respectively. Taken together, the results of these two recent studies (*13*, *14*) and the results of the present study on Japanese subjects support the notion that the appropriate $AC_M$ cutoff level for diagnosis of metabolic syndrome in Japanese females is 78–80 cm.

## Prevalence of Metabolic Syndrome and Cutoff Level for Diagnosis of Visceral Obesity

To illustrate the effect of change in the cutoff level of visceral obesity on the prevalence of metabolic syndrome, we plotted the calculated prevalence of metabolic syndrome in the subjects for a range of $AC_M$ cutoff levels (Fig. 7). The prevalence of NCEP-ATP III–defined metabolic syndrome was less sensitive to change in the $AC_M$ cutoff level than was the prevalence of metabolic syndrome defined by the Japanese criteria, since visceral obesity is not a requisite in the former criteria. As shown in Fig. 7, the prevalences of NCEP-ATP III–defined metabolic syndrome in males were 51.0%, 59.2% and 62.0% for $AC_M$ cutoff levels of 102 cm (NCEP-ATP III), 90 cm (IDF for Asians), and 85 cm (Japanese criteria). The prevalences were reduced to 35.9%, 47.6% and 50.5% when they were calculated for subjects without ASCD. The prevalences in females were 40.5%, 43.9% and 39.6% for $AC_M$ cutoff levels of 88 cm (NCEP-ATP III), 80 cm (IDF for Asians) and 90 cm (Japanese criteria), respectively, and these values were reduced to 34.4%, 38.0% and 34.4%, respectively, when calculated for subjects without ASCD. In contrast, the prevalence of metabolic syndrome defined by the Japanese criteria is strongly dependent on $AC_M$ cutoff levels: male $AC_M$ cutoff levels of 102, 94, 90, and 85 cm give prevalences of metabolic syndrome of 4.6%, 16.0%, 23.8%, and 36.2%, and female $AC_M$ cutoff levels of 88, 80, 90 and 78 cm give prevalences of 10.3%, 19.8%, 8.6% and 25.8%, respectively. Thus, the use of an $AC_M$ cutoff level of 78 cm, which is suggested by the present results, triples the prevalence of metabolic syndrome in the present subjects.

In the recent Tanno-Soubetsu Study (*15*), the prevalence of metabolic syndrome as defined by the modified NECP-ATP III criteria ($AC_M$ cutoff=85 cm) was 25.3% in 808 males undergoing health examinations, and their incidence of cardiovascular events was almost two-fold higher than that in subjects without metabolic syndrome (11.7% *vs.* 6.7%) during a 6-year follow up. The prevalence of metabolic syndrome in the present male subjects was approximately two-fold higher than that in the male subjects in the Tanno-Sobetsu Study, but this is likely to be due to selection bias in the present study. First, the subjects in the present study were older by 3 years (63±14 years old *vs.* 60±12 years old) and preferred in-hospital examination for ASCD and/or known coronary risks. Second, the proportion of subjects with ASCD was higher in this study than in the epidemiological studies. Nevertheless, the present study suggested that the prevalence of metabolic syndrome is lower in females than in males even when an $AC_M$ cutoff of 78–80 cm was used for females. Whether metabolic syndrome in females has the impact on the cardiovascular events that it has in males will need to be investigated in large cohort studies.

## Cutoff Level for Visceral Obesity and ASCD

Recent studies have shown that metabolic syndrome is associated with endothelial dysfunction (*16*), a hallmark of early atherosclerotic change, calcification of the coronary artery (*17*, *18*), and subclinical atherosclerosis of the carotid artery (*19*, *20*). On the other hand, obesity *per se* is an established risk factor of ASCD. Thus, we postulated that the $AC_M$ cutoff to predict ASCD might be larger than that to predict metabolic syndrome, which consists of clustered minor risk factors. However, the $AC_M$ cutoff level to predict metabolic syndrome and that to predict ASCD were very similar (Fig. 5B) in the present study. These results may suggest that the level of visceral obesity does not need to be higher than the level of obesity in metabolic syndrome in order for patients to develop ASCD. Nevertheless, the $AC_M$ cutoff levels for diagnosis of metabolic syndrome appear to also be useful for selecting patients who should be screened for ASCD.

## Limitations in the Present Study

There were several limitations in the present study. First, data collection was formed in a single institute by use of a retrospective and non-randomized method, which could have resulted in selection bias. Second, since this study is cross-sectional, a sequential relationship between visceral obesity and development of ASCD cannot be established. Third, a substantial number of the subjects were receiving treatment, including lifestyle modification and medications. Although the presence of diabetes mellitus does not preclude diagnosis of metabolic syndrome (*7–9*), it has profound effects on the metabolic profiles in patients. Furthermore, a recent Treating to New Targets (TNT) study (*21*) suggested that diabetes mellitus increases the incidence of cardiovascular events in patients with metabolic syndrome. Thus, it may be problematic to determine the VFA cutoff level for diagnosis of visceral obesity by use of mixed data from diabetic and non-diabetic populations. Fourth, we did not perform age-adjustment when calculating the $AC_M$ cutoff, though there was a trend of age-dependent changes in VFA. Therefore, a further investigation using a large population with age-adjustment needs to be performed for obtaining a precise estimation of $AC_M$ cutoff for diagnosis of metabolic syndrome in Japanese.

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## References


1. Castelli WP: Epidemiology of coronary heart disease: the Framingham study. *Am J Med* 1984; **76**: 4–12.
2. National Cholesterol Education Program: Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; **269**: 3015–3023.
3. Reaven GM: Banting lecture 1988: role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
4. Kaplan NM: The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989; **149**: 1514–1520.
5. DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14**: 173–194.
6. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987; **36**: 54–59.
7. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
8. Alberti KG, Zimmet P, Shaw J: Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; **23**: 469–480.
9. Examination Committee of Criteria for 'Obesity Disease' in Japan: Japan Society for the Study of Obesity: New criteria for 'Obesity Disease' in Japan. *Circ J* 2002; **66**: 987–992.
10. Matsuzawa Y: Adipocytokines and metabolic syndrome. *Semin Vasc Med* 2005; **5**: 34–39.
11. Moller DE, Kaufman KD: Metabolic syndrome: a clinical and molecular perspective. *Annu Rev Med* 2005; **56**: 45–62.
12. Task Force for Japanese Metabolic Syndrome Criteria: Diagnostic criteria of metabolic syndrome in Japanese. *Nihon Naika Gakkai Zasshi* 2005; **94**: 794 (in Japanese).
13. Miyawaki T, Hirata M, Moriyama K, *et al*: Metabolic syndrome in Japanese diagnosed with visceral far measurement by computed tomography. *Proc Jpn Acad* 2005; **81**: 471–479.
14. Hara K, Matsushita Y, Horikoshi M, *et al*: A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; **29**: 1123–1124.
15. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. *Hypertens Res* 2005; **28**: 203–208.
16. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, *et al*: Coronary vasomotor abnormalities in insulin-resistant individuals. *Ann Intern Med* 2004; **140**: 700–708.
17. Hunt ME, O'Malley PG, Feuerstein I, Taylor AJ: The relationship between the 'metabolic score' and subclinical atherosclerosis detected with electron beam computed tomography. *Coron Art Dis* 2003; **14**: 317–322.
18. Wong ND, Sciammarella MG, Polk D, *et al*: The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol* 2003; **41**: 1547–1553.
19. Tzou WS, Douglas PS, Srinivasan SR, *et al*: Increased subclinical atherosclerosis in young adults with metabolic syndrome: the Bogalusa Heart Study. *J Am Coll Cardiol* 2005; **46**: 457–463.
20. Hassinen M, Komulainen P, Lakka TA, *et al*: Metabolic syndrome and the progression of carotid intima-media thickness in elderly women. *Arch Intern Med* 2006; **166**: 444–449.
21. Deedwania P, Barter P, Carmena R, *et al*, Treating to New Targets Investigators: Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet* 2006; **368**: 919–928.

# Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort
## The Suita Study

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*Abstract*—Few prospective studies have examined the association between high-normal blood pressure and cardiovascular disease (CVD) in Asia. We examined the impact of high-normal blood pressure on the incidence of CVD in a general urban population cohort in Japan. We studied 5494 Japanese individuals (ages 30 to 79 years without CVD at baseline) after completing a baseline survey who received follow-up through December 2005. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, we documented the incidence of 346 CVD events. The frequencies of high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 18.0%, 20.1%, and 10.1% for men and 15.9%, 15.6%, and 8.8% for women, respectively. Antihypertensive drug users were also classified into the baseline blood pressure categories. Compared with the optimal blood pressure group, the multivariable hazard ratios (95% confidence intervals) of CVD for normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) in men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) in women, respectively. The risks of myocardial infarction and stroke for each blood pressure category were similar to those of CVD. Population-attributable fractions of high-normal blood pressure and hypertension for CVD were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively. In conclusion, high-normal blood pressure is a risk factor for the incidence of stroke and myocardial infarction in a general urban population of Japanese men. (***Hypertension.* 2008; 52:652-659.**)

**Key Words:** cardiovascular diseases ■ epidemiology ■ general population ■ high-normal blood pressure ■ myocardial infarction ■ prospective studies ■ stroke

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD)[1–5] in both developing and developed countries.[2,6,7] The guidelines of the Joint National Committee 7 from the United States has recently introduced a category, designated "prehypertension," for people with blood pressures ranging from 120 to 139 mm Hg for systolic pressure or 80 to 89 mm Hg for diastolic pressure.[8] The European Guidelines[9] and Japanese Society of Hypertension Guidelines,[10] however, divide this population into 2 groups: those with systolic blood pressures between 120 and 129 mm Hg or diastolic blood pressures between 80 and 84 mm Hg are classified as normal, whereas those with systolic blood pressures between 130 and 139 mm Hg or diastolic blood pressures between 85 and 89 mm Hg are classified as high-normal. Although the association of cardiovascular risk with elevated blood pressure is well accepted,[1–4,6] only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. The Framingham Heart Study revealed an association of high-normal blood pressure with increased risk of CVD.[11] The Framingham coronary heart disease prediction functions perform well for whites and blacks in different settings; these findings can be applied to other ethnic groups, like in the ARIC study, after recalibration for differing prevalence of risk factors for coronary heart disease events.[12] Few studies have investigated the association between blood pressure category and the incidence of CVD in Japan,[5,13] where there is a higher incidence of stroke and lower incidence of myocardial infarction (MI) than those in Western countries.[7] We performed a prospective examination of the risk of stroke and MI in men and women according to blood pressure category comparing normal and high-normal blood pressures in a general urban Japanese population.

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## Methods

### Study Subjects

The Suita Study,[5,14,15] an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 12 200 Japanese residents of Suita. As a baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n=208), were missing data (n=170), attended health checkups after April 1994 (n=79), or failed to complete the follow-up health surveys or questionnaires after baseline examination (n=534). After applying these exclusions, 5494 individuals were included in the analysis.

