表３：陰性Ｔ波（コード5-1～5-3）

		1980年	1990年	2000年	2010年
全体	60歳未満・男性	1.9%	1.8%	1.2%	4.9%
	60歳以上・男性	8.9%	7.6%	6.3%	12.3%
	60歳未満・女性	4.1%	3.7%	3.3%	4.2%
	60歳以上・女性	13.5%	9.7%	8.9%	12.2%
側壁	60歳未満・男性	(なし)	1.2%	1.0%	4.1%
	60歳以上・男性		6.8%	4.6%	10.1%
	60歳未満・女性		1.4%	1.2%	1.3%
	60歳以上・女性		6.3%	5.9%	8.9%
下壁	60歳未満・男性	(なし)	0.4%	0.3%	1.2%
	60歳以上・男性		2.3%	1.9%	3.7%
	60歳未満・女性		1.1%	0.8%	1.6%
	60歳以上・女性		2.1%	1.6%	2.7%
前壁	60歳未満・男性	(なし)	1.2%	0.8%	2.2%
	60歳以上・男性		4.2%	4.3%	5.3%
	60歳未満・女性		2.8%	2.4%	2.5%
	60歳以上・女性		7.3%	5.7%	7.3%

表４：異常Ｑ波（コード 1-1～1-2）

		1980 年	1990 年	2000 年	2010 年
全体	60 歳未満・男性	0.4%	0.5%	0.1%	3.6%
	60 歳以上・男性	1.8%	1.4%	2.2%	4.8%
	60 歳未満・女性	0.2%	0.3%	0.5%	1.5%
	60 歳以上・女性	0.9%	0.8%	1.4%	2.6%
側壁	60 歳未満・男性		0.0%	0.2%	0.7%
	60 歳以上・男性	(なし)	0.0%	0.6%	1.4%
	60 歳未満・女性		0.0%	0.1%	0.1%
	60 歳以上・女性		0.0%	0.3%	0.5%
下壁	60 歳未満・男性		0.3%	0.3%	2.7%
	60 歳以上・男性	(なし)	0.9%	0.8%	2.1%
	60 歳未満・女性		0.2%	0.2%	0.1%
	60 歳以上・女性		0.5%	0.8%	1.9%
前壁	60 歳未満・男性		0.1%	0.1%	0.2%
	60 歳以上・男性	(なし)	0.5%	0.9%	1.7%
	60 歳未満・女性		0.1%	0.3%	1.2%
	60 歳以上・女性		0.3%	0.3%	0.6%

表５：左室高電位（コード 3-1or 3-3）

	1980 年	1990 年	2000 年	2010 年
60 歳未満・男性	23.4%	16.6%	9.3%	20.6%
60 歳以上・男性	24.6%	19.0%	13.4%	22.2%
60 歳未満・女性	7.2%	4.8%	3.8%	6.7%
60 歳以上・女性	14.4%	9.6%	9.2%	13.0%

表６：持続性心房細動（コード 8-3-1）

	1980 年	1990 年	2000 年	2010 年
60 歳未満・男性	0.4%	0.4%	0.1%	1.2%
60 歳以上・男性	1.8%	2.5%	1.4%	2.2%
60 歳未満・女性	0.2%	0.0%	0.2%	0.0%
60 歳以上・女性	2.0%	1.2%	0.8%	0.8%

Ⅱ．分担研究報告

④ NIPPON DATA80/90/2010 分析報告

1．NIPPON DATA80 リスクチャートを用いた冠動脈死亡絶対危険度、動脈硬化学会脂質管理カテゴリーと頸部動脈硬化所見との関連の検討

研究分担者　門田　文　（大阪教育大学養護教育講座　准教授）
研究代表者　三浦　克之（滋賀医科大学社会医学講座公衆衛生学部門　教授）
研究分担者　岡村　智教（慶應義塾大学医学部衛生学公衆衛生学　教授）
研究協力者　藤吉　朗　（滋賀医科大学社会医学講座公衆衛生学部門　准教授）
研究分担者　大久保孝義（帝京大学医学部衛生学公衆衛生学講座　教授）
研究協力者　門脇　崇　（滋賀医科大学社会医学講座公衆衛生学部門　客員助教）
研究協力者　高嶋　直敬（滋賀医科大学社会医学講座公衆衛生学部門　特任助教）
研究協力者　久松　隆史（滋賀医科大学アジア疫学研究センター　特任助教）
研究分担者　中村　保幸（京都女子大学家政学部生活福祉学科　教授）
研究協力者　笠置　文善（放射線影響協会放射線疫学調査センター　センター長）
研究協力者　前川　聡　（滋賀医科大学糖尿病内分泌・腎臓・神経内科　教授）
研究協力者　柏木　厚典（滋賀医科大学）
研究分担者　上島　弘嗣（滋賀医科大学アジア疫学研究センター　特任教授）

【目的】NIPPON DATA80 リスクチャートを用いて既知の動脈硬化危険因子から算出された冠動脈疾患死亡絶対危険度（絶対リスク）別、動脈硬化学会の脂質管理カテゴリー別の頸部動脈硬化所見の程度を明らかにする。

【方法】年齢階級別に層別無作為抽出された滋賀県草津市一般住民のうち40 歳から74 歳の男性868 人を解析対象とした。調査は2006 年から2008 年の間に実施した。頸動脈の超音波検査は総頸動脈（CCA）から内頸動脈（ICA）の内膜中膜複合体肥厚（IMT）とプラーク数を計測した。10 年以内の冠動脈疾患死亡絶対リスク（%）は既知の動脈硬化危険因子（性、年齢、血圧、総コレステロール、糖尿病、喫煙）を用いたNIPPON DATA80 リスクチャートの式により算出し、冠動脈疾患死亡絶対リスク別（＜0.5%、≥0.5%、 ≥2.0%、≥5.0%）と動脈硬化学会の脂質管理カテゴリー別の平均IMT とプラーク数を算出した。

【結果】冠動脈疾患死亡絶対リスクが高いほどIMT は肥厚しており、冠動脈疾患死亡リスク≥2.0%、≥5.0% の場合、CCA-IMT の平均はそれぞれ、0.88mm、0.95mmであった。また、冠動脈疾患死亡絶対リスクが高いほど多くのプラークを認めた。動脈硬化学会脂質管理カテゴリーⅠ、Ⅱ、Ⅲの場合、CCA-IMT の平均はそれぞれ、0.70mm、0.81mm、0.88mmであった。カテゴリーⅢについては糖尿病や腎機能障害の有無とも

