly in subjects with GFR of 60 to 89 mL · min^{-1} · 1.73 m^{-2} (4.3 per 1000 person-years, P=0.002) and in those with a GFR <60 mL · min^{-1} · 1.73 m^{-2} (6.5, P<0.001) compared with those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} (2.9). Even after adjustment for potential confounding factors, subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} had a 57% (95% CI 14% to 115%) greater risk of CVD than those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2}. The multivariate-adjusted hazard ratios of CVD increased in a log-linear manner with elevations in blood pressure levels, regardless of GFR levels (all P for trend <0.01).

Conclusions—Our findings suggest that a reduced GFR is a significant risk factor for CVD in the general Japanese population. Additionally, a log-linear association of blood pressure level with CVD risk was observed, without evidence of a J-curve association, regardless of GFR levels. (***Circulation***. **2008;118:2694-2701.)**

Key Words: cardiovascular diseases ■ blood pressure ■ kidney ■ meta-analysis

Kidney disease is increasingly being recognized as a leading public health issue. Chronic kidney disease, most commonly defined by a reduction in glomerular filtration rate (GFR) or the presence of proteinuria, affects 10% to 15% of the adult population in Western countries[1,2] and is associated with an increased risk of cardiovascular disease (CVD)[3–5]; however, there have been few well-designed large prospective studies in general Asian communities to date.[6–8]

Clinical Perspective p 2701

Blood pressure is an important determinant of the risk of CVD in the general population,[9,10] in which it has been well established that treatment for high blood pressure prevents CVD.[11] Blood pressure is commonly elevated in individuals with a reduced GFR,[4,5] which suggests that lowering blood pressure may offer significant benefits in this population. Recent prospective cohort studies, however, have reported that the risk of stroke or death for individuals with a reduced GFR is greater among those with systolic blood pressure levels below 120 mm Hg than among those with higher levels.[12,13] These data have raised concerns that lowering blood pressure may provide less benefit than previously believed, or may even be hazardous, in individuals with kidney dysfunction.

In the present report, we discuss the results of a pooling analysis from the Japan Arteriosclerosis Longitudinal Study–Existing Cohorts Combine (JALS-ECC), which is an overview of individual participant data from 21 community-based

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longitudinal observational studies in Japan.[14] Our aims were to assess the impact of a reduction in GFR on the development of CVD in the general population and to examine the association of blood pressure with the risk of CVD in individuals with a reduced GFR.

Methods

Study Population

The rationale, study design, and methods of the JALS-ECC have been described elsewhere.[14] In brief, cohort studies were eligible for inclusion in this project if they satisfied the following criteria: (1) Japanese population; (2) prospective cohort study; (3) at least 3000 person-years of follow-up; (4) date of birth, sex, height, weight, blood pressure, and serum total cholesterol recorded at baseline; and (5) date of death or the age at death recorded during a follow-up. Quality control of the collected cohort data were performed at the JALS Coordinating Center. The individual records of 66 691 participants in 21 cohort studies were included in the present project, with 82.7% of the participants from 17 community-based cohorts and 17.3% from 4 work-site–based cohorts. Permission to submit each collection of cohort data to the JALS Coordinating Center was obtained from the relevant institutional review boards for ethical issues.

Of the 21 cohort studies, 11 cohorts were excluded from the present analysis for the following reasons: 4 were work-site–based cohorts, 3 did not include creatinine data, 3 lacked many values for relevant variables, and 1 included no event data for either stroke or myocardial infarction. From the remaining 10 cohorts, we excluded participants less than 40 years of age and those 90 years of age or older, those with unavailable examination data at baseline or unavailable event data, those with a history of CVD, and those with an estimated GFR <15 mL · min^{-1} · 1.73 m^{-2}. For the analysis regarding CVD and stroke, the Niigata cohort was excluded, because information on stroke events was unavailable. A final total of 23 033 participants were enrolled in the CVD analysis, 23 084 in the stroke analysis, 30 657 in the myocardial infarction analysis, and 31 374 in the all-cause death analysis. The average follow-up period was 7.4 years.

