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

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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 ⩾7 $mmol\,l^{-1}$ and/or current use of insulin or oral medication for diabetes.
Dyslipidemia: fasting serum total cholesterol of ⩾5.69 $mmol\,l^{-1}$ and/or HDL-C <1.03 $mmol\,l^{-1}$ and/or TG ⩾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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Factors Associated With Onset-to-Door Time in Patients With Transient Ischemic Attack Admitted to Stroke Centers

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Background and Purpose—The aim of this study was to elucidate the factors associated with the time from symptom onset to arrival at a stroke center (onset-to-door time [ODT]) in patients with classically defined transient ischemic attack using data from a multicenter, retrospective study.

Methods—The subjects were patients with transient ischemic attack admitted to 13 stroke centers in Japan within 7 days of onset between 2008 and 2009. A total of 464 patients registered (292 men, 68.5±13.2 years old), and 421 of them (268 men, 68.8±13.1 years old) were included in the analyses. ODT was classified into the following 5 categories: <3 hours, 3 to 6 hours, 7 to 12 hours, 13 to 24 hours, and >24 hours.

Results—There were 233 patients (55.3%) who visited a stroke center within 3 hours of symptom onset. Multiple ordinal logistic regression analysis revealed that motor weakness, speech disturbance, and duration of symptoms >10 minutes were independently associated with a short ODT. Furthermore, a history of transient ischemic attack and hypertension and a referral from another medical facility were independently associated with a long ODT. Patients with a higher $ABCD^2$ score were likely to arrive at a stroke center more quickly.

Conclusions—We identified several factors that were positively and negatively associated with the ODT in patients with transient ischemic attack. (***Stroke*. 2014;45:611-613.**)

Key Words: ischemic attack, transient ■ stroke

A transient ischemic attack (TIA) is a medical emergency associated with a high risk of early recurrent stoke. Urgent assessment and management of patients in a dedicated TIA clinic were found to decrease the 90-day stroke risk by ≈80%.[1,2] Immediate medical attention is essential to reduce the risk of stroke after TIA. Although the behavior of patients after stroke has been studied extensively since the advent of thrombolysis and other potential treatments, little information is available on the behavior of patients after TIA, except for the Oxford Vascular Study.[3-5]

We investigated the factors associated with the time from symptom onset to arrival at a stroke center (onset-to-door time [ODT]) in patients with TIA admitted to stroke centers using data from a multicenter, retrospective study.

Methods

The methods of this retrospective, observational, multicenter study have already been described in detail.[6] In brief, we enrolled patients with TIA admitted to 13 stroke centers in Japan within 7 days after symptom onset between January 2008 and December 2009. The diagnosis of TIA was made if neurological symptoms and signs lasted <24 hours, regardless of the brain imaging findings.

A total of 464 patients registered (292 men, 68.5±13.2 years old), but 43 were excluded as a result of either incomplete data (n=20) or referral from another department within the same stroke center (n=23). Thus, a total of 421 patients (268 men, 68.8±13.1 years old) were included in the analyses.

Based on the study design, ODT was classified into the following 5 categories: <3 hours, 3 to 6 hours, 7 to 12 hours, 13 to 24 hours, and >24 hours. Individual $ABCD^2$ scores were calculated.[7] The clinical outcome was the occurrence of ischemic stroke during acute hospitalization.

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The ODT category was considered an ordinal variable, and ordinal logistic regression analyses were performed to identify the associations between the study variables and ODT. Variables that showed $P<0.1$ in univariate analyses were used in multiple ordinal logistic regression analysis, and this was performed using a cumulative logit model. The ABCD^2 score was excluded from the multivariable model because of confounding factors.

Results

Table 1 shows the characteristics of patients according to ODT. Patients with symptoms on arrival at stroke centers, motor weakness, speech disturbance, and duration of symptoms >10 minutes were more likely to arrive at stroke centers quickly than those without. Patients with a history of TIA and hypertension and those referred from another medical facility were more likely to have a delayed arrival at a stroke center. We found that patients with a higher ABCD^2 score were more likely to arrive at a stroke center quickly. Multiple ordinal logistic regression analysis revealed that motor weakness, speech disturbance, and duration of symptoms >10 minutes were independently associated with a short ODT. Furthermore, a history of TIA and hypertension and a referral from another medical facility were independently associated with a long ODT (Table 2).

Subsequent ischemic stroke occurred during hospitalization in 4 (1.7%) of 233 patients who visited a stroke center within 3 hours, 1 (1.5%) of 65 within 3 to 6 hours, 0 (0%) of 43 within 7 to 12 hours, 1 (3.3%) of 31 within 13 to 24 hours, and 1 (2.0%) of 49 after 24 hours. Events and ODT were not significantly associated.

