Table 2. Age- and multivariable-adjusted hazard ratios and 95% confidence intervals for the incidence of cardiovascular disease according to small dense LDL cholesterol quartiles

	Small dense LDL Cholesterol, mg/dL				
	Q1 (Lower)	Q2	Q3	Q4 (Higher)	per 10 mg/dL
Men and women, range (mean)	6.3-25.5 (19.7)	25.6-35.3 (30.5)	35.4-49.0 (41.4)	49.1-136.6 (63.9)	
Person-years	5,576	5,789	5,527	5,741	
Cardiovascular disease					
Case	21	23	29	43	
Age and sex-adjusted HR	1	0.75 (0.43-1.29)	1.11 (0.68-1.83)	**1.64 (1.04-2.60)**	**1.21 (1.12-1.31)**
Model 1-adjusted HR	1	0.81 (0.45-1.42)	1.08 (0.65-1.81)	1.60 (0.99-2.60)	**1.21 (1.11-1.32)**
Stroke					
Case	14	13	10	16	
Age and sex-adjusted HR	1	0.58 (0.30-1.14)	0.80 (0.43-1.48)	1.21 (0.69-2.12)	**1.17 (1.05-1.30)**
Model 1-adjusted HR	1	0.63 (0.32-1.23)	0.79 (0.41-1.50)	1.19 (0.65-2.16)	**1.18 (1.04-1.33)**
Cerebral infarction					
Case	8	10	6	12	
Age and sex-adjusted HR	1	1.08 (0.45-2.57)	1.14 (0.47-2.73)	1.74 (0.77-3.90)	**1.15 (1.00-1.33)**
Model 1-adjusted HR	1	1.18 (0.48-2.88)	1.16 (0.46-2.89)	1.85 (0.77-4.40)	**1.18 (1.00-1.39)**
Coronary artery disease					
Case	7	10	19	27	
Age and sex-adjusted HR	1	1.36 (0.49-3.77)	2.26 (0.89-5.73)	**3.35 (1.38-8.13)**	**1.29 (1.14-1.45)**
Model 1-adjusted HR	1	1.44 (0.51-4.08)	2.17 (0.83-5.66)	**3.26 (1.29-8.20)**	**1.28 (1.13-1.46)**
Men, range (mean)	6.3-27.8 (21.1)	27.9-38.2 (32.7)	38.3-53.4 (45.3)	53.5-119.6 (67.3)	
Person-years	2,499	2,615	2,519	2,608	
Cardiovascular disease					
Case	19	19	22	36	
Age-adjusted HR	1	1.06 (0.56-2.01)	1.31 (0.70-2.44)	**2.03 (1.16-3.57)**	**1.15 (1.04-1.28)**
Model 1-adjusted HR	1	1.17 (0.61-2.24)	1.36 (0.70-2.62)	**2.12 (1.16-3.86)**	**1.16 (1.04-1.30)**
Stroke					
Case	14	13	10	16	
Age-adjusted HR	1	1.03 (0.48-2.21)	0.87 (0.38-1.99)	1.43 (0.69-2.97)	1.06 (0.92-1.23)
Model 1-adjusted HR	1	1.13 (0.51-2.47)	0.98 (0.40-2.38)	1.55 (0.70-3.41)	1.08 (0.92-1.28)
Cerebral infarction					
Case	8	10	6	12	
Age-adjusted HR	1	1.33 (0.52-3.39)	0.85 (0.29-2.48)	1.81 (0.73-4.48)	1.08 (0.91-1.29)
Model 1-adjusted HR	1	1.43 (0.54-3.78)	0.90 (0.29-2.80)	1.93 (0.70-5.29)	1.10 (0.90-1.36)
Coronary artery disease					
Case	5	6	12	20	
Age-adjusted HR	1	1.24 (0.37-4.07)	2.48 (0.87-7.07)	**3.89 (1.45-10.42)**	**1.27 (1.10-1.47)**
Model 1-adjusted HR	1	1.27 (0.38-4.29)	2.34 (0.78-6.97)	**4.03 (1.42-11.40)**	**1.28 (1.09-1.50)**
Women, range (mean)	7.5-23.9 (18.7)	24.0-33.0 (28.6)	33.1-44.6 (38.5)	44.7-136.6 (59.7)	
Person-years	3,077	3,174	3,008	3,133	
Cardiovascular disease					
Case	7	12	13	23	
Age-adjusted HR	1	1.01 (0.39-2.60)	0.99 (0.39-2.50)	1.73 (0.74-4.06)	**1.31 (1.16-1.47)**
Model 1-adjusted HR	1	1.04 (0.40-2.72)	0.91 (0.35-2.35)	1.52 (0.63-3.68)	**1.29 (1.13-1.48)**
Stroke					
Case	5	8	6	16	
Age-adjusted HR	1	0.95 (0.30-2.94)	0.64 (0.19-2.11)	1.72 (0.62-4.74)	**1.31 (1.13-1.52)**
Model 1-adjusted HR	1	0.98 (0.31-3.14)	0.64 (0.18-2.19)	1.66 (0.58-4.76)	**1.33 (1.12-1.59)**

(Cont Table 2)

	Small dense LDL Cholesterol, mg/dL				
	Q1 (Lower)	Q2	Q3	Q4 (Higher)	per 10 mg/dL
Cerebral infarction					
Case	0	5	4	7	
Age-adjusted HR	1	–	–	–	**1.31 (1.05-1.63)**
Model 1-adjusted HR	1	–	–	–	**1.37 (1.05-1.80)**
Coronary artery disease					
Case	2	4	7	7	
Age-adjusted HR	1	1.22 (0.22-7.76)	1.90 (0.39-9.24)	1.84 (0.38-8.91)	**1.32 (1.08-1.61)**
Model 1-adjusted HR	1	1.27 (0.22-7.33)	1.83 (0.35-9.45)	1.54 (0.30-7.83)	1.23 (0.99-1.53)

Model 1: adjusted for age, (sex), body mass index, smoking, drinking, blood pressure category (optimal, normal, and high-normal blood pressure, hypertension grade 1 and 2 + 3), diabetes, and lipid-lowering drug user
Bold numbers: statistically significant

increased risks of CVD and stroke in the total cohort and in women, but not in men (**Table 3**).

Discussion

This study clearly indicates an increased risk of CVD, stroke, cerebral infarction, and CAD attributed to elevated sd-LDL-C concentrations in a Japanese population without a previous history of CVD. We also showed that HR was significant after multivariable adjustment and by analysis including LDL-C, log-transformed triglyceride, and HDL-C in the same model. Thus, sd-LDL-C measurement with the new test is promising as a new biomarker to predict the risk of CVD.

In addition to traditional risk factors for CVD, such as hypertension, diabetes, and dyslipidemia, other biomarkers are required to better define the risk and refine therapeutic decisions. There is scientific evidence that sd-LDL particles are highly atherogenic and can be a biomarker of CVD[15, 20, 21]. Our data provide additional evidence to show the role of sd-LDL-C as a CVD risk in the general population. Furthermore, measuring sd-LDL-C with this test has an advantage because it is more user-friendly and more applicable than specialized tests such as gradient gel electrophoresis, nuclear magnetic resonance, and gradient ultracentrifugation.

Until now, there have been no target goals of sd-LDL-C to prevent CAD. In this study the HR of the 4th quartile was statistically significant, suggesting that the cutoff of sd-LDL-C is approximately 50 mg/dL, although significance was not obtained in women probably due to the low event rate; therefore, a larger study should be performed to define an appropriate cutoff for sd-LDL-C. Because statins, fibrates, and ezetimibe have been shown to reduce the amount of sd-LDL[25-28], a randomized control study is required to address whether lowering sd-LDL-C to a certain goal by these drugs can prevent the development of CAD.

In this study we found that sd-LDL-C was significantly associated with traditional risk factors, such as hypertension and diabetes. BMI and the prevalence of diabetes increased and HDL-C decreased across the sd-LDL-C quartiles, and more hypertensive subjects were found in second to fourth quartiles than in the first quartile in both genders. We also found that age-adjusted partial correlation coefficients between sd-LDL-C and BMI, log-transformed triglyceride, LDL-C, and HDL-C (Pearson) were 0.305, 0.636, 0.554, and −0.346 ($p<0.0001$), respectively. Thus these data suggest that increased concentrations of sd-LDL-C may be associated with metabolic disorders and that lifestyle modification, such as exercise and weight control, would be effective to reduce sd-LDL in patients with diabetes and metabolic syndrome. Furthermore, we should address whether sd-LDL-C can be used to identify a very high-risk patient with type 2 diabetes, metabolic syndrome, and other metabolic disorders. In contrast to the association with metabolic disorders, an age-related change in sd-LDL-C was found only in women, consistent with the trend of increased atherogenic dyslipidemia in postmenopausal women. Ai *et al.* also found that postmenopausal women had higher levels of sd-LDL-C than premenopausal women in the Framingham Offspring Study[20].