に同様の値であった。

【結論】頸部動脈硬化所見の程度は既知の動脈硬化危険因子により推定された冠動脈疾患死亡絶対リスク、動脈硬化学会脂質管理カテゴリーと一致していた。

Original Article

Carotid Intima-Media Thickness and Plaque in Apparently Healthy Japanese Individuals with an Estimated 10-Year Absolute Risk of CAD Death According to the Japan Atherosclerosis Society (JAS) Guidelines 2012: The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA)

Aya Kadota[1,2], Katsuyuki Miura[1], Tomonori Okamura[3], Akira Fujiyoshi[1], Takayoshi Ohkubo[1,4], Takashi Kadowaki[1], Naoyuki Takashima[1], Takashi Hisamatsu[1], Yasuyuki Nakamura[1,5], Fumiyoshi Kasagi[6], Hiroshi Maegawa[7], Atsunori Kashiwagi[7] and Hirotsugu Ueshima[1,8] for the SESSA Research Group and for the NIPPON DATA80/90 Research Group

[1]Department of Health Science, Shiga University of Medical Science, Otsu, Shiga, Japan
[2]Department of School Nursing and Health Education, Osaka Kyoiku University, Kashiwara, Osaka, Japan
[3]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Tokyo, Japan
[4]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Tokyo, Japan
[5]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Kyoto, Japan
[6]Radiation Effects Association, Tokyo, Tokyo, Japan
[7]Department of Internal Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan
[8]Department of Lifestyle Related Disease Prevention Center, Shiga University of Medical Science, Otsu, Shiga, Japan

Aim: To examine whether subclinical atherosclerosis of the carotid arteries is concordant with the categories in the 2012 atherosclerosis prevention guidelines proposed by the Japan Atherosclerosis Society (JAS guidelines 2012), which adopted the estimated 10-year absolute risk of coronary artery disease (CAD) death in the NIPPON DATA80 Risk Assessment Chart.
Methods: Between 2006 and 2008, 868 Japanese men 40 to 74 years of age without a history of cardiovascular disease were randomly selected from Kusatsu City, Japan. The intima media thickness (IMT) and plaque number from the common to internal carotid arteries were investigated using ultrasonography. The absolute risk of CAD death was estimated based on the individual risk factor data, and the mean IMT and plaque number in Categories I, II and III of the guidelines were examined.
Results: The estimated 10-year absolute risk of CAD was directly related to the IMT (mean IMT (mean±SD) (mm) for a 10-year absolute risk of ≥2.0% and ≥5.0%: 0.88±0.18 and 0.95±0.19, respectively) and the plaque number. These results are compatible with the categories described by the guidelines (mean IMT (mean±SD) (mm) for Categories I, II, and III: 0.70±0.11, 0.81±0.16 and 0.88±0.18, respectively; mean plaque number: 0.9, 2.1 and 3, respectively). These findings were similar for Category III participants with or without DM and CKD.
Conclusions: Subclinical atherosclerosis of the carotid arteries is concordant with the 10-year absolute risk of CAD and the categories in the JAS guidelines 2012.

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Key words: Coronary artery disease (CAD), Coronary heart disease (CHD), Absolute risk, Carotid atherosclerosis, Intima-media thickness, JAS guidelines

Address for correspondence: Aya Kadota, Department of School Nursing and Health Education, Osaka Kyoiku University, 4-698-1 Asahigaoka, Kashiwara, 582-8582, Japan
E-mail: akadota@cc.osaka-kyoiku.ac.jp
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Introduction

Over the past several decades, risk factors for atherosclerotic disease have been identified in epidemiological and experimental studies[1]. Because several risk

factors frequently coexist in a single individual, the risk of atherosclerosis is preferentially assessed from a global viewpoint employing an absolute risk assessment that includes multiple risk factors[2]. Several institutes, including the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) and the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII), have proposed guidelines using risk charts to estimate the absolute risk[3-5].

In 2012, the Japan Atherosclerosis Society proposed comprehensive lipid and risk management guidelines (JAS guidelines 2012) using the NIPPON DATA80 Risk Assessment Chart to estimate the 10-year absolute risk of coronary artery disease (CAD) death and stratified individuals into three categories for the primary prevention of CAD[5]. The NIPPON DATA80 Risk Assessment Chart was developed for the NIPPON DATA80 (National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged), a cohort study of participants of the National Survey of Circulatory Disorders conducted in 1980[6]. Therefore, the degree of subclinical atherosclerosis in the general population based on the new guideline categories should be clarified. Furthermore, the JAS guidelines 2012 classify individuals with diabetes mellitus into Category III, although diabetes mellitus is considered to be a more severe condition requiring secondary prevention, according to the NCEP-ATPIII[4, 5]. In the new guidelines, individuals with chronic kidney disease (CKD) are also classified into Category III. Therefore, the appropriateness of including diabetes mellitus and CKD in Category III for Japanese individuals should also be clarified.

The degree of carotid atherosclerosis can be assessed noninvasively using ultrasonography. Several studies have reported a relationship between cardiovascular disease (CVD) and the intima media thickness (IMT) and plaque number[7-11]. We herein investigated whether the degree of subclinical atherosclerosis of the carotid arteries in the general population today is concordant with the categories in the JAS guidelines 2012 and the estimated 10-year absolute risk of CAD death.