Risk Factors

The JALS Coordinating Center requested individual participant data from the collaborating investigators. Serum creatinine was measured by Jaffe's method in 8 cohorts, by the enzymatic method in 1 cohort, and by both methods in 1 cohort. Serum creatinine values measured by the enzymatic method were corrected for Japanese subjects by the addition of 18.3 μmol/L.[15] GFR was estimated with the 4-variable Modification of Diet in Renal Disease study equation.[4] In accordance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines,[16] GFR levels were classified in the following ranges: ≥90, 60 to 89, and <60 mL · min^{-1} · 1.73 m^{-2}. Blood pressure was measured by a standard sphygmomanometer in all cohorts. Mean values were used in several cohorts that measured 2 or more blood pressure values. Blood pressure levels at baseline were classified into 4 categories (normal, prehypertension, stage 1 hypertension, and stage 2 hypertension) according to the criteria of the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[17] Diabetes was defined as a fasting blood glucose level of ≥7.0 mmol/L, a casual blood glucose level of ≥11.1 mmol/L, current use of insulin or oral medication for diabetes, and/or a history of diabetes. Serum total cholesterol was determined enzymatically. Information on smoking habit was obtained through a standard questionnaire and classified as current habitual use or lack thereof.

End Points

In each cohort, vital status and the development of CVD were ascertained during follow-up by use of death certificates, hospital medical records, and/or questionnaire surveys. All outcomes were classified according to the International Classification of Diseases, 9th Revision (ICD-9). All events were recoded by coordinating center staff members. CVD was defined as the development of either stroke or myocardial infarction. Stroke was defined as an acute disturbance of focal neurological function with symptoms that lasted >24 hours or death caused by a stroke event (ICD-9 codes 430, 431, 433, 434, or 436). Myocardial infarction included both fatal and nonfatal myocardial infarction, which was diagnosed by use of an appropriate clinical history supported by ECG changes and/or elevations of cardiac enzymes or other biochemical markers of myocardial injury (ICD-9 410). Only the first event of the relevant outcome type was included in each analysis.

Statistical Analysis

The SAS software package for Windows, release 9.13 (SAS Institute, Inc, Cary, NC) was used to perform all statistical analyses. The incidence rate of each outcome for the GFR subgroups was calculated by the person-year method and adjusted for the age and sex distribution of the overall population enrolled in the CVD analysis by the direct method, in which the subgroups and study population were subdivided into the same set of age groups (defined by decade) and the age- and sex-specific incidence rates were calculated within each subgroup.[18] The hazard ratios (HRs) and their 95% CIs for the development of events were estimated with the Cox proportional hazards regression model. The cohort effect was adjusted as a fixed effect by taking the study as a strata variable, assuming only proportional hazards within each study and not between studies.[18] Heterogeneity across cohorts was examined with the Cochran Q test and the I^2 statistic.[18] The risks of events according to blood pressure levels were also estimated with the Cox regression model. Trends in relationship between blood pressure levels and the risk of events were assessed by fitting models with a linear term for blood pressure categories according to kidney function status, and the heterogeneity of these relationships between kidney function status subgroups was estimated by the addition of an interaction term of a linear term for blood pressure levels and kidney function status to the relevant model. $P<0.05$ was considered statistically significant in all analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The characteristics of the 10 cohorts examined in the present study are shown in Table 1. Among all subjects, the mean age was 57.6 years, and the proportion of men was 38.0%. The mean value of serum creatinine was 78.6 μmol/L, and the frequency of GFR <60 mL · min^{-1} · 1.73 m^{-2} was 8.2%. During the average follow-up period of 7.4 years, a total of 727 subjects experienced CVD, 592 had strokes, 180 had myocardial infarctions, and a total of 2104 died.

Table 2 shows the baseline characteristics of the 23 033 subjects enrolled in the CVD analysis by sex. Their mean ages were 56.9 years for men and 58.2 years for women, and the frequency of GFR <60 mL · min^{-1} · 1.73 m^{-2} was 5.2% for men and 10.1% for women. The frequencies of normal blood pressure, prehypertension, stage 1 hypertension, and stage 2 hypertension were 19.6%, 41.8%, 26.0%, and 12.6% for men and 24.3%, 41.0%, 24.3%, and 10.4% for women, respectively. Similar findings were observed in subjects enrolled in the analyses of stroke, myocardial infarction, and all-cause death.

