



Impact of Hypertension and Subclinical Organ Damage on the Incidence of Cardiovascular Disease Among Japanese Residents at the Population and Individual Levels — The Circulatory Risk in Communities Study (CIRCS) —

Akihiko Kitamura, MD; Kazumasa Yamagishi, MD; Hironori Imano, MD; Masahiko Kiyama, MD; Renzhe Cui, MD; Tetsuya Ohira, MD; Mitsumasa Umesawa, MD; Isao Muraki, MD; Tomoko Sankai, MD; Isao Saito, MD; Hiroyasu Iso, MD on behalf of the CIRCS Investigators

Background: In Japan, a community-based screening program for cardiovascular disease (CVD) has been effective in preventing stroke and coronary artery disease (CAD). The present study aimed to clarify which risk factors assessed at the screening examinations affect the incidence of CVD and the magnitude of the association after the late 1990s.

Methods and Results: We conducted a 12.5-year prospective study of 10,612 Japanese residents aged 40–74 years between 1995 and 2000, initially free of CVD and who underwent the screening examinations. During the follow-up, 364 cases of stroke and 137 cases of CAD were identified. The population attributable fraction of stroke was the largest for hypertension (HT; 46%), while the relative risk of stroke was the highest for atrial fibrillation (multivariable hazard ratio, 4.9; 95% confidence interval, 2.9–8.3). The population attributable fraction of CAD was relatively large for HT, current smoking, and high non-high-density lipoprotein cholesterol (20–29%). A dose-response relationship was found between the incidence of these cardiovascular events and the number of comorbid hypertensive subclinical organ damage markers: funduscopy changes, ST-T changes on ECG at rest, proteinuria and low estimated glomerular filtration rate.

Conclusions: HT and hypertensive subclinical organ damage are significantly associated with incident stroke and CAD at the population level, suggesting that management of HT and assessment of subclinical organ damage in hypertensive subjects at a screening program are still beneficial for community-based CVD prevention.

Key Words: Coronary artery disease risk; Epidemiology; Hypertension; Stroke prevention; Subclinical organ damage

Cardiovascular disease (CVD) is a major cause of death and disability in all countries, making the primary prevention of CVD a global health priority.¹ In Japan, a national program to prevent CVD was launched in 1982 under the Law of Health and Medical Services for the Elderly. This national program, which includes cardiovascular screening examinations such as blood pressure measurement, urinalysis, blood chemistry, anthropometric measurements, ECG, and retinal photography, has been reported to contribute to preventing stroke and coronary artery disease (CAD) nationwide.^{2,3}

In this study, we evaluated the risk factors assessed at

screening examinations in terms of their effect on the incidence of stroke and CAD at the population and individual levels. In Japan, hypertension (HT) has a greater effect on CVD morbidity than other risk factors (i.e., dyslipidemia, cigarette smoking, and diabetes mellitus), and 3 Japanese cohort studies completed by the early 1990s showed that approximately 40% of excess stroke events were attributable to HT.^{4–6} However, the contributions of HT and other risk factors to the occurrence of CVD events could change with time and have not been examined since the late 1990s in Japan. Furthermore, although representative clinical guidelines for the management of HT have recommended

Received November 6, 2016; revised manuscript received February 17, 2017; accepted February 20, 2017; released online March 29, 2017 Time for primary review: 29 days

Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka (A.K., M.K., I.M.); Tokyo Metropolitan Institute of Gerontology, Tokyo (A.K.); Department of Public Health Medicine (K.Y.), Department of Community Health (T.S.), Faculty of Medicine, University of Tsukuba, Tsukuba; Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka (H. Imano, R.C., H. Iso); Department of Epidemiology, Fukushima Medical University School of Medicine, Fukushima (T.O.); Department of Public Health, Dokkyo Medical University School of Medicine, Mibu (M.U.); and Department of Community Health Systems Nursing, Ehime University Graduate School of Medicine, Toon (I.S.), Japan

Mailing address: Akihiko Kitamura, MD, Research Team for Social Participation and Community Health, Tokyo Metropolitan Institute of Gerontology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015, Japan. E-mail: kitamura@pbhel.med.osaka-u.ac.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

CVD risk evaluation using assessments of subclinical organ damage (i.e., ECG changes, funduscopy changes, and chronic kidney disease),^{7–10} few studies have addressed the CVD risk comparatively for these markers of subclinical organ damage at the population level.

The aim of this study was to investigate the relative and attributable risks associated with stroke and CAD incidence for each component of the screening examination, including markers of subclinical organ damage, in an established cohort of Japanese residents after the late 1990s.