Methods

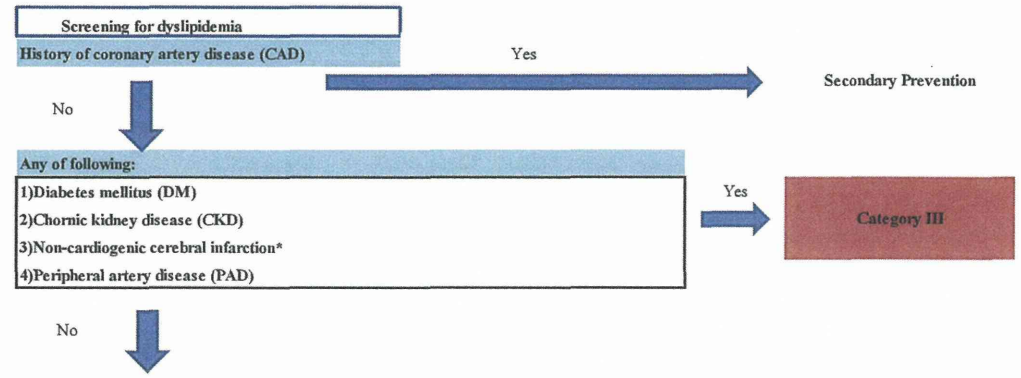
Study Population

Between 2006 and 2008, 2,381 Japanese men 40 to 79 years of age were randomly selected based on age strata from Kusatsu City, Japan and sent an invitation to participate in the baseline survey of the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). Of these men, 1,096 agreed to participate. The population of 40- to 79-year-old men in Kusatsu city was 25,394 in April 2005. Therefore, the extraction rate was 9.4% (2,381/25,394), and the participation rate in this survey was 46% (1,096/2,381) for men. Among these participants, 868 men 40 to 74 years of age without a history of cardiovascular disease who underwent carotid ultrasound examinations were analyzed. The Institutional Review Board of Shiga University of Medical Science approved this study (No. 17-19, 17-83).

Study Examinations

Trained observers collected data regarding smoking, alcohol consumption and medical history using a self-administered questionnaire and physical measurements. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). Blood pressure was measured using an automatic blood pressure measurement machine placed on the right arm of the seated participant after a five-minute rest. The ankle-brachial index (ABI) was estimated by measuring the blood pressure of the brachial and tibial arteries using an automatic measurement machine (Form PWV/ABI, Omron Colin, Japan) with the participant in the supine position after a five-minute rest. Peripheral artery disease (PAD) was defined as an ABI of <0.9 on either side.

Fasting blood samples were obtained. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes and shipped to a laboratory (Shiga Laboratory; MEDIC, Japan) for the blood measurements. The levels of serum triglycerides (TGs) and total cholesterol were measured enzymatically, and that of high-density lipoprotein (HDL) cholesterol was measured after heparin-calcium precipitation. The measurements were standardized according to the Centers for Disease Control and Prevention/US Collaborating Center for Reference Method Laboratory Network Research in Blood Lipids (CDC/CRMLN)[12]. Hypo-HDL cholesterolemia was defined as an HDL cholesterol level of <40 mg/dL. Plasma was collected into siliconized tubes containing sodium fluoride for the enzymatic glucose measurements. The level of hemoglobin A1c (HbA1c) was measured using a latex agglutination inhibition assay according to the standardized method of the Japan Diabetes Society (JDS) and converted into the National Glycohemoglobin Standardization Program (NGSP) value using the following formula: HbA1c (NGSP) (%) $= 1.02 \times$ HbA1c (JDS) (%) $+ 0.25$[13]. In the present study, diabetes mellitus was defined as a



Management categories based on absolute risk for the primary prevention of CAD

10-year probability (absolute risk) of CAD death derived from NIPPON DATA80)	Additional risk	
	No additional risk	One or more of the following: 1) Hypo-HDL-cholesterolemia (HDL-C < 40 mg/dl) 2) Family histroy of premature CAD in first-degree relatives (a man aged < 55years or a woman aged < 65 years)** 3) Impaired glucose tolerance
< 0.5%	Category I	Category II
0.5 to < 2.0%	Category II	Category III
≥ 2.0%	Category III	Category III

Fig. 1. Flow chart for setting management targets of LDL-cholesterol poposed by the Japan Atherosclerosis Society guidelines 2012, which modified for the present study.

This flow chart is not applicable to patients with FH.
*Non-cardiogenic cerebral infarction was excluded as history of stroke for the present study.
**Family history of premature CAD was not considered for the present study.
LDL-cholesterol: low density lipoprotein cholesterol
HDL-cholesterol: high density lipoprotein cholesterol

fasting blood glucose level of ≥126 mg/dL and/or an HbA1c (NGSP) level of ≥6.5% and/or the use of antidiabetic medications, although diabetes mellitus is defined as a casual blood glucose level of ≥200 mg/dL in the original NIPPON DATA80 Risk Chart. Impaired glucose tolerance was defined as a fasting glucose level between 110 mg/dL and 126 mg/dL for only those individuals not taking medications for diabetes mellitus. The serum creatinine level was measured enzymatically. The estimated glomerular filtration rate (eGFR) was calculated using the following formula for men: eGFR (mL/min/1.73 m^2) = 194 × creatinine$^{-1.094}$ × age$^{-0.287}$. Casual urine was collected for the semiquantitative assessment of proteinuria using a dipstick (Uriace-kc, Terumo, Japan). The results were recorded as (−), (±), (+), (2+), (3+) or (4+), which corresponded to approximate protein concentrations of <15, <30, <100, <250, <1,000 and ≥1,000 (mg/dL), respectively. Chronic kidney disease (CKD) was defined as proteinuria ≥ (+) and/or an eGFR of <60 mL/min/1.73 m^2.

The IMT and number of plaques from the common carotid artery (CCA) to the internal carotid artery (ICA) were investigated using an ultrasound device equipped with a 7.5-MHz probe (Xario-660A, Toshiba Medical Systems, Japan) according to a standardized method established and certified by the Ultrasound Research Laboratory of University of Pittsburgh. The details of the scanning procedure have been described elsewhere[7, 14, 15]. In brief, for the CCA, both the far and near wall 1 cm proximal to the bulb were examined, while only the far wall was examined with respect to the bulb and a 1-cm area of the internal carotid artery (ICA). The IMT was traced using the automatic image reading program of the AMS (Chalmers University of Technology, Gotenburg, Sweden). A plaque was defined as a focal thickening lesion with an IMT of ≥1 mm.