The age- and sex-adjusted incidences of CVD and stroke increased with declining GFR levels in the overall population (Table 3); the differences were statistically significant between subjects with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} and

Table 1. Characteristics of Included Cohort Studies

Regions	Cohort Name	No. of Population	Mean Age, y	Men, %	Mean sCr, μmol/L*	GFR <60, %†	Mean SBP/DBP, mm Hg	Mean Fasting Blood Glucose, mmol/L	Mean Total Cholesterol, mmol/L	Current Smoking, %	Follow-Up, y		No. of Events			
											Start-End	Mean	CVD	Stroke	MI	Death
Hokkaido	Tanno/Soubetsu	2066	60.1	43.9	89.6	19.4	133/78	5.1	5.0	25.9	1991–1999	5.5	120	93	27	136
Akita 2	Ikawa	2595	56.1	43.6	76.0	2.6	135/81	6.6	4.9	28.5	1985–1999	10.7	44	41	3	146
Ibaraki	Kyowa	4479	54.8	42.8	76.9	5.3	137/82	6.9	5.0	30.4	1985–1999	10.1	168	128	51	350
Niigata	Tokamachi	8480	58.0	33.1	79.6	7.7	127/73	NA	5.1	18.8	1993–2003	7.8	NA	NA	29	400
Osaka	Yao Minami-takayasu	3855	54.0	34.8	78.7	6.7	132/80	6.0	5.2	27.2	1985–1998	9.6	79	62	18	191
Shiga 1	Shigaraki	2934	56.6	41.1	81.3	10.5	132/78	6.0	5.0	29.4	1992–2001	7.3	82	69	13	260
Hiroshima	Hiroshima	2222	72.1	28.7	84.0	23.8	136/78	6.2	5.6	15.4	1992–2000	3.6	73	63	12	350
Ehime	Ohzu	5300	59.5	33.9	76.9	6.2	130/76	5.3	5.3	15.2	1996–2003	5.5	99	89	10	184
Fukuoka 1	Hisayama	757	60.8	39.5	83.1	9.5	133/78	5.4	5.4	21.1	1990–2000	9.9	57	45	14	86
Kumamoto	...	2465	47.0	70.0	65.4	0.2	127/80	5.7	5.4	46.4	1999–2003	4.2	5	2	3	1
Total	...	35 153	57.6	38.0	78.6	8.2	131/78	6.0	5.2	24.5	1985–2003	7.4	727	592	180	2104

sCr indicates serum creatinine; SBP/DBP, systolic or diastolic blood pressure; MI, myocardial infarction; and NA, not available.

*Serum creatinine was measured by Jaffe's method in 8 cohorts, by enzymatic method in the Ehime cohort, and by either method in the Niigata cohort. The values of serum creatinine measured by the enzymatic method were corrected by the addition of 18.3 μmol/L.

†GFR (unit: mL · min^{-1} · 1.73 m^{-2}) was estimated by the Modification of Diet in Renal Disease formula.

those with a GFR <90 mL · min^{-1} · 1.73 m^{-2} (all $P<0.01$). Subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} showed a significantly higher age- and sex-adjusted incidence of myocardial infarction and all-cause mortality than those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} ($P<0.001$). The age-adjusted incidences of CVD, stroke, and all-cause mortality were significantly higher in subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} than in those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} in both sexes (all $P<0.05$).

The risks of CVD, stroke, myocardial infarction, and all-cause death increased progressively with declining GFR levels in the overall population after adjustment for age and sex (Table 4). Even after adjustment for potential confounding factors, specifically age, sex, cohort, systolic blood pressure, diabetes, serum total cholesterol, body mass index, and current smoking status, the risks of CVD, myocardial infarction, and all-cause death were significantly higher in subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} than in the overall population. There was no evidence of heterogeneity in these associations among study cohorts (all P for heterogeneity >0.6; Q=2.46, I^2=0% for CVD; Q=4.06, I^2=0% for stroke; Q=3.75, I^2=0% for myocardial infarction; and Q=1.14, I^2=0% for all-cause death). Subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} had a significantly greater risk of myocardial infarction and death in men and of CVD, stroke, and death in women.