Methods

Study Cohort

The study cohort comprised residents aged 40–74 years who participated in annual health checkups conducted between 1995 and 2000 in 4 communities in the Circulatory Risk in Communities Study (CIRCS):⁴ Ikawa, a town in Akita Prefecture; Minami-Takayasu, a district in the city of Yao in Osaka Prefecture; Noichi, a town in Kochi Prefecture; and Kyowa, a town in Ibaraki Prefecture in Japan. All residents aged 40 years and older were annually recruited by the municipal government to be assessed for CVD risk factors. The overall participation rate was 37% of the census population. After excluding participants with a history of stroke or CAD, the data for the remaining 10,612 subjects (3,960 men and 6,652 women) were analyzed. Informed consent was obtained from community leaders and was implied by individual participation in health checkups; this was common practice before the year 2000 in Japan, based on the guidelines of the Council for International Organizations of Medical Science.¹¹ The study was approved by the Ethics Committee of the Osaka Center for Cancer and Cardiovascular Disease Prevention, University of Tsukuba, and Osaka University.

Health Checkup Examinations

Height and weight were measured with the subjects wearing socks and light clothing. Systolic and 5th-phase diastolic blood pressures (SBP and DBP) in the right arm were measured using a standard epidemiological method by trained physicians using standard mercury sphygmomanometers with cuffs that were 14 cm wide and 51 cm long.¹² The participants were seated and had rested for 5 min before the measurements. The blood pressure measurement was repeated after 5 deep breaths if SBP \geq 140 mmHg or DBP \geq 90 mmHg. In this study, the first reading was used for the analyses. Dipstick urinalysis was performed with spontaneously voided fresh urine to assess proteinuria, glycosuria, and hematuria.

Blood was drawn from the arm regardless of fasting status and immediately centrifuged to separate the serum. Total serum and high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, and creatinine were measured using standardized methods with a Hitachi 7250 autoanalyzer (Hitachi Medical, Ibaraki, Japan) at the Osaka Medical Center for Cancer and Cardiovascular Diseases laboratory, an international member of the US National Cholesterol Reference Method Laboratory Network.¹³ NonHDL-C was calculated as total cholesterol minus HDL-C. Serum creatinine values, originally measured using the Jaffe method, were converted to those established with the enzymatic method by subtracting 17.68 μ mol/L (0.2 mg/dL). Estimated glomerular filtration

rate (eGFR) was then calculated based on a standardized formula from the Japan Society of Nephrology Chronic Kidney Disease Initiative: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times (\text{serum creatinine [enzyme method]})^{-1.094} \times (\text{age})^{-0.287} \times (0.739 \text{ for women})$.¹⁴

Standard 12-lead ECG was performed at rest in the supine position. Well-trained physicians assessed each ECG using Minnesota codes.¹⁵ A retinal photograph was taken for 1 eye (almost always the right eye) using a non-mydratric fundus camera by medical examiners after 5 min of dark adaptation. Retinal arteriosclerosis was evaluated by well-trained physicians and examiners using the modified Scheie classification criteria.¹⁶ Electrocardiographic and funduscopy diagnoses were conducted by 2 or more researchers who had all received the same training. An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual intake of alcohol and the use of medications for chronic diseases including HT, dyslipidemia and diabetes mellitus.

Subclinical Organ Damage

Assessment of potential subclinical organ damage as an intermediate marker of CVD is recommended in several international clinical guidelines for the management of HT.^{7–10} Although these guidelines list several signs of subclinical organ damage, we adopted the following 4 markers because they could be measured less invasively at the screening examinations: funduscopy changes (defined as modified Scheie classification \geq H1 or \geq S1), resting ECG ST-T changes (Minnesota code 4-1 to 4-3 or 5-1 to 5-3), proteinuria (\geq 1+), and low eGFR ($<$ 60 mL/min/1.73 m²).

Follow-up and Ascertainment of CVD

The subjects were followed to determine the incidence of stroke and CAD up to 2012 for Ikawa and Yao, 2010 for Kyowa, and 2005 for Noichi. Follow-up was terminated at the first incidence of stroke or CAD, exit from the community, or death. During follow-up, 413 (4%) subjects moved out of their community and 1,274 (12%) died. These individuals were censored at the date of moving or death.

Information on the CVD incidents was collected from at least 1 of the followings: death certificate; national health insurance claims; reports from local physicians, public health nurses and health volunteers; annual cardiovascular risk surveys; or a household questionnaire. To confirm the diagnosis of CVD, all living patients were telephoned, visited, or invited to take part in annual health checkups to obtain a medical history. Next, the study physicians reviewed the medical records at local clinics and hospitals. In cases of death with certain underlying causes of death (ICD 10 classification codes: I20–22, I50 and I60–69), medical histories were obtained from families and/or local physicians, and medical records were reviewed.