### Measurement of Blood Pressure and Covariates

Well-trained physicians measured blood pressure 3 times in a seated position with a mercury column sphygmomanometer and an appropriately sized cuff according to standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic blood pressure was measured first to obtain approximate systolic blood pressure levels. Systolic (SBP) and diastolic (DBP) blood pressures were the average of the second and third measurements recorded more than 1 minute apart.

At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal blood pressure (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), hypertension Stage 1 (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg), or hypertension Stage ≥2 (SBP ≥160 mm Hg or DBP ≥100 mm Hg).[9,10] Antihypertensive drug users were classified according to their blood pressure levels at baseline survey. Due to the small sample size for Grade 3 hypertension, both Grades 2 and 3 were combined. Therefore, we compared optimal blood pressure with Grade 1 and Grades 2 plus 3 hypertension in this study. In addition, after antihypertensive drug users were classified into the hypertension Stage ≥1 group, subjects were classified into one of the 4 blood pressure categories: optimal, normal, and high-normal blood pressure and hypertension Stage ≥1 group. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the 2 blood pressure categories.

At the baseline examination, we performed routine blood tests, including serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose levels. Physicians or nurses administered questionnaires regarding individual personal habits and present illnesses. Subjects were classified as current smokers, nonsmokers, and past smokers. We also measured height and body weight in a fasting state. Body mass index was calculated as weight (kg) divided by the square of the height ($m^2$). Hyperlipidemia was defined as total serum cholesterol levels ≥5.7 mmol/L (220 mg/dL) and/or current use of antihyperlipidemic medications. Diabetes was defined as fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) and/or current use of antidiabetic medications. We obtained informed consent from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

### Confirmation of Strokes and Myocardial Infarctions

Five hospitals in the Suita area were capable of performing CT scans and/or MRI, all of which were the major hospitals to which patients with acute stroke and those with MI were admitted. Medical records were reviewed by registered hospital or research physicians who were blinded to the baseline data. Stroke and MI events were registered if they occurred between the date on which the baseline health examination was performed and December 31, 2005. Strokes were defined according to the US National Survey of Stroke criteria,[16] which require rapid onset neurological deficits lasting at least 24 hours or until death. For each stroke subtype (cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definitive diagnosis was established based on CT, MRI or autopsy. Definitive and probable MIs were defined according to the criteria set by the MONICA project,[17] which requires electrocardiographic evidence, cardiac enzyme elevations, and/or autopsy. Sudden death was defined as death of unknown origin occurred within 24 hours from onset.

To complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates without registration of CVD incidence, which were defined as probable stroke or MI. CVD was defined as stroke and MI in this study.

### End Point Determination

The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored). To detect MI and stroke occurrences, each participant's health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. We also obtained informed consent to review in-hospital medical records for 86.2% participants who were suspected to have signs or symptoms related to stroke or MI events.

### Statistical Analysis

Analysis of variance and $\chi^2$ tests were used to compare the mean values and frequencies by sex according to blood pressure category. For each subject, person-years of follow-up were calculated from the date of baseline survey, to the first end point, CVD event, death, emigration, or December 31, 2005. The Cox proportional hazard ratios (HRs) were fit for each blood pressure category after adjusting for age and other potential confounding factors, including age, present illness of hypercholesterolemia or diabetes, smoking status (nonsmoker, past smoker, and current smoker), and drinking status (nondrinker, past drinker, and current drinker) at baseline survey.

To express the impact of blood pressure categories on CVD occurrence in the participants, we estimated the population-attributable fraction (%). Population-attributable fraction was estimated as $Pe \times (HR-1)/HR$, in which Pe is the proportion of incident cases in the blood pressure category and HR is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using SAS statistical package software (release version 8.2; SAS Institute Inc, Cary, NC).

## Results

At baseline, we observed several differences in the distribution of CVD risk factors according to blood pressure categories (Table 1). The percentages of subjects with optimal, normal, and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively. On average, both men and women with higher blood pressure were older and had higher serum total cholesterol levels, higher body mass index, and higher incidences of hyperlipidemia and diabetes than those with optimal blood pressure. The percentages of antihypertensive drug users classified as having hypertension Stages 1 and ≥2 at baseline were 21.3% and 37.7% for men and 24.2% and 40.6% for women, respectively.

**Table 1. Baseline Characteristics of Study Subjects According to Blood Pressure Category**

| Groups and Variables | Blood Pressure Category* | | | | | *P* Values |
|---|---|---|---|---|---|---|
| | Optimal | Normal | High-Normal | Stage 1 | Stage ≥2 | |
| Men | | | | | | |
| No. of subjects | 803 | 502 | 463 | 516 | 286 | |
| Age, years | 50.8±13.2 | 54.0±12.9 | 57.5±12.2 | 60.1±11.7 | 62.0±11.1 | <0.001 |
| SBP, mm Hg | 107.8±7.5 | 121.7±5.4 | 131.4±5.8 | 143.9±8.5 | 167.0±17.4 | <0.001 |
| DBP, mm Hg | 68.2±6.7 | 76.6±6.3 | 81.2±6.9 | 87.5±8.2 | 97.0±11.7 | <0.001 |
| Total cholesterol, mmol/L† | 5.1±0.8 | 5.2±0.9 | 5.3±0.9 | 5.3±0.9 | 5.3±0.9 | <0.001 |
| High-density lipoprotein cholesterol, mmol/L† | 1.3±0.3 | 1.3±0.4 | 1.3±0.3 | 1.3±0.3 | 1.3±0.3 | 0.332 |
| Body mass index, kg/m$^2$ | 22.0±2.7 | 22.7±2.6 | 23.2±2.7 | 23.3±3.0 | 23.6±3.2 | <0.001 |
| Antihypertensive medication, % | 0.6 | 3.9 | 7.7 | 21.3 | 37.7 | <0.001 |
| Hyperlipidemia, % | 23.7 | 27.4 | 30.6 | 34.4 | 31.4 | <0.001 |
| Diabetes, % | 3.8 | 5.3 | 5.6 | 8.9 | 9.7 | <0.001 |
| Current smokers, % | 59.7 | 49.6 | 46.3 | 44.3 | 40.9 | <0.001 |
| Current drinkers, % | 71.7 | 77.0 | 75.0 | 76.8 | 79.6 | 0.045 |
| Women | | | | | | |
| No. of subjects | 1240 | 504 | 465 | 457 | 258 | |
| Age, years | 47.8±11.9 | 54.0±11.5 | 58.9±11.5 | 61.6±9.4 | 62.9±9.6 | <0.001 |
| SBP, mm Hg | 105.5±7.9 | 122.4±4.8 | 132.4±4.9 | 145.7±7.8 | 169.9±14.0 | <0.001 |
| DBP, mm Hg | 66.4±6.6 | 75.5±7.1 | 79.7±6.9 | 85.0±9.0 | 92.3±13.9 | <0.001 |
| Total cholesterol, mmol/L† | 5.2±0.9 | 5.6±1.0 | 5.7±0.9 | 5.9±0.9 | 5.8±1.0 | <0.001 |
| High-density lipoprotein cholesterol, mmol/L† | 1.5±0.3 | 1.4±0.3 | 1.4±0.3 | 1.4±0.3 | 1.4±0.3 | <0.001 |
| Body mass index, kg/m$^2$ | 21.1±2.7 | 22.5±3.0 | 22.8±3.2 | 23.2±3.3 | 23.7±3.7 | <0.001 |
| Antihypertensive medication, % | 0.9 | 4.3 | 11.3 | 24.2 | 40.6 | <0.001 |
| Hyperlipidemia, % | 28.8 | 44.2 | 50.9 | 58.6 | 58.1 | <0.001 |
| Diabetes, % | 1.5 | 3.3 | 4.0 | 6.7 | 5.8 | <0.001 |
| Current smokers, % | 15.6 | 11.7 | 9.2 | 6.9 | 8.9 | <0.001 |
| Current drinkers, % | 37.0 | 32.5 | 27.9 | 29.8 | 25.4 | <0.001 |

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Plus–minus values are means±SD.

†To convert cholesterol values to mg/dL, multiply ×38.67.

During an average 11.7-year follow-up period, we documented 213 strokes (155 definitive strokes and 58 probable strokes) consisting of 141 cerebral infarctions, 32 intracerebral hemorrhages, 22 subarachnoid hemorrhages, and 18 unclassified strokes. We also documented 133 MIs (64 definitive MIs and 69 probable MIs or sudden cardiac deaths). Subjects who moved from Suita (16.8% of the total participants) were censored at that time.

We determined the age- and multivariable-adjusted hazard ratios for CVD, MI, and stroke according to blood pressure categories in the presence or absence of antihypertensive medication (Table 2). In men, the multivariable HRs (95% CIs) of CVD incidence were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) for men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) for women with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively. The risks of MI and stroke for each blood pressure category were similar to the risk of CVD. In a combined analysis of men and women, the multivariable HR of CVD incidence were 1.62 (1.08 to 2.43), 2.08 (1.42 to 3.05), 2.06 (1.42 to 2.98), and 3.53 (2.43 to 5.13) for the normal and high-normal blood pressure and hypertension Stages 1 and ≥2 groups, respectively (data not shown). In addition, the multivariable HR of CVD incidence in men and women younger than 60 years old were similar to those seen in men and women older than 60 years of age (data not shown).