Discussion

Our study revealed that motor weakness, speech disturbance, and long duration of symptoms were associated with a short ODT. Patients with a higher ABCD^2 score were more likely to arrive at a stroke center quickly. The results of our study are consistent with those of previous studies.[3,5,8] Two reports using data from the Oxford Vascular Study[3,5] demonstrated that patients with motor weakness, speech disturbance, and symptom duration >60 minutes were less likely than other patients to delay in seeking medical attention. Patients with a higher predicted stroke risk were more likely to act quickly due apparently to the influence of weakness and prolonged symptom duration on behavior, although there was no association between the recognition of symptoms and the urgency of action.[3]

We found that a history of recent TIA and hypertension, both known risk factors for stroke after TIA, was associated with delayed arrival at a stroke center. These relationships were not found in a study by Chandratheva et al.[5] They reported that prior stroke and atrial fibrillation tended to be associated with less delay. We also showed that a referral from another medical facility was associated with a longer delay in arrival at a stroke center. A systematic review found that there

Table 1. Comparison of Characteristics According to Onset-to-Door Time

		Onset-to-Door Time					
	Overall n=421	>3 h n=233	3–6 h n=65	7–12 h n=43	13–24 h n=31	>24 h n=49	*P* Value
Age, y (mean±SD)	68.8±13.1	68.8±12.4	70.9±14.3	67.0±12.6	70.0±15.3	66.5±13.0	0.566
Men, %	63.7	64.0	53.9	62.8	64.5	75.5	0.546
Symptoms, %							
Motor	68.5	76.4	59.4	59.5	50.0	62.5	<0.001
Sensory	28.0	26.8	26.6	36.8	32.3	25.5	0.591
Speech	39.2	45.9	35.4	41.9	12.9	26.5	<0.001
Visual	8.8	6.9	10.8	4.7	12.9	16.3	0.067
Presence of symptoms on arrival, %	42.8	46.8	46.2	51.2	22.6	24.5	0.005
Duration of symptoms >10 min, %	85.9	90.5	91.5	94.3	88.5	48.9	<0.001
History, %							
Stroke	23.5	24.5	21.5	27.9	16.1	22.5	0.599
TIA	18.5	15.7	13.6	13.5	26.9	40.0	0.009
Hypertension	68.2	63.1	73.9	76.7	74.2	73.5	0.017
Diabetes mellitus	20.2	18.0	21.5	25.6	19.4	24.5	0.218
Dyslipidemia	39.4	34.8	56.9	27.9	51.6	40.8	0.109
Atrial fibrillation	12.4	12.8	13.9	11.6	19.4	4.1	0.482
Median ABCD^2 score, (IQR)	4 (3–5)	5 (4–5.75)	4 (3–5)	5 (3–6)	4 (3–5)	4 (2–5)	<0.001
Referral from another medical facility, %	29.9	17.6	46.2	39.5	54.8	42.9	<0.001

IQR indicates interquartile range; and TIA, transient ischemic attack.

Table 2. Factors Associated With Onset-to-Door Time by Multivariate Analysis

	Estimate	SE	*P* Value
Motor disturbance	−0.276	0.127	0.029
Speech disturbance	−0.233	0.114	0.041
Visual disturbance	0.137	0.215	0.524
Presence of symptoms on arrival	−0.078	0.115	0.493
Duration of symptoms >10 min	−0.438	0.154	0.005
History of TIA	0.296	0.136	0.030
History of hypertension	0.258	0.122	0.034
Referral from another medical facility	0.605	0.114	<0.001

TIA indicates transient ischemic attack.

was an association between delay in seeking medical attention and referral from a general physician in patients with TIA or minor stroke.[9] The finding that patient factors are related to delayed arrival at stroke centers might be important insofar as action that could mitigate these factors. The present findings suggest that educating the general public and general physicians about TIA as a medical emergency and stroke risk factors, including hypertension, is essential to minimize the delay in arriving at a stroke center.

The present study has several limitations. First, there was a selection bias in this study because only patients with TIA admitted to a stroke center were enrolled. Second, this study had a retrospective design, and there were missing data on some baseline characteristics. Third, we were unable to investigate substantially an association between ODT and stroke risk because of the small number of patients who had stroke after TIA. Whether the hyperacute stroke treatment aphorism, time is brain, is applicable to TIA remains unclear.

In conclusion, we identified several factors that were positively and negatively associated with ODT in patients with TIA admitted to stroke centers. Further study is needed to clarify whether the same patterns of behavior after TIA would be observed in other populations.

Sources of Funding

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Disclosures

None.

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Clinical Significance of Fluid-Attenuated Inversion Recovery Vascular Hyperintensities in Transient Ischemic Attack

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Background and Purpose—Fluid-attenuated inversion recovery vascular hyperintensity (FVH) is often identified in patients with acute ischemic stroke. The purpose of this study was to determine the clinical significance of FVH in patients with transient ischemic attack (TIA).

Methods—Consecutive inpatients with TIA who underwent MRI within 24 hours of symptom onset were studied. The frequency, relative factors, and time course of FVH were determined.