In addition to type 2 diabetes and metabolic syn-

Table 3. Relationship between major lipid variables and cardiovascular disease

	Cardiovascular disase	Stroke	Cerebral infarction	Coronary artery disease
Men and women				
Age and sex-adjusted	**1.21 (1.12-1.31)**	**1.17 (1.05-1.30)**	**1.15 (1.00-1.33)**	**1.29 (1.14-1.45)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.21 (1.11-1.32)**	**1.18 (1.04-1.33)**	**1.18 (1.00-1.39)**	**1.28 (1.13-1.46)**
Model A				
Sd-LDL-C/10 mg/dL	**1.26 (1.11-1.43)**	**1.26 (1.06-1.50)**	**1.29 (1.02-1.62)**	**1.29 (1.07-1.55)**
LDL-C/10 mg/dL	0.96 (0.89-1.04)	0.94 (0.85-1.04)	0.93 (0.81-1.06)	0.99 (0.88-1.11)
Model B				
Sd-LDL-C/10 mg/dL	**1.20 (1.01-1.42)**	**1.35 (1.07-1.71)**	1.31 (0.96-1.78)	1.05 (0.81-1.36)
LDL-C/10 mg/dL	0.98 (0.90-1.06)	0.93 (0.83-1.03)	0.92 (0.80-1.07)	1.05 (0.93-1.19)
ln_TG	1.15 (0.71-1.86)	0.76 (0.40-1.46)	0.86 (0.37-1.96)	1.82 (0.87-3.81)
HDL-C/10 mg/dL	0.94 (0.81-1.08)	1.00 (0.84-1.20)	0.93 (0.73-1.18)	0.80 (0.61-1.04)
Men				
Age-adjusted	**1.15 (1.04-1.28)**	1.06 (0.92-1.23)	1.08 (0.91-1.29)	**1.27 (1.10-1.47)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.16 (1.04-1.30)**	1.08 (0.92-1.28)	1.10 (0.90-1.36)	**1.28 (1.09-1.50)**
Model A				
Sd-LDL-C/10 mg/dL	**1.17 (1.00-1.38)**	1.17 (0.92-1.48)	1.20 (0.90-1.60)	1.18 (0.94-1.48)
LDL-C/10 mg/dL	0.99 (0.89-1.09)	0.94 (0.82-1.08)	0.93 (0.79-1.09)	1.07 (0.93-1.24)
Model B				
Sd-LDL-C/10 mg/dL	1.10 (0.88-1.38)	1.28 (0.92-1.77)	1.28 (0.87-1.90)	0.96 (0.70-1.31)
LDL-C/10 mg/dL	1.01 (0.90-1.13)	0.92 (0.78-1.07)	0.91 (0.76-1.10)	1.14 (0.97-1.33)
ln_TG	1.23 (0.66-2.26)	0.75 (0.32-1.76)	0.86 (0.31-2.38)	1.87 (0.75-4.62)
HDL-C/10 mg/dL	0.96 (0.80-1.14)	1.05 (0.85-1.28)	1.08 (0.94-1.40)	0.72 (0.50-1.03)
Women				
Age-adjusted	**1.31 (1.16-1.47)**	**1.31 (1.13-1.52)**	**1.31 (1.05-1.63)**	**1.32 (1.08-1.61)**
Multivariable-adjusted Sd-LDL-C/10 mg/dL	**1.29 (1.13-1.48)**	**1.33 (1.12-1.59)**	**1.37 (1.05-1.80)**	1.23 (0.99-1.53)
Model A				
Sd-LDL-C/10 mg/dL	**1.44 (1.17-1.77)**	**1.48 (1.13-1.94)**	**1.62 (1.08-2.43)**	1.33 (0.94-1.89)
LDL-C/10 mg/dL	0.92 (0.81-1.04)	0.92 (0.79-1.08)	0.88 (0.69-1.11)	0.94 (0.75-1.16)
Model B				
Sd-LDL-C/10 mg/dL	**1.35 (1.03-1.77)**	**1.47 (1.04-2.08)**	1.33 (0.78-2.29)	1.12 (0.70-1.79)
LDL-C/10 mg/dL	0.93 (0.81-1.07)	0.92 (0.78-1.09)	0.92 (0.72-1.19)	0.98 (0.78-1.24)
ln_TG	1.19 (0.53-2.69)	0.91 (0.31-2.68)	0.86 (0.17-4.25)	1.84 (0.47-7.15)
HDL-C/10 mg/dL	0.92 (0.72-1.19)	0.92 (0.67-1.26)	0.56 (0.31-1.00)	0.92 (0.60-1.41)

Multivariable adjusted for age, sex, body mass index, smoking, drinking, blood pressure category (optimal, normal, and high-normal bloodpressure, hypertension grade 1 and 2 + 3), diabetes, and antilipidemic drug user
Model A: sd-LDL-C per 10 mg/dL and LDL-C per 10 mg/dL in the same model
Model B: sd-LDL-C per 10 mg/dL, LDL-C per 10 mg/dL, ln(TG), and HDL-C per 10 mg/dL in the same model
Sd-LDL-C, small dense LDL cholesterol; ln_TG, logarithmical transformed TG
Bold numbers: statistically significant

drome, sd-LDL-C is increased in familial combined hyperlipidemia and postprandial hyperlipidemia[29, 30]. Hirano *et al.* demonstrated that sd-LDL-C determined by this simple precipitation method is useful for screening familial combined hyperlipidemia in large populations[13]. Because the prevalence of familial combined hyperlipidemia is high in the general population and the increase of sd-LDL particles as well as large VLDL particles is a characteristic feature of familial combined hyperlipidemia, this assay would be quite useful for its diagnosis. Although sd-LDL is decreased by lipid-lowering drugs, such as statins and fibrates, the effect of adequate combination therapy on sd-LDL-C has not yet been confirmed; therefore, this assay would be also useful in determining the therapeutic strategy for patients with a high serum level of sd-LDL-C.

There are some limitations in our study. First, we

used plasma stored at −80℃, and there is no guarantee that we would have obtained the same results if we had used fresh serum; however, our results are consistent with those reported by Hirano *et al.*, who measured sd-LDL-C in a Japanese general population with the same method, and comparison studies performed in Japan indicate virtually identical results with the use of fresh vs. frozen plasma for sd-LDL-C[13]. Second, the single measurement of sd-LDL-C at the baseline survey and the fact we did not evaluate the longitudinal trend for each risk factor including lipid-lowering agents may have caused us to underestimate the relationship between these conditions and CAD due to regression dilution bias, although we statistically adjusted for the use of lipid-lowering agents at the baseline survey. Third, serum LDL-C was measured by the direct homogeneous assay, which failed to meet the National Cholesterol Education Program total error goals for diseased individuals, although it met these goals in non-diseased individuals[31]. However, the present study is a cohort study of community-dwelling citizens without a history of CVD. Furthermore, the serum levels of LDL-C determined by direct homogeneous assay are almost consistent with those calculated by the Friedewald formula in a large Japanese cohort.

Conclusions

In this large urban cohort study conducted in Japan, we demonstrated that sd-LDL-C is significantly associated with the development of CVD, providing evidence of sd-LDL-C as an important biomarker to predict CVD. A large intervention study is required to determine the appropriate target level of sd-LDL-C.

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Disclosures

Dr. Arai has received an unrestricted grant from Denka Seiken. Drs Ito and Minagawa are employees of Denka Seiken. The other authors have no conflicts to declare.

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ORIGINAL ARTICLE

Alcohol consumption and cardiovascular disease incidence in men with and without hypertension: the Suita study

This article has been corrected since Advance Online Publication, and a corrigendum is also printed in this issue.

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The relationship between alcohol consumption and the risk for cardiovascular disease (CVD) is U-shaped, whereas alcohol drinking is linearly associated with blood pressure, and the CVD risk also increases linearly according to blood pressure level. Accordingly, we investigated the net effect of alcohol consumption and hypertension on CVD and its subtypes in this study. A 13-year prospective study of 2336 Japanese men who were free from CVD was performed; ex-drinkers were excluded. The participants were divided into eight groups classified by the combination of the presence of hypertension (systolic/diastolic blood pressure ⩾140/90 mm Hg) and alcohol consumption (never-, current- (light, moderate and heavy) drinkers). Multivariate-adjusted hazard ratios (HRs) for the incidence of CVD, coronary artery disease (CAD) and stroke due to the combination of hypertension and alcohol consumption were calculated and compared with non-hypertensive never-drinkers. The HRs for CVD and its subtypes were higher in hypertensives than those in non-hypertensives; in hypertensives without medication for hypertension, the relationship between alcohol consumption and the risks for CVD and CAD was U-shaped, with the highest and most significant increase in never-drinkers. The risk for total stroke was the highest in heavy-drinkers, which was significant. In non-hypertensives, there was no evident increase or decrease in the HRs for CVD and its subtypes in drinkers. Accordingly, controlling blood pressure is important to prevent CVD. In hypertensives, heavy drinking should be avoided to prevent CVD, although light-to-moderate drinking could be protective for CAD. Furthermore, in non-hypertensives, drinkers may need to continuously monitor their blood pressure.
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Keywords: epidemiological study; hazard ratio; prospective study

INTRODUCTION

The relationship between alcohol consumption and the risk for cardiovascular disease (CVD) has been reported to be U-shaped in previous studies.[1,2] However, drinking alcohol is also well known to be positively associated with the development of hypertension.[3] Alcohol consumption is linearly related to increased blood pressure,[4,5] and the CVD risk also linearly increases according to the blood pressure level.[6] Thus, several previous studies have investigated the relationships among alcohol consumption, hypertension and CVD risk in hypertensive patients,[7–9] but few studies were performed in the general population including both hypertensives and non-hypertensives.