Stroke was defined as a constellation of neurological deficits that were sudden or rapid in onset and lasted at least 24 h or until death. Stroke subtypes were classified as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (lacunar infarction or large-artery occlusive infarction) primarily by using CT or MRI,¹⁷ which were available for 89% of total stroke cases. Stroke cases without imaging studies were subclassified according to the clinical criteria⁴ as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke and stroke of undetermined type. The criteria for CAD were modified

Table 1. Baseline Characteristics for Study Participants Developing Stroke or CAD or Remaining Free of Cardiovascular Disease (CIRCS 1995–2000)

	Men (n=3,960)			Women (n=6,652)		
	Stroke	CAD	Free of CVD	Stroke	CAD	Free of CVD
n	188	94	3,678	176	43	6,433
Age, years	63.3 [§]	61.6 [†]	58.4	64.2 [§]	63.5 [§]	57.1
Systolic BP, mmHg	139.8 [§]	136.4	133.9	135.9 [†]	130.4	131.5
Diastolic BP, mmHg	86.6 [§]	83.9	82.7	81.9 [†]	81.7	79.3
Antihypertensive medication use, %	30.0 [§]	24.7	17.3	33.2 [§]	37.3 [§]	16.2
Hypertension, %	73.0 [§]	62.0	52.4	64.3 [§]	64.3 [†]	45.0
NonHDL-C, mmol/L	3.79	4.13 [§]	3.76	3.91	4.03	4.02
HDL-C, mmol/L	1.38	1.25 [§]	1.40	1.49	1.46	1.54
Lipid-lowering medication, %	4.9	2.9	2.8	2.3	4.5	5.6
High nonHDL-C, %	56.5	72.4 [†]	55.3	59.8	57.1	65.6
Low HDL-C, %	13.9	28.5 [§]	13.6	6.4	1.5	5.6
Hypertriglyceridemia, %	23.4 [*]	30.1 [†]	17.6	11.4	15.6	12.8
Hyperglycemia, %	27.8 [†]	30.9 [†]	18.6	14.7 [†]	4.4	9.5
Antidiabetic medication, %	4.1	7.0 [†]	2.9	5.3 [†]	0.0	2.1
Atrial fibrillation, %	4.4 [§]	0.8	1.1	3.2 [§]	4.5 [§]	0.2
Current smoking, %	54.5	58.2	49.0	6.8	13.2 [*]	5.6
Heavy smoking, %	36.1	51.5 [†]	34.9	1.1	2.8	1.8
Current drinking, %	75.6	60.0 [†]	73.3	10.7	12.8	14.1
Heavy drinking, %	37.6 [†]	22.7	27.9	0.8	0.2	0.6
BMI, kg/m ²	23.7	23.8	23.4	24.1 [†]	24.0	23.4
MetS, %	13.1	21.7	15.4	13.7	9.6	10.5
Funduscopy changes, %	40.7 [§]	29.6 [†]	17.0	30.9 [§]	24.3	15.3
ECG ST-T changes, %	11.6 [§]	12.0 [†]	5.0	10.0	5.2	6.8
Proteinuria, %	7.3 [†]	8.4 [†]	3.2	2.5	0.0	1.2
Low eGFR, %	20.8 [†]	21.8 [*]	14.4	17.2 [†]	24.0 [†]	10.4

Values are means or prevalence, adjusted for age and community. *P<0.1, †P<0.05, ‡P<0.01, §P<0.001 (difference from 'Free of CVD'). BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CIRCS, Circulatory Risk in Communities Study; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

from those of the World Health Organization Expert Committee,¹⁸ as previously reported in detail.¹⁹ In brief, the indication for definite myocardial infarction (MI) was typical severe chest pain (lasting ≥30 min and with no definite nonischemic cause) accompanied by new, abnormal, and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. If the electrocardiographic and enzyme levels were nondiagnostic or not obtainable, but the patient had typical chest pain, a diagnosis of possible MI was made. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or with the use of sublingual nitroglycerin. Sudden cardiac death (SCD) was defined as death within 1 h of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by ≥1 h of symptoms. We excluded SCD cases in which the cause of death was diagnosed as stroke, lethal arrhythmia, cardiomyopathy, or other organic heart diseases. CAD was defined as including definite or probable MI, angina pectoris, and SCD. The final diagnosis of stroke and CAD was made by a panel of 3 or 4 study physicians who were blinded to the baseline data.