Results—Of the 202 patients who were enrolled (76 women, mean age, 69.0±13.2 years), FVH was identified in 41 patients (20%). Multivariate analysis showed that atrial fibrillation (odds ratio, 7.14; 95% confidence interval [CI], 2.69–18.1), arterial occlusive lesion (odds ratio, 4.89; 95% CI, 3.03–12.2), and hemiparesis (odds ratio, 2.81; 95% CI, 1.17–7.48) was independently associated with FVH. Of 23 recurrence-free patients with FVH positive undergoing follow-up MRI at a median of 7 days after the onset, FVH was no longer positive in 15 patients (65%). Atrial fibrillation was more common (P=0.027) and arterial occlusive lesion was less common (P<0.001) in patients with transient FVH compared with those with persistent FVH. Within 90 days after the onset, 13 patients developed recurrent TIA or ischemic stroke. After Cox proportional hazard analysis, FVH (hazard ratio, 3.65; 95% CI, 1.09–12.7), arterial occlusive lesion (hazard ratio, 4.15; 95% CI, 1.18–17.1), and coexistence of FVH and arterial occlusive lesion (hazard ratio, 13.9; 95% CI, 3.36–71.0) were significantly associated with recurrent TIA or ischemic stroke.

Conclusions—The presence of FVH early after symptom onset may help to diagnosis TIA, to identify the potential mechanisms of TIA and to predict recurrence risk after a TIA. **(*Stroke*. 2013;44:1635-1640.)**

Key Words: acute stroke ■ atrial fibrillation ■ fluid-attenuated inversion recovery ■ magnetic resonance angiography ■ transient ischemic attack

High signal intensity within blood vessels on fluid-attenuated inversion recovery (FLAIR), otherwise known as FLAIR vascular hyperintensity (FVH), is often observed in patients with acute ischemic stroke (AIS) attributable to large artery stenosis or occlusion.[1–9] Altered hemodynamics, such as stationary and slow blood flow often from collateral circulation through leptomeningeal anastomosis, has been suggested to be the leading cause of FVH.[4,10]

A transient ischemic attack (TIA) is a medical emergency associated with a high risk of subsequent stroke. Ten percent to 15% of patients with TIA develop stroke within 90 days, with half of such strokes occurring within the first 48 hours.[11] Thus, the clinical importance of early diagnosis and management of TIA should be emphasized to prevent the development of stroke. Several guidelines recommend that patients with TIA undergo urgent neuroimaging evaluation (at least within 24 hours of symptom onset).[12,13] Diffusion-weighted imaging (DWI) reflects brain tissue damage that can be caused by ischemia. Vascular imaging, such as computed tomography angiography, MR angiography (MRA), and ultrasonography, can detect large arterial occlusive lesions (AOL). However, most culprit lesions are DWI negative,[13] and large AOL may be the collateral evidence of a TIA. In contrast, identification of FVH might provide additional information on disturbed blood flow and the important evidence of a TIA. The purpose of this study was to determine the detection rate, related factors, and significance of FVH as a predictor of recurrent TIA or ischemic stroke (IS) in patients with TIA.

Methods

Patient Selection and Definition

From a database of patients admitted to our department between January 2005 and December 2011, consecutive inpatients with TIA who underwent MRI and MRA within 24 hours of symptom onset were retrospectively selected. The diagnosis of TIA was made by neurologists if clinical symptoms lasted <24 hours regardless of imaging findings (such as DWI positivity) according to the third edition of *Cerebrovascular Disease Classification* by the National Institute of Neurological Disorders and Stroke.[14] Patients who underwent thrombolysis or endovascular therapy were excluded

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from the study. In our institute, patients who arrived within 24 hours after TIA onset were principally treated during hospitalization. Basically, patients with TIA having mechanisms of cardioembolic stroke underwent anticoagulant therapy, whereas the other patients were treated with antiplatelet agent. The hospital's ethics committee approved this series of clinical studies on the basis of the database of our stroke/TIA inpatients.

MRI Methods and Analysis

MRI, including DWI, FLAIR imaging, and time-of-flight MRA, was performed at 1.5 T (Magnetom Sonata or Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany). DWI was performed using the following parameters for the Magnetom Sonata (parameters for the Magnetom Vision were the same as those for the Magnetom Sonata, unless noted in parentheses): repetition time, 3000 ms (4000 ms); echo time, 72 ms (100 ms); matrix, 128×128; field of view, 23 cm; section thickness, 4 mm; intersection gap, 2 mm; and *b* values, 0 and 1000 s/mm^2. FLAIR images were as follows: repetition time, 9000 ms; echo time, 119 ms (105 ms); inversion time, 2500 ms (2400 ms); matrix, 182×256; field of view, 23 cm; flip angle, 150° (180°); section thickness, 5 mm (4 mm); and intersection gap, 1 mm (2 mm). Time-of-flight MRA was obtained using the following parameters: repetition time, 37 ms (35 ms); echo time, 7.15 ms (7.6 ms); flip angle, 25° (20°); field of view, 200 mm; matrix, 230×512 (224×512); and slice thickness, 0.6 mm.

The criterion for FVH was either dotted hyperintensity identified in the subarachnoid space on 2 or more axial slices (Figure 1A) or serpentine hyperintensity on 1 or more axial slices (Figure 1B). FLAIR images were independently estimated by 2 board-certified neurologists (J.K. and K.E.), who were informed about the patients' symptoms and neurological signs. They re-evaluated all FLAIR images after 1 month. When the judgment of the 2 neurologists was inconsistent, a decision was made by discussion without considering the information other than FLAIR imaging.