Japanese men have been reported to drink more alcohol,[10] have a higher prevalence of hypertension,[11,12] and have a higher prevalence of stroke[13] than Westerners. Therefore, an investigation of the net effect of hypertension and alcohol consumption on the risk for CVD and its subtypes is important in Asian populations, including the Japanese.

To investigate the relationships among alcohol consumption, hypertension and the risk for CVD and its subtypes, a 13-year cohort study of an urban Japanese male population was conducted.

METHODS

Study participants

The Suita study,[14,15] a cohort study of CVD, was established in 1989. In this study, 6485 participants who were randomly selected from the municipal population registry participated in a baseline survey at the National Cardiovascular Center (NCVC, currently, National Cerebral Cardiovascular Center) between September 1989 and February 1994. The present study excluded 821 participants who had a past history of CVD at the baseline survey or who were

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lost to follow-up, as well as 3093 female participants because the alcohol consumption of women was much less than that of men (prevalence of drinking alcohol >23 g ethanol per day in women: 6.3%). In addition, 235 men were excluded for the following reasons: non-fasting visit ($n=83$), missing information at the baseline survey ($n=58$) and being an ex-drinker ($n=94$). The data for the remaining 2336 men aged 30–79 years were then analyzed. Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the NCVC.

Baseline examination

Well-trained nurses obtained information on smoking, alcohol consumption and the medical histories of the participants. The assessment of alcohol consumption was previously reported.[16] Briefly, current drinkers were asked about the frequency of alcohol consumption during a typical week and the total alcohol intake on each occasion, and the alcohol intake per week was calculated. This value was then divided by seven to obtain the average alcohol intake per day. The usual daily intake of alcohol was assessed in units of 'gou' (a traditional Japanese unit of measurement, corresponding to 23 g of ethanol) and then converted to grams of ethanol per day. In the present study, half a gou was defined as one drink (11.5 g of ethanol), a value nearly equal to a 'standard drink' in other countries.[17] According to the guidelines for lifestyle changes in Japan (Health Japan 21), the recommended amount of alcohol consumption for men was not more than two drinks per day.[18] Thus, the participants were classified as never-drinkers, light-drinkers (≤2.0 drinks per day), moderate-drinkers (>2.0 and ≤4.0 drinks per day) and heavy-drinkers (>4.0 drinks per day).

Well-trained physicians measured the participants' blood pressure in the right arm three times with the participant in a seated position after 5 min rest using a standard mercury sphygmomanometer. The average of the second and third measurements was used in the analyses. Height in socks and weight in light clothing were measured. The body mass index was calculated as weight (kg) divided by the square of height (m^2). Blood samples were collected at the NCVC after the participants had fasted for at least 8 h. The samples were centrifuged immediately, and a routine blood examination that included serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride and glucose levels was then conducted.

Follow-up and endpoint determination

The follow-up method has been described elsewhere.[14,15] Briefly, the endpoints of the present study were as follows: (1) the date of the first stroke or coronary artery disease (CAD) event; (2) the date of death; (3) the date of leaving Suita city; and (4) 31 December 2007. The survey for the stroke and CAD events involved checking the health status of the participants by repeated clinical visits to the NCVC or interview by mail or telephone, followed by checking the in-hospital medical records of the participants who were suspected of having had a stroke or CAD. The criteria for stroke were defined according to the US National Survey of Stroke criteria.[19] For each stroke subtype (cerebral infarction (thrombotic or embolic), intracerebral hemorrhage and subarachnoid hemorrhage), a definitive diagnosis was established based on computed tomography, magnetic resonance imaging or autopsy. In the present study, cerebral infarction was defined as an ischemic stroke, and intracerebral hemorrhage and subarachnoid hemorrhage were defined as hemorrhagic strokes. The criteria for myocardial infarction were defined according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) project,[20] which requires evidence from an electrocardiogram, cardiac enzymes and/or autopsy. In addition to acute myocardial infarction, the criteria for a diagnosis of CAD included sudden cardiac death within 24 h after the onset of acute symptoms or CAD followed by coronary artery bypass or angioplasty. Furthermore, to complete the surveillance for fatal strokes and myocardial infarctions, a systematic search for death certificates was conducted.

Statistical analyses

Hypertension was defined as an average systolic/diastolic blood pressure ≥140/90 mm Hg.[21] Dyslipidemia was defined as total cholesterol ≥5.69 mmol l^{-1} (220 mg dl^{-1}) and/or HDL-C <1.03 mmol l^{-1} (40 mg dl^{-1}) and/or triglyceride ≥1.69 mmol l^{-1} (150 mg dl^{-1})[22] and/or current use of oral medication for dyslipidemia. Diabetes was defined as a fasting blood glucose ≥7.06 mmol l^{-1} (126 mg dl^{-1})[23] and/or current use of insulin or oral medication for diabetes.

To show the baseline risk characteristics of the six groups classified by alcohol drinking status (never, light, moderate and heavy) and the presence of hypertension (absent and present), the mean or median was calculated for continuous variables, and the percentage was calculated for dichotomous variables.

The Cox proportional hazards model was used to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals of alcohol consumption in those with and without hypertension for the incidence of CVD, CAD, stroke and stroke subtypes after adjustment for age, body mass index, the presence of dyslipidemia and diabetes (absent or present) and smoking status (current or non-current). When the HRs were calculated, never-drinkers without hypertension were defined as the 'reference' group. The estimation of the HRs was also performed after excluding the participants with medication for hypertension at the baseline survey.

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) statistical software version 15.0 J (SPSS, Tokyo, Japan), and $P<0.05$ (two-tailed) was considered significant.

RESULTS

The mean age of the participants was 55 ± 13 years. Table 1 summarizes the baseline characteristics of the participants divided into eight groups classified by the combination of the presence of hypertension and alcohol consumption. The participants with hypertension were older than those without hypertension, and current drinkers were younger than never-drinkers. The percentage of current smoking was the highest among heavy-drinkers both in those with and without hypertension. In those with hypertension, the triglyceride median increased according to alcohol consumption.

The mean follow-up period was 13 years, and 109 CAD, 78 ischemic stroke and 29 hemorrhagic stroke events occurred. Table 2 shows the age- and multivariate-adjusted HRs (95% confidence intervals) for CVD and its subtypes of the eight groups classified by the combination of alcohol consumption and the presence of hypertension compared with never-drinkers without hypertension in all participants. In non-hypertensives, the HRs for CVD and CAD in current drinkers were consistently lower than that in the reference group. Additionally, the HRs for total and ischemic stroke were similar or slightly higher in the light-drinkers and lower in the moderate- and heavy-drinkers than those in the reference group. However, there was no evident increase or decrease in the HRs for CVD and its subtypes. Among hypertensives, the HRs for CVD and CAD were consistently higher than those in the reference group, and the relationship between alcohol consumption and the risks for CVD and CAD was U-shaped, with the highest and most significant increase in never-drinkers. The HRs for total and ischemic stroke were also consistently higher than those in the reference group, with the highest and most significant increase in heavy-drinkers for total stroke and in light-drinkers for ischemic stroke. For hemorrhagic stroke, the risk associated with alcohol consumption could not be assessed because of the small number of these events (data not shown in the table).

Table 3 shows the age- and multivariate-adjusted HRs (95% confidence intervals) for CVD and its subtypes of the eight groups in the participants without medication for hypertension at the baseline survey. For CVD and CAD, the results were similar to those in Table 2. For total and ischemic stroke, the results in non-hypertensives were also similar to those in Table 2; in hypertensives, the HRs were consistently increased in all groups compared with those in the reference group, and an increase in the HR for both total and ischemic stroke was statistically significant and the highest in heavy-drinkers.

