Cerebral Infarction and Patent Foramen Ovale (PFO) in the Elderly: Is PFO the Culprit or Not?

Key words: cerebral infarction, patent foramen ovale, paradoxical brain embolism

Recent studies have found that paradoxical brain embolism through patent foramen ovale (PFO) is a major cause of cryptogenic cerebral infarction (CI) in younger patients (1, 2). Although it was reported that the frequency of PFO decreases with age (3), PFO might be no less important cause of CI in the elderly than in younger patients (4), because the size of PFO (3) and the incidence of deep vein thrombosis (5) increases with age. Using transesophageal echocardiography (TEE) in consecutive patients with CI (mean age over 60 years), there was a higher prevalence of PFO in patients with cryptogenic CI compared to that in those with a known cause (40% vs. 25%, retrospectively) (6). However, it sometimes becomes difficult to prove a causal relationship between PFO and CI in elderly patients, because they often have other vascular risk factors such as lifestyle-related diseases or heart disease.

Yasaka et al (7) demonstrated that 52.9% of patients with PFO had other embolic sources and only 3.2% of those met the definite criteria for paradoxical brain embolism and the clinical and neuroradiological features of PFO with sinus rhythm and PFO with atrial fibrillation were quite different. They concluded that not only paradoxical brain embolism through the PFO but also other causes of stroke may contribute to stroke development in stroke patients with PFO (7). This study proposed a very interesting consideration of the mechanism of stroke in elderly patients with several risk factors, and indicates that risk factors other than PFO probably have a stronger impact on the incidence of CI.

See also p 434.

We think it is preferable to investigate the size of PFO (8) and the presence of atrial septal aneurysm (9) which both increase the risk of paradoxical brain infarction. It is also interesting to investigate whether deep vein thrombosis associated with hemiplegia after stroke increases the risk in patients with PFO more than does in those without PFO. Recent study has demonstrated the significant difference in the size of PFO among race-ethnic groups (10). A further larger prospective study is necessary here in Japan to clarify the role of PFO in CI patients with other vascular risk factors.

In CI patients with PFO, there was no significant difference in the efficacy against recurrent stroke between aspirin and warfarin (11). Consequently, when we encounter a CI patient with PFO, we should maximize the effort to detect embolic sources, especially in patients with cardioembolic stroke who must receive warfarin to prevent recurrence. After excluding cardioembolic stroke, anti-platelet treatment should be considered for CI patients with PFO, other vascular risk factors, or both. If the patient meets the definitive criteria for paradoxical brain embolism, surgical or percutaneous PFO closure is also promising (12) though reduction in the event rate has not been fully demonstrated.

In conclusion, CI in elderly patients has multiple causative mechanisms, and we need to recognize PFO as the culprit only after fully investigating other causes of CI.

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Good correlations between Serum Adiponectin Levels and other Hematological markers of Cardiovascular Disease's risks in patients with past history of Stroke

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Purpose: Adiponectin, a newly found adipose tissue-specific collagen-like protein, has been noted as an important antiatherogenic protein, and its serum levels have been reported to be lower in patients with atherogenic diseases, such as diabetes or dyslipidemia. Our purpose of this study was to explore the correlations between adiponectin and other hematological markers of cardiovascular disease's risks in patients with a past history of stroke.

Subjects and Methods: One hundred and three patients (mean age 69.0 years, 53.4 % male) with a past history of stroke (79 ischemic and 24 hemorrhagic) were enrolled. We determined the levels of insulin, HbA1c, total cholesterol (TC), high density lipoprotein cholesterol (HDL), triglycerides (TG), apolipoprotein A1 (apo-A1), apolipoprotein B (apo-B), adiponectin, high sensitive CRP (hs CRP), and plasminogen activator inhibitor type1 (PAI-1). Correlations between them were calculated with Spearman rank correlation coefficient.

Results: Adiponectin levels showed significant inverse correlations with insulin ($p = 0.0002$), HbA1c ($p = 0.0266$), TG ($p = 0.0036$), apo-B ($p = 0.0009$), hsCRP ($p = 0.0024$), and PAI-1 ($p = 0.0157$) levels,

whereas positively correlated with HDL ($p = 0.0002$) and apo-A1 ($p = 0.0039$) levels. There was no significant correlation between adiponectin and TC ($p = 0.6630$) levels.
Conclusion: In patients with past history of stroke, serum adiponectin levels correlated well with other markers of cardiovascular disease's risk, indicating necessity of investigating whether or not adiponectin levels could be a reliable marker of stroke recurrence.