Statistical Analysis

Age- and community-adjusted mean values or prevalence of baseline characteristics were compared between participants with and without subsequent stroke and CAD using

analysis of covariance or χ^2 tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for stroke and CAD were calculated with the referent group consisting of individuals without each risk factor by Cox proportional hazards models. Person-years were calculated as the sum of individual follow-up duration until the occurrence of stroke or CAD, death, or moving from the community, whichever occurred first.

We adjusted for age, sex and community in the initial model calculating HRs, and further adjusted for other potential confounding variables including HT (SBP/DBP ≥140/90 mmHg or current use of antihypertensive medication), high nonHDL-C (≥3.62 mmol/L or current use of cholesterol-lowering medication), low HDL-C (<1.03 mmol/L), hypertriglyceridemia (fasting serum triglycerides ≥1.69 mmol/L or non-fasting serum triglycerides ≥2.82 mmol/L), hyperglycemia (fasting serum glucose ≥6.11 mmol/L or non-fasting serum glucose ≥7.77 mmol/L,²⁰ or current use of antidiabetic medication), atrial fibrillation (Minnesota code 8-3-1 or 8-3-2), current smoking (or heavy smoking defined as ≥20 cigarettes/day) and current drinking (or heavy drinking defined as ≥46 g ethanol/day) in the multivariable-adjusted model. Multivariable HRs for metabolic syndrome (MetS) defined from the modified Japanese definition²¹ were adjusted for age, sex, community, high nonHDL-C, atrial fibrillation, and smoking and drinking status. We calculated the population attributable

Table 2. HR and PAF of Stroke and CAD in CIRCS 1995–2000

	No. at risk	Person-years	Stroke				
			No. of cases	Crude incidence, per 1,000 person-years	Age-, sex- and community-adjusted HR (95% CI)	Multivariable HR (95% CI)	PAF, %
Hypertension	5,156	62,624	279	4.5	2.6 (2.0–3.3) [§]	2.5 (2.0–3.3) [§]	46 (35–56)
High nonHDL-C	6,446	81,498	216	2.7	1.0 (0.8–1.2)	0.9 (0.7–1.1)	–
Low HDL-C	907	10,530	39	3.7	1.2 (0.8–1.6)	1.1 (0.8–1.5)	–
Hypertriglyceridemia	1,566	19,417	66	3.4	1.2 (0.9–1.6)	1.0 (0.8–1.4)	–
Hyperglycemia	1,401	15,873	86	5.4	1.6 (1.3–2.1) [§]	1.4 (1.1–1.8) [‡]	7 (2–12)
Atrial fibrillation	67	624	15	24.1	4.6 (2.7–7.8) [§]	4.9 (2.9–8.3) [§]	3 (1–5)
Current smoking	2,335	28,409	104	3.7	1.1 (0.8–1.5)	1.1 (0.8–1.6)	–
Heavy smoking	1,520	18,489	59	3.2	1.0 (0.7–1.5)	1.0 (0.7–1.5)	–
Current drinking	3,814	46,464	149	3.2	1.0 (0.8–1.4)	0.9 (0.7–1.3)	–
Heavy drinking	1,129	13,956	65	4.7	1.5 (1.0–2.1) [*]	1.2 (0.8–1.8)	–
MetS	1,308	15,866	51	3.2	2.7 (1.6–4.4) [§]	2.8 (1.7–4.7) [§]	9 (5–13)

	CAD				
	No. of cases	Crude incidence, per 1,000 person-years	Age-, sex- and community-adjusted HR (95% CI)	Multivariable HR (95% CI)	PAF, %
Hypertension	93	1.5	1.8 (1.2–2.6) [‡]	1.8 (1.2–2.5) [‡]	29 (9–45)
High nonHDL-C	67	0.8	1.7 (1.1–2.6) [†]	1.4 (0.9–2.2)	20 (0–40)
Low HDL-C	28	2.7	2.2 (1.4–3.3) [§]	1.7 (1.1–2.6) [†]	8 (0–16)
Hypertriglyceridemia	35	1.8	1.8 (1.2–2.7) [‡]	1.4 (1.0–2.2) [*]	7 (0–17)
Hyperglycemia	33	2.1	1.6 (1.1–2.4) [†]	1.4 (1.0–2.2) [*]	7 (0–16)
Atrial fibrillation	3	4.8	–	–	–
Current smoking	57	2.0	1.8 (1.1–3.2) [†]	2.0 (1.1–3.5) [†]	21 (4–34)
Heavy smoking	46	2.5	2.4 (1.3–4.4) [‡]	2.6 (1.4–4.8) [‡]	21 (8–31)
Current drinking	59	1.3	0.6 (0.4–0.8) [‡]	0.5 (0.3–0.8) [‡]	–
Heavy drinking	19	1.4	0.5 (0.3–0.9) [†]	0.4 (0.2–0.8) [‡]	–
MetS	25	1.6	1.7 (0.9–3.2) [*]	1.7 (0.9–3.2)	–

