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Absolute risk score for stroke, myocardial infarction, and all cardiovascular disease: Japan Arteriosclerosis Longitudinal Study

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Abstract

To develop a risk chart or score that is based on recent data and applicable to the Japanese people, we need a large cohort study representative of the Japanese people without a need for long-term follow-up. The purpose of the present study was to develop a risk scoring system to estimate the 5- and 10-year absolute and cumulative incidence risk of stroke and acute myocardial infarction (AMI), composite outcome of stroke and AMI, and death from all cardiovascular disease (CVD). The cumulative incidence risk ratios were calculated using a multiple Poisson regression model and data from the Japan Arteriosclerosis Longitudinal Study, which included 67,969 men and women aged 40–89 years. An absolute risk scoring system for 5- and 10-year risk was developed. For blood pressure categories, the risk ratios for all outcomes increased from normal blood pressure (systolic blood pressure (SBP) 120–129 mmHg and diastolic blood pressure (DBP) 80–89 mmHg) to grade III hypertension (SBP ≥ 180 and/or DBP ≥ 110) based on the 2014 Guidelines for the Management of Hypertension compared to the reference optimal blood pressure (SBP < 120 and DBP < 80). Grade II (SBP 160–179 and/or DBP 100–109) and III hypertension treated with medication showed a lower risk compared to counterparts without medication. Other risk factors showed reasonable figures. The total of scores for each risk factor indicated the estimated absolute risk for stroke and AMI, the composite outcome of stroke and AMI, and all CVD. This scoring system may contribute to patient education and to the development of strategies for reducing CVD in the population.

Keywords Cardiovascular disease · Myocardial infarction · Risk score · Risk prediction model · Stroke

Introduction

Several risk charts and scoring systems for cardiovascular disease (CVD) [1–8] have been published for patient education and risk assessment for treatment indication in the Japanese population since the NIPPON DATA80 risk chart [1]. To develop a risk chart or scoring system that is based on the most recent data and applicable to the Japanese people, we need a large cohort study representative of the Japanese people without requiring long-term follow-up.

The purpose of the present study was to develop a risk scoring system to estimate the 5- and 10-year absolute and cumulative incidence risk of stroke and acute myocardial infarction (AMI), the composite outcome of stroke and AMI and death from all CVD.

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Methods

Population

A total of 96,705 participants (aged ≥ 18 years) in 22 cohorts from Hokkaido to Okinawa were eligible to participate in the Japan Arteriosclerosis Longitudinal Study (JALS) with follow-up. The baseline survey was conducted from 2002 to 2004. The participants were followed from the date of the baseline survey until Dec 31, 2010. The present analyses were conducted after excluding following participants: 6739 participants with a past history of stroke and heart diseases; participants with an ambiguous last follow-up date for stroke ($n = 271$); one cohort without AMI surveys ($n = 1619$); three cohorts for which cause of death was not verified against national vital statistics ($n = 8677$); participants aged >90 years or <40 years; and those with missing adjusting covariates (Stoke: $n = 13,389$; AMI: $n = 13,229$; CVD death: $n = 8687$). A total of 67,969 participants were included in the present analyses for stroke risk, 66,602 for AMI, and 65,876 for death from all CVD (see Supplemental web Figure, available at the Hypertension Research website).

The mean participant age at baseline was 61.5 years, and the median follow-up period was 6.9 years. Approximately, 40% of the participants were men (Table 1), and 33.1% had hypertension (grades I–III).

Standardization

Several workshops involving the principal investigators for each cohort and their associates were conducted to discuss the study purpose, survey items, and criteria for incidence of stroke and coronary heart disease (CHD). Then, we outlined the standardized survey methods and developed operation manuals for blood pressure measurement, the self-administered questionnaire, and criteria for the incidence of stroke and CHD and their case report forms. Cases of mortality were also reported to the central data managing office, where the underlying cause of death was matched to indexes of age, sex and area code [9]. The international classification of diseases-10 (ICD-10) codes were used for all CVD (I00–I99).

Blood was drawn under non-fasting and fasting conditions. For serum total cholesterol and high-density lipoprotein (HDL) cholesterol, each laboratory received a quality control test from the standardization laboratory of Japan, which participated in the cholesterol quality control program and has been certified by the US Centers for Disease Control and Prevention and the Cholesterol Reference Methods Laboratory Network (CRMLN) [10].

Physical examination and questionnaire administration

For blood pressure measurement, an automatic blood pressure measurement device from any company using the oscillometric method was used. The mean of two blood SBP and DBP measurements was used for the analyses; the blood pressure measurements were obtained using cuffs of appropriate size while sitting after 5 min of rest and in the absence of conversation. Weight and height were measured, and body mass index (BMI) (weight/height^2, kg/m^2) was calculated. Standard 12-lead electrocardiography was performed at rest, and the Minnesota code was recorded [11].

A standardized self-administered questionnaire that was checked by a health professional was used to assess the past history and prevalence of disease, antihypertensive medication use (yes, no), smoking status and the year of smoking initiation, physical activity, and dietary habits.

Blood chemistry analyses

Blood was drawn in either fasting or nonfasting states with the time of the last meal recorded. Samples were sent to local laboratories for blood chemistry analysis, including serum total cholesterol, HDL cholesterol, triglycerides (TG), glucose, hemoglobin A1c (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (γ-GTP), and creatinine levels. Non-HDL cholesterol was calculated as follows: non-HDL cholesterol (mg/dL) = total cholesterol (mg/dL) − HDL cholesterol (mg/dL).

The estimated glomerular filtration ratio (eGFR) was calculated based on the following equation defined by the Japan Association of Chronic Kidney Disease Initiatives (J-CKDI): eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × (0.739 for females) [12].

Diagnostic criteria for stroke and AMI

The incidence of stroke and subtype were reported according to the standard form, which includes findings from computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain and signs and symptoms according to the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project criteria for stroke [13, 14].