MRA and carotid ultrasound were performed for all patients, and digital subtraction angiography was performed for some. Assessments of extracranial internal carotid arteries on digital subtraction angiography, MRA, and carotid echography were made by North American Symptomatic Carotid Endarterectomy Trial (NASCET)-based methodology.[15] Stenosis in major intracranial arteries on digital subtraction angiography and MRA was evaluated by Warfarin Aspirin Symptomatic Intracranial Disease (WASID)-style methodology.[16] An AOL was defined as >50% stenosis, or as occlusion of extra- and intracranial large arteries assessed by MRA or digital subtraction angiography without recanalization on the follow-up examination. Vascular imaging was repeated for patients initially exhibiting steno-occlusive findings.

To assess whether FVH was persistent or transient, some of the patients with FVH positive underwent follow-up MRI and MRA around the seventh hospital day.

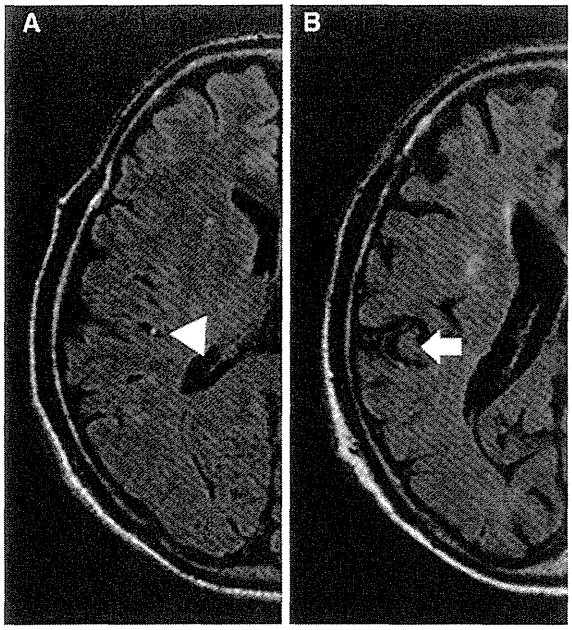

Figure 1. Representative images of fluid-attenuated inversion recovery vascular hyperintensity. **A**, Dot-like hyperintense signal in the Sylvian fissure (arrowhead). **B**, Serpentine hyperintense signal in the distal to Sylvian fissure (arrows).

Clinical Characteristics

The patients' clinical background characteristics, including sex, age, cardiovascular risk factors, history of TIA or stroke, blood pressure levels on arrival, clinical symptoms of TIA, symptom duration, and presence or absence of symptoms on arrival were collected from medical charts. Individual ABCD^2 scores, which use a simple scoring system to predict the risk of stroke after TIA, were calculated.[17] ECG and 24-hour electrocardiographic monitoring were performed in all patients. Atrial fibrillation (AF) was diagnosed on the basis of either documentation of the examinations or a confirmed history.

Cardiovascular Event After a TIA

Patients were routinely reassessed at 90 days by attending stroke neurologists in outpatient clinic, and the timing of the occurrence of stroke, TIA, acute coronary syndrome, undergoing vascular intervention, and death within 90 days was recorded. If the patient could not visit the clinic for follow-up, follow-up was performed by telephone interview or by a mail-in survey. We assessed recurrent stroke on the basis of the neurological examination and the new DWI-positive lesions on brain MRI.

Statistical Analysis

Continuous variables were expressed as the mean±SD (age and blood pressure), and as the median and interquartile range (ABCD^2 score and symptom duration). Categorical data were summarized as percentages. Differences between groups were analyzed using the Student *t* test and Mann–Whitney *U* test for continuous values and Pearson χ^2 test and Fisher exact test for categorical variables as appropriate. Multivariate analyses were performed to find predictors for the presence of FVH on the basis of the variables listed in Table 1. A backward selection procedure was performed using $P>0.10$ for the likelihood ratio test for exclusion. Factors that were independently associated with TIA or IS recurrence were determined using the Cox proportional hazard model on the basis of the ABCD^2 score, sex, AF, DWI positivity, FVH, and AOL (forced-entry method). A *P* value of <0.05 was considered statistically significant. Cohen κ values were calculated to quantify the level of agreement regarding the presence of FVH to determine inter- and intraobserver variability. All statistical analyses were conducted using JMP 9.0.2 statistical software (SAS Institute, Inc, Cary, NC).

Results

Two hundred seventy patients with TIA were admitted to our hospital during this investigation period. Of these, 12 patients were excluded because of contraindication for MRI by implanted cardiac devices, 54 were excluded because the initial MRI was performed >24 hours after symptom onset, and 2 were excluded because of lack of carotid imaging. No patients received thrombolysis or endovascular therapy. As a result, a total of 202 patients (76 women, mean age, 69.0±13.2 years) were enrolled in this study.