Table 1. Characteristics of study participants according to estimated absolute 10-year risk for CAD death among men aged 40 to 74 years

	Total	Estimated 10-year absolute risk for CAD death				
		<0.5%	0.5≤risk<2.0%	2.0≤risk<5.0%	5%≤	*p* for trend
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Number of participants (%)	868 (100)	201 (23.2)	348 (40.1)	199 (22.9)	120 (13.8)	
Age at exam (years)	61.8±9.1	49.8±6.7	62.4±5.5	67.8±5.0	70.3±4.2	<0.001
BMI (kg/m^2)	23.6±3.0	23.8±3.2	23.3±2.9	23.7±2.8	24.1±3.2	0.327
Systolic blood pressure (mmHg)	136±19	124±14	134±17	144±19	147±19	<0.001
Diastolic blood pressure (mmHg)	80±11	77±10	80±10	82±13	81±10	<0.001
Pulse (beat/min)	65±10	64±9	64±10	66±11	66±11	0.012
Total cholesterol (mg/dL)	211±33	200±32	208±31	218±32	224±34	<0.001
Triglycerides (mg/dL)	130±85	122±73	130±92	127±68	152±102	0.011
HDL-cholesterol (mg/dL)	59±17	59±15	60±18	59±18	56±15	0.226
Creatinine (mg/dL)	0.8±0.2	0.8±0.1	0.8±0.2	0.8±0.1	0.9±0.2	<0.001
eGFR (mL/min/1.73 m^2)	74±14	81±12	74±14	72±12	68±15	<0.001
Glucose (mg/dL)	102±21	98±20	97±14	105±21	120±28	<0.001
Hemoglobin A1c (NGSP) (%)	6.0±0.8	5.6±0.6	5.8±0.5	6.1±0.8	7.0±1.1	<0.001
Medication for hypertension (%)	26.4	10.4	24.7	36.2	41.7	<0.001
Medication for dyslipidemia (%)	11.9	7.5	11.5	10.6	22.5	<0.001
Medication for diabetes mellitus (%)	9.6	0.0	4.3	13.1	35.0	<0.001
Diabetes mellitus (%)	21.0	2.0	6.6	27.1	84.2	<0.001
Peripheral artery diseases (%)	1.2	0	1.1	0.5	4.2	<0.001
Choronic kidney disease (%)	16.1	3.0	16.7	18.6	32.5	<0.001
Current Smoker (%)	34.9	37.8	33.6	32.2	38.3	<0.001
Current Drinker (%)	78.3	82.1	80.2	74.4	73.3	<0.001

CAD: coronary artery disease, BMI: body mass index, HDL-cholesterol: high density lipoprotein cholesterol, eGFR: estimated glomeruler filtration rate

Categorization of the Participants and Estimation of the 10-Year Absolute Risk of CAD Death

First, we estimated the 10-year absolute risk of CAD using the original NIPPON DATA80 Risk Chart based on the baseline age (years), sex, current smoking status (yes/no), systolic blood pressure (mmHg), total cholesterol level (mg/dL) and presence of diabetes mellitus (yes/no)[6].

Next, we classified the participants into the three categories proposed by the JAS guidelines 2012 for the purpose of LDL-c management: "Category I" (low risk), "Category II" (intermediate risk) and "Category III" (high risk)[5]. The classification steps are shown in **Fig. 1**. According to the guidelines, in the first step, individuals with either DM, CKD, a history of noncardiogenic cerebral infarction or PAD were *per se* considered to be at high risk for CAD death, with a rate equivalent to ≥2% within 10 years, and were classified into Category III without any further risk assessment. In the second step, the 10-year absolute risk of CAD death was estimated using the methods of the JAS guidelines 2012, and the participants were classified into three categories: "Category I" (an estimated absolute risk of <0.5%), "Category II" (0.5% to <2.0%) and "Category III" (≥2.0%). The presence of any of the following risk factors ("additional risk factors") resulted in an upgrade from Category I or II to Category II or III, respectively: hypo-HDL cholesterolemia, a family history of premature CAD and/or impaired glucose tolerance. In the present analysis, we categorized the participants similarly, with two exceptions: (1) none of the study participants had a history of noncardiogenic cerebral infarction because a history of any type of stroke was an exclusion criterion for the cohort; (2) a family history of premature CAD was not assessed because we did not obtain the pertinent information. In the subanalyses, we further stratified the participants in Category III according to the presence or absence of diabetes mellitus and CKD to compare the carotid ultrasonography findings between these groups. We also analyzed the participants using stratification according to the median age (<63 years

Table 2. Intima media thickness and plaque prevalence of carotid artery according to estimated 10-year absolute risk for CAD death among men aged 40 to 74 years

	Total	Estimated 10-year absolute risk for CAD death				
		<0.5%	0.5≤risk<2.0%	2.0≤risk<5.0%	5%≤	*p* for trend
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Number of participants (%)	868 (100)	201 (23.2)	348 (40.1)	199 (22.9)	120 (13.8)	
Mean IMT (mm)	0.83±0.18	0.71±0.11	0.82±0.16	0.88±0.18	0.95±0.19	<0.001
Mean IMT of CCA (mm)	0.81±0.16	0.69±0.12	0.80±0.14	0.87±0.17	0.92±0.16	<0.001
Mean IMT of ICA (mm)	0.72±0.26	0.64±0.16	0.72±0.24	0.75±0.27	0.82±0.36	<0.001
Mean IMT of BULB (mm)	0.97±0.31	0.80±0.20	0.98±0.31	1.03±1.03	1.14±0.35	<0.001
1 mm<mean IMT of CCA (%)	11.3	0.0	8.3	15.6	30.8	<0.001
Plaque (%)	75.3	50.2	80.7	80.9	92.5	<0.001
Number of plaque (numerical value)*	2.3±2.3	1.0±1.3	2.2±2.1	2.9±2.7	4.0±2.6	<0.001

CAD: coronary artery disease, IMT: intima media thickness, CCA: common carotid artery, ICA: internal carotid artery
*Individuals without plaques are included in the estimation.

(mean±SD: 54.4±6.9), ≥63 years (mean±SD: 68.9±3.7)) because carotid atherosclerosis is strongly associated with age, which is a classification factor in this category.

Statistical Methods

Differences in the characteristics of the participants were examined using an analysis of variance for continuous variables and the χ^2-test for dichotomized variables according to the estimated absolute risk. All confidence intervals (CIs) were estimated at the 95% level. A p-value of <0.05 was considered to be statistically significant. The Statistical Package for the Social Sciences, version 17.0J software program (SPSS Japan Inc., Tokyo, Japan) was used for all analyses.

Results

Table 1 shows the characteristics of the study participants according to the estimated 10-year absolute risk of CAD death. The mean age of the participants was higher and the levels of traditional atherosclerotic risk factors, such as blood pressure, lipids and glucose, were less favorable among the participants with a higher 10-year absolute risk. Conversely, current drinkers were more frequent among those with a lower risk. The prevalence of current smokers tended to be higher in the lower risk groups; however, the value of the lowest risk group was 37.8%, which is similar to the value of the highest risk group (38.3%). The proportion of participants with a 10-year absolute risk of CAD death ≥2% was 36.7% among the present study population.