In a second analysis in which all antihypertensive drug users were categorized to the Stage ≥1 group, we determined the age- and multivariable-adjusted HRs for CVD, MI, and stroke according to blood pressure category (Table 3). In men, the multivariable HRs (95% CIs) of CVD incidence were 1.83 (1.05 to 3.20), 2.11 (1.22 to 3.64), and 3.20 (2.01

**Table 2. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category With and Without Antihypertensive Medications**

| | Blood Pressure Category* | | | | |
|---|---|---|---|---|---|
| Groups and Variables | Optimal | Normal | High-Normal | Stage 1 | Stage ≥2 |
| Men | | | | | |
| Person-years | 9724 | 5889 | 5127 | 5611 | 3025 |
| Cardiovascular disease | | | | | |
| Case | 23 | 34 | 43 | 57 | 52 |
| Age-adjusted | 1 | 2.03 (1.19–3.46) | 2.42 (1.45–4.03) | 2.44 (1.49–3.99) | 3.71 (2.25–6.16) |
| Multivariable-adjusted | 1 | 2.04 (1.19–3.48) | 2.46 (1.46–4.14) | 2.62 (1.59–4.32) | 3.95 (2.37–6.58) |
| MI | | | | | |
| Case | 10 | 14 | 19 | 25 | 20 |
| Age-adjusted | 1 | 2.07 (0.92–4.68) | 2.56 (1.18–5.53) | 2.45 (1.16–5.17) | 3.47 (1.60–7.51) |
| Multivariable-adjusted | 1 | 2.14 (0.94–4.86) | 2.65 (1.20–5.85) | 2.72 (1.26–5.84) | 3.89 (1.76–8.56) |
| Stroke | | | | | |
| Case | 13 | 20 | 24 | 32 | 32 |
| Age-adjusted | 1 | 2.13 (1.06–4.30) | 2.39 (1.21–4.71) | 2.49 (1.30–4.78) | 4.17 (2.17–8.01) |
| Multivariable-adjusted | 1 | 2.12 (1.04–4.30) | 2.43 (1.21–4.86) | 2.62 (1.35–5.09) | 4.38 (2.24–8.56) |
| Women | | | | | |
| Person-years | 15 438 | 6100 | 5391 | 5272 | 2812 |
| Cardiovascular disease | | | | | |
| Case | 25 | 17 | 28 | 29 | 38 |
| Age-adjusted | 1 | 1.05 (0.56–1.95) | 1.48 (0.85–2.59) | 1.32 (0.75–2.30) | 3.00 (1.77–5.09) |
| Multivariable-adjusted | 1 | 1.12 (0.59–2.13) | 1.54 (0.85–2.78) | 1.35 (0.75–2.43) | 2.86 (1.60–5.12) |
| MI | | | | | |
| Case | 7 | 5 | 10 | 9 | 14 |
| Age-adjusted | 1 | 1.09 (0.34–3.48) | 1.71 (0.63–4.59) | 1.38 (0.50–3.80) | 3.56 (1.39–9.08) |
| Multivariable-adjusted | 1 | 1.44 (0.42–4.90) | 2.27 (0.78–6.57) | 1.69 (0.56–5.10) | 5.24 (1.85–14.85) |
| Stroke | | | | | |
| Case | 18 | 12 | 18 | 20 | 24 |
| Age-adjusted | 1 | 1.05 (0.50–2.19) | 1.39 (0.71–2.75) | 1.29 (0.66–2.52) | 2.83 (1.49–5.39) |
| Multivariable-adjusted | 1 | 1.05 (0.49–2.24) | 1.29 (0.63–2.67) | 1.21 (0.61–2.45) | 2.20 (1.07–4.50) |

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified according to their blood pressure levels at baseline survey.

to 5.09) for normal and high-normal blood pressure subjects without antihypertensive medication and subjects with hypertension Stage ≥1 with or without antihypertensive medication, respectively. In women, the multivariable HR of CVD incidence was 2.13 (1.25 to 3.62) for the hypertension Stage ≥1 group with or without antihypertensive medications. The risks of MI and stroke for high-normal blood pressure and hypertension Stage ≥1 group were observed in men (HR=2.32, 95% CI: 1.02 to 5.27 and HR=3.35, 95% CI: 1.64 to 6.80 for MI; HR=2.04, 95% CI: 1.00 to 4.22 and HR=3.33, 95% CI: 1.80 to 6.15 for stroke, respectively). HRs for CVD according to prehypertensive category excluding subjects taking antihypertensive drugs (Table 3) were similar but slightly lower than that category including subjects taking antihypertensive drugs (Table 2).

Using the HRs, we estimated the positive fraction of CVD attributable to exposure for each blood pressure category at baseline by sex (Figure). For men, 8.3%, 12.2%, 16.8%, and 18.5% of CVD incidence were excessive incidence due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2 with values of 1.3%, 7.1%, 5.4%, and 18.0%.

## Discussion

In this cohort study of a general Japanese urban population, we determined that high-normal blood pressure was a risk factor for the incidence of stroke and MI in men in comparison to subjects with optimal blood pressure. In this study, 20.5% and 8.4% of CVD incidence may derive from prehypertension cases in men and women, respectively. This is the

**Table 3. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category**

| Groups and Variables | Blood Pressure Category* | | | |
|---|---|---|---|---|
| | Optimal | Normal | High-Normal | Stage ≥1 |
| Men | | | | |
| Person-years | 9670 | 5662 | 4805 | 9243 |
| Cardiovascular disease | | | | |
| Case | 23 | 28 | 35 | 123 |
| Age-adjusted | 1 | 1.80 (1.03–3.13) | 2.09 (1.23–3.55) | 3.00 (1.91–4.72) |
| Multivariable-adjusted | 1 | 1.83 (1.05–3.20) | 2.11 (1.22–3.64) | 3.20 (2.01–5.09) |
| MI | | | | |
| Case | 10 | 11 | 16 | 51 |
| Age-adjusted | 1 | 1.71 (0.72–4.03) | 2.27 (1.02–5.03) | 2.98 (1.49–5.93) |
| Multivariable-adjusted | 1 | 1.78 (0.75–4.22) | 2.32 (1.02–5.27) | 3.35 (1.64–6.80) |
| Stroke | | | | |
| Case | 13 | 17 | 19 | 72 |
| Age-adjusted | 1 | 1.93 (0.93–3.98) | 2.01 (1.00–4.08) | 3.18 (1.75–5.79) |
| Multivariable-adjusted | 1 | 1.92 (0.92–3.97) | 2.04 (1.00–4.22) | 3.33 (1.80–6.15) |
| Women | | | | |
| Person-years | 15 293 | 5890 | 4834 | 9002 |
| Cardiovascular disease | | | | |
| Case | 24 | 12 | 20 | 81 |
| Age-adjusted | 1 | 0.80 (0.39–1.61) | 1.28 (0.69–2.36) | 2.12 (1.30–3.44) |
| Multivariable-adjusted | 1 | 0.86 (0.42–1.72) | 1.32 (0.69–2.53) | 2.13 (1.25–3.62) |
| MI | | | | |
| Case | 7 | 4 | 7 | 27 |
| Age-adjusted | 1 | 0.91 (0.26–3.14) | 1.38 (0.47–4.01) | 2.23 (0.94–5.28) |
| Multivariable-adjusted | 1 | 1.17 (0.31–4.34) | 1.83 (0.58–5.75) | 2.97 (1.11–7.91) |
| Stroke | | | | |
| Case | 17 | 8 | 13 | 54 |
| Age-adjusted | 1 | 0.76 (0.32–1.79) | 1.22 (0.58–2.58) | 2.12 (1.17–3.83) |
| Multivariable-adjusted | 1 | 0.77 (0.32–1.83) | 1.11 (0.50–2.49) | 1.89 (1.00–3.58) |

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified into the hypertension Stage ≥1 group.

first cohort study to examine the impact of high-normal blood pressure on the risks of stroke and MI incidence in a general Japanese urban population, who have a relatively higher incidence of stroke and lower incidence of MI than those seen in Western countries.[7]

Compared with the previous studies, this study has several methodological strengths. First, we evaluated a large prospective cohort of people selected randomly from a general population in Japan, which allowed us to perform subanalyses by age and CVD subtype. Second, our cohort population was selected from an urban population in contrast to the majority of other cohorts in Japan, which have been selected from rural populations. Because approximately 66% of the Japanese population lives in urban areas, this is an important strength of our analysis. The health status of each participant was examined every 2 years during a clinical visit at the National Cardiovascular Center. In addition, a health questionnaire was administered to each participant yearly by mail or telephone. In combination with frequent evaluation of the CVD registry, we could effectively examine the incidence of CVD events in this population. Finally, we examined the risk of CVD incidence, which is a more direct measure of CVD risk than risk of CVD mortality, because mortality from CVD is significantly influenced by treatment.

This study revealed that normal and high-normal blood pressures were risk factors for CVD in Japanese urban men. The results of a multiple ethnic groups investigation has demonstrated that high-normal blood pressure is a risk factor for incidence of coronary heart disease in both men and women.[11] Compared with optimal blood pressure, the relative risk of CVD was 2.33 (1.85 to 2.92) for high-normal blood pressure and was 1.81 (1.47 to 2.22) for normal blood pressure among blacks.[19] An inverse association of optimal blood pressure and a positive association of Stage 1 hyper-

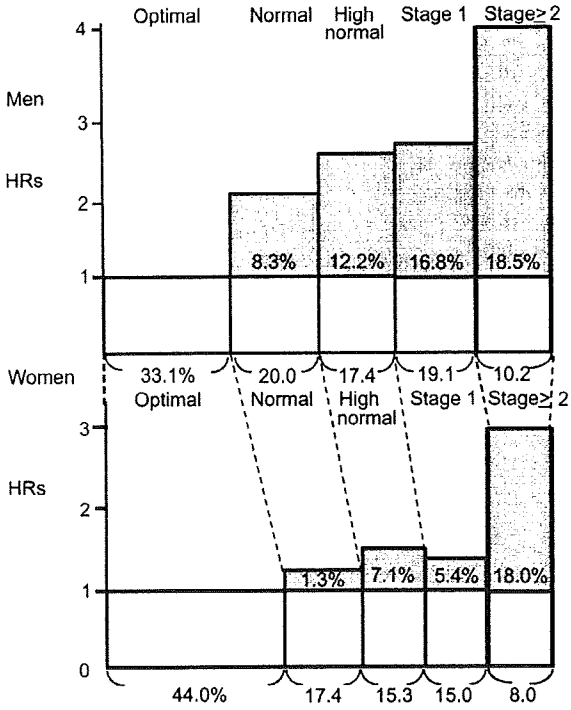


**Figure.** The HRs and positive fraction attributable to exposure to each blood pressure category (optimal, normal, and high-normal blood pressures and hypertension Stages 1 and ≥2) at baseline for CVD were estimated by sex. The gray area displays excessive incidence of CVD due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2.

tension with coronary heart disease were observed in men compared with normal blood pressure.[12] The Framingham Heart Study revealed that 17.6% and 37.3% of subjects with baseline normal and high-normal blood pressure, respectively, were diagnosed with hypertension within 4 years. High-normal blood pressure has also been associated with increased risk of carotid atherosclerosis,[20] altered cardiac morphological features,[21] and diastolic ventricular dysfunction,[22] all of which may be precursors of incidence of CVD.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al demonstrated a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan.[5] Sairenchi et al revealed that high-normal blood pressure was associated with an increased risk of CVD mortality in Japanese men.[23] The NIPPON DATA 80 also indicated that high blood pressure was a risk factor for mortality from all causes as well as death from CVD among Japanese.[24] All of these studies used end points of mortality. The risk of CVD incidence, like used in this study, is a more direct measure of CVD risk than is the risk of CVD mortality, which is heavily influenced by treatment.