FVH was identified in 41 patients (20%). The κ coefficients for intraobserver agreement of FVH by the 2 examiners were

Table 1. Patient Characteristics

	All Patients (n=202)	Positive FVH (n=41)	Negative FVH (n=161)	*P* Value
Women, n (%)	76 (38%)	15 (37%)	61 (38%)	1.000
Age, y (mean±SD)	69.0±13.2	70.9±12.3	68.5±13.4	0.287
Risk factor				
Diabetes mellitus, n (%)	35 (17%)	7 (17%)	28 (17%)	1.000
Hypertension, n (%)	150 (74%)	35 (85%)	115 (71%)	0.075
Hyperlipidemia, n (%)	99 (49%)	17 (41%)	82 (51%)	0.299
Atrial fibrillation, n (%)	51 (25%)	20 (49%)	31 (19%)	<0.001
Previous stroke or TIA, n (%)	58 (29%)	17(41%)	41(25%)	0.053
SBP on arrival, mm Hg (mean±SD)	152±27	151±28	152±27	0.830
DBP on arrival, mm Hg (mean±SD)	83±16	85±16	83±16	0.423
Characteristics of TIA				
Clinical features, n (%)				
Unilateral weakness	136 (67%)	33 (80%)	103 (64%)	0.152
Isolated speech disturbance	18 (9%)	2 (5%)	16 (10%)	
Other symptoms	48 (24%)	6 (15%)	42 (26%)	
Symptom duration, median (IQR), min	60 (20–275)	20 (10–300)	90 (30–273)	0.013
Presence of symptoms on arrival, n (%)	68 (34%)	10 (24%)	58 (36%)	0.196
ABCD² score, median (IQR)	5 (4–5)	5 (4–5)	5 (4–5)	1.000
DWI lesion, n (%)	36 (18%)	13 (32%)	23 (14%)	0.020
AOL, n (%)	60 (30%)	20 (49%)	40 (25%)	0.004
AOL at the initial examination, n (%)	73 (36%)	30 (73%)	43 (27%)	<0.001
Recanalization, n (%)	13 (18%)	10 (33%)	3 (7%)	0.005

AOL indicates arterial occlusive lesion; DBP, diastolic blood pressure; DWI, diffusion-weighted imaging; FVH, fluid-attenuated inversion recovery vascular hyperintensity; IQR, interquartile range; SBP, systolic blood pressure; and TIA, transient ischemic attack.

0.810 and 0.726, and that for interobserver agreement of FVH was 0.783. Thirty-nine patients had FVHs in the middle cerebral artery territory, and 2 patients had FVHs in the posterior cerebral artery territory. There were no patients presenting with FVH in multiple vascular territories. In all 41 patients, FVH was identified in the clinically relevant side, ipsilateral to the DWI lesion in the 13 patients with DWI-positive, and contralateral to the clinical symptoms in the remaining 28 DWI-negative patients.

Factors Related to FVH

Baseline characteristics of the patients are shown in Table 1. AF (P<0.001), a DWI lesion (P=0.020), and AOL (P=0.004) were more common and the duration of symptoms was shorter (P=0.013) in the FVH-positive group than in the FVH-negative group. Multivariate logistic regression analysis showed that AF (odds ratio, 7.14; 95% confidence interval [CI], 2.69–18.1), AOL (odds ratio, 4.89; 95% CI, 3.03–12.2), and hemiparesis (odds ratio, 2.81; 95% CI, 1.17–7.48) were independently associated with FVH (Table 2).

Time Course of FVH According to Follow-up MRI

Of 41 patients with FVH positive, 23 patients received follow-up MRI during their acute hospitalization (median, 7 days; interquartile range, 6–11 days) without episodes of recurrent TIA or IS before the follow-up MRI. There were no significant differences in patient characteristics shown in Table 1 between patients having the follow-up MRI or not. FVH was no longer positive in 15 patients (65%; transient FVH). In the transient FVH group, AF was more common (67% versus 13%; P=0.027) and AOL was less common (0% versus 88%; P<0.001) than in the 8 patients with persistent FVH. Particularly in the 9 patients with FVH positive without a DWI lesion or AOL at the initial assessment, all FVHs completely resolved, and DWI revealed hyperintense lesions that were compatible with the initial symptom of TIA in 4 of these 9 patients (Figure 2).

Recurrent TIA/Stroke and FVH

One hundred eighty-one patients (90%) had catamnestic follow-up at 90 days. Nine patients developed recurrent TIA, 4 developed IS, 1 developed hemorrhagic stroke, and none

Table 2. Multivariate Logistic Regression Analysis of Parameters for Independent Relative Factors of FVH

Characteristics	Odds Ratio	95% CI	*P* Value
The presence of FVH			
Hypertension	2.47	0.93–7.53	0.710
AF	7.14	2.69–18.1	<0.001
AOL	4.89	3.03–12.2	<0.001
Hemiparesis	2.81	1.17–7.48	0.020

The presence of FVH was adjusted by characteristics selected by a backward selection procedure on the basis of the variables listed in Table 1.

AF indicates atrial fibrillation; AOL, arterial occlusive lesion; CI, confidence interval; and FVH, fluid-attenuated inversion recovery vascular hyperintensity.