*P<0.1, †P<0.05, ‡P<0.01, §P<0.001. ^{||}Adjusted for age, sex, community, and other confounding variables including hypertension, high nonHDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation (only for stroke), smoking and drinking status. For MetS, HR was adjusted for age, sex, community, high nonHDL-C, atrial fibrillation (only for stroke), and smoking and drinking status. HRs and PAFs were calculated only when there were ≥5 cases. PAF was calculated only when the HR with adjustment for age, sex, and community was statistically significant (P<0.05). CI, confidence interval; HR, hazard ratio; PAF, population attributable fraction. Other abbreviations as in Table 1.

fraction (PAF) to estimate the contribution of each risk factor to the total stroke or CAD events with a standard formula: $PAF = \text{prop} \times (HR - 1) / HR$, where prop is the proportion of cases falling into each category and HR is the multivariate HR in the category.²²

We also calculated the risk of stroke and CAD associated with 4 markers indicating subclinical organ damage with HT. We conducted tests for trends across categories based on the number of markers of subclinical organ damage by assigning median values for each category (0, 1, 2, 3 or more) and testing for effect modification with sex using an interaction term generated by multiplying the median value for each category by sex. Probability values for statistical tests were 2-tailed. P<0.05 was regarded as statistically significant. SAS (version 9.4, SAS Institute, Cary, NC, USA) was used for all analyses.

Results

After a mean follow-up of 12.5 years (median, 13.1 years), we documented 364 strokes (188 in men, 176 in women) and 137 CAD events (94 in men, 43 in women). Stroke subtypes consisted of 126 hemorrhagic strokes, including 87 intraparenchymal hemorrhages and 39 subarachnoid hemorrhages; 232 ischemic strokes, including 127 lacunar infarctions, 67 large-artery occlusive infarctions and 38 unclassified infarctions; 6 strokes were of undetermined type. CAD consisted of 74 cases of MI, 35 of angina pectoris, and 28 of SCD.

Table 1 shows the age- and community-adjusted means and prevalence of baseline characteristics for stroke and CAD cases and for those who remained free of CVD. Among men and women who developed stroke, there was more HT, higher prevalence of hyperglycemia, atrial fibrillation, fundoscopic changes, and lower eGFR. Furthermore, men who developed stroke had higher prev-

Table 3. HR of Stroke and CAD for the Markers of Subclinical Organ Damage With Hypertension in CIRCS 1995–2000

	No. at risk	Person-years	Stroke				CAD			
			No. of cases	Crude incidence, per 1,000 person-years	Age-, sex- and community-adjusted HR (95% CI)	Multivariable HR (95% CI) [†]	No. of cases	Crude incidence, per 1,000 person-years	Age-, sex- and community-adjusted HR (95% CI)	Multivariable HR (95% CI) [†]
Nonhypertensive subjects	5,443	70,161	85	1.2	1.0	1.0	44	0.6	1.0	1.0
Hypertensive subjects with										
Funduscopy changes	1,157	13,801	100	7.2	3.8 (2.8–5.2) [†]	3.8 (2.8–5.1) [†]	33	2.4	2.5 (1.6–4.0) [†]	2.6 (1.6–4.2) [†]
ECG ST-T changes	456	5,199	40	7.7	4.0 (2.7–5.9) [†]	3.8 (2.5–5.6) [†]	13	2.5	3.0 (1.6–5.6) [†]	2.8 (1.5–5.4) [†]
Proteinuria	163	1,629	18	11.0	5.1 (2.9–8.7) [†]	4.9 (2.8–8.4) [†]	7	4.3	4.0 (1.8–9.0) [†]	3.9 (1.7–8.8) [*]
Low eGFR	781	8,724	75	8.6	3.7 (2.7–5.2) [†]	3.6 (2.6–5.0) [†]	27	3.1	3.0 (1.8–4.9) [†]	2.7 (1.6–4.5) [†]
No. of subclinical organ damage markers [§]										
0	2,451	30,528	88	2.9	2.0 (1.5–2.7) [†]	1.9 (1.4–2.6) [†]	31	1.0	1.3 (0.8–2.1)	1.4 (0.9–2.2)
1	1,366	16,448	79	4.8	2.5 (1.8–3.4) [†]	2.5 (1.8–3.4) [†]	30	1.8	2.0 (1.2–3.2) [*]	2.0 (1.2–3.2) [*]
2	352	3,937	45	11.4	5.7 (4.0–8.3) [†]	5.6 (3.8–8.1) [†]	18	4.6	4.7 (2.7–8.2) [†]	4.6 (2.6–8.1) [†]
3+	57	547	11	20.1	8.0 (4.0–16.0) [†]	8.2 (4.1–16.5) [†]	3	5.5	–	–
P for trend					<0.001	<0.001			<0.001	0.001
HR for an increase of 1 category number					1.7 (1.5–1.9) [†]	1.7 (1.5–1.9) [†]			1.6 (1.3–1.8) [†]	1.5 (1.3–1.8) [†]