Here, definite cases, which were confirmed using the MONICA Project criteria [14] by surveying medical records, and probable cases, i.e., those with insufficient data to confirm them as definite cases, were used as the outcomes. Probable cases without medical record surveys were identified and recorded as possible cases. These possible

Table 1 Baseline characteristics of Japan Arteriosclerosis Longitudinal Study cohorts in 2002–2004, and number of outcome cases during follow-up years of 2002–2010

Regions	Cohort name	Follow-up (years) Median	n	Sex Men	(%)	Age (years)	Blood pressure at baseline[a] Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3	CVD death	Observed endpoints Total stroke (TS)	CI	CH	MI	TS + MI
Hokkaido	Tanno/Soubetsu	7.4	1,345	502	37.3	64.0	326	217	204	342	189	67	22	12	3	7	0	12
Akita1	Akita	8.6	2,164	807	37.3	61.3	417	361	381	624	261	120	24	84	53	26	8	87
Iwate1	Iwate-KENCO	4.8	24,136	8247	34.2	63.0	8969	4383	4023	5109	1357	295	458	592	346	181	69	658
Iwate2	Higashiyama	5.0	965	465	48.2	59.3	373	218	150	167	48	9	11	15	10	3	3	13
Iwate3	Ohasama	8.6	1367	499	36.5	62.8	258	290	280	370	127	42	16	52	34	10	–	–
Ibaraki	Kyowa	7.1	2404	1025	42.6	59.9	430	372	528	717	279	78	64	37	25	6	9	45
Chiba	Kamogawa	6.6	1483	613	41.3	65.5	383	252	261	403	132	52	22	20	15	5	4	24
Niigata1/Gunma	Nagaoka(Yoita), Kusatsu	7.5	1334	482	36.1	67.4	339	248	304	341	82	20	18	22	13	5	6	27
Niigata2	Sado	7.5	6594	2768	42.0	64.2	2197	1265	1147	1450	434	101	157	140	92	35	40	176
Toyama worker		7.7	3939	2429	61.7	49.6	1912	706	524	598	166	33	17	47	22	14	12	59
Aichi worker		8.7	1778	1463	82.3	50.4	639	438	299	305	80	17	–	12	6	4	4	16
Shiga	Takashima	8.6	3785	1393	36.8	62.0	1,032	624	641	1014	374	100	56	60	49	7	19	79
Wakayama	Hidaka(Miyama, Nakatsu)	7.4	489	206	42.1	64.4	115	96	91	136	40	11	13	9	7	1	6	14
Akita2	Ikawa	7.6	1340	542	40.4	61.3	291	245	292	405	86	21	22	27	16	7	1	28
Osaka1	Minamitakayasu, Yao City	7.8	1621	514	31.7	60.1	409	266	252	455	183	56	16	13	5	5	12	25
Osaka worker		7.6	315	286	90.8	50.5	99	73	68	60	13	2	–	0	0	0	0	0
Hiroshima1	Hiroshima	7.5	1559	517	33.2	69.7	380	321	308	387	118	45	40	48	40	7	8	56
Ehime1	Hassei	8.3	5684	2019	35.5	62.2	844	859	976	1864	858	283	160	132	89	27	22	153
Ehime2	Imabari	8.4	104	28	26.9	70.7	36	16	19	24	9	0	7	5	4	1	1	6
Fukuoka	Hisayama	8.3	1,430	617	43.1	50.4	551	284	243	235	86	31	3	19	12	3	6	24
Okinawa	Ishigaki	6.3	2990	1088	36.4	59.9	788	703	689	677	112	21	22	5	2	3	3	8
Saga	Arita	6.3	1143	420	36.7	64.2	335	214	186	292	90	26	21	0	0	0	1	1
Total		6.9	67,969	26,930	39.6	61.5	21,123	12,451	11,866	15,975	5,124	1430	1169	1351	843	357	234	1511

CVD cardiovascular disease, CI cerebral infarction, CH cerebral hemorrhage, MI myocardial infarction, TS total stroke

[a]Guidelines for the Management of Hypertension 2014 (JSH2014)

cases were censored at event occurrence and excluded from this analysis. All stroke cases were classified based on CT and MRI findings and event symptoms into cerebral hemorrhage (CH), cerebral infarction, subarachnoid hemorrhage, and unknown type.

The criteria for AMI were also based on the MONICA Project [13]. In addition to the MONICA criteria, findings such as a thrombus or >75% stenosis of the culprit vessel on coronary angiography, abnormal movement of the myocardium on echocardiography, and rupture of the myocardium identified on a CT or during an autopsy for sudden death were considered definite cases. As for strokes, definite and probable cases were used for AMI.

The registration forms for both stroke and AMI include flow charts that guide diagnosis and classification (into definite and probable cases). Sudden deaths were also recorded on registration forms. If stroke or AMI were possible causes of sudden death, the form for stroke or AMI was used for diagnosis.

To calculate incidence rates, only the first definite or probable stroke (regardless of subtype) or AMI was considered. If a person had both stroke and AMI, both events were included.

Data coordination center and ethical approval

All participants agreed to participate in the JALS follow-up study and provided written informed consent to participate during the baseline survey. All data from each cohort were sent to the central data coordinating office at Tokyo University (located at Chuo University since April 2016) and underwent systematic quality checks according to established protocols. If the data were insufficient for a cohort, additional or corrected data were requested from the data coordinating office.

This study complied with the 2000 revision of the Declaration of Helsinki. The ethical committees of Shiga University of Medical Science (No. 22-63) and Chuo University (No. 2107-9) approved the JALS study, and all local principal investigators obtained approval for the study from their respective institutions.

Statistical analyses

We applied pooled mixed effect Poisson regression to estimate the incidence of stroke, AMI, and the composite outcome of stroke and AMI in relation to their risk factors. In addition, the risk ratio for death from all CVD (ICD-10, I00–I99) was estimated in the same manner. All categories of variables used in the analysis are listed in Table 2. To calculate risk ratios by blood pressure classification, the reference group was optimal blood pressure without antihypertensive medication, and risk ratios were obtained for

normal blood pressure; high-normal blood pressure; and grade I–III hypertension with/without medication following the Japanese Hypertension Society Guidelines for the Management of Hypertension (JSH 2014) [15]. We adjusted for the use of antihypertensive medication by modeling the impact of a participant's blood pressure differently on the basis of the use of such medications. For each participant, multiple observations with the same number of follow-up years (until event occurrence) were generated. The response variable in each observation except the last year was coded 0, and 1 or 0 was assigned in the last year depending on whether the participant experienced an event. As the offset (fixed constant) of the Poisson regression, the observed fraction of the year (1 except in the last year) in each observation was assigned. The cohort effect was treated as a random normal variable, and the age of the subject was included in the model as a categorical time-dependent covariate.