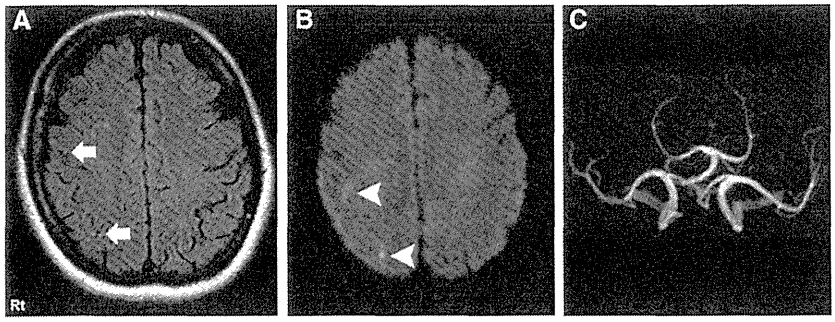

Figure 2. Brain MRI of a 53-year-old woman with transient ischemic attack (TIA) caused by paradoxical embolism. **A**, Initial fluid-attenuated inversion recovery (FLAIR) images 80 min after a 1-min attack of left hemiparesis showing 2 dot-like high intensities in the right middle cerebral artery territory (arrows). Initial diffusion-weighted imaging (DWI) showing no abnormal findings. **B**, Follow-up DWI showing hyperintense lesions close to the area where the fluid-attenuated inversion recovery vascular hyperintensity (FVH) are initially identified (arrowhead). Follow-up FLAIR images 6 d after the attack showing disappearance of the FVHs. **C**, MRA showing no arterial occlusive lesions at the initial assessment. The patient was diagnosed as having a patent foramen ovale and protein S deficiency during hospitalization. She did not experience a TIA or stroke after the initial TIA episode.

developed acute coronary syndrome, received vascular intervention, or died within 90 days. Figure 3A shows the cumulative rate of recurrent TIA or IS. In the FVH-positive group, 3 patients developed recurrent TIA and 4 patients developed IS on the ipsilateral side of FVH; 5 of these 7 patients developed these events within the initial week. In the FVH-negative group, 1 patient developed recurrent TIA and 5 patients developed IS; 5 of these 6 patients developed these events within the initial week. Cox proportional hazard analysis showed that FVH (hazard ratio, 3.64; 95% CI, 1.08–12.6) and AOL (hazard ratio, 3.82; 95% CI, 1.07–15.8) were independently associated with the events (Table 3, Model A). Because a significant association was found between FVH and AOL in this study, the analysis was repeated using 4 subgroups divided according to FVH and AOL: 20 patients with both FVH and AOL, 40 patients with only AOL, 21 patients with only FVH, and 100 patients without FVH or AOL. Patients having both FVH and AOL were independently associated with the events (hazard ratio, 12.8; 95% CI, 3.09–64.4; Table 3, Model B; Figure 3B).

Discussion

This is the first study to determine the frequency and clinical significance of FVH, and the association between FVH and recurrence of TIA or IS in patients with TIA. The first major finding of this study was that FVH was identified in 20% of patients with TIA on the clinically relevant side. The second major finding was that AF and AOL were independently associated with FVH; AF was especially associated with transient FVH and AOL with persistent FVH. Third, AOL and FVH were predictive of recurrence of TIA or IS within 90 days.

Patients with AIS often have FVH associated with large-vessel stenosis or occlusion.[2–9] In patients with AIS receiving intravenous thrombolysis within 3 hours from symptom onset, the frequency of FVH was 57% at baseline, 44% at 2 hours, and 25% at 24 hours; large artery occlusion was identified in 91% of the patients with FVH positive and 63% of the patients with FVH negative at baseline.[18] In another study, FVH was detected in 45% of patients within 24 hours after AIS onset, and all patients with FVH had large-vessel occlusion or severe stenosis.[4] In a study on TIA patients, FVH was identified in 33%, and again had a strong association with large-vessel occlusion or severe stenosis.[19] In contrast, only a report of a patient with AIS indicated that AF caused transient FVH without large AOLs.[1] In our series, FVH was identified only in 20% of the present patients within 24 hours after TIA onset, and only 49% of patients with FVH showed AOL. The incidence of FVH and large artery occlusive lesions in this study was obviously lower than those in the studies on AIS.