Table 2 shows the IMT values and plaque numbers in the carotid artery according to the estimated 10-year absolute risk of CAD death assessed using the original NIPPON DATA80 Risk Chart. The mean IMT of the CCA, ICA and bulb all increased in association with an increase in the estimated 10-year absolute risk. The number of plaques also increased from one for an estimated 10-year absolute risk of <0.5% to up to four for a risk of ≥5%. All of these trends were statistically significant among the four categories of estimated 10-year absolute risk (p for trend <0.001).

Table 3 (A) shows the IMT values and plaque numbers according to the categories described in the JAS guidelines 2012. The IMT and plaque number increased in association with the category number. Among the category Ⅲ participants, the mean IMT values at all sites were higher, the prevalence of plaque was as high as 83% and the mean number of plaques was three. We further stratified the participants in category Ⅲ according to the presence or absence of diabetes mellitus (**Table 3 (B)**). The mean IMT and plaque number in the participants with diabetes mellitus were similar to those of the nondiabetic category Ⅲ participants. The prevalence of a CCA IMT of >1.0 mm was significantly higher among the participants with diabetes mellitus; however, when we estimated the prevalence of a CCA IMT >1.1 mm, no statistically significant differences were found (5.2% in the nondiabetic participants, 7.1% in the participants with diabetes mellitus, p for the difference was 0.421) (not shown in the table). **Table 3 (C)** shows the presence of carotid atherosclerosis in the category Ⅲ participants stratified according to the presence or absence of CKD. There were no statistical differences between the participants with and without CKD.

Table 3. (A) Intima media thickness and plaque of carotid artery according to the category for LDL-c management proposed by the JAS guidelines 2012
(B) Intima media thickness and plaque of carotid artery of the non-diabetec category Ⅲ participants and participants with diabetes mellitus
(C) Intima media thickness and plaque of carotid artery of the non-CKD category Ⅲ participants and participants with CKD

(A)	Category for LDL-c management proposed by JAS2012 Guideline			*p* for trend
	Ⅰ Mean ± SD	Ⅱ Mean ± SD	Ⅲ Mean ± SD	
Number of participants (%)	170 (19.6)	245 (28.2)	453 (52.2)	
Mean IMT (mm)	0.70 ± 0.11	0.81 ± 0.16	0.88 ± 0.18	<0.001
Mean IMT of CCA (mm)	0.68 ± 0.11	0.79 ± 0.15	0.86 ± 0.16	<0.001
Mean IMT of ICA (mm)	0.64 ± 0.16	0.70 ± 0.23	0.77 ± 0.30	<0.001
Mean IMT of BULB (mm)	0.81 ± 0.21	0.97 ± 0.33	1.04 ± 0.30	<0.001
1 mm < mean IMT of CCA (%)	0.6	7.3	17.4	<0.001
Plaque (%)	48.2	79.5	83.2	<0.001
Number of plaque (numerical value)*	0.9 ± 1.3	2.1 ± 1.9	3.0 ± 2.6	<0.001

(B)	Ⅲ (excluding diabetes) Mean ± SD	Diabetes mellitus Mean ± SD	*p* for difference
Number of participants (%)	271 (31.2)	182 (21.0)	
Mean IMT (mm)	0.88 ± 0.17	0.89 ± 0.19	0.440
Mean IMT of CCA (mm)	0.86 ± 0.16	0.87 ± 0.17	0.324
Mean IMT of ICA (mm)	0.77 ± 0.30	0.75 ± 0.28	0.462
Mean IMT of BULB (mm)	1.02 ± 0.27	1.06 ± 0.34	0.133
1 mm < mean IMT of CCA (%)	14.0	22.5	0.023
Plaque (%)	80.8	86.8	0.097
Number of plaque (numerical value)*	2.9 ± 2.5	3.1 ± 2.7	0.315

(C)	Ⅲ (excluding CKD) Mean ± SD	CKD Mean ± SD	*p* for difference
Number of participants (%)	313 (36.1)	140 (16.1)	
Mean IMT (mm)	0.88 ± 0.17	0.88 ± 0.19	0.850
Mean IMT of CCA (mm)	0.86 ± 0.16	0.87 ± 0.17	0.730
Mean IMT of ICA (mm)	0.76 ± 0.28	0.77 ± 0.32	0.740
Mean IMT of BULB (mm)	1.04 ± 0.30	1.03 ± 0.30	0.820
1 mm < mean IMT of CCA (%)	18.2	15.7	0.593
Plaque (%)	83.4	82.9	0.892
Number of plaque (numerical value)*	3.0 ± 2.6	2.9 ± 2.5	0.580

LDL: low density lipoprotein, CKD: chronic kidney disease, IMT: intima media thickness, CCA: common carotid artery, ICA: internal carotid artery
Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL and/or HbA1c (NGSP) ≥ 6.5% and/or medication for diabetes mellitus.
Chronic kidney disease (CKD) was defined as proteinuria ≥ (+) and/or eGFR < 60 mL/min/1.73 m^2.
*Individuals without plaques are included in the estimation.

Table 4. Intima media thickness and plaque prevalence of carotid artery according to the category for LDL-c management proposed by the JAS guidelines 2012 among men aged 40 to 74 years with stratification by median age ((A) < 63 years old, (B) ≥ 63 years old)