Variable selection was conducted in a backward manner, with the remaining threshold p value being 0.05—that is, the variable with the largest p value (>0.05) in the regression model was removed successively from the full model with all candidate covariates.

The absolute and cumulative incidence of 5- and 10-year risk were calculated based on selected risk factors for stroke, AMI, composite outcomes of stroke and AMI and all CVD death. To obtain a risk score, each 10-point increment in the score was assigned a 2.0 increment in risk. The 5-year cumulative incidence risk (%) was calculated using a simple approximate formula: $\{1 - \exp\ [-(5 \times 1\text{-year cumulative incidence rate for total score} = 0) \times (1.0718^{\text{Total score}})]\} \times 100$, where 1.0718 is the incidence rate ratio (IRR) per 1-point increment in the total score determined by $2^{0.1}$. The 10-year absolute cumulative incidence risk was estimated by combining the first and last 5-year risk as follows: $1 - (1 - (\text{first 5-year risk})) \times (1 - (\text{last 5-year risk}))$, where the last 5-year risk was calculated using the next age-category score. Model predictivity was evaluated using C-statistics. SAS software package for Windows, release 9.4 (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses.

Results

Table 2 shows the IRRs for stroke and the scores assigned for selected variables. The reference category with IRR 1 and a score of 0 was assigned for no atrial fibrillation (AF), normal blood pressure, age in the 40 s, no diabetes mellitus (DM), non-smoker and woman. BMI, HDL cholesterol, eGFR and non-HDL cholesterol did not have significant P values in the final model. Two models with/without AF were also estimated. The highest IRR was 4.18 for AF

Table 2 Risk ratio and score for stroke incidence, 67,969 participants with 6.9 mean follow-up years, JALS

Variables	Categories		No atrial fibrillation model			Atrial fibrillation model		
			IRR	Confidence interval	Score[a]	IRR	Confidence interval	Score[a]
Atrial fibrillation		No	–			1.00		0
		Yes	–			4.18	(3.27–5.34)	21
BMI (kg/m^2)		<18.5	–			–		
		18.5–25.0	–			–		
		25≤	–			–		
HDL-cholesterol (mg/dl)		<40	–			–		
		40–59	–			–		
		60≤	–			–		
Blood pressure[b]	No antihypertensive medication	Optimal BP	1.00		0	1.00		0
		Normal BP	1.64	(1.30–2.08)	7	1.65	(1.30–2.10)	7
		High-normal BP	1.64	(1.29–2.09)	7	1.64	(1.29–2.09)	7
		Grade I hypertension	2.65	(2.15–3.26)	14	2.69	(2.18–3.31)	14
		Grade II hypertension	4.23	(3.31–5.40)	21	4.25	(3.33–5.43)	21
		Grade III hypertension	6.32	(4.60–8.68)	27	6.50	(4.73–8.94)	27
	Antihypertensive medication	Optimal BP	2.33	(1.65–3.27)	12	2.22	(1.58–3.12)	11
		Normal BP	2.61	(1.92–3.54)	14	2.57	(1.89–3.48)	14
		High-normal BP	2.52	(1.90–3.33)	13	2.52	(1.90–3.34)	13
		Grade I hypertension	3.44	(2.75–4.31)	18	3.41	(2.73–4.27)	18
		Grade II hypertension	3.80	(2.89–5.00)	19	3.84	(2.92–5.05)	19
		Grade III hypertension	3.80	(2.46–5.86)	19	3.73	(2.42–5.75)	19
Age (years)		40–49	1.00		0	1.00		0
		50–59	1.32	(0.92–1.91)	4	1.31	(0.91–1.89)	4
		60–69	2.45	(1.72–3.49)	13	2.41	(1.69–3.42)	13
		70–79	5.10	(3.59–7.24)	24	4.93	(3.47–7.00)	23
		80≤	8.68	(6.03–12.49)	31	8.33	(5.78–11.99)	31
eGFR (mL/min/1.73 m^2)		<45	–			–		
		45–60	–			–		
		60–90	–			–		
		90≤	–			–		
Non-HDL-cholesterol (mg/dl)		<130	–			–		
		130–149	–			–		
		150–169	–			–		
		170≤	–			–		
Diabetes mellitus		No	1.00		0	1.00		0
		Yes	1.51	(1.30–1.74)	6	1.49	(1.29–1.73)	6
Sex		Men	1.38	(1.22–1.56)	5	1.31	(1.16–1.49)	4
		Women	1.00		0	1.00		0
Current smoking		No	1.00		0	1.00		0
		Yes	1.60	(1.38–1.85)	7	1.64	(1.42–1.89)	7
AUC			0.764			0.772		

IRR incidence rate ratio, *BMI* body mass index, *HDL* high-density lipoprotein, *BP* blood pressure, *eGFR* estimated glomerular filtration ratio by the equation of Japan Association of Chronic Kidney Disease Initiative (J-CKDI), *AUC* area under the curve

[a]Scores are determined by a formula $\log_2(IRR) \times 10$ in total score

[b]Blood pressure categories were defined as follows; "Optimal BP" as systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mmHg for "Normal BP," 130–139 or 85–89 mmHg (whichever was greater) for "high-normal BP," 140–159 or 90–99 mmHg for "Grade I hypertension," 160–179 or 100–109 mmHg for "Grade II hypertension" and ≥180 or ≥110 mmHg for "Grade III hypertension", respectively

(yes), and the score was 21. For blood pressure, the higher the category, the higher the IRR for participants with and without antihypertensive medication. Even in the normal blood pressure group, the risk ratios for those without antihypertensive medication and those with anti-hypertensive medication were 1.65 and 2.57, respectively, compared with the optimal blood pressure group. However, those with grade II and III hypertension who were being treated with medication had lower IRRs than those without medication (4.25 vs. 3.84 ($p = 0.46$) and 6.50 vs. 3.73 ($p = 0.02$) for grade II and III, respectively). The IRRs for DM, men, and current smokers were 1.49, 1.31, and 1.64, respectively. In terms of age, the risk of very old people (aged ≥ 80 years) was approximately 8 times higher com-pared with 40–49 years old. There were no substantial differences in the IRRs for variables in the models with/without AF.