Table 1 Baseline characteristics of the participants; the Suita study: 1989–2007

	Hypertension (−)				*Hypertension (+)*			
		Current drinkers				*Current drinkers*		
	Never-drinkers	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (⩽4.0 drinks per day)*	*Never-drinkers*	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (⩽4.0 drinks per day)*
Number of participants	380	684	348	214	141	276	178	115
Age (years)	56±14	54±13	52±12	47±11	65±10	61±12	59±11	56±10
Body mass index ($kg\,m^{-2}$)	22.3±3.0	22.5±2.7	22.6±2.7	23.0±2.6	23.7±3.6	23.2±3.0	23.4±2.6	23.9±3.0
Systolic blood pressure (mm Hg)	116±13	118±12	119±12	118±11	153±15	152±16	150±16	154±19
Diastolic blood pressure (mm Hg)	72±9	74±9	76±8	75±8	88±10	92±10	91±10	93±10
Total cholesterol ($mmol\,l^{-1}$)	5.20±0.88	5.17±0.85	5.12±0.85	5.09±0.85	5.38±1.03	5.33±0.88	5.30±0.85	5.25±0.98
HDL-cholesterol ($mmol\,l^{-1}$)	1.16±0.31	1.27±0.31	1.34±0.36	1.34±0.36	1.14±0.28	1.27±0.31	1.40±0.36	1.34±0.39
Triglycerides ($mmol\,l^{-1}$)	1.30	1.24	1.24	1.37	1.29	1.34	1.39	1.56
Dyslipidemia (%)	59.5	52.3	47.1	54.2	69.5	60.1	63.5	61.7
Diabetes (%)	2.4	4.1	5.5	5.1	9.9	6.9	7.3	13.9
Current smoking (%)	53.2	47.4	62.1	65.0	34.8	33.0	52.2	61.7

Abbreviation: HDL, high-density lipoprotein.
Values are mean±s.d. unless specified otherwise. Values of triglycerides are median.
Hypertension: average systolic/diastolic blood pressures of ⩾140/90 mm Hg.
Diabetes: fasting blood glucose of $\geqslant 7\,mmol\,l^{-1}$ and/or current use of insulin or oral medication for diabetes.
Dyslipidemia: fasting serum total cholesterol of $\geqslant 5.69\,mmol\,l^{-1}$ and/or HDL-C $<1.03\,mmol\,l^{-1}$ and/or TG $\geqslant 1.69\,mmol\,l^{-1}$ and/or current use of oral medication for dyslipidemia.

When we additionally adjusted for pulse pressure in the estimation of the HRs presented in Tables 2 and 3, the results were equivalent, although the HRs for CAD in hypertensives were slightly attenuated (data not shown).

DISCUSSION

In the present study, the multivariate-adjusted HRs for CVD and its subtypes were consistently higher in the hypertensive participants compared with the non-hypertensive never-drinkers, irrespective of alcohol consumption. In hypertensives without medication for hypertension, the relationship between alcohol consumption and the risks for CVD and CAD was U-shaped, with the highest and most significant increase in never-drinkers. The risk for total and ischemic stroke was the highest in heavy-drinkers, which was significant. In non-hypertensives, there was no evident increase or decrease in the HRs for CVD and its subtypes in drinkers.

One of the strengths of this study was that we compared the risk for CVD and its subtypes due to alcohol consumption among those with and without hypertension. Another strength was that we also estimated the HRs only among the individuals without medication for hypertension at the baseline survey, although the number of events was small. Furthermore, this study is the first to show the relationships among alcohol consumption, hypertension diagnosed by the current definition and the risk for CAD in an Asian population. Although Kiyohara *et al.*[24] investigated the net effect of alcohol consumption on ischemic and hemorrhagic stroke stratified by the presence of hypertension in a Japanese population (Hisayama study), they did not investigate the risk for CAD, and their diagnosis of hypertension was defined as 160/95 mm Hg.

For CAD, the results in the present study were similar to those in previous studies involving hypertensive Western populations. In the previous studies, light-to-moderate alcohol consumption in hypertensives was associated with a reduced risk for CVD mortality or a reduced incidence of myocardial infarction.[7–9] A possible mechanism of reduced risk for CAD in hypertensive drinkers in the present study might be as follows: although they were under high risk for hypertension because of lineally increasing blood pressure due to alcohol drinking[4,5] and high risk for CAD due to hypertension,[6] there might be cardio-protective effects, such as decreased platelet aggregation[25] and increased fibrinolytic activity.[26] An increase in the serum level of HDL-C may be another cardio-protective effect of alcohol.[27] Such cardio-protective effects of alcohol drinking and the relatively higher incidence of CAD compared with that in the previous study in Japan[28] might explain the clear U-shaped relationship between alcohol consumption and the risk for CVD among hypertensives in the present study.

With respect to stroke, Kiyohara *et al.*[24] investigated the combined effects of alcohol drinking and hypertension on stroke in a prospective study of the general Japanese population. The participants were classified as non-drinkers, light-drinkers (<34 g of ethanol per day) and heavy-drinkers (⩾34 g of ethanol per day) and were followed up for 26 years. Among the hypertensive subjects (⩾160/95 mm Hg), the risk for cerebral hemorrhage was significantly increased in heavy-drinkers compared with non-drinkers; the relationship between alcohol consumption and the risk for cerebral infarction was U-shaped, with a significant increase in heavy-drinkers compared with light-drinkers. However, an increase in the risk for hemorrhagic and cerebral stroke was not shown in any drinkers among the non-hypertensives (<160/95 mm Hg). It was observed both in the previous and present studies that the highest risk for stroke was in hypertensive heavy-drinkers, although there was no U-shaped pattern for cerebral infarction herein.

Table 2 Risk for CVD and its subtypes according to the presence of hypertension and alcohol drinking in all participants; the Suita study: 1989–2007

	Hypertension (−)				*Hypertension (+)*			
		Current drinkers				*Current drinkers*		
	Never-drinkers	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (>4.0 drinks per day)*	*Never-drinkers*	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (>4.0 drinks per day)*
Number of participants	380	684	348	214	141	276	178	115
Person-years	4869	8698	4564	2916	1496	3244	2140	1361
CVD								
Number of cases	34	42	17	9	35	46	23	16
Age-adjusted HR (95% CI)	1.00	0.77 (0.49–1.21)	0.76 (0.42–1.36)	0.82 (0.39–1.73)	2.13 (1.32–3.42)	1.55 (0.99–2.41)	1.28 (0.76–2.18)	1.90 (1.05–3.44)
Multivariate-adjusted HR (95% CI)[a]	1.00	0.80 (0.51–1.26)	0.74 (0.41–1.33)	0.79 (0.37–1.66)	2.14 (1.32–3.47)	1.62 (1.03–2.54)	1.23 (0.72–2.10)	1.68 (0.92–3.09)
CAD								
Number of cases	19	17	8	6	24	20	9	6
Age-adjusted HR (95% CI)	1.00	0.55 (0.29–1.06)	0.61 (0.27–1.41)	0.92 (0.36–2.34)	2.72 (1.48–5.01)	1.23 (0.65–2.30)	0.90 (0.41–1.99)	1.25 (0.50–3.14)
Multivariate-adjusted HR (95% CI)[a]	1.00	0.58 (0.30–1.11)	0.63 (0.27–1.44)	0.91 (0.36–2.32)	2.72 (1.46–5.08)	1.28 (0.68–2.43)	0.88 (0.40–1.96)	1.18 (0.47–2.99)
All stroke								
Number of cases	15	25	9	3	11	26	14	10
Age-adjusted HR (95% CI)	1.00	1.05 (0.55–2.00)	0.95 (0.41–2.18)	0.67 (0.19–2.32)	1.46 (0.67–3.18)	1.94 (1.03–3.67)	1.77 (0.85–3.66)	2.73 (1.23–6.10)
Multivariate-adjusted HR (95% CI)[a]	1.00	1.08 (0.57–2.06)	0.88 (0.38–2.02)	0.61 (0.18–2.15)	1.47 (0.66–3.24)	2.03 (1.07–3.88)	1.67 (0.80–3.49)	2.28 (1.01–5.18)
Ischemic stroke								
Number of cases	9	18	6	2	8	21	7	7
Age-adjusted HR (95% CI)	1.00	1.27 (0.57–2.83)	1.05 (0.37–2.98)	0.72 (0.15–3.38)	1.76 (0.68–4.59)	2.61 (1.19–5.71)	1.49 (0.56–4.01)	3.18 (1.18–8.55)
Multivariate-adjusted HR (95% CI)[a]	1.00	1.33 (0.59–2.97)	0.96 (0.34–2.75)	0.63 (0.13–2.98)	1.66 (0.63–4.38)	2.69 (1.21–5.95)	1.33 (0.49–3.61)	2.43 (0.88–6.68)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
Hypertension: average systolic/diastolic blood pressures of ⩾140/90 mm Hg.
Dyslipidemia: fasting serum total cholesterol of ⩾5.69 mmol l^{-1} and/or high-density lipoprotein cholesterol <1.03 mmol l^{-1} and/or triglyceride ⩾1.69 mmol l^{-1} and/or current use of oral medication for dyslipidemia.
[a]Multivariate-adjusted HR was calculated after adjustment for age, body mass index, presence of dyslipidemia and diabetes, and smoking status (current or non-current).