*P<0.01, †P<0.001. ‡Adjusted for age, sex, community, and other confounding variables including high nonHDL-C, low HDL-C, hypertriglyceridemia, hyperglycemia, atrial fibrillation (only for stroke), and smoking and drinking status. §Indicate the number of subclinical organ damage markers comprising funduscopy changes, ECG ST-T changes, proteinuria, or low eGFR. HRs were calculated only when there were ≥5. Abbreviations as in Tables 1,2.

alence of heavy drinking, ST-T changes on ECG and proteinuria, while women developing stroke had higher mean body mass index. Men who developed CAD had higher prevalence of dyslipidemia, hyperglycemia, heavy smoking, funduscopy changes, ECG ST-T changes, proteinuria, and lower prevalence of current drinking compared with those who did not develop CVD. Women who developed CAD had more HT, higher prevalence of atrial fibrillation and low eGFR, and tended to have higher prevalence of current smoking.

Table 2 shows the HRs and PAFs of stroke and CAD in the presence of each risk factor. Atrial fibrillation was associated with the strongest risk of stroke (multivariable-adjusted HR, 4.9) followed by MetS, HT and hyperglycemia. In contrast, the PAF of stroke was the largest for HT at 46%, which was much larger than for other risk factors. These results were similar for men and women (**Table S1**). When stratified by hemorrhagic and ischemic strokes, HT and MetS were associated with increased risk of both types of stroke, but their associations were appeared stronger for hemorrhagic than for ischemic stroke (**Table S2**). Atrial fibrillation markedly increased the risk of ischemic stroke (multivariable-adjusted HR, 6.0), and hyperglycemia also increased the risk of ischemic stroke. HT had the largest

PAFs of both hemorrhagic and ischemic stroke: 57% and 42%, respectively.

The risk for CAD adjusted for age, sex, and community was 1.6–2.4-fold higher in the presence of every risk factor except alcohol consumption, which was associated with a 40–50% lower risk of CAD (**Table 2**). Multivariable adjustment did not weaken the positive associations for HT and current or heavy smoking with CAD. PAFs of CAD were relatively larger for HT, current or heavy smoking, and high nonHDL-C (20–29%) than for other risk factors. The PAFs of CAD tended to vary by sex (**Table S1**). In men, high nonHDL-C had the largest PAF (38%) of CAD, followed by heavy smoking (28%), whereas, in women, the PAF due to HT was the largest (48%).

Table 3 shows the risk of stroke and CAD associated with 4 markers of subclinical organ damage in the presence of HT. Compared with non-hypertensive subjects, the multivariable HRs for each marker of hypertensive subclinical organ damage were 3.6–4.9 for stroke and 2.6–3.9 for CAD. There was no interaction with sex (P for interaction >0.05). The risk of stroke and CAD was linearly associated with the number of comorbid hypertensive subclinical organ damage markers. The dose-response relationship was more noticeable for stroke than for CAD, for which

the HR at ≥ 3 subclinical organ damage markers was not calculated because of the small number of cases. Compared with the non-hypertensive group, the multivariable HR (95% CI) for hypertensive subjects with ≥ 2 markers of subclinical organ damage was 5.9 (4.1–8.4) for stroke and 4.5 (2.6–7.8) for CAD.

Discussion

This 12.5-year follow-up study of more than 10,000 Japanese residents revealed that, as in the late 1990s, HT still had the largest effect on the incidence of stroke and CAD at the population level, despite a downward trend in blood pressure levels and an increasing prevalence of anti-hypertensive medication use over the last decades of the 20th century in Japan.²³ The PAF of HT for stroke in the present study was 46%, which was consistent with findings from a recent international study in 32 countries²⁴ and 3 previous Japanese cohort studies from the late 1980s⁵ and early 1990s.^{4,6}

Comparing the individual effects of risk factors on stroke, it was apparent that atrial fibrillation was strongest risk factor for stroke, with an HR of approximately 5. On the other hand, the PAF of stroke due to atrial fibrillation was only 3% because of the very low prevalence of atrial fibrillation (0.6% in men and women). However, we may have underestimated the prevalence of atrial fibrillation because we examined only the standard ECG from a single health checkup, therefore the assessment of paroxysmal atrial fibrillation was insufficient.