HDL cholesterol and non-HDL cholesterol were risk factors for AMI (Table 3), as were high blood pressure, DM, and current smoking. For blood pressure treated with medication, the IRR for grade II and III hypertension was not significantly lower than that for grade I (1.56 vs. 2.14 ($p = 0.82$) and 1.86 vs. 2.14 ($p = 0.42$)), and the results did not show a stepwise relationship. BMI and eGFR were not retained as risk factors in the final model. The risk factors for AMI included HDL-C and non-HDL-C, which were different from the risk factors for stroke. The contribution of DM was greater for AMI than for stroke.

Risk factors for the composite outcomes of stroke and AMI were between those of stroke and AMI but closer stroke risk factors because of the larger number of cases of stroke than AMI (Table 4).

For CVD death, all variables except non-HDL choles-terol were included in the regression model and were sig-nificant (Table 5). The weight of AF risk was lower than that of the composite outcome of stroke and AMI. Lower BMI and lower HDL cholesterol were risk factors. DM, although a significant risk factor, was weaker than for stroke, AMI, and the composite outcome. Again, those with grade II and III hypertension treated with medication had a lower risk than those without medication. Regardless of whether AF was included in the regression models, most variables showed similar risk levels.

Table 6 shows the 5- and 10-year absolute risk for stroke, AMI, composite outcomes of stroke and AMI and mortality from CVD by age category. The scores in Table 6 represent residual scores calculated by subtracting the age score from the total score. For example, using Table 2 and Table 6 to assess stroke risk, if a man (score = 4) is 75 years old (score = 23), has grade II hypertension without medication (score = 21), does not have diabetes (score = 0) and is a nonsmoker (score = 0), then his stroke score is 25 (total score 48) and the corresponding 5-year absolute risk for

stroke is 3.08%. The 10-year absolute incidence risk was estimated by combining the first and last 5-year absolute risk, where the last 5-year absolute risk was calculated using the next age category score. Using the previous example, the 10-year absolute risk of stroke for a 75-year-old male is 8.07% in the score = 25 row and 70–79 years column, where last 5-year absolute risk was calculated using the age score for an 80–89-year old.

The threshold on the target blood pressure level and diagnosis of hypertension set in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines [16] and the threshold for treating blood pressure set in the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines [17] is 130/80 mmHg. Supplemental tables S1-S5 show the results considering a target threshold change in the ACC/AHA and ESC/ESH guidelines.

Discussion

This large-scale, standardized cohort study of the Japanese population reports the most recent risk scoring system (years 2002–2010) based on age, sex, blood pressure (JSH2014) [15], antihypertensive medication use, smoking status, non-HDL cholesterol level, HDL cholesterol level, DM, BMI, and eGFR and provides scores for the incidence of stroke, AMI, the composite outcome of stroke and AMI, and mortality from all CVD. Although this cooperative cohort study does not include a randomized sample drawn from all over Japan as in the NIPPON DATA80 [1], the participants include individuals from Hokkaido (the north island) and Okinawa and Kyushu (south islands). Therefore, the absolute risks estimated by this scoring system are expected to be applicable to the Japanese population in 2010.

Although previously developed risk scoring systems and risk charts used to educate and motivate patients to make appropriate lifestyle changes and take medications [1–8] are still useful, the estimated absolute risks do not necessarily represent present day risks, as both the incidence of and mortality from CVD have changed with changes in risk factors. In addition, both the incidence of and mortality from CHD are lower in Japan than in Western countries [18, 19]; thus, there are only few cohort studies on AMI risk charts, scoring systems [1, 5, 7, 8] and the incidence risk of AMI. When treated with medication, grade II and III hypertension did not have a higher IRR than grade I hypertension. The reason is not clear, and this result may be due to the relatively small number of AMI cases.

These scoring systems may be useful for planning public health policy in a given area or population. If we could determine the risk status of a population, we could calculate

Table 3 Risk ratio and score for incidence of acute myocardial infarction, 66,602 participants with 6.9 mean follow-up years, JALS

	Categories	No atrial fibrillation model			Atrial fibrillation model		
		IRR	Confidence interval	score[a]	IRR	Confidence interval	Score[a]
Atrial fibrillation	No	–			1.00		0
	YES	–			2.41	(1.12–5.14)	13
BMI (kg/m²)	<18.5	–			–		
	18.5–25.0	–			–		
	25≤	–			–		
HDL-cholesterol (mg/dl)	<40	2.12	(1.38–3.25)	11	2.11	(1.38–3.24)	11
	40–59	1.64	(1.18–2.27)	7	1.64	(1.18–2.27)	7
	60≤	1.00		0	1.00		0
Blood pressure[b]	No antihypertensive medication Optimal BP	1.00		0	1.00		0
	Normal BP	1.23	(0.73–2.06)	3	1.23	(0.73–2.07)	3
	High-normal BP	1.47	(0.89–2.43)	6	1.47	(0.89–2.43)	6
	Grade I hypertension	1.65	(1.04–2.61)	7	1.66	(1.05–2.63)	7
	Grade II hypertension	1.82	(0.99–3.36)	9	1.83	(0.99–3.36)	9
	Grade III hypertension	3.18	(1.45–6.96)	17	3.21	(1.46–7.03)	17
	Antihypertensive medication Optimal BP	1.18	(0.42–3.37)	2	1.15	(0.40–3.29)	2
	Normal BP	2.64	(1.34–5.17)	14	2.61	(1.33–5.13)	14
	High-normal BP	3.15	(1.80–5.54)	17	3.17	(1.81–5.57)	17
	Grade I hypertension	2.14	(1.27–3.60)	11	2.14	(1.27–3.60)	11
	Grade II hypertension	1.56	(0.73–3.31)	6	1.56	(0.74–3.32)	6
	Grade III hypertension	1.88	(0.57–6.22)	9	1.86	(0.56–6.14)	9
Age (years)	40–49	1.00		0	1.00		0
	50–59	2.19	(1.02–4.69)	11	2.18	(1.02–4.67)	11
	60–69	2.55	(1.20–5.45)	14	2.53	(1.18–5.39)	13
	70–79	4.38	(2.06–9.31)	21	4.31	(2.03–9.15)	21
	80≤	7.14	(3.20–15.94)	28	6.99	(3.13–15.61)	28
eGFR (mL/min/1.73m2)	<45	–			–		
	45–60	–			–		
	60–90	–			–		
	90≤	–			–		
Non-HDL-cholesterol (mg/dl)	<130	1.00		0	1.00		0
	130–149	1.94	(1.28–2.93)	10	1.96	(1.30–2.96)	10
	150–169	2.41	(1.60–3.62)	13	2.43	(1.61–3.66)	13
	170≤	3.22	(2.17–4.76)	17	3.24	(2.19–4.79)	17
Diabetes mellitus	No	1.00		0	1.00		0
	Yes	1.87	(1.36–2.55)	9	1.85	(1.35–2.54)	9
Sex	Men	3.21	(2.32–4.44)	17	3.16	(2.28–4.37)	17
	Women	1.00		0	1.00		0
Current smoking	No	1.00		0	1.00		0
	Yes	2.04	(1.52–2.75)	10	2.05	(1.52–2.77)	10
AUC		0.812			0.814		