Table 3 Risk for CVD and its subtypes according to the presence of hypertension and alcohol drinking in men without medication for hypertension at baseline; the Suita study: 1989–2007

	Hypertension (−)				*Hypertension (+)*			
		Current drinkers				*Current drinkers*		
	Never-drinkers	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (>4.0 drinks per day)*	*Never-drinkers*	*Light (⩽2.0 drinks per day)*	*Moderate (>2.0 and ⩽4.0 drinks per day)*	*Heavy (>4.0 drinks per day)*
Number of participants	368	663	335	207	99	193	133	90
Person-years	4767	8449	4431	2834	1110	2341	1641	1077
CVD								
Number of cases	28	38	15	8	23	28	14	11
Age-adjusted HR (95% CI)	1.00	0.85 (0.52–1.39)	0.82 (0.44–1.54)	0.90 (0.41–2.00)	2.24 (1.28–3.90)	1.59 (0.94–2.69)	1.37 (0.72–2.60)	2.14 (1.06–4.31)
Multivariate-adjusted HR (95% CI)[a]	1.00	0.88 (0.54–1.44)	0.80 (0.42–1.51)	0.86 (0.39–1.92)	2.10 (1.19–3.71)	1.62 (0.96–2.76)	1.26 (0.66–2.42)	2.05 (1.01–4.15)
CAD								
Number of cases	17	16	7	5	15	14	6	4
Age-adjusted HR (95% CI)	1.00	0.59 (0.30–1.17)	0.62 (0.25–1.50)	0.89 (0.33–2.46)	2.48 (1.23–5.00)	1.32 (0.65–2.69)	0.96 (0.38–2.43)	1.27 (0.43–3.80)
Multivariate-adjusted HR (95% CI)[a]	1.00	0.63 (0.32–1.25)	0.66 (0.27–1.61)	0.89 (0.32–2.45)	2.33 (1.13–4.77)	1.39 (0.68–2.85)	0.89 (0.35–2.28)	1.25 (0.42–3.74)
All stroke								
Number of cases	11	22	8	3	8	14	8	7
Age-adjusted HR (95% CI)	1.00	1.27 (0.61–2.61)	1.14 (0.45–2.85)	0.90 (0.25–3.27)	1.92 (0.77–4.79)	2.01 (0.91–4.43)	2.10 (0.81–5.00)	3.49 (1.35–9.06)
Multivariate-adjusted HR (95% CI)[a]	1.00	1.25 (0.60–2.58)	1.02 (0.40–2.56)	0.83 (0.23–3.02)	1.79 (0.70–4.56)	1.98 (0.89–4.41)	1.86 (0.74–4.70)	3.25 (1.24–8.51)
Ischemic stroke								
Number of cases	6	15	5	2	5	10	5	5
Age-adjusted HR (95% CI)	1.00	1.58 (0.61–4.07)	1.26 (0.38–4.17)	1.02 (0.20–5.14)	2.26 (0.69–7.46)	2.68 (0.97–7.38)	2.33 (0.71–7.62)	4.45 (1.35–14.66)
Multivariate-adjusted HR (95% CI)[a]	1.00	1.57 (0.60–4.06)	1.09 (0.33–3.64)	0.88 (0.17–4.48)	1.93 (0.57–6.53)	2.59 (0.93–7.23)	2.02 (0.61–6.71)	3.78 (1.13–12.61)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
Hypertension: average systolic/diastolic blood pressures of ⩾140/90 mm Hg.
Dyslipidemia: fasting serum total cholesterol of ⩾5.69 mmol l^{-1} and/or high-density lipoprotein cholesterol <1.03 mmol l^{-1} and/or triglyceride ⩾1.69 mmol l^{-1} and/or current use of oral medication for dyslipidemia.
[a]Multivariate-adjusted HR was calculated after adjustment for age, body mass index, presence of dyslipidemia and diabetes, and smoking status (current or non-current).

However, these results in Japanese hypertensives were not consistent with those in Western populations,[7,8] that is, the risk for stroke was lower in any drinkers compared with never-drinkers in Westerners.[7,8] This inconsistency between the Western and Japanese populations might be due to a difference in the incidence of stroke events and in the percentage of stroke subtypes. Specifically, the incidence of hemorrhagic stroke, which could be affected by heavy alcohol drinking,[2,29] and hypertension[30,31] has been much lower than that of ischemic stroke in Western populations.[32] Furthermore, for ischemic stroke, the frequency of cortical infarction or cerebral embolism was high in Western populations,[33,34] and a pathological study revealed that moderate alcohol intake has a weak inverse association with atherosclerosis in large, cerebral arteries.[35] Thus, even in a hypertensive condition, the risk for stroke associated with alcohol consumption could be low or not evidently increased in Western populations. In contrast, in a Japanese population, the incidence of hemorrhagic stroke is considered to be higher than that in Western populations.[2,31] Additionally, lacunar infarction due to small-vessel disease was the most common among Japanese individuals.[36] Moreover, a pathological study revealed that moderate alcohol intake did not have an inverse association with atherosclerosis in small cerebral arteries.[35] Thus, these factors might have an influence on the additive effect of alcohol and hypertension on stroke in the Japanese population.[24]

In non-hypertensive participants, neither an evident increase nor decrease was shown in the risk for CAD and stroke with increased alcohol consumption. As the numbers of non-hypertensive participants and CVD event cases were small in the present study, the risk for CVD and its subtypes of alcohol drinking in non-hypertensives should be investigated in other large-scale prospective studies.

As shown in the present study, hypertension is the key to determine the risk for CVD and its subtypes. As heavy drinking was associated with a significant increase in the risk for both CAD and stroke in hypertensives, individuals with hypertension should avoid heavy alcohol drinking. In addition, lowering high levels of alcohol consumption is associated with a reduction in blood pressure.[37] Thus, a reduction in alcohol consumption is expected to be followed by both a decrease in blood pressure and particularly a decrease in the risk for stroke, although the association between the reduction of alcohol consumption in hypertensives and the risk for stroke incidence should be examined in future studies among Asian populations. In non-hypertensives, drinkers need to pay attention to their blood pressure and avoid heavy drinking, not only for the prevention of CVD, but also for the prevention of other alcohol-induced diseases.

The present study had several limitations. First, the relationships among alcohol drinking, hypertension and hemorrhagic stroke could not be assessed because of the small number of cases. In addition, we could not assess the risk for CVD and its subtypes in moderate- and heavy-drinkers separately with and without hypertension due to the small number of events. Second, single blood pressure measurements and a single questionnaire for alcohol consumption at the baseline survey might have underestimated the relationships among alcohol drinking, hypertension and CVD due to regression dilution bias.[38] Third, the effects of the type of alcoholic beverage[17] and genetic differences, such as acetaldehyde dehydrogenase genotypes,[39] could not be investigated. Fourth, we potentially could not fully remove the influence of age differences among the groups at the baseline, although we adjusted for age in the estimation of the HRs.

In conclusion, compared with never-drinkers without hypertension, the risks for CVD, CAD, stroke and ischemic stroke were increased in those with hypertension, irrespective of alcohol consumption. The risk for CAD was the highest in hypertensive never-drinkers, whereas the risk for stroke was the highest in hypertensive heavy-drinkers. In non-hypertensives, there was no evident increase or decrease in the HRs for CVD and its subtypes in drinkers. Accordingly, controlling blood pressure is important to prevent CVD. In hypertensives, heavy drinking should be avoided to prevent CVD, although light-to-moderate drinking could be protective for CAD. Furthermore, in non-hypertensives, drinkers may need to continuously monitor their blood pressure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Prognostic values of bundle branch blocks for cardiovascular mortality in Japanese (24 year follow-up of NIPPON DATA80)☆

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Abstract

Aims: Left bundle branch block (LBBB) is generally considered to be associated with a poorer prognosis in comparison with normal controls. However, there are some studies that showed no difference in prognosis of LBBB in comparison with normal controls.

Methods and Results: We studied prognostic values of BBBs on cardiovascular disease (CVD) and total mortality using the NIPPON DATA80 database with a 24-year follow-up. At the baseline in 1980, data were collected on study participants, ages 30 years and over, from randomly selected areas in Japan. We followed 9,090 participants (44% men, mean age 51). During the 24 year follow-up, there were 886 CVD, and 2,597 total mortality cases. Among participants, 0.2% of them were in LBBB, 1.3% in RBBB, 4.3% in other ventricular conduction defect (VCD) groups. The multivariate-adjusted hazard ratio (HR) using the Cox model including biochemical and other ECG variables revealed that LBBB was significantly positively associated with CVD (HR = 2.71, 95% confidence intervals [CI]: 1.35–5.45, P = 0.005), and total (HR = 2.07, 95%CI: 1.26-3.39, P = 0.004) mortality in men and women combined compared to participants without VCD. RBBB and other VCDs did not carry any significant risk for CVD or total mortality.

Conclusions: We found significant positive associations of LBBB with CVD and total mortality independent of confounding factors including other ECG changes.

Keywords: Electrocardiography; Bundle branch blocks; Total mortality; Cardiovascular mortality

Introduction

Among ventricular conduction defects (VCD), complete left (LBBB) and right bundle branch (RBBB) are distinct findings of ECG.[1] RBBB is generally considered to be benign in the absence of any underlying cardiac abnormality such as congenital heart disease.[2–5] LBBB, on the other hand, is generally considered to be associated with a poorer

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prognosis in comparison with normal controls.[5,6] However, there are some studies that showed no difference in prognosis of LBBB in comparison with normal controls.[2,7–9] There are not many epidemiological studies evaluating the prognostic significance of LBBB and RBBB in general populations, and studies that incorporate lifestyle related and blood chemical risk factors into analyses are quite rare. The aim of the present study was to assess the independent prognostic values of LBBB, RBBB and other VCDs for CVD and total mortality in a large cohort of participants obtained from randomly selected health districts in Japan.[10,11]

Methods

Participants

Cohort studies of the National Survey on Circulatory Disorders, Japan, are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere.[10,11]

Three hundred health districts throughout Japan were randomly selected. The overall population, ages 30 years and over, in the participating health districts was 13,771. All of them were invited to participate in the study. Among them, a total of 10,546 community-based participants agreed to participate in the study. The participation rate was 76.6 % (10,546 of 13,771) before exclusion for reasons mentioned below. The survey consisted of history-taking, physical examinations, blood tests, a standard 12-lead ECG recording in the supine position, and a self-administered questionnaire on lifestyle. For the present study, participants were followed up to 2004 (NIPPON DATA 80, 1980–2004).