	Total	Category for LDL-c management proposed by JAS2012 Guideline			
		I	II	III	*p* for trend
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
(A) Age < 63 years					
Participants number (%)	423 (100)	164 (38.8)	134 (31.7)	125 (29.6)	
Mean IMT (mm)	0.76 ± 0.15	0.70 ± 0.11	0.78 ± 0.13	0.82 ± 0.18	< 0.001
Mean IMT of CCA (mm)	0.75 ± 0.16	0.68 ± 0.11	0.76 ± 0.14	0.81 ± 0.20	< 0.001
Mean IMT of ICA (mm)	0.68 ± 0.19	0.64 ± 0.16	0.68 ± 0.19	0.71 ± 0.22	0.003
Mean IMT of BULB (mm)	0.88 ± 0.24	0.81 ± 0.21	0.90 ± 0.21	0.95 ± 0.28	< 0.001
1 mm < mean IMT of CCA (%)	6.1	0.6	6.7	12.8	< 0.001
Plaque (%)	66.6	49.4	75.2	80.0	< 0.001
Number of plaque (numerical value)*	1.7 ± 2.0	1.0 ± 1.3	1.7 ± 1.6	2.5 ± 2.7	< 0.001
(B) Age ≥ 63 years					
Participants number (%)	445 (100)	6 (1.3)	111 (24.9)	328 (73.7)	
Mean IMT (mm)	0.89 ± 0.18	0.71 ± 0.12	0.85 ± 0.18	0.91 ± 0.17	< 0.001
Mean IMT of CCA (mm)	0.86 ± 0.15	0.74 ± 0.16	0.81 ± 0.15	0.88 ± 0.15	< 0.001
Mean IMT of ICA (mm)	0.77 ± 0.31	0.59 ± 0.13	0.73 ± 0.27	0.79 ± 0.32	0.028
Mean IMT of BULB (mm)	1.06 ± 0.33	0.77 ± 0.11	1.05 ± 0.42	1.07 ± 0.30	0.123
1 mm < mean IMT of CCA (%)	16.2	0.0	8.1	19.2	0.005
Plaque (%)	83.6	16.7	84.7	84.5	0.069
Number of plaque (numerical value)*	3.0 ± 2.5	0.7 ± 1.6	2.5 ± 2.2	3.2 ± 2.5	0.002

IMT: intima media thickness, CCA: common carotid artery, ICA: internal carotid artery
*Individuals without plaques are included in the estimation.

Similar results were also observed with respect to stratification according to the median age (< 63 years (mean ± SD: 54.4 ± 6.9), ≥ 63 years (mean ± SD: 68.9 ± 3.7)) (**Table 4**). We also performed a sensitivity analysis restricted to the participants not taking medications for hypertension, dyslipidemia or diabetes mellitus. The mean IMT and number of plaques were similar to the results shown in **Table 3** (data not shown).

Discussion

We found that the mean carotid IMT and plaque number are concordant with the risk stratification of the lipid management guidelines proposed by the JAS guidelines 2012, estimating the 10-year absolute risk of CAD death using the NIPPON DATA80 Risk Assessment Chart. To the best of our knowledge, this is the first report to clarify carotid ultrasonography findings according to the absolute risk of CAD in the general population, especially in Asia, where stroke is the predominant cause of CVD mortality.

Previous studies have demonstrated that the IMT and the presence of carotid plaque are associated with future risk of cardiovascular events, including stroke and CAD[7-11, 16-19]. In Japan, Kitamura *et al.* reported that an increased IMT of the CCA and the presence of uncalcified plaque in the ICA predict the risk of stroke in the general elderly population[11]. The reported value of the relative risk of an increased IMT varies with respect to different study participants and end points[18, 19]. A systematic review and meta-analysis of cohort studies in Western countries concluded that the relative risk per IMT difference is slightly higher for stroke than for CAD[20]. However, most risk factors, even those for stroke, are common to both the coronary and carotid arteries, although the impact of each risk factor can differ. Therefore, the results of the present study showing that the presence of carotid atherosclerosis is concordant with the estimated 10-year absolute risk of CAD are acceptable.

The NIPPON DATA is a cohort study of participants of the National Survey on Circulatory Disorders of Japan conducted by the Ministry of Health, Labour and Welfare of Japan[6, 21-24]. The baseline data of the NIPPON DATA80 were obtained in 1980, more than 30 years ago. Since then, the lifestyle and

risk profiles of individuals in Japan have changed dramatically[1]. Nevertheless, our findings regarding carotid atherosclerosis in the present population are concordant with the estimated 10-year absolute risk and the categories described in the JAS guidelines 2012.

In the present study, we found that the mean IMT values at all sites were higher in the participants in Category III than in those belonging to other categories and that the prevalence of plaque was as high as 83%, with a mean number of three plaques in the Category III participants. These atherosclerotic findings were confirmed, irrespective of age group and medications. Therefore, the present study showed that making a global assessment using the JAS guidelines 2012 also provides information regarding the prevalence of carotid atherosclerosis in the clinical setting. Guidelines, including the JAS guidelines 2012, that adopt an absolute risk assessment classify individuals with a higher absolute risk of CHD into the high-risk group requiring active risk management[2-5, 25-27]. Although epidemiological studies of the relationship between lipid profiles and carotid atherosclerosis in Japan remain insufficient, the comprehensive risk management proposed in the JAS guidelines 2012 may be beneficial for preventing carotid atherosclerosis.

Prospective studies reporting an association between the IMT and CAD in the general population are very scarce in Japan, likely due to the low incidence of CAD. However, the IMT has been reported to be associated with the severity and likelihood of CAD and to predict the likelihood of future CAD in diabetic patients[28, 29]. Therefore, our results showing an increased IMT in the Category III participants suggest the possibility that an increased IMT is associated with the likelihood of CAD. However, it should be noted that a recent meta-analysis reported that the addition of IMT measurement to an assessment of the absolute risk is associated with a small improvement in the ability to predict the risk of myocardial infarction[30].

Diabetes mellitus is a high risk factor for the development of atherosclerosis, the pathophysiology of which is complicated[31-34]. The ESC/EAS guidelines classify individuals with diabetes mellitus into class I for primary prevention, which represents a very high risk, requiring active management of all risk factors[3]. In the United States, diabetes mellitus is considered to be a more severe condition, being compatible with secondary prevention[4]. Although individuals with hyperglycemia frequently have other risk factors, such as dyslipidemia and hypertension, few diabetic patients meet the target levels of the above-mentioned risk factors[35-37]. Therefore, the JAS guidelines 2012 classify diabetes mellitus into Category III for primary prevention, not the category of secondary prevention. Furthermore, the guidelines recommend that the LDL-C level in diabetic individuals be <120 mg/dL[5]. In the present study, we compared the participants with diabetes mellitus and those without diabetes in Category III separately and found that the carotid ultrasonography findings were similar between the two groups. Our findings therefore support the JAS guidelines 2012, which place diabetes mellitus into Category III. However, we also found that the prevalence of plaque tended to be higher among the participants with diabetes mellitus than those without. Our study participants were by and large relatively healthy individuals from the general population and did not include severely diabetic patients with poor glycemic control. Therefore, further studies are needed to clarify the target lipid levels in Japanese patients with diabetes mellitus.