IRR incidence rate ratio, *BMI* body mass index, *HDL* high-density lipoprotein, *BP* blood pressure, *eGFR* estimated glomerular filtration ratio by the equation of Japan Association of Chronic Kidney Disease Initiative (J-CKDI), *AUC* area under the curve

[a]Scores are determined by a formula $\log_2(IRR) \times 10$ in total score

[b]Blood pressure categories were defined as follows; "Optimal BP" as systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mmHg for "Normal BP," 130–139 or 85–89 mmHg (whichever was greater) for "high-normal BP," 140–159 or 90–99 mmHg for "Grade I hypertension," 160–179 or 100–109 mmHg for "Grade II hypertension" and ≥180 or≥ 110 mmHg for "Grade III hypertension", respectively

the future risk of the population and develop a preventive plan with possible risk modification based on these tools [1].

It is noteworthy that in the present JALS study, those with grade II and III hypertension treated with anti-hypertensive medication showed a lower risk than those not

Table 4 Risk ratio and score for incidence of composite outcome of stroke and acute myocardial infarction, 66,602 participants with 6.9 mean follow-up years, JALS

		Categories	No atrial fibrillation model			Atrial fibrillation model		
			IRR	Confidence interval	Score[a]	IRR	Confidence interval	Score[a]
Atrial fibrillation		No	–			1.00		0
		Yes	–			3.98	(3.14–5.03)	20
BMI (kg/m^2)		<18.5	–			–		
		18.5–25.0	–			–		
		25≤	–			–		
HDL-cholesterol (mg/dl)		<40	1.30	(1.09–1.55)	4	1.29	(1.08–1.55)	4
		40–59	1.13	(1.01–1.26)	2	1.13	(1.01–1.26)	2
		60≤	1.00			1.00		
Blood pressure[b]	No antihypertensive medication	Optimal BP	1.00		0	1.00		0
		Normal BP	1.55	(1.25–1.94)	6	1.57	(1.25–1.95)	6
		High-normal BP	1.67	(1.34–2.09)	7	1.68	(1.34–2.10)	7
		Grade I hypertension	2.54	(2.09–3.08)	13	2.58	(2.13–3.13)	14
		Grade II hypertension	3.82	(3.03–4.81)	19	3.84	(3.05–4.84)	19
		Grade III hypertension	5.95	(4.40–8.04)	26	6.12	(4.53–8.27)	26
	Antihypertensive medication	Optimal BP	2.11	(1.52–2.93)	11	2.02	(1.45–2.80)	10
		Normal BP	2.68	(2.03–3.55)	14	2.64	(1.99–3.50)	14
		High-normal BP	2.65	(2.05–3.43)	14	2.67	(2.07–3.45)	14
		Grade I hypertension	3.20	(2.60–3.95)	17	3.18	(2.58–3.92)	17
		Grade II hypertension	3.35	(2.57–4.36)	17	3.38	(2.60–4.40)	18
		Grade III hypertension	3.46	(2.27–5.27)	18	3.41	(2.24–5.19)	18
Age (years)		40–49	1.00		0	1.00		0
		50–59	1.46	(1.05–2.05)	5	1.45	(1.04–2.03)	5
		60–69	2.52	(1.82–3.49)	13	2.47	(1.78–3.43)	13
		70–79	5.04	(3.64–6.98)	23	4.88	(3.52–6.76)	23
		80≤	8.35	(5.94–11.74)	31	8.03	(5.71–11.29)	30
eGFR (mL/min/1.73 m^2)		<45	–			–		
		45–60	–			–		
		60–90	–			–		
		90≤	–			–		
Non-HDL-cholesterol (mg/dl)		<130	–			–		
		130–149	–			–		
		150–169	–			–		
		170≤	–			–		
Diabetes Mellitus		No	1.00		0	1.00		0
		Yes	1.56	(1.36–1.78)	6	1.54	(1.35–1.77)	6
Sex		Men	1.51	(1.35–1.70)	6	1.44	(1.29–1.62)	5
		Women	1.00		0	1.00		0
Current smoking		No	1.00		0	1.00		0
		Yes	1.66	(1.46–1.90)	7	1.70	(1.48–1.94)	8
AUC			0.764			0.771		

IRR incidence rate ratio, *BMI* body mass index, *HDL* high-density lipoprotein, *BP* blood pressure, *eGFR* estimated glomerular filtration ratio by the equation of Japan Association of Chronic Kidney Disease Initiative (J-CKDI), *AUC* area under the curve

[a]Scores are determined by a formula $\log_2(\text{IRR}) \times 10$ in total score

[b]Blood pressure categories were defined as follows; 'Optimal BP' as systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mmHg for "Normal BP," 130–139 or 85–89 mmHg (whichever was greater) for "high-normal BP," 140–159 or 90–99 mmHg for "Grade I hypertension," 160–179 or 100–109 mmHg for "Grade II hypertension" and ≥180 or ≥110 mmHg for "Grade III hypertension", respectively

using medication not only for the incidence risk of stroke and AMI but also for mortality from CVD. Previous cohort studies have shown that patients using antihypertensive medication are always at a higher risk than those not using medication [20–23]. The findings from previous cohort studies have suggested that patients with hypertension

Table 5 Risk ratio and score for all cardiovascular death, 65,876 participants with 6.9 mean follow-up years, JALS