Table 2. Baseline Characteristics of the Study Population by Sex

Risk Factors	Men (n=9574)	Women (n=13 459)
Age, y	56.9 (11.1)	58.2 (11.4)
Serum creatinine, μmol/L	87.3 (16.7)	71.6 (13.6)
GFR, mL · min^{-1} · 1.73 m^{-2}	87.3 (20.2)	81.0 (19.1)
GFR levels (mL · min^{-1} · 1.73 m^{-2}), %		
≥90	39.0	27.1
60–89	55.9	62.8
<60	5.2	10.1
Systolic blood pressure, mm Hg	133.6 (19.1)	132.3 (19.8)
Diastolic blood pressure, mm Hg	81.1 (11.5)	77.9 (11.0)
Blood pressure levels, %		
Normal	19.6	24.3
Prehypertension	41.8	41.0
Stage 1 hypertension	26.0	24.3
Stage 2 hypertension	12.6	10.4
Diabetes, %	9.5	5.2
Serum total cholesterol, mmol/L	5.0 (0.9)	5.4 (1.0)
Body mass index, kg/m^2	23.2 (3.0)	23.2 (3.3)
Current smoking, %	56.2	7.1

Values are means (SD) or frequencies.

The Figure shows the log-linear relationship between blood pressure levels at baseline and the hazard of CVD, stroke, and all-cause death regardless of kidney function status after adjustment for potential confounding factors (all P for trend <0.01). There was no evidence of heterogeneity of the patterns in the association of blood pressure levels with the risk of outcomes between subgroups of kidney function status (all P for heterogeneity >0.7). The age- and sex-adjusted HR of myocardial infarction increased in a log-linear fashion with increasing blood pressure levels in the normal, prehypertension, stage 1 hypertension, and stage 2 hypertension groups in subjects with a GFR ≥60 mL · min^{-1} · 1.73 m^{-2} (HR 0.56 [95% CI 0.33 to 0.95], 1.00 [reference], 1.60 [1.08 to 2.37], and 1.75 [1.06 to 2.87]; P for trend 0.03) and in those with a GFR <60 mL · min^{-1} · 1.73 m^{-2} (0.19 [0.02 to 1.47], 1.00 [reference], 1.72 [0.80 to 3.70], and 2.36 [1.02 to 5.44]; P for trend 0.04). The number of myocardial infarctions in subjects with normal blood pressure levels was too small to assess reliably for multivariate-adjusted analysis.

We also performed sensitivity analyses to assess the risk of CVD according to GFR levels estimated by the MDRD formula corrected according to the Japanese coefficient of 0.881.[15] The correction shifted the GFR distribution to a