Participants were excluded from follow-up because of missing baseline data (N = 139), a past history of coronary heart disease (CHD) or stroke at the baseline (N = 153), or loss to follow-up (N = 1,104). The latter group was excluded because of the absence of a permanent address that was needed to link to vital statistical records. We also excluded participants with baseline ECG abnormalities including moderate or major Q wave abnormalities (Minnesota Code (MC), 1-1- or 1-2-), third-degree atrio-ventricular block (MC 6–1), and Wolf-Parkinson-White syndrome (MC 6-4-) (N = 60).[12,13] There were no participants with Mobitz type II AV block or with artificial ventricular pacemaker. The final sample comprised 9,090 participants (3,970 men and 5,120 women). There were no significant differences between participants who were lost to follow-up and those who were included in the current study in terms of several risk factors.

Biochemical and baseline examinations

The baseline surveys were conducted at public health centers according to a standardized manual. Blood pressure was measured by trained research nurses using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, use of antihypertensive agents or any combination of these. Height and weight were measured in stocking feet and light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also carried out using a self-administered questionnaire. Participants were asked about their alcohol drinking habit (never, past, occasional, and daily drinkers). Reported information was confirmed by public health nurses through interviews with the study participants regarding smoking, drinking habit, and present and past medical histories.

Casual blood samples were drawn and centrifuged within 60 min of collection and stored at −70 °C until analyses as described previously.[10,11,14,15] Serum concentrations of glucose were measured by the cupric-neocuproline method, and the value was converted so as to better correspond with the more widely used hexokinase method.[16]

The ECG findings were independently evaluated by 2 trained researchers independent of the NIPPON DATA research group in each of 12 institutions according to the MC as previously described.[17] Codes in agreement were accepted, whereas inconsistent codes were decided by a panel of study epidemiologists and cardiologists.[17] Major ECG findings for the present study were LBBB (MC7-1-1, -2), RBBB (MC7-2-1, -2), and other VCDs (MC7-3 to 7–7). There were no participants with code 7.4 plus codable Q wave. Additional ECG findings (www.sph.umn.edu/epi/ecg/mncode.pdf[13]) that we examined were minor Q wave abnormality (MC1-3-) (yes/no), first- or second-degree atrio-ventricular block (1° or 2° AV block) (MC6-2-2, 6-2-3 or 6–3) (yes/no), atrial or ventricular premature beats (APC or VPC) (MC8-1-) (yes/no), atrial fibrillation or flutter (AF or AFL) (MC8-3-) (yes/no). The following ECG codes were suppressed in the presence of LBBB according to MC: MC ([1-2-3, 1-2-7, 1-2-8: these three were in the exclusion criteria in the present study], 1-3-2, 1-3-6, all 2-, 3-, 4-, and 5-codes, 7–7, 9–2, 9–4, 9–5).[18] Most of these MCs were also suppressed in the presence of RBBB Thus, these codes were not entered in the analyses.

Endpoint determination

To determine the cause of death after 24 years follow-up, we used the National Vital statistics database of Japan with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and ICD-10 from the beginning of 1995. The details of classification in the present study are described elsewhere.[19–21] CVD (ICD-9: 393 to 459 and ICD-10: I00 to I99) was identified. Approval for the study was obtained from the Institutional review Board of Shiga University of Medical Science (No. 12–18, 2000).

Statistical analysis

SAS version 9.2 for Windows (SAS Institute, Cary, NC) was used throughout the analyses. Variables were compared among the four groups according to ECG findings of VCDs (normal, LBBB, RBBB and other VCDs). The chi-square test was used to compare dichotomous variables, followed

Table 1
Baseline characteristics and mortality according to ventricular conduction defect categories NIPPON DATA80, 1980-2004.

Type	Normal	LBBB	RBBB	Other VCDs	P
N (% of total N)	8558 (94.1%)	20 (0.2%)	117 (1.3%)	395 (4.3%)	
Age (y)	50.3 ± 13.0	65.0 ± 10.3†	64.2 ± 12.4†	54.1 ± 14.1†	<0.001
Men (%)	42.8	50.0	65.0†	55.7†	<0.001
BMI (kg/m^2)	23.0 ± 15.3	22.0 ± 3.5	22.0 ± 3.2	21.6 ± 3.2	0.301
Hypertension (%)	44.8	65.0	63.3†	49.4	<0.001
Smoker (%)	32.0	45.0	40.2	40.8†	<0.001
Alcohol drinker (%)	43.6	35.0	42.7	48.9	0.182
Total Cholesterol (mg/dl)	188.7 ± 33.6	187.4 ± 30.4	184.0 ± 32.8	188.3 ± 31.9	0.514
BS (mg/dl)	101.3 ± 30.3	104.2 ± 30.8	105.0 ± 30.8	101.9 ± 29.9	0.549
Creatinine (mg/dl)	0.92 ± 0.23	1.03 ± 0.34	1.03 ± 0.23†	0.96 ± 0.17*	<0.001
CVD death (%)	9.5	40.0†	18.8†	11.9	<0.001
Total death (%)	27.5	80.0†	64.1†	38.0†	<0.001

Values are shown as the mean ± SD, or in %. P values are from the chi-square test, or from a one-way analysis of variance. * P < 0.05, † P < 0.01 compared to the normal group. Baseline characteristics, CVD and total mortality were compared among the four groups according to VCD type (normal, LBBB, RBBB, and others). The chi-square test was used to compare dichotomous variables, followed by a post hoc application of Bonferroni's method when P < 0.05. A one-way analysis of variance was used to compare means among the groups, followed by a post hoc application of Dunnett's test when the F value showed a significant difference at P < 0.05. VCD = ventricular conduction defect, BMI = body mass index, Alcohol drinker = those participants who admitted to drinking alcohol daily, Smoker = those participants who admitted to smoking currently, Total Cholesterol = serum total cholesterol concentration, BS = blood glucose concentration, CVD = cardiovascular diseases.

by a post hoc application of Bonferroni's method when P < 0.05. A one-way analysis of variance was used to compare means among the groups, followed by a post hoc application of Dunnett's test when the F value showed a significant difference at p < 0.05.

To examine the factors associated with CVD, and total mortality, multivariate-adjusted hazard ratios (HR) and P values were calculated using a Cox proportional hazards model. Men and women were combined. Covariates in model 1 were sex, age, and VCD categories (normal, LBBB, RBBB, and other VCDs). Model 2: model 1 covariates + BMI (5 categories divided at 18.5, 23, 25, and 30 kg/m^2; 18.5-23: a reference), hypertension, cigarette smoking (never and past smokers, 3 current smokers categories divided at 20, and 40 cigarettes/day; never smokers: a reference), alcohol drinking (ex-drinker or current drinker, never-drinker; never drinkers: a reference), serum total cholesterol, and blood glucose concentrations (standardized to have the mean = 0 and standard deviation = 1), serum creatinine (divided at 75 percentile,1.0 mg/dl), and interaction terms (age x hypertension, age x smoking, and age x standardized blood glucose). These interaction terms were entered because they contributed significantly. Model 3: model 2 covariates + other ECG findings separately (minor Q wave, 1° or 2° atrio-ventricular block [except for Mobitz type II], atrial or ventricular premature contractions, atrial fibrillation or atrial flutter), and interaction terms. Model 3 analysis stratified by sex was also performed.

Results

Descriptive statistics

During follow-up for 24 years (191,942 person-years), 886 CVD deaths (429 in men, 457 in women), and 2,597 total deaths (1,374 in men, 1,223 in women) were confirmed.

Baseline characteristics, CVD and total mortality according to VCD groups are shown in Table 1. Among participants, 0.2% of them were in LBBB, 1.3% in RBBB, 4.3% in other VCD groups. Mean age in the three VCD groups was higher than in the normal group, and mean creatinine in RBBB and other VCD groups were higher than in that in normal groups. Prevalence of men, hypertension, and smokers were different among the groups. Mean BMI, total cholesterol, blood sugar and prevalence of alcohol drinkers were not different among the groups. CVD mortality in LBBB and RBBB were higher than in the normal group. Total mortality in the three VCD groups were higher than in the normal group.

Baseline ECG characteristics according to VCD groups are shown in Table 2. Prevalence of 1° or 2° AV block (except for Mobitz type II) in other VCD group was higher than in the normal group. Other ECG findings were not different among the groups.

Associations of VCD types with CVD, and total mortality

Results of Cox analyses on the associations of VCD types with CVD and total mortality are shown in Table 3. With

Table 2
Baseline ECG characteristics (%) according to ventricular conduction defect type – NIPPON DATA80, 1980-2004.