Previous epidemiological studies have demonstrated that CKD is a high risk factor for CVD[38-40]. Therefore, the JAS guidelines 2012 classify individuals with CKD into Category III for primary prevention and recommend a target level of LDL-C of <120 mg/dL[5]. In the present study, we confirmed that the degree of carotid atherosclerosis in the participants with CKD was as severe as that observed in the participants in Category III without CKD, which supports the classification of the guidelines.

Several limitations regarding the present study should be noted. First, family history was not considered during risk classification in this study. Second, we conducted this study in men only; thus, the results may not be applicable to women. Finally, we used the IMT as a surrogate marker of subclinical atherosclerosis, although the predictive value of the progression of IMT is in debate[41]. Further studies using CAD as a study end point are required to confirm the validity of the guidelines.

In conclusion, the carotid IMT and prevalence of plaque, as assessed using ultrasonography, are concordant with the risk stratification described in the lipid and comprehensive risk management guidelines proposed by the JAS guidelines 2012. Individuals classified as belonging to the higher category should adequately control their risk factors, including the lipid levels, with lifestyle modification and medications in order to prevent CVD.

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Conflicts of Interest

None.

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Appendix

Research Group Members

The SESSA Research Group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-chairpersons: Katsuyuki Miura (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Research members: Minoru Horie, Takashi Yamamoto, Atsunori Kashiwagi, Hiroshi Maegawa (Shiga University of Medical Science, Otsu, Shiga), Yoshihiko Nishio (Kagoshima University, Kagoshima), Kiyoshi Murata, Kenichi Mitsunami (Shiga University of Medical Science, Otsu, Shiga), Toru Kita (Kobe City Medical Center General Hospital, Kobe, Hyogo), Takeshi Kimura (Kyoto University, Kyoto), Yasuyuki Nakamura (Kyoto Women's University, Kyoto), Tomonori Okamura (Keio University, Tokyo), Akira Sekikawa, Emma JM Barinas-Mitchell (University of Pittsburgh, Pittsburgh, PA), Kazuhiko Nozaki, Akihiko Shiino, Ikuo Toyama, Isao Araki, Akihiko Tsuru, Hisakazu Ogita, Toshinaga Maeda, Yoshikuni Kita (Shiga University of Medical Science, Otsu, Shiga), Takayoshi Ohkubo (Teikyo University, Tokyo), Aya Kadota (Osaka Kyoiku University, Kashiwara, Osaka), Akira Fujiyoshi, Naoyuki Takashima, Takashi Kadowaki, Sayaka Kadowaki, Yoshitaka Murakami, Naomi Miyamatsu (Shiga University of Medical Science, Otsu, Shiga), Atsushi Hozawa (Tohoku University, Sendai, Miyagi), Nagako Okuda (National Institute of Health and Nutrition, Tokyo), Aya Higashiyama (Hyogo College of Medicine, Nishinomiya, Hyogo), Shinya Nagasawa (Kanazawa Medical University, Kanazawa, Ishikawa), Takashi Hisamatsu, Naoko Miyagawa, Sayuki Torii, Yoshino Saito (Shiga University of Medical Science, Otsu, Shiga).

The NIPPON DATA80/90 Research Group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-chairpersons: Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo) for the NIPPON DATA80, and Tomonori Okamura (Department of Preventive Medicine and Public Health, Keio University, Tokyo) for the NIPPON DATA90.

Research members: Shigeyuki Saitoh (Sapporo Medical University School of Health Science, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Iwate), Atsushi Hozawa (Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Miyagi), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima), Yosikazu Nakamura (Department of Public Health, Jichi Medical University, Shimotsuke, Tochigi), Yasuhiro Matsumura (Faculty of Health and Nutrition, Bunkyo University, Chigasaki, Kanagawa), Nobuo Nishi (Project for the National Health and Nutrition Survey, National Institute of Health and Nutrition, Tokyo), Nagako Okuda (Department of Nutrition Epidemiology, National Institute of Health and Nutrition, Tokyo), Fumiyoshi Kasagi (Institute of Radiation Epidemiology, Radiation Effects Association, Tokyo), Toru Izumi (Faculty of Medicine, Kitasato University, Sagamihara, Kanagawa), Takayoshi Ohkubo (Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo), Toshiyuki Ojima (Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka), Koji Tamakoshi (Department of Public Health and Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya, Aichi), Hideaki Nakagawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Katsuyuki Miura, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Yasuyuki Nakamura (Cardiovascular Epidemiology, Kyoto Women's University, Kyoto), Katsushi Yoshita (Osaka City University Graduate School of human life science, Osaka), Aya Kadota (Department of School Nursing and Health Education, Osaka Kyoiku University, Kashiwara, Osaka), Kazunori Kodama (Radiation Effects Research Foundation, Hiroshima) and Yutaka Kiyohara (Department of Environmental Medicine, Kyushu University, Fukuoka).

2．ヘモグロビンA1cと総死亡，循環器疾患死亡の関連　-NIPPON DATA90-

研究協力者　櫻井　勝　（金沢医科大学医学部公衆衛生学講座　准教授）
研究分担者　斎藤　重幸（札幌医科大学保健医療学部看護学科基礎臨床医学講座　教授）
研究代表者　三浦　克之（滋賀医科大学社会医学講座公衆衛生学部門　教授）
研究分担者　中川　秀昭（金沢医科大学医学部公衆衛生学講座　教授）
研究協力者　大西　浩文（札幌医科大学医学部公衆衛生学講座　准教授）
研究協力者　赤坂　憲　（札幌医科大学医学部内科学第二講座　助教）
研究分担者　門田　文　（大阪教育大学養護教育講座　准教授）
研究分担者　喜多　義邦（滋賀医科大学社会医学講座公衆衛生学部門　助教）
研究分担者　早川　岳人（福島県立医科大学衛生学・予防医学講座　准教授）
研究分担者　大久保孝義（帝京大学医学部衛生学公衆衛生学講座　教授）
研究分担者　岡山　明　（結核予防会第一健康相談所　所長）
研究分担者　岡村　智教（慶應義塾大学医学部衛生学公衆衛生学　教授）
研究分担者　上島　弘嗣（滋賀医科大学アジア疫学研究センター　特任教授）