Table 3. Incidence Rate of CVD According to Kidney Function Status

GFR Levels, mL · min^{-1} · 1.73 m^{-2}	Overall				Men				Women			
	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*
CVD												
GFR ≥90	105	7199	51 203	2.9 (2.1–3.6)	78	3672	23 964	4.4 (3.3–5.6)	27	3527	27 239	1.8 (0.9–2.8)
GFR 60–89	489	13 957	104 334	4.3 (3.9–4.7)†	245	5404	39 794	5.5 (4.8–6.2)	244	8563	64 540	3.5 (3.1–3.9)†
GFR <60	133	1857	12 013	6.5 (5.0–8.0)‡	49	498	3018	9.1 (5.7–12.5)‡	84	1369	8995	4.7 (3.6–5.8)‡
Stroke												
GFR ≥90	84	7206	51 315	2.2 (1.6–2.8)	61	3676	24 033	3.5 (2.5–4.5)	23	3530	27 281	1.4 (0.6–2.1)
GFR 60–89	404	14 003	104 808	3.5 (3.2–3.9)†	192	5433	40 160	4.2 (3.6–4.8)	212	8570	64 648	3.0 (2.6–3.4)†
GFR <60	104	1875	12 092	5.0 (3.7–6.4)‡	33	501	3048	6.8 (3.5–9.7)§	71	1374	9044	4.0 (3.0–5.0)‡
Myocardial Infarction												
GFR ≥90	25	8360	60 807	0.6 (0.2–0.9)	21	4179	28 164	0.9 (0.4–1.4)	4	4171	32 643	0.4 (−0.2–0.9)
GFR 60–89	116	19 796	151 527	0.7 (0.6–0.8)	72	7345	54 855	1.1 (0.9–1.4)	44	12 441	96 672	0.4 (0.3–0.5)
GFR <60	39	2521	16 926	1.4 (0.9–1.9)‡	21	643	4039	2.4 (1.3–3.6)‡	18	1878	12 887	0.7 (0.4–1.1)
All-cause death												
GFR ≥90	289	8445	62 754	7.6 (6.4–8.7)	217	4225	29 119	11.4 (9.7–13.1)	72	4220	33 635	5.1 (3.5–6.6)
GFR 60–89	1388	20 230	161 168	7.0 (6.7–7.4)	809	7529	58 344	10.4 (9.7–11.1)	579	12 751	102 824	4.8 (4.4–5.2)
GFR <60	427	2649	18 935	12.9 (10.2–15.5)‡	184	681	4540	21.3 (14.9–27.7)‡	243	1968	14 395	7.3 (5.9–8.6)‡

PY indicates person-years.

*Incidence rates were adjusted for age by the direct standardized method. Overall results were additionally adjusted for sex.

†$P<0.01$, ‡$P<0.001$, §$P<0.05$ vs GFR ≥90 mL · min^{-1} · 1.73 m^{-2}.

lower level. Consequently, more participants (21%) were assigned to the group whose GFR was <60 mL · min^{-1} · 1.73 m^{-2}, and the age- and sex-adjusted risk of CVD among these subjects relative to those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} was attenuated by 85% (95% CI 32% to 160%), although it was still significant. Similarly, a log-linear relationship between blood pressure levels and the risk of CVD was still observed in the subgroup whose GFR was <60 mL · min^{-1} · 1.73 m^{-2}, even after correction with the Japanese coefficient (Data Supplement Figure).

Discussion

In the present study, we demonstrated a clear association between reduced GFR and high risk of CVD. To the best of our knowledge, this is the first overview of this issue in a Japanese community-based longitudinal study. Furthermore, the relationship between blood pressure levels at baseline and CVD risk was found to be strong and continuous, regardless of kidney function status.

There have been few studies showing the association of reduced GFR with an increased risk of CVD or mortality in the general Japanese population.[6–8] The findings of the Hisayama study revealed that a GFR <60 mL · min^{-1} · 1.73 m^{-2} was a significant risk factor for the development of coronary heart disease in men and of CVD and stroke in women.[6] In a large cohort study conducted by Irie et al,[7] reduced GFR was strongly associated with mortality due to CVD or stroke. A report from NIPPON DATA 90 also showed an association between a GFR <30 mL · min^{-1} · 1.73 m^{-2} and a high risk of cardiovascular death.[8] In the present study, we demonstrated a clear association between reduced GFR and the risks of CVD, stroke, myocardial infarction, and death in an overview of 10 Japanese cohort studies. These results, therefore, highlight the importance of taking kidney function status into consideration in trying to reduce the burden of CVD in the general Japanese population.