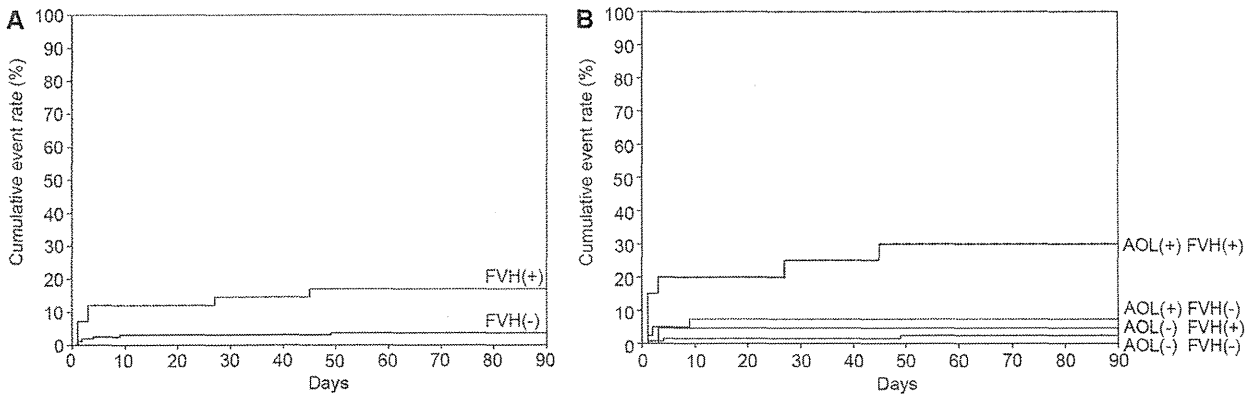

Figure 3. Cumulative rate of recurrent transient ischemic attack or ischemic stroke. **A**, The rate between patients with and without fluid-attenuated inversion recovery vascular hyperintensity (FVH). **B**, The rate among 4 groups classified according to the presence of FVH and arterial occlusive lesion (AOL).

Table 3. Cox Proportional Hazard Analysis for Factors Associated With Recurrent TIA and Ischemic Stroke Within 90 Days

	Model A			Model B		
Characteristics	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sex	1.18	0.33–3.86	0.785	1.16	0.33–3.77	0.812
ABCD^2	1.00	0.65–1.60	0.998	1.00	0.65–1.60	0.997
DWI positivity	1.06	0.26–3.75	0.926	1.03	0.25–3.67	0.964
AF	0.73	0.14–2.89	0.664	0.79	0.16–3.05	0.743
FVH	3.64	1.08–12.6	0.037	...	...	...
AOL	3.82	1.07–15.8	0.039	...	...	...
FVH(–) AOL(–)	...	...	...	1.00	(Reference)	...
FVH(+) AOL(–)	...	...	...	1.97	0.10–17.3	0.593
FVH(–) AOL(+)	...	...	...	2.80	0.50–15.7	0.232
FVH(+) AOL(+)	...	...	...	12.8	3.09–64.4	<0.001

AF indicates atrial fibrillation; AOL, arterial occlusive lesion; CI, confidence interval; DWI, diffusion-weighted imaging; FVH, fluid-attenuated inversion recovery vascular hyperintensity; HR, hazard ratio; and TIA, transient ischemic attack.

In addition, transient FVH was significantly associated with AF. These observations demonstrate that transient FVH could be caused by early recanalization of emboli in patients with TIA. We suggest that transient FVH in patients with transient neurological disturbances can be an objective evidence of a TIA. Along with FVH, perfusion-weighted imaging can demonstrate an evidence of ischemic nature in patients with TIA.[20,21] To add both FVH and perfusion-weighted imaging to DWI can contribute to enhance the accuracy of TIA diagnosis.

The positive association between hemiparesis and FVH might be mainly because AOL often leads to broad ischemia and severe neurological deficits, including hemiparesis on the one hand and FVH has strong relationship with AOL on the other hand.

Predicting recurrent IS after TIA is important to consider adequate strategies for managing patients with TIA according to risk. The ABCD^2 score is a prognostic tool for prediction of the risk of early recurrent stroke after TIA in primary care.[17] The presence of ischemic lesions on DWI or large artery occlusion is another predictor for recurrent stroke after TIA.[22–26] Although the association between FVH and poor outcome in patients with IS was demonstrated,[27,28] the association between FVH and recurrence of TIA or IS after TIA has been merely reported.[29] In the present study, Cox proportional hazard analysis showed that recurrence within 90 days after onset was associated with AOL and FVH, as well as coexistence of these 2. AOL accompanied by FVH has been reported to indicate diminished vascular reserve,[22] and diminished reserve because of symptomatic arterial occlusive disease is associated with recurrent stroke.[30,31] The combination of FVH and vascular imaging findings may provide useful information on the risk assessment of TIA to prevent recurrence.

This study has some limitations. First, the single-center retrospective study design might cause selection bias and statistical errors. Second, follow-up imaging examinations of patients with FVH positive were only performed on a small sample size. Third, although AOL in the present definition primarily indicates atherothrombotic disease, some patients with cardioembolic occlusion who did not show early recanalization may have been included among the patients with AOL.

In conclusion, FVH could be interpreted as a marker of altered hemodynamics in patients with TIA with AF and in those with AOL. The results of this study suggest that the presence of FVH early after symptom onset may help to differentiate TIA from stroke mimic, to identify the potential mechanisms of TIA, and to predict recurrence risk after a TIA.

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Disclosures

None.