		Categories	No atrial fibrillation model			Atrial fibrillation model		
			IRR	Confidence interval	Score[a]	IRR	Confidence interval	Score[a]
Atrial fibrillation		No	–			1.00		0
		Yes	–			3.53	(2.73–4.56)	18
BMI (kg/m^2)		<18.5	1.55	(1.23–1.95)	6	1.57	(1.25–1.97)	7
		18.5–25.0	1.00		0	1.00		0
		25≤	0.91	(0.80–1.04)	−1	0.90	(0.79–1.03)	−2
HDL-cholesterol (mg/dl)		<40	1.24	(1.02–1.51)	3	1.22	(1.00–1.48)	3
		40–59	0.93	(0.82–1.06)	−1	0.94	(0.83–1.06)	−1
		60≤	1.00		0	1.00		0
Blood pressure[b]	No antihypertensive medication	Optimal BP	1.00		0	1.00		0
		Normal BP	1.02	(0.80–1.30)	0	1.03	(0.81–1.32)	0
		High-normal BP	1.29	(1.03–1.62)	4	1.30	(1.04–1.64)	4
		Grade I hypertension	1.32	(1.07–1.62)	4	1.35	(1.09–1.67)	4
		Grade II hypertension	2.06	(1.60–2.66)	10	2.11	(1.64–2.71)	11
		Grade III hypertension	2.39	(1.65–3.47)	13	2.51	(1.73–3.64)	13
	Antihypertensive medication	Optimal BP	1.64	(1.19–2.26)	7	1.56	(1.13–2.16)	6
		Normal BP	1.78	(1.33–2.39)	8	1.79	(1.33–2.40)	8
		High-normal BP	1.25	(0.93–1.67)	3	1.28	(0.95–1.71)	4
		Grade I hypertension	1.53	(1.22–1.93)	6	1.55	(1.23–1.96)	6
		Grade II hypertension	1.76	(1.33–2.33)	8	1.81	(1.36–2.40)	9
		Grade III hypertension	1.43	(0.87–2.35)	5	1.41	(0.86–2.32)	5
Age (years)		40–49	1.00		0	1.00		0
		50–59	1.52	(0.83–2.75)	6	1.51	(0.83–2.74)	6
		60–69	3.06	(1.74–5.37)	16	3.02	(1.72–5.29)	16
		70–79	11.32	(6.54–19.59)	35	11.01	(6.36–19.05)	35
		80≤	47.97	(27.62–83.30)	56	46.20	(26.60–80.25)	55
eGFR (mL/min/1.73 m^2)		<45	2.15	(1.70–2.71)	11	2.10	(1.66–2.65)	11
		45–60	1.18	(1.02–1.37)	2	1.17	(1.01–1.36)	2
		60–90	1.00		0	1.00		0
		90≤	1.10	(0.89–1.35)	1	1.11	(0.90–1.36)	2
Non-HDL-cholesterol (mg/dl)		<130	–			–		
		130–149	–			–		
		150–169	–			–		
		170≤	–			–		
Diabetes mellitus		No	1.00		0	1.00		0
		Yes	1.30	(1.10–1.52)	4	1.28	(1.09–1.50)	4
Sex		Men	1.57	(1.38–1.79)	7	1.51	(1.33–1.73)	6
		Women	1.00		0	1.00		0
Current smoking		No	1.00		0	1.00		0
		Yes	1.86	(1.60–2.17)	9	1.89	(1.62–2.20)	9
AUC			0.828			0.832		

IRR incidence rate ratio, *BMI* body mass index, *HDL* high-density lipoprotein, *BP* blood pressure, *eGFR* estimated glomerular filtration ratio by the equation of Japan Association of Chronic Kidney Disease Initiative (J-CKDI), *AUC* area under the curve

[a]Scores are determined by a formula $\log_2(IRR) \times 10$ in total score

[b]Blood pressure categories were defined as follows; "Optimal BP" as systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg; the corresponding systolic and diastolic blood pressure values were 120–129 and 80–84 mmHg for "Normal BP," 130–139 or 85–89 mmHg (whichever was greater) for "high-normal BP," 140–159 or 90–99 mmHg for "Grade I hypertension," 160–179 or 100–109 mmHg for "Grade II hypertension" and ≥180 or ≥110 mmHg for "Grade III hypertension", respectively

treated with medication had a higher risk with other confounding CVD risk factors, e.g., long-term hypertension with organ damage, compared to those whose blood pressure levels were the same at baseline but were not using medication. These explanations have been accepted, although the treatment of hypertension undoubtedly lowers blood pressure and reduces CVD risk [15, 24]. The present JALS study is the first to report that patients with hypertension using antihypertensive medication were at lower risk than those not using medication. It may be that patients

Table 6 Five-and 10-year absolute risk for incidence of stroke, acute myocardial infarction and composite outcome of stroke and acute myocardial infarction, and death for cardiovascular diseases[a]