There are several possible explanations for the association of reduced GFR with CVD.[3] First, reduced GFR is associated with a high prevalence of traditional CVD risk factors, such as aging, hypertension, diabetes, smoking habits, and dyslipidemia.[19] In the present study, reduced GFR was found to be a significant risk factor for the development of stroke after adjustment for demographic factors, but not after adjustment for potential traditional CVD risk factors, which suggests that an accumulation of traditional CVD risk factors in individuals with reduced GFR increases the risk of stroke. In contrast, the risks of CVD, myocardial infarction, and all-cause death in individuals with reduced GFR were also attenuated, although still significant, after adjustment for traditional CVD risk factors. Reduced GFR has been shown to be associated with increased levels of novel CVD risk factors, such as inflammation, asymmetric dimethylarginine, oxidative stress, and thrombogenic factors.[19,20] Second, reduced GFR may be a marker of vascular disease; it is well recognized that renal arteriosclerosis and glomerular sclerosis are closely related to systemic atherosclerosis.[21]

In the present study, reduced GFR was associated with a high risk of stroke in men after adjustment for demographic factors but not after adjustment for potential confounding factors; however, this relationship was still observed in women even after adjustment for confounding factors. This sex difference may be a consequence of the effects of residual confounding factors, specifically, hypercoagulable states[22] or gonadal steroids,[23] in women. Furthermore, the lack of a significant association between reduced GFR and a high risk of myocardial infarction is probably due to the relatively small number of events.

Table 4. Effects of Kidney Function on Development of CVD

	Age- and Sex-Adjusted*		Multivariate-Adjusted†	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.41 (1.13–1.75)	0.002	1.24 (0.98–1.58)	0.07
GFR <60	2.26 (1.71–2.99)	<0.001	1.57 (1.14–2.15)	0.005
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.40 (1.10–1.79)	0.007	1.24 (0.95–1.61)	0.11
GFR <60	2.06 (1.51–2.81)	<0.001	1.41 (0.99–2.00)	0.06
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.32 (0.84–2.08)	0.22	1.26 (0.77–2.05)	0.35
GFR <60	3.35 (1.94–5.79)	<0.001	2.37 (1.29–4.34)	0.005
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.01 (0.88–1.15)	0.94	1.10 (0.96–1.27)	0.17
GFR <60	1.70 (1.44–2.00)	<0.001	1.65 (1.38–1.97)	<0.001
Men				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.21 (0.93–1.58)	0.16	1.01 (0.75–1.35)	0.95
GFR <60	2.13 (1.45–3.11)	<0.001	1.47 (0.94–2.29)	0.09
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.17 (0.86–1.57)	0.32	0.99 (0.71–1.38)	0.95
GFR <60	1.69 (1.08–2.65)	0.02	1.10 (0.64–1.89)	0.72
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.25 (0.75–2.07)	0.39	1.05 (0.61–1.81)	0.85
GFR <60	3.95 (2.07–7.55)	<0.001	2.56 (1.24–5.27)	0.01
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	0.97 (0.83–1.14)	0.72	1.06 (0.90–1.25)	0.48
GFR <60	1.75 (1.42–2.16)	<0.001	1.73 (1.37–2.17)	<0.001
Women				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.93 (1.28–2.92)	0.002	1.81 (1.17–2.79)	0.008
GFR <60	2.84 (1.79–4.52)	<0.001	1.97 (1.19–3.29)	0.009
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	2.01 (1.28–3.14)	0.002	1.81 (1.14–2.89)	0.01
GFR <60	2.89 (1.75–4.79)	<0.001	1.98 (1.15–3.42)	0.01
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.60 (0.55–4.60)	0.39	2.14 (0.63–7.24)	0.22
GFR <60	2.93 (0.93–9.23)	0.07	2.79 (0.74–10.56)	0.13
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.13 (0.87–1.47)	0.35	1.23 (0.94–1.62)	0.13
GFR <60	1.79 (1.34–2.38)	<0.001	1.68 (1.24–2.30)	<0.001

GFR was measured in mL · min^{-1} · 1.73 m^{-2}.

*Sex was removed from model for the analysis stratified by sex.

†Estimates were adjusted for age, sex, cohort, systolic blood pressure, diabetes, serum total cholesterol, body mass index, and current smoking status. Sex was removed from model for the analyses stratified by sex.