Type	Normal	LBBB	RBBB	Other VCDs	P
Minor Q wave (MC1-3-) (%)	1.43	0	1.71	1.52	0.945
1° or 2° AV block (%)	2.15	5.00	4.27	4.05*	0.033
APC or VPC (%)	1.11	5.00	0.85	2.03	0.141
AF or AFL (%)	0.61	0	1.71	1.01	0.355

Values are shown as in %. Baseline ECG characteristics were compared among the four groups according to the VCD type (normal, LBBB, RBBB, and others; normal: as a reference). The chi-square test was used, followed by a post hoc application of Bonferroni's method. * P < 0.05, † P < 0.01 compared to normal controls. BBB = bundle branch block, VCD = ventricular conduction defect, AV = atrioventricular, APC = atrial premature contractions, VPC = ventricular premature contractions, AF = atrial fibrillation, AFL = atrial flutter.

Table 3
Ventricular conduction defect categories and mortality – NIPPON DATA80, 1980-2004.

	LBBB			RBBB			Other VCDs		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
CVD									
Model 1	2.65	1.32–5.32	0.006	0.78	0.51–1.19	0.775	0.86	0.64–1.15	0.301
Model 2	2.62	1.30–5.26	0.007	0.73	0.48–1.12	0.731	0.88	0.65–1.18	0.879
Model 3	2.71	1.35–5.45	0.005	0.75	0.49–1.15	0.190	0.85	0.63–1.14	0.264
Total									
Model 1	2.11	1.29–3.45	0.003	1.04	0.83–1.32	0.726	0.99	0.84–1.17	0.939
Model 2	2.03	1.24–3.33	0.005	1.01	0.80–1.28	0.916	0.99	0.84–1.17	0.991
Model 3	2.07	1.26–3.39	0.004	1.03	0.81–1.30	0.833	0.97	0.82–1.14	0.709

Covariates in model 1 were sex, age, and VCD categories. Model 2: model 1 + BMI, hypertension, cigarette smoking, alcohol drinking, serum total cholesterol, and blood glucose concentrations, serum creatinine, and interaction terms. Model 3: model 2+ other ECG findings (minor Q wave, 1° or 2° atrioventricular block [except for Mobitz type II], atrial or ventricular premature contractions, atrial fibrillation or atrial flutter), and interaction terms. BBB = bundle branch block, VCD = ventricular conduction defect.

adjustment for age and sex, statistical significances were noted for CVD and total mortality in LBBB. Statistical significance of CVD and total mortality in LBBB remained in the fully adjusted model (Model 3). In comparison with the normal group, HR and 95% confidence intervals (CI) for CVD mortality in LBBB were 2.71 (95%CI: 1.35-5.45, P = 0.005), and were 2.07 (95%CI: 1.26-3.39, P = 0.004) for total mortality. In model 3 analyses stratified by sex, statistical significances of LBBB in men remained (CVD: HR = 5.60 [95%CI: 2.44-12.82], P < 0.001; total: HR = 2.42 [95%CI: 1.24-4.70], P = 0.009), but statistical significances disappeared in women (CVD: HR = 1.09 [95%CI: 0.27-4.39], P = 0.904; total: HR = 1.69 [95%CI: 0.80-3.55], P = 0.171).

Kaplan-Meier survival curves for CVD and total mortality of LBBB and normal groups are shown in Figs. 1 and 2. For the both mortality curves, lines diverge obviously after 5 years of follow-up.

Discussion

We found a significant positive association of LBBB with CVD and total mortality. We also found that RBBB and other VCDs did not carry any significant risk for CVD or total mortality.

The results of previous studies on the prognostic significance of LBBB have been conflicting. Rotman et al. performed a follow-up study of 394 participants with RBBB and 125 participants with LBBB out of over 237,000 individuals at the United States Air Force (USAF) School of Aerospace Medicine.[2] They observed no differences in follow-up morbidity of CVD or mortality with LBBB or RBBB compared to normal controls with a mean follow-up period of 10.8 years. In a cohort study in Iceland, Hardarson et al. found that mortality from coronary artery disease or hypertension was not increased in those with LBBB.[8] Kreger et al. reported the results of the Framingham study with over 18 years of follow-up. They found that age-adjusted incidence of myocardial infarction, angina pectoris, and coronary death were unrelated to baseline QRS prolongation, and that participants with LBBB fared no worse than those with RBBB.[9] However, in more recent cohort studies with a larger number of participants and with a longer duration of follow-up, it has been shown that LBBB is associated with a poorer prognosis. Imanishi et al. studied 17,361 participants over a 40-year period in Hiroshima and Nagasaki in the follow-up program of atomic bomb survivors, and they found

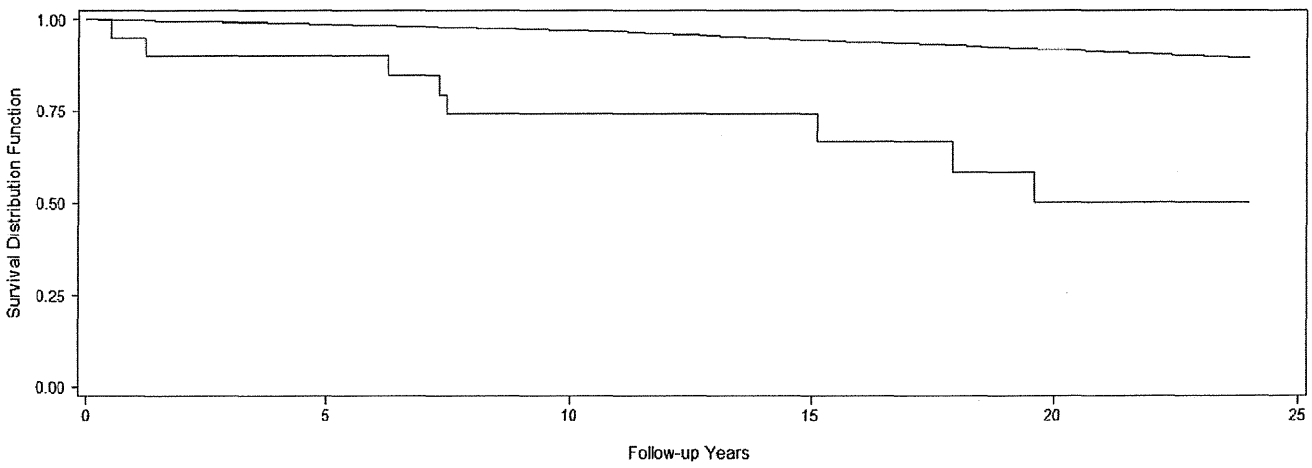

Fig. 1. Kaplan-Meier Survival Curve for CVD Mortality of LBBB and the For the Normal Groups. Upper line indicates survival for the participants with no ventricular conduction defects, and lower line with LBBB.

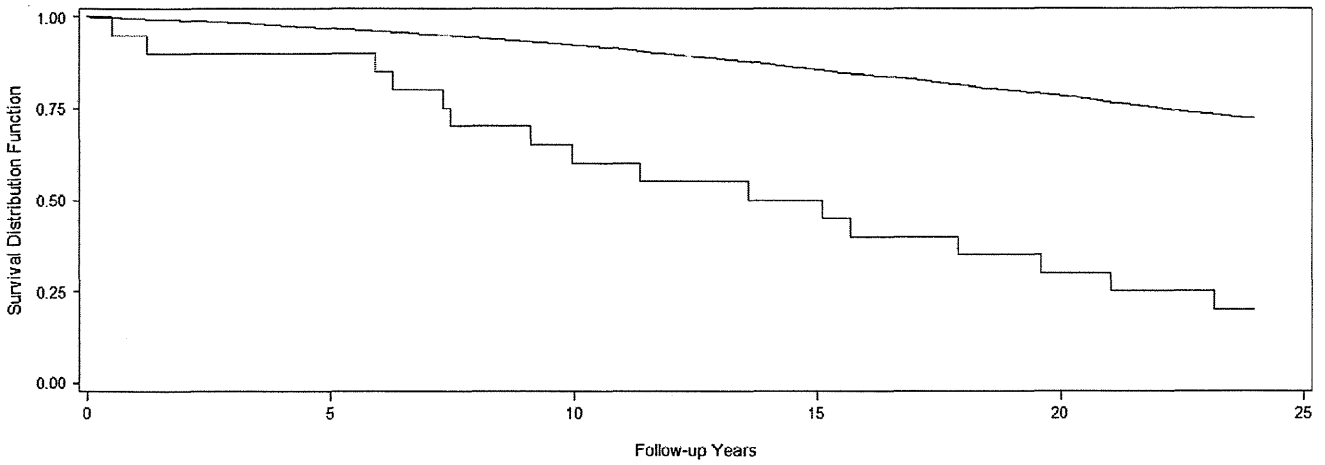

Fig. 2. Kaplan-Meier Survival Curve for Total Mortality of LBBB and the Normal Groups. Upper line indicates survival for the participants with no ventricular conduction defects, and lower line for LBBB.

that LBBB predicted mortality from heart failure, but not for all-cause mortality.[6] Zhang et al. evaluated mortality risk associated with BBBs during 14 years of follow-up in 66,450 participants from the Women's Health Initiative study, and found that prevalent LBBB in CVD-free women was a significant predictor of coronary heart disease mortality.[5] Differences in the results of previous studies on the prognostic significance of LBBB may be related to differences in the number of cases and the durations of follow-up. In a USAF study, the majority of participants were flyers in exceptionally good health.[2,22] The chance of unnoticed inclusion of participants with subclinical underlying heart disease must be minimal in such a study.