Score[b]	40–49		50–59		60–69		70–79		80–89	
	5 year	10 year	5 year	10 year	5 year	10 year	5 year	10 year	5 year	10 year
Stroke model (AF is included)										
0	0.11	0.26	0.15	0.42	0.27	0.82	0.55	1.48	0.93	1.85
5	0.16	0.37	0.21	0.59	0.38	1.16	0.78	2.08	1.31	2.61
10	0.22	0.52	0.29	0.83	0.54	1.63	1.10	2.93	1.85	3.67
15	0.32	0.73	0.42	1.17	0.76	2.30	1.55	4.12	2.61	5.15
20	0.45	1.03	0.59	1.65	1.07	3.24	2.19	5.77	3.67	7.20
25	0.63	1.46	0.83	2.33	1.52	4.55	3.08	8.07	5.15	10.03
30	0.89	2.05	1.17	3.28	2.14	6.37	4.33	11.21	7.20	13.88
35	1.26	2.89	1.65	4.61	3.01	8.89	6.06	15.48	10.03	19.05
40	1.78	4.06	2.33	6.45	4.23	12.33	8.47	21.17	13.88	25.83
45	2.51	5.70	3.28	9.00	5.92	16.98	11.76	28.57	19.05	34.47
50	3.52	7.96	4.60	12.49	8.27	23.14	16.21	37.86	25.83	44.99
55	4.95	11.07	6.44	17.20	11.50	31.08	22.13	48.97	34.47	57.05
60	6.92	15.29	8.99	23.42	15.86	40.93	29.80	61.38	44.99	69.74
AMI model (AF is included)										
0	0.01	0.02	0.02	0.03	0.02	0.05	0.03	0.08	0.05	0.09
5	0.01	0.03	0.02	0.04	0.02	0.06	0.04	0.11	0.07	0.13
10	0.01	0.04	0.03	0.06	0.03	0.09	0.06	0.15	0.09	0.19
15	0.02	0.06	0.04	0.09	0.05	0.13	0.08	0.21	0.13	0.26
20	0.03	0.09	0.06	0.13	0.07	0.18	0.12	0.30	0.19	0.37
25	0.04	0.12	0.08	0.18	0.10	0.26	0.16	0.43	0.26	0.53
30	0.05	0.17	0.12	0.25	0.14	0.36	0.23	0.60	0.37	0.74
35	0.08	0.24	0.17	0.36	0.19	0.52	0.33	0.85	0.53	1.05
40	0.11	0.34	0.23	0.50	0.27	0.73	0.46	1.20	0.74	1.48
45	0.15	0.48	0.33	0.71	0.38	1.03	0.65	1.69	1.05	2.09
50	0.21	0.68	0.47	1.00	0.54	1.45	0.92	2.38	1.48	2.94
55	0.30	0.96	0.66	1.41	0.76	2.04	1.29	3.35	2.09	4.14
60	0.43	1.35	0.93	1.99	1.07	2.88	1.82	4.71	2.94	5.80
Composite model (AF is included)										
0	0.12	0.29	0.17	0.46	0.29	0.86	0.57	1.51	0.94	1.88
5	0.17	0.41	0.24	0.65	0.41	1.22	0.81	2.13	1.33	2.64
10	0.24	0.58	0.34	0.92	0.58	1.72	1.14	3.00	1.88	3.72
15	0.33	0.82	0.48	1.30	0.82	2.42	1.62	4.22	2.64	5.22
20	0.47	1.15	0.68	1.84	1.16	3.41	2.28	5.91	3.72	7.30
25	0.67	1.62	0.97	2.59	1.64	4.79	3.20	8.25	5.22	10.16
30	0.94	2.29	1.36	3.64	2.31	6.70	4.50	11.47	7.30	14.06
35	1.33	3.22	1.92	5.11	3.25	9.35	6.30	15.83	10.16	19.29
40	1.87	4.52	2.71	7.14	4.56	12.96	8.80	21.62	14.06	26.15
45	2.63	6.34	3.80	9.95	6.39	17.82	12.21	29.15	19.29	34.86
50	3.70	8.84	5.34	13.78	8.91	24.24	16.82	38.57	26.15	45.46
55	5.20	12.27	7.46	18.91	12.37	32.46	22.93	49.80	34.86	57.57
60	7.27	16.91	10.39	25.65	17.03	42.60	30.81	62.26	45.46	70.25
CVD model (AF is included)										
0	0.07	0.17	0.10	0.30	0.20	0.94	0.74	3.77	3.05	6.01

Table 6 (continued)

| Score[b] | Age categories (year) | | | | | | | | | |
| | 40–49 | | 50–59 | | 60–69 | | 70–79 | | 80–89 | |
	5 year	10 year	5 year	10 year	5 year	10 year	5 year	10 year	5 year	10 year
5	0.10	0.24	0.14	0.43	0.29	1.32	1.04	5.29	4.29	8.40
10	0.13	0.34	0.20	0.61	0.40	1.87	1.47	7.39	6.01	11.67
15	0.19	0.48	0.29	0.86	0.57	2.63	2.07	10.29	8.40	16.09
20	0.27	0.67	0.40	1.21	0.81	3.70	2.91	14.24	11.67	21.97
25	0.38	0.95	0.57	1.70	1.14	5.19	4.09	19.53	16.09	29.59
30	0.54	1.34	0.81	2.40	1.61	7.26	5.74	26.45	21.97	39.12
35	0.76	1.89	1.14	3.38	2.27	10.10	8.02	35.24	29.59	50.43
40	1.07	2.66	1.61	4.74	3.19	13.98	11.15	45.91	39.12	62.93
45	1.51	3.74	2.26	6.64	4.48	19.19	15.40	58.06	50.43	75.43
50	2.13	5.24	3.18	9.26	6.28	26.01	21.06	70.74	62.93	86.26
55	2.99	7.33	4.47	12.84	8.76	34.69	28.43	82.41	75.43	93.96
60	4.21	10.21	6.27	17.66	12.16	45.26	37.68	91.44	86.26	98.11

[a]Values mean 5- and 10-year absolute absolute risks for stroke, AMI, and the composite outcomes of stroke and AMI, and for mortality from CVD, according to age categories.

[b]Score mean subtract values age score from total score.

For example, score "0" for 75 year means woman having no risk factors except for age score. Stroke score for 75 year (score = 23) man (score = 4) in grade II hypertension without medication (score = 21), nondiabetes (score = 0) and nonsmoking (score = 0) is 25 (total score 48), and corresponding 5-year absolute risk of stroke is 3.08%.

Absolute incidence risks for 10 years were estimated by combining the first and last 5-year absolute risks, where the last 5-year risk was calculated using the next age category score. For the previous example, 10-year absolute risk of stroke for 75 year could be referred 8.07% in the score = 25 row and 70–79 year column, where last 5 year risk was calculated using age score with 80–89 year

whose hypertension is treated with medication had better risk control not only for blood pressure but also other risk factors compared to those who do not take medication, although this assertion was not confirmed by repeated measurement of risk factors during follow-up.

For stroke, AF has a high risk score compared with other factors, except for old age, which is consistent with the findings of previous cohort studies [18, 19, 25–29]. Non-HDL cholesterol and HDL cholesterol are not risk factors for stroke. These findings are also comparable to those of other previous cohort studies [18, 19, 25–29]. DM and smoking had similar risk ratios to those obtained in previous cohort studies [18, 30]. On the contrary, non-HDL cholesterol and HDL cholesterol were risk factors for AMI [18, 19, 25–29].

eGFR was not significantly related to stroke, AMI, or CVD. These findings imply that traditional risk factors, including age, were more strongly related to outcomes and exhibited collinearity with other risk factors. Regarding other possible causes, recent studies have shown that proteinuria, rather than eGFR, is a risk factor for CVD among elderly people, whereas a relation with eGFR is observed for younger cohorts [31, 32]. High eGFR caused by glomerular hyper-filtration or decreasing muscle volume is also thought to be a risk factor [33, 34]. Our results, which show that eGFR was not a risk factor for CVD, may be attributable the inclusion of a large number of elderly people. Our risk score model does not include proteinuria because it could not be measured as a risk factor in all study groups. This is a limitation of this study. BMI was not a risk factor, nor was eGFR. This result is also not unexpected, as BMI is a mediator of blood pressure, serum cholesterol, and TG [35].