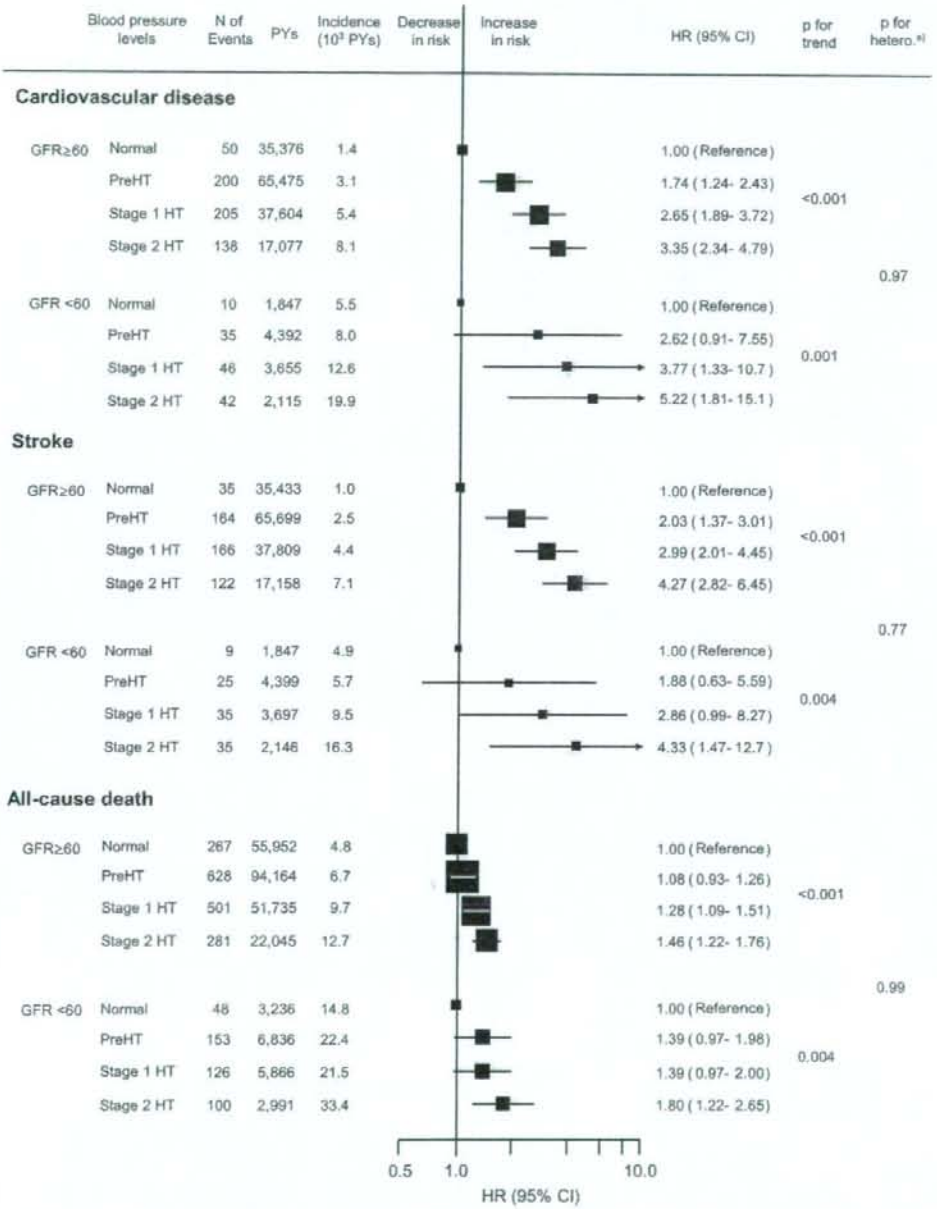

Figure. Effects of blood pressure levels on the development of CVD according to kidney function status. Estimates were adjusted for age, sex, cohort, diabetes, serum total cholesterol, body mass index, and current smoking status. Solid boxes represent estimates on the risk of outcomes for each blood pressure level. Areas of the boxes are proportional to the number of events. "*P* for trend" tested the log-linear relationship between blood pressure levels at baseline and the risk of outcomes by kidney function status. "*P* for hetero." tested the heterogeneity of the association of blood pressure levels with the risk of outcomes between kidney function status subgroups. HT indicates hypertension; PYs, person-years.