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Sleep–disordered breathing in patients with recent Ischaemic Stroke

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Introduction: Several studies reported a higher frequency of sleep disordered breathing (SDB) among ischaemic stroke patients. Many showed prevalence between 43% and 72%, taking the apnoea hypopnoea index (AHI) of ≥10. Hypertension and coronary heart disease are known risk factors of stroke, which are also consequences of SDB that can contribute to stroke mortality and morbidity.
Objectives: The objectives were to determine the frequency of SDB in patients with recent ischaemic stroke admitted to HUKM and the relationship between SDB and known risk factors of ischaemic stroke.
Method: This was a cross-sectional prospective study involving 28 consequtive acute ischaemic stroke patients admitted to HUKM over three months. Sleep studies were done within 1 to 4 weeks after stroke onset using ResMed Autoset portable 11 plus system.
Results: The prevalence of SDB in ischaemic stroke depending on the AHI cut off was: 92.8% for AHI ≥ 5, 78.5% for AHI ≥ 10, 44.5% for AHI ≥ 15 and 37.7% for AHI ≥ 20. We discovered that diabetes mellitus (DM) and smoking history were important factors predicting significant SDB (AHI ≥ 15) in recent ischaemic stroke.
Conclusion: There was a high prevalence of SDB in recent ischaemic stroke patients in HUKM comparable to other studies. DM and smoking history were strong predictors of the occurrence of SDB after an ischaemic stroke.

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Hyperhomocysteinemia as a Risk Factor for Ischemic Stroke

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Background: The aim of this study is to investigate the correlation between plasma Homocysteine (Hcy) level and ischemic stroke by better controlling risk factors for the ischemic stroke and factors affecting the levels of plasma Hcy.
Method: We conducted a case-control study with 31 cases who had never had a Transient Ischemic Attack (TIA), all within one week of their first-ever ischemic stroke. Both the patients and control subjects were paired for age, sex, cardiac disease, hypertension and smoking status. Their total fasting plasma Hcy level was determined, using High-Performance Liquid Chromatography (HPLC) method.
Results: Mean plasma Hcy level was significantly higher in cases than controls (mean, 20.79 ± 11.938 versus 14.45 ± 8.028 μmol/L; $P < 0.017$). After using the multivariate logistic regression model, we found a significant correlation between plasma Hcy level and stroke (OR = 1.149 with 95% CI of 1.032-1.280 for each 1μmol/L increment).
Conclusion: This finding indicates a correlation between increasing plasma Hcy level and ischemic stroke; although further researches is needed to prove the cause and effect relationship between the two.

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Stroke in South West Nigeria – a ten year review

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Background and Purpose: Stroke is a significant economic, social and medical problem worldwide. This retrospective follow-up study aimed to review the pattern, types and case fatality of stroke in Nigeria.
Methods: Records of all stroke patients admitted into Ogun State University Teaching Hospital (OSUTH), sagamu, from December 1993 to November 2003 were reviewed. Patients were classified into haemorrhage or infarct using the WHO criteria. Information was obtained as to the time of death in those who died and case fatality at 24 hours, 7 days, 30 days and 6 months recorded. Autopsy records were also reviewed.
Results: A total of 708 stroke patients were reviewed and this constituted 2.4% of all emergency admissions. On clinical grounds, 49% of the patients had cerebral infarction (CI), 45% intracerebral haemorrhage (ICH) while 6% had subarachnoid haemorrhage (SAH). Stroke constituted 1.8% of all deaths at the emergency unit and the case-fatality was 9% at 24 hours, 28% at 7 days, 40% at 30 days and 46% at 6 months.
Conclusion: Stroke constitutes a significant cause of mortality and the need for prompt institution of intensive treatment is emphasised. A changing pattern with an increasing frequency of haemorrhagic stroke in our population is suspected. However, as this was a retrospective study based on clinical examination in a highly selected stroke population, neuro-imaging confirmation would be needed for any future prospective hospital or population-based studies.

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Pure agraphia for Romaji, the third Japanese writing system utilizing alphabet and phonological rules

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We report a Japanese man who developed pure agraphia selectively affecting Romaji. Romaji is an alphabetic writing system for Japanese based on phonological rules, the third Japanese writing system after Kana and Kanji, which is in general used exclusively for typewriting. The patient was a 51-year-old right-handed Japanese clerical worker with 12 years of education, who was referred to us because of difficulty in typing. MRIs revealed an infarct affecting a lower part of the precentral gyrus and pars opercularis of the inferior frontal gyrus. Hand-writing was defective as well. Neurological examination was unremarkable including spoken language and praxia. The agraphia had following features: (1) many errors in Romaji, occasional errors in Kana (syllabograms), and no error in Kanji (morphograms); (2) the same nature of errors in oral spelling, hand-writing, and typing of Romaji; (3) errors consisting mainly of substitution with another letters with proper consonant/vowel structure in a syllable. These findings suggest that the basic defect of the Romaji agraphia in this patient is a selective functional disruption within the phoneme-to-grapheme conversion system, and that the neural mechanism processing consonants is distinct for that for vowels in Japanese.