Another limitation of the present JALS findings is that only one baseline measurement was performed, and no repeated data collection was performed during the follow-up period 2002–2010. Therefore, the estimation of risk may be slightly diluted. However, this regression dilution effect may be overcome to some extent by the large sample size used to estimate the risk ratios.

In conclusion, this absolute incidence and mortality risk scoring system for Japanese people is based on the most recent data (2002–2010) and a large-scale, standardized cohort study. This scoring system could be used not only for patient education but also to develop population strategies to reduce the risk of CVD among the public.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J. 2006;70:1249–55.
2. Arima H, Yonemoto K, Doi Y, Ninomiya T, Hata J, Tanizaki Y, et al. Development and validation of a cardiovascular risk prediction model for Japanese: the Hisayama study. Hypertens Res. 2009;32:1119–22.
3. Matsumoto M, Ishikawa S, Kayaba K, Gotoh T, Nago N, Tsutsumi A, et al. Risk charts illustrating the 10-year risk of myocardial infarction among residents of Japanese Rural Communities: the JMS Cohort Study. J Epidemiol. 2009;19:94–100.
4. Ishikawa S, Matsumoto M, Kayaba K, Gotoh T, Nago N, Tsutsumi A, et al. Risk charts illustrating the 10-year risk of stroke among residents of Japanese Rural Communities: the JMS Cohort Study. J Epidemiol. 2009;19:101–6.
5. Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, et al. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events—the JALS-ECC. Circ J. 2010;74:1346–56.
6. Yatsuya H, Iso H, Yamagishi K, Kokubo Y, Saito I, Suzuki K, et al. Development of a point-based prediction model for the incidence of total stroke: Japan public health center study. Stroke. 2013;44:1295–302.
7. Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, et al. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study. J Atheroscler Thromb. 2014;21:784–98.
8. Yatsuya H, Iso H, Li Y, Yamagishi K, Kokubo Y, Saito I, et al. Development of a risk equation for the incidence of coronary artery disease and ischemic stroke for middle-aged Japanese—Japan Public Health Center-Based Prospective Study. Circ J. 2016;80:1386–95.
9. Harada A, Okayama A, Kita Y, Ohashi Y, Ueshima H, Yasumura S, Japan Arteriosclerosis Longitudinal Study Group. Problems of the identification cause of death using Vital statistics in large cohort study in Japan (in Japanese). J Health Welf Stat. 2012;59:1–8.
10. 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;10:145–53.
11. Blackburn H. Classification of the electrocardiogram for population studies: Minnesota code. J Electrocardiol. 1969;2:305–10.
12. 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;53:982–92.
13. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation. 1994;90:583–612.
14. Asplund K, Tuomilehto J, Stegmayr B, Wester PO, Tunstall-Pedoe H. Diagnostic criteria and quality control of the registration of stroke events in the MONICA project. Acta Med Scand Suppl. 1988;728:26–39.
15. 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 H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res. 2014;37:253–390.
16. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–324.
17. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104.
18. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al. Cardiovascular disease and risk factors in Asia: a selected review. Circulation. 2008;118:2702–9.
19. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb. 2007;14:278–86.
20. Lindholm L, Ejlertsson G, Schersten B. High risk of cerebro-cardiovascular morbidity in well treated male hypertensives. A retrospective study of 40-59-year-old hypertensives in a Swedish primary care district. Acta Med Scand. 1984;216:251–9.
21. Ibsen H. Antihypertensive treatment and risk of cardiovascular complications: is the cure worse than the disease? J Hypertens. 2009;27:221–3.
22. Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, et al. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. J Hypertens. 2009;27:357–64.
23. Asayama K, Satoh M, Murakami Y, Ohkubo T, Nagasawa SY, Tsuji I, et al. Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis. Hypertension. 2014;63:1189–97.
24. Lenfant C, Chobanian AV, Jones DW, Roccella EJ, Joint National Committee on the Prevention DE, Treatment of High Blood P. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension. 2003;41:1178–9.
25. Tanaka T, Okamura T. Blood cholesterol level and risk of stroke in community-based or worksite cohort studies: a review of Japanese cohort studies in the past 20 years. Keio J Med. 2012;61:79–88.
26. Hirata A, Okamura T, Sugiyama D, Kuwabara K, Kadota A, Fujiyoshi A, et al. The relationship between very high levels of serum high-density lipoprotein cholesterol and cause-specific mortality in a 20-year follow-up study of Japanese General Population. J Atheroscler Thromb. 2016;23:800–9.
27. Ito T, Arima H, Fujiyoshi A, Miura K, Takashima N, Ohkubo T, et al. Relationship between non-high-density lipoprotein

cholesterol and the long-term mortality of cardiovascular diseases: NIPPON DATA 90. Int J Cardiol. 2016;220:262–7.

28. Satoh M, Ohkubo T, Asayama K, Murakami Y, Sakurai M, Nakagawa H, et al. Combined effect of blood pressure and total cholesterol levels on long-term risks of subtypes of cardiovascular death: evidence for Cardiovascular Prevention from Observational Cohorts in Japan. Hypertension. 2015;65:517–24.

29. Nagasawa SY, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, et al. Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65,594 individuals from 10 cohort studies in Japan. J Am Heart Assoc. 2012;1:e001974.

30. Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care. 2003;26:360–6.

31. Nagata M, Ninomiya T, Kiyohara Y, Murakami Y, Irie F, Sairenchi T, et al. Prediction of cardiovascular disease mortality by proteinuria and reduced kidney function: pooled analysis of 39,000 individuals from 7 cohort studies in Japan. Am J Epidemiol. 2013;178:1–11.

32. van der Velde M, Bakker SJL, de Jong PE, Gansevoort RT. Influence of age and measure of eGFR on the association between renal function and cardiovascular events. Clin J Am Soc Nephrol. 2010;5:2053–9.

33. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ. Renal hyperfiltration as a novel marker of all-cause mortality. J Am Soc Nephrol. 2015;26:1426–33.

34. Naimark DM, Grams ME, Matsushita K, Black C, Drion I, Fox CS, et al. Past decline versus current eGFR and subsequent mortality risk. J Am Soc Nephrol. 2016;27:2456–66.

35. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383:970–83.