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神経

脳卒中のクリニカル・パール

上原敏志・豊田一則

脳卒中は発症後できるだけ早く対応すべき救急疾患である

脳卒中は，脳梗塞，脳出血，くも膜下出血に大別される．そのなかで最も多いのは脳梗塞であり全体の約7割を占める．脳梗塞に対しては，発症4.5時間以内のrt-PA(アルテプラーゼ)静注による血栓溶解療法や発症8時間以内の血管内治療などの超急性期治療が可能である．これらの治療は発症から治療開始までの時間が早ければ早いほど効果が期待できるため，一刻を争って対応しなければいけない．救急外来でのベッドサイド処置としては，意識・呼吸・血圧・脈拍などのバイタルサインチェックをしながら同時並行で，病歴聴取，神経学的診察を行う．併せて，心電図，静脈ルート確保，血液検査，胸部X線検査を行ったうえで，頭部CT，MRIなどの画像検査へと進めていく．

脳卒中を疑う症例が搬送された場合，まず安静臥床にする

これは，血圧変動に対して脳血流量を一定に保つ脳循環自動調節能が脳梗塞急性期では障害されているため，頭部挙上が脳の灌流圧の低下を招き，虚血領域の増大につながる可能性があるためである．

脳梗塞急性期は原則として降圧を行わない

脳梗塞急性期には血圧が上昇していることが多いが，前述した脳循環自動調節能の障害により降圧が症状悪化につながる可能性がある．例外として，収縮期血圧220 mmHg以上または拡張期血圧120 mmHg以上の極度の高血圧が持続する場合や，大動脈解離，急性心筋梗塞，心不全，腎不全などを合併している場合に限り，慎重な降圧を行う．また，rt-PA静注療法を予定する例で収縮期血圧185 mmHg以上または拡張期血圧110 mmHg以上の場合は静注降圧薬の単回投与により降圧を行う．

脳卒中かどうかを判断するうえで問診は大きな手がかりとなる

問診では，発症様式，症状，症状の経過，高血圧や心房細動などの危険因子の有無などについて的確に聴取することが重要である．脳卒中の臨床症候の特徴は「突然発症する意識障害，片麻痺，一側の感覚障害，言語障害などの神経脱落症候」であり，こうした特徴があれば脳卒

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中を疑う．ただし，数日かけて徐々に症状が出現することもあるので注意を要する．くも膜下出血の場合は，突然発症の激しい頭痛や意識障害が特徴である．

脳卒中発症時刻の定義は「無症状であることが最後に確認された時刻（最終未発症時刻）」である

rt-PA 静注療法の適応を考えるうえで発症時刻を確認することが必要である（**表 1**）．治療開始可能時間を計算するうえで基準となる発症時刻とは，「患者自身，あるいは症状出現時に目撃した人が報告した時刻」，あるいはこうした情報が得られない場合では「患者が無症状であることが最後に確認された時刻（最終未発症時刻）」であり，発見された時刻ではない．起床時に症状を有していた場合は，就寝前あるいはその途中で無症状であることが確認された時刻となる．「倒れていたところを発見された」場合，家族などの第三者により無症状であったことが確認されていた最後の時刻が発症時刻となる．階段状増悪の場合，最初に症状が発現した時点が発症時刻である[1]．

脳卒中とまぎらわしい疾患との鑑別が必要である

脳卒中の診断においては，低血糖などの代謝性疾患，薬物中毒，ほかの脳疾患（てんかん，脳炎，脳腫瘍など），脊髄疾患，末梢神経疾患，さらには感染症などの全身疾患による脱力衰弱などの除外が必要である．片麻痺などの局所症状は，低血糖，高浸透圧性ケトン性昏睡やけいれん後片麻痺（Todd 麻痺）などでも出現する可能性があるため注意を要する．

表 1　アルテプラーゼ静注療法のチェックリスト
（文献 1 より引用）

適応外（禁忌）
発症～治療開始時刻 4.5 時間超
既往歴
非外傷性頭蓋内出血
1 カ月以内の脳梗塞（一過性脳虚血発作を含まない）
3 カ月以内の重篤な頭部脊髄の外傷あるいは手術
21 日以内の消化管あるいは尿路出血
14 日以内の大手術あるいは頭部以外の重篤な外傷
治療薬の過敏症
臨床所見
くも膜下出血（疑）
急性大動脈解離の合併
出血の合併（頭蓋内，消化管，尿路，後腹膜，喀血）
収縮期血圧（降圧療法後も 185 mmHg 以上）
拡張期血圧（降圧療法後も 110 mmHg 以上）
重篤な肝障害
急性膵炎
血液所見
血糖異常（<50 mg/dL，または>400 mg/dL）
血小板 100,000/mm^3 以下
血液所見：抗凝固療法中ないし凝固異常症において
PT-INR>1.7
aPTT の延長（前値の 1.5 倍［目安として約 40 秒］を超える）
CT/MR 所見
広汎な早期虚血性変化
圧排所見（正中構造偏位）

軽度片麻痺を見つけるのにはコツがある

片麻痺は脳卒中でみられる最も多い症状である．片麻痺をみるために Barre 徴候をチェックする．上肢の場合は，閉眼して両腕を前に伸ばして手掌を上に向けて挙上させる．麻痺側は健側の腕よりも下垂する．軽い麻痺であれば両腕とも同じ高さで挙上保持できるが，もし片方の腕が回内していれば軽度片麻痺があると判断する．手掌を下にして前方に提出させた時に，小指が薬指にくっつかず外側にそれる第 5 手指徴候も軽度の麻痺を示唆する徴候である．下肢の Barre 徴候を診る時は通常腹臥位にし，両側の下腿を 45° 挙上させ保持させる．しかし，脳卒中急性期には腹臥位になるのが難しいこと