In prospective studies examining the incidence of CVD in Japanese populations, the Ohasama study demonstrated that high-normal blood pressure was a risk factor for stroke by using homed blood pressure, but not by using causal blood pressure.[13] The Hisayama study, which observed the natural course of untreated hypertension in a general Japanese elderly population over a 32-year period, indicated that high-normal blood pressure was not a risk factor for cerebral infarction.[4] This cohort was approximately half the size of our cohort, and the subjects were older and observed for longer periods of time. Hypertensive risk for CVD decreased with advancing age.[25] Over very long periods, confounding factors, including advancing aging, menopause, lifestyle modifications, and medication, will affect blood pressure classification. The Tanno-Sobetu study determined that high-normal blood pressure, determined according to the 1999 World Health Organization/International Society of Hypertension criteria, was not a risk factor for CVD in comparison to optimal and normal blood pressures.[26]

In this study, we did not find an association between high-normal blood pressure and CVD incidence in women. The association between blood pressure category and coronary heart disease is well documented to be weaker in women than in men.[12] For each racial/ethnic group, the mean SBP and DBP values in men were 6 to 7 and 3 to 5 mm Hg higher, respectively, than the values in women.[27] Postmenopausal effects have been associated with elevated blood pressure.[28] Therefore, the period of hypertension exposure tends to be shorter in women than in men. The incidence of CVD was lower in women (3.9 per 1000 person-year) than in men (7.1 per 1000 person-years) in this study. The percentages of those with hypertension who were aware, treated, and controlled were higher for women than men.[27]Because the frequency of white coat hypertension is higher in women than in men,[29,30] blood pressure at baseline examination may be overestimated in women, which may result in the absence of an association between high-normal blood pressure and CVD incidence in women.

The multivariable HR of CVD incidence for normal blood pressure was 2-fold higher than that for optimal blood pressure. In the Honolulu heart program and the Puerto Rico heart health program, the multivariable HRs of CVD incidence for normal blood pressure were approximately 2-fold higher than those for optimal blood pressure.[12] Thus, lower blood pressure appears to prevent the incidence of CVD.

The crude 10-year cumulative incidences of CVD in this subjects who had optimal, normal, and high-normal blood pressure were approximately 2%, 6%, and 8% for men and 2%, 3%, and 5% for women, respectively (data not shown). In the Framingham Heart Study, those were 5%, 8%, and 10% for men and 1%, 3%, and 6% for women, respectively.[12] Compared with the Framingham Heart Study, the incidences of CVD for optimal blood pressure in the Suita study tend to be lower in men and similar in women.

Our study has several limitations. The primary limitation is a dilution bias[31]; this study was based on a single-day measurement of blood pressure, which may lead to a misclassification of blood pressure levels. Previous epidemiological evidence has suggested, however, that blood pressure measurements taken on a single day are accurate.[32] Second, approximately 10% of subjects who underwent baseline survey did not respond to our questionnaires thereafter. However, we found no clinical background difference be-

tween participants and nonparticipants, because the main denial reason for participation in this study was not a health problem. Age- and sex-adjusted systolic blood pressures were 127 mm Hg for participants and 128 mm Hg for nonparticipants ($P$=0.08). To achieve a minimum of failure study subjects, we performed close follow-up with health questionnaires annually and health checkups every 2 years.

In conclusion, high-normal blood pressure is a risk factor for MI and stroke in general Japanese urban men. Approximately 20% and 8% of CVD incidences can be attributed to normal and high-normal blood pressure in both men and women, respectively. To prevent the incidence of CVD, it is necessary for subjects with high-normal blood pressure to attempt to control these values through lifestyle modifications.

## Perspectives

Although it is well accepted that hypertension is a strong risk factor for total mortality and CVD all over the world, only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. In this study, the impact of high-normal blood pressure on the incidence of CVD was examined in a general urban population cohort in Japan. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, 346 CVD events were identified. Compared with the optimal blood pressure group, the multivariable HR of CVD for high-normal blood pressure was 2.5 times in men but was not statistically significant in women. This might be due to a postmenopausal effect, higher frequency of controlled or medication for hypertension, and white coat hypertension in women compared with those in men, but it should be researched further whether these reasons can be applied in women. The risks of MI and stroke for each blood pressure category were similar to those of CVD. Approximately 20% and 8% of CVD incidences can be attributed to prehypertension in men and women, respectively. It is a remarkable finding that one fifth of CVD incidence is derived from prehypertension in men. Our results suggest that it is necessary for subjects with high-normal blood pressure to attempt to control blood pressure through lifestyle modifications to prevent the incidence of CVD.

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## Disclosures

None.

## References

1. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*. 1996;275:1571–1576.
2. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. *Lancet*. 1998;352:1801–1807.
3. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med*. 1993; 153:598–615.
4. Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, Tanaka K, Ohkubo K, Nakamura H, Abe I, Fujishima M, Iida M. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med*. 2003;163:361–366.
5. Murakami Y, Hozawa A, Okamura T, Ueshima H. Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension*. 2008;51:1483–1491.
6. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med*. 2000;342:1–8.
7. Tanaka H, Yokoyama T, Yoshiike N, Kokubo Y. Cerevrovascular disease. In: Detels R, McEwen J, Beaglehole R, Tanaka H, eds. *Oxford Textbook of Public Health: The Scope of Public Health*, IV ed. Oxford: Oxford University Press; 2002:1193–1254.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42: 1206–1252.
9. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
10. Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2004). *Hypertens Res*. 2006;29(suppl):S1–S105.
11. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297.
12. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
13. Asayama K, Ohkubo T, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by self-measurement of blood pressure at home versus casual screening blood pressure measurement in relation to the Joint National Committee 7 classification: the Ohasama study. *Stroke*. 2004;35:2356–2361.
14. Inamoto N, Katsuya T, Kokubo Y, Mannami T, Asai T, Baba S, Ogata J, Tomoike H, Ogihara T. Association of methylenetetrahydrofolate reductase gene polymorphism with carotid atherosclerosis depending on smoking status in a Japanese general population. *Stroke*. 2003;34: 1628–1633.
15. Iwai N, Kajimoto K, Kokubo Y, Tomoike H. Extensive genetic analysis of 10 candidate genes for hypertension in Japanese. *Hypertension*. 2006; 48:901–907.
16. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12(suppl 1):I13–I44.
17. 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.
18. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88:15–19.
19. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med*. 2006;119:133–141.
20. Lonati L, Cuspidi C, Sampieri L, Boselli L, Bocciolone M, Leonetti G, Zanchetti A. Ultrasonographic evaluation of cardiac and vascular changes in young borderline hypertensives. *Cardiology*. 1993;83:298–303.
21. Kimura Y, Tomiyama H, Nishikawa E, Watanabe G, Shiojima K, Nakayama T, Yoshida H, Kuwata S, Kinouchi T, Doba N. Characteristics of cardiovascular morphology and function in the high-normal subset of hypertension defined by JNC-VI recommendations. *Hypertens Res*. 1999; 22:291–295.
22. Escudero E, De Lena S, Graff-Iversen S, Almiron M, Cingolani HE. Left ventricular diastolic function in young men with high normal blood pressure. *Can J Cardiol*. 1996;12:959–964.
23. Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, Saito Y, Ota H, Nose T. Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertens Res*. 2005;28:901–909.
24. Lida M, Ueda K, Okayama A, Kodama K, Sawai K, Shibata S, Tanaka S, Keijnkai T, Horibe H, Minowa M, Yanagawa H, Hashimoto T. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese–Nippon data 80. *J Hum Hypertens*. 2003;17:851–857.
25. Selmer R. Blood pressure and twenty-year mortality in the city of Bergen, Norway. *Am J Epidemiol*. 1992;136:428–440.
26. Obara F, Saitoh S, Takagi S, Shimamoto K. Influence of hypertension on the incidence of cardiovascular disease in two rural communities in Japan: the Tanno-Sobetsu [corrected] study. *Hypertens Res*. 2007;30: 677–682.
27. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*. 1995;25:305–313.
28. Zanchetti A, Facchetti R, Cesana GC, Modena MG, Pirrelli A, Sega R. Menopause-related blood pressure increase and its relationship to age and body mass index: the SIMONA epidemiological study. *J Hypertens*. 2005;23:2269–2276.
29. James GD, Marion R, Pickering TG. White-coat hypertension and sex. *Blood Press Monit*. 1998;3:281–287.
30. Gualdiero P, Niebauer J, Addison C, Clark SJ, Coats AJ. Clinical features, anthropometric characteristics, and racial influences on the 'white-coat effect' in a single-centre cohort of 1553 consecutive subjects undergoing routine ambulatory blood pressure monitoring. *Blood Press Monit*. 2000;5:53–57.
31. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.
32. Markovic N, Olomu IN, Bunker CH, Huston SL, Ukoli FA, Kuller LH. Adequacy of a single visit for classification of hypertensive status in a Nigerian civil servant population. *Int J Epidemiol*. 1994;23:723–729.

# Circulating CD34-Positive Cell Number Is Associated With Brain Natriuretic Peptide Level in Type 2 Diabetic Patients

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Patients with type 2 diabetes often suffer from asymptomatic left ventricular (LV) injury, including increased LV mass, without apparent myocardial ischemia. The mechanisms underlying diabetic LV injury remain unclear; however, it has been suggested that endothelial dysfunction plays a role. Accumulating evidence indicates that bone marrow–derived endothelial progenitor cells (EPCs) contribute to neovascularization of ischemic tissue and endothelialization of denuded endothelium. Recent studies have shown that circulating bone marrow–derived immature cells, including $CD34^+$ cells, contribute to the maintenance of the vasculature, both as a pool of EPCs and as the source of growth/angiogenesis factors (1). We hypothesized that circulating $CD34^+$ cells might be associated with LV dysfunction in patients with type 2 diabetes. Therefore, we studied the correlation between circulating $CD34^+$ cell levels and plasma brain natriuretic peptide (BNP) levels, an LV dysfunction marker, in type 2 diabetic patients.

## RESEARCH DESIGN AND METHODS

The institutional review board of the National Cardiovascular Center approved this study, and all subjects provided informed consent. We examined 26 patients with type 2 diabetes (12 men and 14 women, duration of diabetes 16.1 ± 10.7 years) who were over 60 years of age (70.5 ± 6.4 years). Statin was given to nine subjects. ACE inhibitor or angiotensin receptor blocker was given to nine subjects, and thiazolidinedione was given to two subjects. Subjects were excluded from the study if they had known cardiovascular disease or chronic renal failure (defined as serum creatinine ≥180 μmol/l). No study subject showed hypokinesis by echocardiography or electrocardiogram change, indicating myocardial ischemia. Systolic (SBP) and diastolic (DBP) blood pressure and anthropometric parameters were determined. Blood samples were taken after 12-h fasting to measure circulating $CD34^+$ cells, plasma BNP, fasting plasma glucose (FPG), and A1C. Circulating $CD34^+$ cells were quantified by flow cytometry according to the manufacturer's protocol (ProCOUNT; Becton Dickinson Biosciences) as previously reported (2). BNP was quantified by enzyme immunoassay (Tohso, Tokyo, Japan). We further examined LV fractional shortening (LVFS), LV mass index (LVMI) (3), and peak flow velocity of the early filling wave (E), the late filling wave (A), and the E/A-wave ratio (E/A) by echocardiography. All echocardiograms were performed by several expert physicians who were blinded to $CD34^+$ cell level.