Several underlying mechanisms involved in apparently healthy participants with LBBB from general populations have been postulated. These include subclinical myocarditis,[23] a degenerative fibrotic process involving the conduction system,[24–27] and silent coronary artery disease.[2] Furthermore, without evident heart disease, LBBB may induce abnormalities in left ventricular performance due to abnormal asynchronous contraction patterns.[28–30] Asynchronous electrical activation of the ventricles causes regional differences in workload which may lead to asymmetric hypertrophy, left ventricular dilatation, and increased wall mass in late-activated regions.[31] These may aggravate preexisting left ventricular pumping performance or even induce it. Some reports showed that patients with LBBB and normal left ventricular dimensions and the normal ejection fraction at rest, but presented with an abnormal increase in pulmonary artery pressure during exercise, production of lactate during high-rate pacing, and abnormal ultrastructural findings on myocardial biopsy.[30,32,33]

Horibe et al. studied the NIPPON DATA80 dataset with 19 years of follow-up, and reported that total mortality in those with RBBB was significantly higher without any adjustment.[17] In the present study, RBBB was not associated with any mortality risk when adjusted for age and sex. Lack of prognostic significance of RBBB and other VCDs in our study is consistent with previous studies.[2–5]

We had a large cohort of participants obtained from randomly selected health districts in Japan. The participants in our study were observed for 24 years, which is along follow-up period and this increases the value of our study.

Study limitations

There are some limitations to the current study. Firstly, we had a relatively large number of lost to follow-up: 1,104 participants (about 10%). However, there were no significant differences between participants who were lost to follow-up and those who were included in the current study in terms of several risk factors. Therefore, the potential bias regarding the participants lost to follow-up may be negligible. However, unobserved information related to outcomes may have led participants to drop out of our study early. We cannot exclude the fact that this may lead to a bias. Secondly, we used a single ECG at the baseline. It is well recognized that single biologic measurements are subject to variability and ECG abnormalities could have changed over time. However, this possible variability generally tends to result in underestimate of the risk. Third, MC was coded by visual reading in our study. Computerized ECG analysis is reportedly superior to visual reading in terms reliability[34]; however, computerized ECG analysis was not available in the 1980s, and ECG readings in the study were performed under the best standardized quality control by well trained physicians. Fourth, we have no data on PQ prolongation. Fifth, the number of participants with LBBB was small, and thus we could not perform subclass CVD analysis. However, the statistical significance of HR remained with several statistical adjustments. This supports lack of confounding, and supports also that LBBB are independent predictors of CVD and total mortality.

Conclusions

We found a significant positive association of LBBB with CVD and total mortality independent of confounding factors including other ECG changes.

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The Effectiveness of a Stroke Educational Activity Performed by a Schoolteacher for Junior High School Students

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Background: The purpose of this study was to determine whether our stroke education system can help junior high school students acquire stroke knowledge when performed by a schoolteacher. *Methods:* A stroke neurologist gave a stroke lesson to 25 students (S group) and a schoolteacher through our stroke education system. After instruction, the schoolteacher performed the same lesson using the same education system to another 75 students (T group). Questionnaires on stroke knowledge were examined at baseline, immediately after the lesson (IL), and at 3 months after the lesson (3M). We analyzed the results of stroke knowledge assessment by linear mixed effects models adjusted for gender and class difference using the student number. *Results:* We assessed 24 students in the S group and 72 students in the T group. There were no significant differences in the changes of predicted scores of symptoms and risk factors adjusted for gender, class difference, and each student knowledge level until 3M between the 2 groups. Correct answer rates for the meaning of the FAST (facial droop, arm weakness, speech disturbance, time to call 119) at IL were 92% in the S group and 72% in the T group, respectively. At 3M, they were 83% in the S group and 84% in the T group. The correct answer rates of FAST at 3M were not significantly different adjusted for group, gender, class difference, and correct answer rate at IL. *Conclusions:* A schoolteacher can conduct the FAST message lesson to junior high school students with a similar outcome as a stroke neurologist using our stroke education system. **Key Words:** School-based intervention—stroke enlightenment—FAST—online system.

Introduction

Stroke is the leading cause of disability and a main cause of death in Japan. The number of stroke patients and the burden of the elderly population will increase as society ages. With the advantage of acute thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator for stroke outcome,[1,2] shortening the time between symptom onset and hospital arrival is essential for improving stroke outcome. Although the

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European Cooperative Acute Stroke Study III led to the expansion of the therapeutic time window of thrombolysis for acute ischemic stroke,[3] only a small proportion of patients arrive at the hospital within the time window.[4] Improving stroke awareness is an important factor for rapid access to the acute stroke center at symptom onset.

Although several studies have reported that stroke educational campaigns improve public knowledge about stroke in adults,[5-9] only a few studies have examined stroke education programs for children. Stroke enlightenment for youth is a promising strategy for the prevention of cardiovascular disease. Because of compulsory education, implementing stroke lessons in the education programs of elementary or junior high school is a promising means for spreading stroke knowledge in Japan. We developed a stroke education system that is performed by stroke neurologists for junior high school students.[10] As the next step, to extend stroke enlightenment all over the country, we investigated whether this education system was effective when schoolteachers rather than physicians present the stroke lessons to students. The aim of this study was to verify the effectiveness of our education system in junior high schools when performed by a schoolteacher.

Methods

The research was carried out in partnership with the Suita City Board of Education. The Suita City Board of Education approved this study, and this study obtained exempted approval from the institutional review board based on our domestic guideline because of using only an anonymized and unconnectable data set of questionnaire responses.

Subjects

This study was conducted at a public junior high school at Suita City, Osaka Prefecture, Japan, from July 2011 to October 2011. Subjects were 100 students in 4 classes of the third grade (40 girls, 14-15 years old). The subjects were divided into 2 groups: 1 class with 25 students received a 45-minute stroke lesson by a stroke neurologist (S group), and the remaining 3 classes with 75 students in total received a 45-minute lesson by a schoolteacher of health and physical education (T group).

Stroke Education System and Items with FAST Message

Our stroke education system consisted of an online system and the lecture materials were Power Point files including stroke risk factors, signs, symptoms, and the FAST massage (facial droop, arm weakness, speech disturbance, time to call 119).[5] All junior high schools in Suita City have their own computer systems, and each student could use the online systems during the stroke lesson. At first, a stroke neurologist (T.A.) gave the stroke lesson to 25 students (S group) using our online stroke education system (Fig 1, A). A schoolteacher monitored the lecture and received instructions on how to use the stroke education system. Within 2 weeks after the instruction, the schoolteacher performed the lesson using the same system to the other 75 students (T group). Education items of a pen, file, magnet, and sticky note, all recorded with the FAST message (Fig 1, B), were distributed to all the students after the lesson.

Assessments

A questionnaire on stroke knowledge (a total of 12 items for stroke signs and 10 items for risk factors) was examined using the online system in all the students before (baseline [BL]) and immediately after the lesson (IL). At 3 months after the lesson (3M), the same questionnaire was applied. The questionnaire comprised multiple choice questions and close-ended questions, which assessed stroke signs and risk factors. The 12 items for stroke signs included 6 symptoms of stroke ("headache," "vision loss," "facial weakness," "speech disturbance," "numbness on 1 side of the body," and "weakness on 1 side of the body") and 6 incorrect or atypical symptoms ("chest pain," "dyspnea," "weakness on 4 limbs," "abdominal pain," "edema in feet," and "joint pain"). The 10 items for risk factors consisted of 7 stroke risk factors ("alcohol intake every day," "smoking," "hypertension," "dyslipidemia," "hyperglycemia," "obesity," and "arrhythmia") and 3 incorrect or atypical risk factors ("constipation," "urinary frequency," and "stiffness of neck"). Furthermore, the meaning of the FAST message, such as each word of F, A, S, and T, was also examined by a single choice test, at IL and 3M.

Analysis of Data

Statistical analysis was performed using the JMP 8.0 statistical software (SAS Institute Inc., Cary, NC) or Stata software, version 12.0 (StatCorp LP, College Station, TX). We collected individual results of questionnaires on stroke knowledge at each time point until 3M using the unconnectable student number. Results of the questionnaire in each group at BL were compared with those at 3 months and those at IL by the Fisher exact test. For calculating scores, the student got 1 point if he chose a correct answer or did not choose an incorrect answer. Therefore, the scores of questionnaires on stroke signs and risk factors ranged from 0 to 12 and 0 to 10, respectively. In each questionnaire on stroke signs and risk factors, we summed these points of each student in assessing stroke knowledge. Because each student's score was measured repeatedly in a longitudinal manner, linear mixed effects models adjusted for gender and class difference and were used to analyze the association between the score of knowledge for symptoms or risk and lessons