背景：ヘモグロビンA1cと循環器疾患との関連が欧米諸国を中心に報告されているが，循環器疾患の分布が欧米と大きく異なるアジア人においても，HbA1cが欧米人と同様に循環器疾患のリスクとなるかは定かではない．

対象と方法：NIPPON DATA90の参加者のうち，循環器疾患の既往のない7,120名（男性2,962名，女性4,158名）を，15年間追跡し死亡を確認した．糖尿病のない対象者をベースラインのHbA1c(NGSP)値をもとに5群に分類し(5.0%未満，5.0-5.4%，5.5-5.9%，6.0-6.4%，and 6.5%以上)，比例ハザードモデルを用いて総死亡および循環器疾患死亡の調整ハザード比を算出した．

結果：15年の観察期間中に1,104名の死亡を確認した．このうち，循環器疾患死亡は304名（冠動脈疾患61名；脳卒中127名，うち脳梗塞78名，脳出血25名，分類不能の脳卒中24名）であった．HbA1cの上昇に伴い，総死亡，および循環器疾患死亡リスクは連続的に上昇した．HbA1c 5.0%未満群を基準とした，性，年齢，生活習慣や他の循環器疾患危険因子で調整したハザード比（95%信頼区間）は，HbA1c 5.0-5.4%群で1.31(0.93-1.84)，5.5-5.9%群1.38（0.93-2.04)，6.0-6.4%群2.18（1.22-3.87)，6.5%以上群2.75（1.43-5.28)，糖尿病治療中のもの2.04（1.19-3.05）であった．同様にHbA1cの上昇にともない冠動脈疾患死亡および脳梗塞死亡リスクは上昇する傾向を認めたが，脳出血とは関連を認めなかった．

結語：これまでの欧米の報告同様に，日本人においても非糖尿病者の HbA1c は総死亡，循環器疾患死亡，特に冠動脈疾患，脳梗塞による死亡と関連していた．

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HbA_{1c} and the Risks for All-Cause and Cardiovascular Mortality in the General Japanese Population

NIPPON DATA90

MASARU SAKURAI, MD[1,2]
SHIGEYUKI SAITOH, MD[3]
KATSUYUKI MIURA, MD[4]
HIDEAKI NAKAGAWA, MD[1]
HIROFUMI OHNISHI, MD[3]
HIROSHI AKASAKA, MD[3]
AYA KADOTA, MD[5]
YOSHIKUNI KITA, PHD[4]
TAKEHITO HAYAKAWA, PHD[6]
TAKAYOSHI OHKUBO, MD[4,7]
AKIRA OKAYAMA, MD[8]
TOMONORI OKAMURA, MD[9]
HIROTSUGU UESHIMA, MD[4]
FOR THE NIPPON DATA90 RESEARCH GROUP*

OBJECTIVE—Associations between HbA_{1c} and cardiovascular diseases (CVD) have been reported mainly in Western countries. It is not clear whether HbA_{1c} measurements are useful for assessing CVD mortality risk in East Asian populations.

RESEARCH DESIGN AND METHODS—The risk for cardiovascular death was evaluated in a large cohort of participants selected randomly from the overall Japanese population. A total of 7,120 participants (2,962 men and 4,158 women; mean age 52.3 years) free of previous CVD were followed for 15 years. Adjusted hazard ratios (HRs) and 95% CIs among categories of HbA_{1c} (<5.0%, 5.0–5.4%, 5.5–5.9%, 6.0–6.4%, and ≥6.5%) for participants without treatment for diabetes and HRs for participants with diabetes were calculated using a Cox proportional hazards model.

RESULTS—During the study, there were 1,104 deaths, including 304 from CVD, 61 from coronary heart disease, and 127 from stroke (78 from cerebral infarction, 25 from cerebral hemorrhage, and 24 from unclassified stroke). Relations to HbA_{1c} with all-cause mortality and CVD death were graded and continuous, and multivariate-adjusted HRs for CVD death in participants with HbA_{1c} 6.0–6.4% and ≥6.5% were 2.18 (95% CI 1.22–3.87) and 2.75 (1.43–5.28), respectively, compared with participants with HbA_{1c} <5.0%. Similar associations were observed between HbA_{1c} and death from coronary heart disease and death from cerebral infarction.

CONCLUSIONS—High HbA_{1c} levels were associated with increased risk for all-cause mortality and death from CVD, coronary heart disease, and cerebral infarction in general East Asian populations, as in Western populations.

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From the [1]Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, Japan; the [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; the [3]Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan; the [4]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; the [5]Department of School Nursing and Health Education, Osaka Kyoiku University, Osaka, Japan; the [6]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; the [7]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan; the [8]First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo, Japan; and the [9]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan.
Corresponding author: Masaru Sakurai, m-sakura@kanazawa-med.ac.jp.
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*A complete list of members of the NIPPON DATA Research Group can be found in Supplementary Data online.

Since the association between HbA_{1c} and microangiopathy was established in patients with diabetes, HbA_{1c} has been used for not only the determination of glucose control among patients with diabetes but also the diagnosis of diabetes (1). Measurement of HbA_{1c} is also recommended for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (2) because the association between HbA_{1c} and the risk for cardiovascular disease (CVD) in general populations has been reported, mainly from Western countries (3–10).

There have been only a few studies regarding the associations between HbA_{1c} and CVD in Asian populations (11–13). Furthermore, these studies were from Japan, and HbA_{1c} measurements were expressed mainly using Japan Diabetes Society (JDS) values rather than National Glycohemoglobin Standardization Program (NGSP) values; thus, we cannot compare these results with those from Western countries. Recently, the JDS provided an equation for the conversion from HbA_{1c} (JDS) to HbA_{1c} (NGSP) units (14), which allows a comparison of the results from Japanese studies and previous studies from Western countries.

CVD in East Asian people is characterized by a higher rate of stroke and lower rate of coronary heart disease compared with CVD in Western populations (15). In one previous study evaluating the association between HbA_{1c} and incidence of stroke in Japan, ischemic stroke, but not hemorrhagic stroke, was associated with HbA_{1c} in Asian populations (12). Other studies from Japan (11,13) showed a significant association between HbA_{1c} and CVD; however, the number of participants and CVD events were too small to calculate the risk by subtype of CVD, such as coronary heart disease, stroke, cerebral infarction, and cerebral hemorrhage.

The current study was performed to examine the association between HbA_{1c} using NGSP values and the risks for death from all causes and from CVD (coronary