All statistical analyses were performed using JMP version 5.1.1 software (SAS Institute). Data are expressed as means ± SD. Comparisons of number of $CD34^+$ cells by sex were made using the two-tailed unpaired *t* test. Correlations between number of $CD34^+$ cells and clinical parameters were assessed by univariate liner regression analysis and multiple regression analysis. LVMI and plasma BNP concentrations were analyzed after logarithmic transformation.

## RESULTS

FPG levels, A1C levels, and BMIs in the study subjects were measured to be 9.5 ± 2.6 mmol/l, 9.2 ± 1.8%, and 26.4 ± 4.3 $kg/m^2$, respectively. A total of 88% of the patients had hypertension (SBP 142 ± 18 mmHg, DBP 75.7 ± 13.5 mmHg). Plasma BNP levels were measured to be 95 ± 319 pg/ml. Although it has been reported that the level of BNP ≥100 pg/ml has a sensitivity of 90% of diagnosing congestive heart failure (CHF) in patients with CHF symptoms (4), none of the subjects in this study, including subjects with ≥100 pg/ml of BNP, showed symptoms of CHF. The level of circulating $CD34^+$ cells was measured to be 0.76 ± 0.39 cells/μl, and there was no significant difference between sexes. The range of LVMI was 73.3–340.2, and 11 subjects applied to the definition of LV hypertrophy (LVMI ≤131 in men and ≤100 in women) (3).

Plasma BNP levels had a significant inverse correlation with the number of circulating $CD34^+$ cells (Fig. 1*A*), whereas FPG, A1C, BMI, SBP, DBP, and age showed no significant correlations. There was a significant correlation between the number of circulating $CD34^+$ cells and LVMI by echocardiography (Fig. 1*B*). LVFS and E/A were not associated with circulating $CD34^+$ cell numbers (LVFS $r = -0.07$, $P = 0.72$; E/A $r = -0.11$, $P = 0.59$). There was also a significant correlation between BNP levels and LVMI ($r = 0.59$, $P = 0.001$).

In multiple regression analysis, the

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Abbreviations: BNP, brain natriuretic peptide; CHF, congestive heart failure; DBP, diastolic blood pressure; EPC, endothelial progenitor cell; FPG, fasting plasma glucose; LV, left ventricular; LVFS, LV fractional shortening; LVMI, LV mass index; SBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

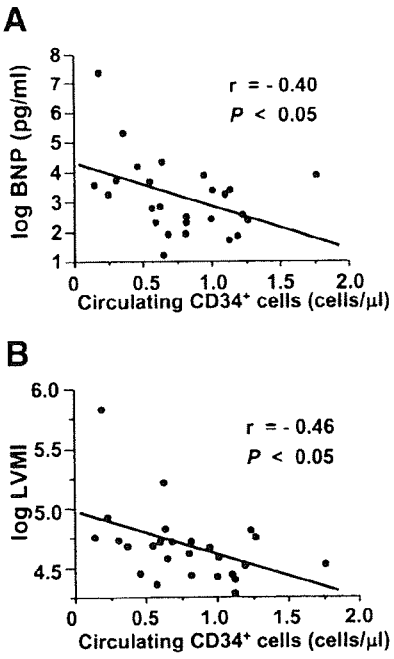


**Figure 1**—*Correlation between CD34$^+$ cell numbers and plasma BNP levels (A) and correlation between CD34$^+$ cell numbers and LVMI (B) in type 2 diabetic patients* (n = 26).

level of CD34$^+$ cells was an independent correlate of both BNP ($\beta = -1.64$, $P = 0.017$) and LVMI ($\beta = -0.337$, $P = 0.031$) in the model including age, A1C, SBP, BMI, and medication (ACE inhibitor/angiotensin receptor blocker, statin, and thiazolidinedione).

**CONCLUSIONS** — In this study, circulating CD34$^+$ cell number was found to significantly correlate with plasma BNP level, a marker of LV dysfunction. To the best of our knowledge, this is the first report that circulating bone marrow–derived cells are associated with diabetic LV abnormality. Circulating CD34$^+$ cell numbers also significantly correlated with LVMI, whereas they did not correlate with LVFS (an LV systolic function marker) or E/A (an LV diastolic function marker). LV hypertrophy is a well-known predictor of cardiovascular events independent of coronary artery disease. The Framingham Heart Study identified an association between diabetes and increased LV wall thickness and mass (5). Although the precise mechanisms underlying the association between diabetes and LV hypertrophy remain unknown, our results suggest that reduced circulating CD34$^+$ cell numbers may be involved in the progression of LV hypertrophy in diabetic patients. However, further investigations are necessary to demonstrate this hypothesis.

We measured the level of CD34$^+$ cells in this study but not the levels of circulating CD34$^+$/kinase insert domain receptor (KDR)$^+$ cells that are regarded as EPCs. Circulating CD34$^+$ cell levels are associated with ischemic stroke (6), and administration of CD34$^+$ cells ameliorates cerebral ischemia in mice (7). This indicates that CD34$^+$ cells may be involved in cardiovascular disease. Indeed, another recent report indicated that levels of circulating CD34$^+$ cells are more strongly correlated with cardiovascular risk than levels of EPCs (8). Therefore, our results suggest that measurement of CD34$^+$ cells may provide an indicator for diabetic LV hypertrophy.

Our study had several limitations. First, the study was performed only by cross sectional analysis; therefore, a prospective study is needed to clarify whether circulating CD34$^+$ cell numbers predict LV injury in diabetic patients. Second, although systemic blood pressure did not significantly associate with CD34$^+$ cell numbers, further investigation of normotensive diabetic patients is needed to exclude the possible effects of hypertension on circulating CD34$^+$ cell numbers, as most of the subjects in this study were hypertensive. Despite this caveat, these results may be of practical use in elderly patients with type 2 diabetes, as hypertension is a very common comorbid condition in this population.

In conclusion, reduced circulating CD34$^+$ cell numbers are significantly associated with plasma BNP concentration and LVMI in elderly patients with type 2 diabetes. These results suggest that decreased circulating CD34$^+$ cells may be involved in LV hypertrophy and that measurement of circulating CD34$^+$ cell numbers may be useful for the identification of diabetic patients at high risk of LV injury.

**References**

1. Majka M, Janowska-Wieczorek A, Ratajczak J, Ehrenman K, Pietrzkowski Z, Kowalska MA, Gewirtz AM, Emerson SG, Ratajczak MZ: Numerous growth factors, cytokines, and chemokines are secreted by human CD34(+) cells, myeloblasts, erythroblasts, and megakaryoblasts and regulate normal hematopoiesis in an autocrine/paracrine manner. *Blood* 97:3075–3085, 2001
2. Kikuchi-Taura A, Soma T, Matsuyama T, Stern DM, Taguchi A: A new protocol for quantifying CD34(+) cells in peripheral blood of patients with cardiovascular disease. *Jex Heart Inst J* 33:427–429, 2006
3. Devereux RB, Reichek N: Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 55:613–618, 1977
4. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AHB, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS, BNP multinational study investigators. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Property (BNP) Multinational Study. *Circulation* 106: 416–422, 2002
5. Galderisi M, Anderson KM, Wilson PW, Levy D: Echocardiographic evidence for existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 68:85–89, 1991
6. Taguchi A, Matsuyama T, Moriwaki H, Hayashi T, Hayashida K, Nagatsuka K, Todo K, Mori K, Stern DM, Soma T, Naritomi H: Circulating CD34-positive cells provide an index of cerebrovascular function. *Circulation* 109:2972–2975, 2004
7. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, Tsukamoto Y, Iso H, Fujimori Y, Stern DM, Naritomi H, Matsuyama T: Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. *J Clin Invest* 114:330–338, 2004
8. Fadini GP, de Kreutzenberg SV, Coracina A, Baesso I, Agostini C, Tiengo A, Avogaro A: Circulating CD34+ cells, metabolic syndrome, and cardiovascular risk. *Eur Heart J* 27:2247–2255, 2006

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# Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study

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ABSTRACT

*Objective:* Only a small number of population-based cohort studies have directly compared the predictive value of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDLC) for coronary artery disease in Asian populations, such as Japan.
*Methods:* We performed an 11.9-year cohort study of 4694 men and women, aged 30–74 years, selected randomly from an urban general population in Japan. Baseline LDL-C levels were estimated using the Friedewald formula. The predictive values of LDL-C and non-HDLC for myocardial infarction (MI) and stroke were compared.
*Results and conclusion:* During the follow-up period, there were 80 incident cases of MI and 139 of stoke, comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke. The Hazard ratio (HR) for MI was highest in the top quintile of LDL-C (HR: 3.03, 95% CI, 1.32–6.96) when male and female data were combined. The HR for MI was also highest in the top quintile of non-HDLC (HR: 2.97, 95% CI, 1.26–6.97). Analysis of trends showed a significant positive relationship between MI incidence and serum LDL-C and non-HDLC levels (both $P = 0.02$). However, there was no relationship between the incidence of any subtype of stroke and either LDL-C or non-HDLC. The predictive value of LDL-C and non-HDLC for MI, assessed by calculating the differences in the −2 logarithm likelihood (−2 ln [L]) and area under the curve (AUC), were almost similar.



## 1. Introduction

The causal relationship between high levels of serum low-density lipoprotein cholesterol (LDL-C) and coronary artery disease (CAD) is well established [1–5]. Blood LDL-C levels are therefore the main target for lipid management in the majority of guidelines of developed countries for preventing atherosclerotic disease [3–5]. Some US cohort studies have also suggested that non-high-density lipoprotein (non-HDLC) may be a better predictor of CAD [6,7]. However, to our knowledge, only one population-based cohort study has directly compared the predictive value of these lipid markers for CAD in an Asian population [8], which have a lower incidence of coronary artery disease, but a higher risk of stroke than Western populations [9–12]. Furthermore, although it has not been shown that there is a positive relationship between the risk of any type of stroke and high serum levels of total cholesterol (TC) in the Japanese population [9,10], the effects on stroke incidence of the closely related lipid fractions, LDL-C and non-HDLC, have not been evaluated.

The purpose of this study was therefore to investigate the predictive value of LDL-C and non-HDLC for the incidence of CAD and stroke in a Japanese urban population over an 11.9-year period. Our *a priori* hypothesis was that both LDL-C and non-HDLC may be useful predictors of CAD risk, but not of stroke risk.