In contrast to stroke, the relative risk of CAD was similar for a variety of risk factors (HT, low HDL-C, hypertriglyceridemia, hyperglycemia and smoking). Significant associations between these factors and incident CAD were in general agreement with previous findings from Japanese epidemiological studies.^{25–28} The present study also showed that HT, smoking, and high nonHDL-C were the top 3 contributors to incident CAD, with PAFs of 20–29%, suggesting that combined control may be more effective in preventing CAD.

Another novel finding of the present analysis was that each of the 4 markers of hypertensive subclinical organ damage (funduscopic changes, resting ECG ST-T changes, proteinuria, and low eGFR) was associated with approximately 3- and 4-fold higher risks of CAD and stroke, respectively, and these markers cumulatively increased the individual risk for CVD in a dose-response fashion. Compared with non-hypertensive subjects, those with HT and had ≥ 2 markers of subclinical organ damage exhibited a 5-fold increase in the risk of both stroke and CAD. These markers were considered to be reflective of the severity and duration of HT. To our knowledge, this is the first prospective study in a population-based sample to demonstrate the cumulative magnitude of markers of subclinical organ damage that are assessable at a screening examination, although a study in Copenhagen²⁹ showed that CVD risk increased with higher numbers of damaged organs, as assessed by echocardiography, pulse wave velocity, carotid ultrasound, and the urinary albumin/creatinine ratio. Although international clinical guidelines for the management of HT recommend assessing subclinical organ damage before deciding on a therapeutic strategy,^{7–10} our finding suggests that subclinical organ damage assessment for hypertensive subjects at the screening examination might be useful for preventing CVD as a population

strategy.

Study Limitations

First, the relatively small number of incident cases led to wide CIs for PAF due to several risk factors and difficulties in generating sex-specific results. Second, our criteria for CAD did not include unstable angina. This failure might have resulted in underestimation of the CAD burden in the present study, because recent progress in coronary intervention therapies has decreased the incidence of typical MI. Third, although we found a high risk of CVD associated with hypertensive subclinical organ damage, evaluating their predictive ability for CVD incidence is necessary in future studies. Fourth, the study participants were limited to Japanese residents, so it is uncertain whether our findings can be generalized to other populations. However, we infer that the magnitude of hypertensive subclinical organ damage markers for CVD incidence would be similar in other countries where CVD is a major burden, because HT is the most prevalent risk factor for stroke across major regions of the world.²⁴ Fifth, among the surveyed areas, Noichi had a short follow-up period for ascertainment of CVD because of discontinuation of the investigation in 2005 resulting from municipal mergers. However, when we excluded the subjects (2,582 residents at risk, 59 stroke and 19 CAD events) from Noichi, the magnitude of the association between each risk factor and the incidence of CVD was similar to the present findings that included the subjects from Noichi, while retaining the proportionality of a Cox proportional hazard model (data not shown). Therefore, we included the subjects from Noichi in the analysis to increase the statistical power. Finally, each risk factor was measured only once, which may have weakened the associations with the incidence of CVD, resulting in dilution bias, because of temporal changes and random errors in measurement of the exposure variables.³⁰ We did not evaluate the dilution bias using replicated measurements of the risk factors during the follow-up period in this study.

In summary, this population-based study of Japanese residents revealed that HT still has the largest effect on the incidence of stroke and CAD at the population level since the late 1990s: the PAF of stroke and CAD due to HT was 46% and 29%, respectively. Atrial fibrillation had a strong individual-level effect on ischemic stroke, and smoking and dyslipidemia were associated with the incidence of CAD. Hypertensive subclinical organ damage was cumulatively associated with the risk of incident stroke and CAD, suggesting ECG, retinal photography, urinalysis and estimation of GFR for hypertensive persons are useful components of a community-based screening examination to prevent CVD. From a public health perspective, we infer that blood pressure measurement and less invasive assessments of subclinical organ damage in hypertensive subjects would be beneficial in other countries where CVD is a major burden, because Japan has achieved successful prevention of stroke and CAD using this screening examination in a national prevention program.^{2,3}

Acknowledgments

The authors thank the study physicians, clinical laboratory technologists, public health nurses, nutritionists, nurses, engineers, clerks, and officers of the CIRCS collaborating research institutes and the affiliated institutions in Ikawa, the Minami-Takayasu district of Yao, Noichi, and Kyowa for their collaboration.