## 2. Methods

### 2.1. Populations

The Suita study [13,14], a cohort study of cardiovascular disease, was established in 1989 and included 12,200 Japanese urban residents of Suita City, Osaka. The participants, aged 30–79 years,

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were selected randomly from the municipality population registry. Of these, 6485 men and women had a baseline medical examination at the National Cardiovascular Center between September 1989 and March 1994 (participation rate: 53.2%). Of the 6485 participants, a total of 1791 were excluded for the following reasons: past history of coronary heart disease or stroke ($n$ = 208), nonperiodical participation in baseline survey ($n$ = 79), aged 75 or older ($n$ = 343), non-fasting visit ($n$ = 153), use of lipid-lowering agents such as statins ($n$ = 106), serum triglyceride ≥4.5 mmol/l (400 mg/dl) ($n$ = 98) and missing information at the baseline survey or lost to follow-up ($n$ = 804). The data of the remaining 4694 participants (2169 men and 2525 women) were then analyzed. Informed consent was obtained from all participants. This cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

### 2.2. Baseline examination

Blood samples were collected at the National Cardiovascular Center (NCVC) after the participants had fasted for at least 12 h. The samples were centrifuged immediately and a routine blood examination that included serum total cholesterol (TC), HDL cholesterol, triglyceride and glucose levels then carried out. LDL-C was estimated using the Friedewald formula [15]. Non-HDLC was calculated by subtracting HDL-C from TC.

Blood pressures were measured in triplicate on the right arm in the seated position after 5 min rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used in the analyses. Hypertension was defined as either a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose ≥7.0 mmol/l (126 mg/dl), the use of anti-diabetic agents, or both. Height in stockings and weight in light clothing were measured. Public health nurses obtained information on the smoking, drinking and medical histories of the participants.

### 2.3. Endpoint determination

The participants were followed until December 31, 2005. The first step in the survey involved checking the health status of all participants by repeated clinical visits every 2 years and yearly questionnaires sent by mail or conducted by telephone. Informed consent for review of in-hospital medical records was obtained from 86.2% participants who were suspected of having had a myocardial infarction (MI) or stroke. The medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline information.

The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [16], which requires evidence from an electrocardiogram (ECG), cardiac enzymes and/or autopsy. Stroke was defined according to the National Survey of Stroke criteria [17], which requires the rapid onset of a constellation of neurological deficits lasting at least 24 h or until death. The strokes were classified as either ischemic stroke (thrombotic or embolic), intracerebral hemorrhage, subarachnoid hemorrhage or undetermined type. A definite stroke was defined by autopsy or on the basis of diagnostic imaging, such as computed tomography or magnetic resonance imaging.

Cases with typical clinical symptoms, detected in the clinical visit during follow-up surveillance, but without informed consent for an in-hospital medical records survey, were defined as possible MI or stroke. Furthermore, to complete the surveillance for fatal MI and stroke, we conducted a systematic search for death certificates. All death certificates in Japan are forwarded to the Ministry of Health, Welfare, and Labor and coded for National Vital Statistics. We classified fatal MI and stroke listed on the death certificate, but not registered on our surveillance system, as possible MI and stroke.

### 2.4. Statistical analysis

Sex-specific analysis was performed. We set the cut-off points for serum LDL-C and non-HDLC according to the quintile ranges. For baseline characteristics, analysis of variance for means or Chi-square tests for proportions were used. The multivariable-adjusted hazard ratio (HR) of LDL-C and non-HDLC for MI or stroke was calculated using proportional hazards model adjusted for age, hypertension, diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker). Sex-combined analysis with further adjustment for sex was also carried out.

Separate models with LDL-C or non-HDLC levels as ordinal variables (median of LDL-C or non-HDLC quintile) were fitted to the other risk factor adjusted models (test for trend). The differences between the −2 logarithm likelihood (−2 ln [L]) in each lipid added model and the −2 ln [L] in other risk factor adjusted models were calculated. These differences had an approximate $\chi^2$ distribution with 1 d.f. These $\chi^2$ values assess which lipid had the greatest predictive value in other risk factor adjusted models. The ability to predict which people developed cardiovascular disease was also assessed by calculating the area under the receiver-operating characteristic (ROC) curve (AUC). This curve showed the predictive probability of the variables using logistic regression analysis and the same covariates used in the multivariable model of test for trend. Furthermore, the predictive values of the ratio of LDL-C to HDL-C (LDL-C/HDL-C) and the ratio of non-HDLC to HDL-C (non-HDLC/HDL-C) for myocardial infarction (MI) and stroke were also compared.

All confidence intervals were estimated at the 95% level and significance was set at a $P$ value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

## 3. Results

The mean and standard deviation of serum LDL-C in the baseline survey was 3.23 ± 0.82 mmol/l (124.9 ± 31.7 mg/dl) in men and 3.49 ± 0.90 mmol/l (134.8 ± 34.9 mg/dl) in women. The mean baseline serum non-HDLC was 3.90 ± 0.89 mmol/l (151.1 ± 34.5 mg/dl) in men and 4.01 ± 1.01 mmol/l (155.2 ± 39.1 mg/dl) in women.

Table 1 shows the baseline characteristics of the participants in each LDL-C quintile. In both sexes, there were significant differences in the mean values for age, non-HDLC, HDL-C and BMI. These variables, with the exception of HDL-C, tended to be higher in the higher LDL-C groups. Serum HDL-C levels were lower in the higher LDL-C groups. There was no significant difference in the prevalence of hypertension and diabetes in the quintiles for men, whereas the prevalence of these conditions in women was higher in the higher LDL-C groups. In both sexes, the proportion of current drinkers was lower in the higher LDL-C groups, whereas the proportion of current smokers was highest in the lowest LDL-C group. The relationships between non-HDLC quintiles and the above-mentioned baseline characteristics were almost similar (data not shown in the table).

The total person-years studied was 56,196 (25,420 for men and 30,776 for women), with a mean follow-up period of 11.9 years. During the follow-up period, there were 80 incident cases of MI (41 definite and 39 probable MIs) and 139 of stoke (102 definite and 37

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**Table 1**
Sex-specific mean and prevalence of risk characteristics at baseline in an 11.9-year prospective study of 4694 Japanese men and women

| LDL cholesterol quintiles | Q1 | Q2 | Q3 | Q4 | Q5 | *P*-values |
|---|---|---|---|---|---|---|
| Men | | | | | | |
| Numbers | 447 | 435 | 427 | 438 | 422 | |
| LDL cholesterol (Stratum Mean), mmol/l | 2.13 | 2.80 | 3.22 | 3.66 | 4.40 | |
| Age, year | 54.0 (12.7) | 53.8 (12.6) | 52.5 (12.4) | 54.7 (12.1) | 55.6 (11.0) | 0.005 |
| Non-HDL cholesterol, mmol/l | 2.84 (0.52) | 3.44 (0.39) | 3.87 (0.34) | 4.31 (0.32) | 5.13 (0.56) | <0.001 |
| HDL cholesterol, mmol/l | 1.33 (0.39) | 1.29 (0.36) | 1.29 (0.32) | 1.26 (0.30) | 1.21 (0.28) | <0.001 |
| BMI, kg/m$^2$ | 22.1 (2.9) | 22.6 (2.8) | 22.9 (2.8) | 23.2 (2.6) | 23.4 (2.7) | <0.001 |
| Hypertension, % | 29.5 | 27.4 | 30.4 | 31.3 | 33.6 | 0.364 |
| Diabetes, % | 8.1 | 4.6 | 4.4 | 4.6 | 5.9 | 0.091 |
| Drinking | | | | | | |
| Usual/ex-/never-, % | 81.9/2.7/15.4 | 78.2/2.8/19.1 | 79.6/1.6/18.7 | 71.7/5.3/23.1 | 70.4/4.7/24.9 | <0.001 |
| Smoking | | | | | | |
| Current/ex-/never-, % | 59.3/25.5/15.2 | 55.4/26.9/17.7 | 46.6/31.1/22.2 | 46.6/31.1/22.4 | 48.1/31.8/20.1 | 0.002 |
| Women | | | | | | |
| Numbers | 524 | 498 | 513 | 498 | 492 | |
| LDL cholesterol (Stratum Mean), mmol/l | 2.33 | 2.98 | 3.44 | 3.92 | 4.82 | |
| Age, year | 45.5 (11.4) | 49.9 (11.9) | 52.7 (11.3) | 56.3 (10.6) | 57.8 (9.1) | <0.001 |
| Non-HDL cholesterol, mmol/l | 2.77 (0.42) | 3.47 (0.32) | 3.96 (0.31) | 4.50 (0.32) | 5.46 (0.71) | <0.001 |
| HDL cholesterol, mmol/l | 1.54 (0.36) | 1.49 (0.36) | 1.48 (0.35) | 1.45 (0.33) | 1.40 (0.31) | <0.001 |
| BMI, kg/m$^2$ | 21.0 (2.7) | 21.8 (3.2) | 22.3 (3.3) | 22.6 (3.2) | 23.2 (3.3) | <0.001 |
| Hypertension, % | 12.8 | 19.3 | 23.4 | 29.9 | 37.8 | <0.001 |
| Diabetes, % | 1.5 | 2.8 | 3.1 | 4.0 | 4.7 | 0.050 |
| Drinking | | | | | | |
| Usual/ex-/never-, % | 41.8/2.3/55.9 | 36.5/1.0/62.4 | 32.7/1.4/65.9 | 28.3/1.8/69.9 | 29.1/1.6/69.3 | <0.001 |
| Smoking | | | | | | |
| Current/ex-/never-, % | 16.4/4.6/79.0 | 12.7/3.8/83.5 | 9.6/2.1/88.3 | 10.8/3.4/85.7 | 11.6/3.7/84.8 | 0.015 |

HDL means high-density lipoprotein. LDL means low-density lipoprotein. S.D. means standard deviations. Brackets indicate standard deviation. Analysis of variance was used for comparisons of multiple group means and the Chi-square test was used to compare frequencies.

probable strokes), comprised of 23 intracerebral hemorrhages, 85 cerebral infarctions and 31 other types of stroke.