Disclosures

None.

Grants

This work was supported by a Grant-in-Aid for Scientific Research (Grant no. 26460791) from the Japan Society for the Promotion of Science and Comprehensive Research on Cardiovascular and Life-Style Related Diseases, the Japan Arteriosclerosis Prevention Fund for the Japan Arteriosclerosis Longitudinal Study (2001–2012) and H26-Junkankitou [Seisaku]-Ippan-001 from the Ministry of Health, Labour and Welfare of Japan.

References

- World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: WHO, 2014.
- Ikeda N, Saito E, Kondo N, Inoue M, Ikeda S, Satoh T, et al. What has made the population of Japan healthy? *Lancet* 2011; **378**: 1094–1105.
- Iso H. A Japanese health success story: Trends in cardiovascular diseases, their risk factors, and the contribution of public health and personalized approaches. *EPMA J* 2011; **2**: 49–57.
- Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, et al. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: The Circulatory Risk in Communities Study (CIRCS). *Stroke* 2009; **40**: 1571–1577.
- Fukuhara M, Arima H, Ninomiya T, Hata J, Yonemoto K, Doi Y, et al. Impact of lower range of prehypertension on cardiovascular events in a general population: The Hisayama Study. *J Hypertens* 2012; **30**: 893–900.
- Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: The JPHC Study. *Am J Hypertens* 2009; **22**: 273–280.
- Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281–1357.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; **42**: 1206–1252.
- Taryn K, Kate L, Mark C, Terry M, Bryan W. Management of hypertension: Summary of NICE guidance. *BMJ* 2011; **343**: d4891.
- Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, et al; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of hypertension guidelines for the management of hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–239.
- Council for International Organizations of Medical Sciences. International guidelines for ethical review of epidemiological studies. *Law Med Health Care* 1991; **19**: 247–258.
- Kirkendall WM, Feinleib M, Freis ED, Mark AL. Recommendations for human blood pressure determination by sphygmomanometers: Subcommittee of the AHA Postgraduate Education Committee. *Circulation* 1980; **62**: 1146A–1155A.
- Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003; **10**: 145–153.
- Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
- Ohira T, Iso H, Imano H, Kitamura A, Sato S, Nakagawa Y, et al. Prospective study of major and minor ST-T abnormalities and risk of stroke among Japanese. *Stroke* 2003; **34**: e250–e253.
- Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriosclerosis. *Arch Ophthalmol* 1953; **49**: 117–138.
- Iso H, Rexrode K, Hennekens CH, Manson JE. Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. *Ann Epidemiol* 2000; **10**: 81–87.
- WHO Expert Committee. Arterial hypertension and ischemic heart disease, preventive aspect: WHO technical report series no. 231. Geneva: World Health Organization, 1962.
- Kitamura A, Noda H, Nakamura M, Kiyama M, Okada T, Imano H, et al. Association between non-high-density lipoprotein cholesterol levels and the incidence of coronary heart disease among Japanese: The Circulatory Risk in Communities Study (CIRCS). *J Atheroscler Thromb* 2011; **18**: 454–463.
- Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
- Irie F, Iso H, Noda H, Sairenchi T, Otaka E, Yamagishi K, et al. Associations between metabolic syndrome and mortality from cardiovascular disease in Japanese general population, findings on overweight and non-overweight individuals: Ibaraki Prefectural Health Study. *Circ J* 2009; **73**: 1635–1642.
- Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.
- Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan: Where are we now? *Circ J* 2013; **77**: 2226–2231.
- O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet* 2016; **388**: 761–775.
- Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, et al. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: The Suita Study. *Stroke* 2009; **40**: 2674–2679.
- Konishi M, Iso H, Iida M, Naito Y, Sato S, Komachi Y, et al. Trends for coronary heart disease and its risk factors in Japan: Epidemiologic and pathologic studies. *Jpn Circ J* 1990; **54**: 428–435.
- Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: A 26-year follow-up, Hiroshima/Nagasaki study. *Jpn Circ J* 1990; **54**: 414–421.
- Kitamura A, Iso H, Naito Y, Iida M, Konishi M, Folsom AR, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. *Circulation* 1994; **89**: 2533–2539.
- Sehstedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C, et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J* 2010; **31**: 883–891.
- Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; **150**: 341–353.

Supplementary Files

Supplementary File 1

Table S1. HR and PAF of stroke and CAD according to sex in CIRCS 1995–2000

Table S2. HR and PAF of hemorrhagic and ischemic strokes in CIRCS 1995–2000

Appendix S1

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-16-1129>