Table 2 shows the number of incident cases and multivariable-adjusted HRs for MI and cerebral infarction stratified by LDL-C quintile. In women, the bottom and second quintiles and the third and fourth quintiles were combined into two categories due to the small number of cardiovascular events. In both sexes, the HR for MI was highest in the top quintile of LDL-C, although the value in women was not statistically significant (HR 3.73; 95% CI 1.25–11.1 for men: HR 1.78; 95% CI 0.66–4.77 for women). In the test for trend, serum LDL-C showed a significant positive association with MI when the data from men and women were combined

**Table 2**
The numbers of cases and multivariable-adjusted HRs and 95% C.Is for myocardial infarction and cerebral infarction according to serum LDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

| LDL cholesterol quintiles | LDL-C range (mmol/l) | No. of persons | Person-years | Myocardial infarction | | | Cerebral infarction | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of events | HR[a] | 95% C.I. | No. of events | HR[a] | 95% C.I. |
| Men | | | | | | | | | |
| Q1 | <2.54 | 447 | 5,129 | 4 | 1.00 | | 14 | 1.00 | |
| Q2 | 2.54–3.03 | 435 | 5,122 | 15 | 3.56 | 1.18, 10.8 | 9 | 0.61 | 0.26, 1.42 |
| Q3 | 3.04–3.43 | 427 | 4,945 | 9 | 2.60 | 0.80, 8.5 | 15 | 1.31 | 0.63, 2.72 |
| Q4 | 3.44–3.90 | 438 | 5,201 | 10 | 2.25 | 0.70, 7.2 | 13 | 0.90 | 0.42, 1.94 |
| Q5 | 3.91– | 422 | 5,023 | 18 | 3.73 | 1.25, 11.1 | 6 | 0.42 | 0.16, 1.10 |
| | | | | | *P* for trend | 0.08 | | *P* for trend | 0.22 |
| Women | | | | | | | | | |
| Q1 + Q2[b] | <3.21 | 1022 | 12,473 | 6 | 1.00 | | 7 | 1.00 | |
| Q3 + Q4[b] | 3.22–4.22 | 1011 | 12,279 | 5 | 0.45 | 0.14, 1.49 | 11 | 0.82 | 0.31, 2.15 |
| Q5 | 4.23 | 492 | 6,023 | 13 | 1.78 | 0.66, 4.77 | 10 | 1.13 | 0.42, 3.02 |
| | | | | | *P* for trend | 0.14 | | *P* for trend | 0.88 |
| Men and women combined | | | | | | | | | |
| Q1 | | 971 | 11,548 | 7 | 1.00 | | 19 | 1.00 | |
| Q2 | | 933 | 11,176 | 18 | 2.37 | 0.97, 5.61 | 11 | 0.53 | 0.25, 1.12 |
| Q3 | | 940 | 11,102 | 11 | 1.57 | 0.61, 4.08 | 18 | 0.95 | 0.49, 1.82 |
| Q4 | | 936 | 11,323 | 13 | 1.40 | 0.56, 3.55 | 21 | 0.84 | 0.44, 1.59 |
| Q5 | | 914 | 11,046 | 31 | 3.03 | 1.32, 6.96 | 16 | 0.63 | 0.32, 1.24 |
| | | | | | *P* for trend | 0.02 | | *P* for trend | 0.47 |

LDL means low-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 2.73 between Q1 and Q2, and 3.68 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

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**Table 3**
The numbers of cases and multivariable-adjusted HRs and 95% C.I.s for myocardial infarction and cerebral infarction according to serum non-HDL cholesterol level in an 11.9-year prospective study of 4694 Japanese men and women

| Non-HDL cholesterol quintiles | Non-HDLC range (mmol/l) | No. of persons | Person-years | Myocardial infarction | | | Cerebral infarction | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of events | HR[a] | 95% C.I. | No. of events | HR[a] | 95% C.I. |
| Men | | | | | | | | | |
| Q1 | <3.18 | 445 | 5,123 | 6 | 1.00 | | 11 | 1.00 | |
| Q2 | 3.18–3.68 | 450 | 5,195 | 14 | 2.34 | 0.89, 6.16 | 13 | 1.21 | 0.54, 2.73 |
| Q3 | 3.69–4.12 | 426 | 5,077 | 7 | 1.21 | 0.40, 3.64 | 12 | 1.26 | 0.54, 2.91 |
| Q4 | 4.13–4.63 | 428 | 5,041 | 10 | 1.49 | 0.53, 4.16 | 11 | 0.97 | 0.41, 2.31 |
| Q5 | 4.64 | 420 | 4,982 | 19 | 2.61 | 1.00, 6.80 | 10 | 0.98 | 0.40, 2.40 |
| | | | | | *P* for trend | 0.12 | | *P* for trend | 0.79 |
| Women | | | | | | | | | |
| Q1 + Q2[b] | <3.70 | 1043 | 12,821 | 4 | 1.00 | | 7 | 1.00 | |
| Q3 + Q4[b] | 3.71–4.87 | 1010 | 12,205 | 7 | 0.76 | 0.21, 2.72 | 11 | 0.67 | |
| Q5 | 4.88 | 472 | 5,750 | 13 | 1.77 | 0.50, 6.25 | 10 | 0.80 | |
| | | | | | *P* for trend | 0.10 | | *P* for trend | |
| Men and women combined | | | | | | | | | |
| Q1 | | 998 | 11,931 | 7 | 1.00 | | 15 | 1.00 | |
| Q2 | | 940 | 11,208 | 17 | 2.35 | 0.97, 5.69 | 16 | 1.03 | 0.50, 2.10 |
| Q3 | | 947 | 11,412 | 11 | 1.38 | 0.53, 3.60 | 14 | 0.83 | 0.40, 1.76 |
| Q4 | | 917 | 10,911 | 13 | 1.40 | 0.55, 3.57 | 20 | 1.03 | 0.51, 2.06 |
| Q5 | | 892 | 10,732 | 32 | 2.97 | 1.26, 6.97 | 20 | 0.99 | 0.48, 2.03 |
| | | | | | *P* for trend | 0.02 | | *P* for trend | 0.96 |

HDL means high-density lipoprotein.

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, hypertension, diabetes, HDL cholesterol, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.

[b] These groups were combined due to small number of cardiovascular event. The cut-off points were 3.21 between Q1 and Q2, and 4.26 between Q3 and Q4, respectively.

[c] Sex-specific quintiles were used for analysis.

($P = 0.02$). A similar trend was observed when the endpoint was limited to definite MIs by the criteria of the MONICA project ($P = 0.01$, data not shown in the table). The incidence for cerebral infarction was not related to LDL-C levels in either sex. The incidences of intra-cerebral hemorrhage, other types of stroke and total stroke were also not associated with LDL-C levels (data not shown in the table).

Table 3 shows the results stratified by non-HDLC. The HR for MI was highest in the top quintile of non-HDLC in both sexes, although in women the value did not reach statistical significance (HR 2.61; 95% CI 1.00–6.8 for men: HR 1.77; 95% CI 0.50–6.25 for women). In men, the HR for MI was highest in the top quintile of non-HDLC (HR 2.61; 95% CI 1.00–6.80). In the test for trend, serum non-HDLC showed a significant positive association with MI when the data of men and women were combined ($P = 0.02$). A similar trend was observed when the endpoint was limited to define MIs ($P = 0.01$, data not shown in the table). The incidence of cerebral infarction was not associated with non-HDLC levels in either sex. The other types of stroke and total stroke were also not associated with non-HDLC level (data not shown in the table).

To determine the predictive values of LDL-C and non-HDLC, the difference between the −2 ln [L] of model including each lipid and the −2 ln [L] of other variable-adjusted models was calculated. The $\chi^2$ values for LDL-C and non-HDLC were almost the same at 5.71 ($P = 0.02$) for LDL-C and 5.49 ($P = 0.02$) for non-HDLC. Furthermore, the AUC of the ROC curves based on predictive probability targeting for MI were also estimated. The AUC of LDL-C and non-HDLC were the same at 0.82.

We calculated the hazard ratios of LDL-C/HDL-C and non-HDLC/HDL-C, and compared the predictive values of these for the incidence of MI and stroke. Both ratios were significantly associated with the increased risk for MI but not with any types of stroke. The multivariable HRs of LDL-C/HDL-C and non-HDLC/HDL-C for MI were 1.32 [95% CI, 1.07–1.61] and 1.25 [95% CI, 1.07–1.47], respectively. Furthermore, the $\chi^2$ values between the −2 ln (L) of each lipid added model and non-added model for LDL-C/HDL-C and non-HDLC/HDL-C were almost the same at 7.34 ($P = 0.01$) for LDL-C/HDL-C and 7.06 ($P = 0.01$) for non-HDLC/HDL-C. The AUC of the ROC curves based on predictive probability were also the same. Apparently, because non-HDLC/HDLC was expressed as [(TC/HDLC) − 1], the HR and predictive value for TC/HDLC were just the same as those of non-HDLC/HDLC.

When the participants were divided in two groups using the median value of serum triglycerides (1.12 mmol/l, 99 mg/dl), the results of all the analyses listed above were similar.

## 4. Discussion

This 11.9-year cohort study of a Japanese urban population showed a positive association between serum LDL-C or non-HDLC levels and increased risk of MI, but not with any type of stroke. Furthermore, we found there was no substantial difference in the predictive value for MI incidence between LDL-C and non-HDLC. To our knowledge, this is the first cohort study in an urban Japanese population on the relationship between serum lipids and cardiovascular events.

The role of LDL-C in the development of atherosclerosis and the beneficial effect of LDL-C lowering therapy are well established, especially in Western populations [1–4] Our study indicated there is also a positive relationship between serum LDL-C and CAD events in community-dwelling Japanese with no history of cardiovascular disease or use of lipid-lowering agents, such as statins. A recent large clinical trial in Japan [18], the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study), also have shown an 18% reduction in mean LDL-C (from 4.05 mmol/l to 3.31 mmol/l) was associated with a 33% decreased risk for CAD. These results suggested strongly that management of serum LDL-C levels is as effective for reducing CAD in Japan as it is in Western countries.

Non-HDLC levels are thought to be an alternative predictor that can substitute for LDL-C in patients with hypertriglycemia

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[3]. Non-HDLC reflects the total cholesterol concentration of all atherogenic lipoproteins. Several previous studies in US communities [6,7,9,19,20] or patients with type 2 diabetes [21,22] showed that the non-HDLC level was a stronger predictor for CAD risk than LDL-C. In the Lipid Research Clinics Program Follow-up Study [6], differences of 0.78 mmol/l (30 mg/dl) in non-HDLC and LDL-C levels corresponded to increases in CVD risk of 19% and 15% in men, and 11% and 8% in women, respectively. In contrast, Chien et al. showed that the hazard ratio of the top quintile and area under the ROC curve for CAD incidence were almost similar for LDL-C and non-HDLC in ethnic Chinese living in Taiwan [8].

Our results are consistent with the Taiwan study described above [8], which to date represents the only report from a non-Western community. As we calculated serum LDL-C levels using the Friedewald formula, our results were not applicable to the population with serum triglyceride levels equal to or greater than 4.5 mmol/l (≥400 mg/dl). However, even if the predictive values of LDL-C and non-HDLC are similar in the Japanese population, non-HDLC may be the more convenient indicator to use for primary prevention in the community. Both TC and HDL-C are included in routine biochemistry measurements because of convenience and low cost, and can be measured directly even in non-fasting serum. Accordingly, non-HDLC may be a good serum marker for risk assessment of CAD in a community-based setting.

In the present study, the positive association between serum lipids levels and MI in women was less evident than that in men. We believe it was mainly due to small number of MI in women. Continued community surveillance in Japan showed that incidence of MI for women was about one third of men [23]. In the present study, incidence of MI for women was only 0.78 per 1000 person-years. Because most MI cases (22 of 24) were post-menopausal women, the low incidence of MI in pre-menopausal women was one reason for sex-difference. However, it was difficult to perform further analysis because of small sample size of MI cases.

Similar to previous studies that have explored the relationship between TC and stroke in Japan [9,24,25], we found no association between LDL-C or non-HDLC levels and stroke events. A large meta-analysis of individual data from 61 prospective studies [26], the majority of which were from the US, European and Japanese populations, showed an absence of an independent positive association between TC or non-HDLC and ischemic and total stroke mortality. Recently, the death probability over a 10-year period due to MI and stroke have been calculated and displayed as color risk score charts by combining 10-year age, systolic blood pressure, smoking, and serum total cholesterol and glucose levels by NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) Research group [27]. NIPPON DATA Risk chart for MI clearly showed the positive relationship between TC and MI, however, the risk chart for stroke showed the color gradient, which was shown death probability, for stroke was not affected by TC levels.

The lack of a relationship between TC and ischemic stroke in Japanese studies may be due to a lower prevalence of thrombotic type cortical infarctions (large-artery occlusive) than in Western populations [28], a condition that is associated with atherosclerosis secondary to hypercholesterolemia. Furthermore, the Atherosclerosis Risk in Communities (ARIC) Study also indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (thrombotic type cortical infarction), but not with lacunar or embolic stroke [29]. The effect of LDL-C or non-HDLC on ischemic stroke may be weak in populations with a low prevalence of large-artery occlusive infarctions, such as in Japan. However, a meta-analysis of randomized control trials by statin therapy has indicated a reduction of stroke [30]. Even in Japanese patients with hypercholesterolemia, statin therapy showed a non-significant but inverse association with cerebral infarction [18]. Accordingly, high serum levels of LDLC or non-HDLC should be dealt with caution as a potential risk factor for ischemic stroke.

Previous studies indicated that CAD or MI morality in Japanese people was still lower than in Westerners [9–12]. However, recently, there were evidences that serum levels of TC and LDL-C in Japanese were as high as those reported in the US population [31]. However, CAD mortality has been shown to be higher in large urbanized areas in Japan such as Tokyo and Osaka compared to the rest of Japan [32]. These two cities are among the most urbanized areas in Asia. The present study therefore provides additional evidence supporting the usefulness of LDL-C and non-HDLC as predictors of future risk for MI in screening of the urbanized Japanese population. Although in Asian countries hypertension rather than LDL-C remains the most important manageable cardiovascular risk factor [33], the present study showed that, at least in urbanized areas, lowering of LDL-C levels should also be considered as an important public health issue.

The present study had some limitations. Firstly, the single LDL-C or non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and CAD due to regression dilution bias. Secondly, we did not measure serum apolipoprotein B (apoB), which some previous studies have shown as a stronger predictor for CAD than non-HDLC [8,20]. Furthermore, measurement of apoB is not required fasting status and is estimated to be cost-efficient [34]. Further cohort studies with measurement of apoB are needed in Japanese community-dwelling populations. Thirdly, in order to accurately compare the predictive value of non-HDLC and LDL-C, serum levels of LDL-C should be measured by direct measurement of LDL-C, rather than by the Friedewald formula. Exclusion of participants with a high serum triglyceride level (≥400 mg/dl) may reduce the predictive potential of non-HDLC. Finally, the relationship between serum lipids and cerebral infarction warrants further investigation, as we did not evaluate the effect of serum LDL-C and non-HDLC on each subtype of cerebral infarction due to small sample size, especially for thrombotic type cortical infarctions.

In conclusion, higher levels of serum LDL-C and non-HDLC are both associated with an increased risk of MI, but not with cerebral infarction in a Japanese urban population. Although the predictive value of non-HDLC for MI is almost similar to that of LDL-C calculated by the Friedewald formula, non-HDLC may be recommended as an alternative screening marker for primary prevention of CAD in the community, as it is less expensive and more convenient.

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## References

[1] Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med 1990;322:1700–7.
[2] Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 1992;85:37–45.
[3] Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[4] Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
[5] Teramoto T, Sasaki J, Ueshima H, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerosis cardiovascular diseases for Japanese. J Atheroscler Thromb 2007;14:267–77.
[6] Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 2001;161:1413–9.
[7] Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol 2006;98:1363–8.
[8] Chien KL, Hsu HC, Su TC, Chen MF, Lee YT, Hu FB. Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. J Lipid Res 2007;48:2499–505.
[9] Okamura T, Tanaka H, Miyamatsu N, et al. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis 2007;190:216–23.
[10] Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003;32:563–72.
[11] Sekikawa A, Horiuchi BY, Edmundowicz D, et al. A "natural experiment" in cardiovascular epidemiology in the early 21st century. Heart 2003;89:255–7.
[12] van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world Seven Countries Study Research Group. N Engl J Med 2000;342:1–8.
[13] Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: the Suita Study. Arch Intern Med 2000;160:2297–303.
[14] Murakami Y, et al. Relation of blood pressure and all-cause mortality in 180000 Japanese participants. Pooled analysis of 13 cohort studies. Hypertension 2008;51:1483–91.
[15] Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the ultracentrifuge. Clin Chem 1972;18:499–502.
[16] World Health Organization. Document for meeting of MONICA Principal Investigators. In: WHO, editors. MONICA Project: Event Registration Data Component, MONICA Manual, Version 1.1; 1986:S-4:9–11.
[17] Walker AE, Robins M, Weinfeld FD. The national survey of stroke. Clinical findings. Stroke 1981;12(2 Pt Supp 1):I13–44.
[18] Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled trial. Lancet 2006;368(9542):1155–63.
[19] Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294:326–33.
[20] Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005;112:3375–83.
[21] Jiang R, Schulze MB, Li T, et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. Diabetes Care 2004;27:1991–7.
[22] Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care 2003;26:16–23.
[23] Rumana N, Kita Y, Turin TC, et al. Trend of increase in the incidence of acute myocardial infarction in a Japanese population: Takashima AMI Registry 1990–2001. Am J Epidemiol 2008;167:1358–64.
[24] Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H. NIPPON DATA80 Research Group: what cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–80.
[25] Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616–22.
[26] Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. Lancet 2007;370:1829–39.
[27] 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.
[28] Tanaka H, Iso H, Yokoyama T, Yoshiike N, Kokubo Y. Cerebrovascular disease. In: Detels R, McEwen J, Beaglehole R, editors. Oxford text book of public health: the scope of public health, 3, 4th edition Oxford, UK: Oxford University Press; 2002. p. 1193–254.
[29] Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley Jr TH, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke 2006;37:2493–8.
[30] Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
[31] Sekikawa A, Ueshima H, Kadowaki T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in White Men in the United States in the Post-World War II Birth Cohort. Am J Epidemiol 2007;165:617–24.
[32] Okayama A, Ueshima H, Marmot M, Elliott P, Choudhury SR, Kita Y. Generational and regional differences in trends of mortality from ischemic heart disease in Japan from 1969 to 1992. Am J Epidemiol 2001;153:1191–8.
[33] Ueshima H, Zhang XH, Choudhury SR: epidemiology of hypertension in China and Japan. J Hum Hypertens 2000;14:765–9.
[34] Chan DC, Watts GF. Apolipoproteins as markers and managers of coronary risk. QJM 2006;99:277–87.

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# Masked Hypertension: Subtypes and Target Organ Damage

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*Masked hypertension has been drawing attention recently because this condition is often seen in untreated and treated individuals and is associated with target organ damage and a poor cardiovascular prognosis. Although masked hypertension is defined as normal office blood pressure with elevated ambulatory or home blood pressure, there are several subtypes. Morning hypertension is the most common form of masked hypertension, and is caused by natural circadian variation, evening alcohol consumption, and the use of short-acting antihypertensive drugs. Daytime hypertension may be caused by lifestyle factors such as habitual smoking and mental or physical stress. Nighttime hypertension is seen in various conditions that produce non-dipping status, including a high salt intake, renal dysfunction, obesity, sleep apnea, and autonomic failure. Advanced target organ damage such as increases in the left ventricular mass, carotid artery intima-media thickness, and urinary albumin excretion, is often present both in untreated and treated subjects with masked hypertension. In our study, the presence of the reverse white-coat effect is independently associated with those indices of organ damage among treated hypertensive patients. It is important to identify individuals with masked hypertension, to evaluate them with including the search for the subtype, and to treat each patient appropriately according to the cause of this condition.*

**Keywords** masked hypertension, target organ damage, ambulatory blood pressure monitoring, home blood pressure

## Introduction

Masked hypertension, which is also called reverse white-coat hypertension or isolated ambulatory hypertension, has been drawing attention recently (1–3). Masked hypertension is defined as normal office blood pressure (BP) with elevated ambulatory or home BP. Although the term of masked hypertension was originally applied to untreated subjects, this condition is also frequently seen in treated hypertensive

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patients. The prevalence of masked hypertension has been reported to be about 10% in normotensive (defined by casual BP) subjects and about 20% among treated hypertensive patients (1,4–6). There is increasing evidence that masked hypertension is associated with advanced target organ damage and a poor cardiovascular prognosis (7–11).

Masked hypertension can be classified into several subtypes according to the pattern of ambulatory BP and underlying mechanisms. These subtypes include morning, daytime, and nighttime hypertension (3). Detecting the subtype and underlying mechanism may be helpful for the appropriate management of each patient with masked hypertension. Regarding the target organ damage in masked hypertension, obtained information may not be enough, especially for treated patients. In this review, we describe the subtypes and organ damage of masked hypertension, including the results of our studies.

## Subtypes of Masked Hypertension

### *Morning Hypertension*

Morning hypertension is the most common form of masked hypertension (see Table 1). The circadian rhythm of BP is well known. Usually, BP elevates sharply with waking in the early morning, decreases slightly from the late morning to early afternoon, increases again in the early evening, decreases in the late evening, and then falls largely with sleeping. It has been shown that home BP in the early morning is somewhat higher than that in the late evening (6,12). It is possible that this physiological change in BP causes masked hypertension, if office BP is measured in the late morning or early afternoon in the absence of the white-coat effect. Morning hypertension is also caused by lifestyle-related factors such as habitual alcohol intake. We observed that evening alcohol consumption decreases nighttime BP but increases daytime BP in

**Table 1**
Subtypes of masked hypertension

| Subtypes | Causes | Management |
|---|---|---|
| Morning hypertension (morning surge) | Natural circadian rhythm | Alcohol restriction |
| | Alcohol | Long-acting drug |
| | Antihypertensive drug (short-acting) | Evening drug administration |
| | | Alpha blockers (evening) |
| Daytime hypertension (worksite hypertension) | Smoking | Smoking cessation |
| | Stress (mental, physical) | Stress management |
| | | Beta blockers (morning) |
| Nighttime hypertension (non-dipper) | Salt, renal dysfunction | Salt restriction |
| | Obesity, sleep apnea | Weight reduction |
| | Autonomic failure | Diuretics |
| | | Treatment of sleep apnea |