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Combined Occlusive Anterior Cerebral Artery in patients with Acute Middle Cerebral Artery Occlusion

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Background: Leptomeningeal collateral flow (LCF) from anterior cerebral artery (ACA) and/or posterior cerebral artery (PCA) can be a potential source of blood supply in the territory distal to the occluded middle cerebral artery (MCA).
Methods: We reviewed clinical and angiographic findings in 29 patients with acute MCA occlusion. Digital subtraction angiography was

□ ORIGINAL ARTICLE □

Clinical Characteristics of First-Ever Atherothrombotic Infarction or Lacunar Infarction with Hyperlipidemia (J-STARS-C): An Analysis of Data from the Stroke Data Bank of Japan

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Abstract

Objective **The clinical trial, Japan Statin Treatment Against Recurrent Stroke (J-STARS), is being carried out to investigate the efficacy of statin treatment against recurrent stroke. To participate in J-STARS, patients must have a past history of ischemic stroke excluding cardioembolic events, and must be clinically diagnosed with hyperlipidemia (HL). Before starting J-STARS, we needed to be aware of the clinical characteristics of the patients who were eligible to participate in this study.**

Methods **Between 1999 and 2002, 7,149 patients with ischemic stroke were enrolled in a stroke data bank developed by the Japan Standard Stroke Registry Study Group. From this, we acquired the data on 1,487 patients with first-ever atherothrombotic infarction (ATI) or lacunar infarction (LI) with a satisfactory functional outcome on discharge.**

Results **Patients with HL were significantly younger (65.3±11.0 vs 68.4±10.9, $p<0.0001$) and showed a higher frequency of concomitant hypertension (70.9% vs 61.0%, $p=0.0002$), diabetes mellitus (42.2% vs 25.7%, $p<0.0001$) or both (31.7% vs 16.4%, $p<0.0001$) compared to those without HL. The ratio of ATI to LI and the frequency of prior ischemic heart disease (IHD) did not differ between the 2 groups. Among 467 patients with HL, 52.7% did not receive treatment on admission.**

Conclusion **ATI or LI patients with HL had an earlier age of onset and higher frequency of other lifestyle-related diseases, and this probably includes many with metabolic syndrome, whereas the frequency of IHD was not different between these 2 groups.**

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Key words: atherothrombotic infarction, lacunar infarction, hyperlipidemia, stroke data bank, J-STARS-C, J-STARS

Introduction

Hyperlipidemia (HL) is an important risk factor for ischemic heart disease (IHD), and is probably linked to an increased risk of ischemic stroke (1). 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, potently block cholesterol synthesis. A recent meta-analysis of data obtained from large-scale clinical trials showed that statins decrease the incidence of cardiovascular events in hypercholesterolemic and atherosclerotic patients (2). The meta-analysis also found a significant reduction in the occurrence of strokes most being primary in nature, although the efficacy of statins against recurrent strokes has not been fully investigated (3).

A clinical trial called the Japan Statin Treatment Against Recurrent Stroke (J-STARS) is now being carried out to investigate the efficacy of preventive treatment using pravastatin against recurrent stroke. The basic enrollment criteria for J-STARS is that each patient must have had an ischemic stroke within the past 1 month to 3 years excluding cardioembolic events, and must be clinically diagnosed with HL. Blood samples were taken within 1 month before agreeing to participate in J-STARS, and their serum level of total cholesterol was required to be between 180–240 mg/dl.

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To examine the enrollment criteria in detail, we needed to be aware of the clinical characteristics of the patients who met the basic enrollment criteria, especially regarding their age distribution, ratio of ATI to LI, and frequency of past history of hypertension (HT), diabetes mellitus (DM), and IHD. Before starting J-STARS, we planned a cross-sectional study called J-STARS-C (J-STARS-Cross-sectional), for which we acquired data on patients who had first-ever ATI or LI with HL and good functional outcome on discharge from the stroke data bank developed by the Japan Standard Stroke Registry Study (JSSRS) Group, we then investigated their clinical characteristics compared with patients without HL. In addition, we examined the enrollment criteria of J-STARS in detail by referring to the results of this study.

Methods

JSSRS, which was supported by the Ministry of Health and Welfare for 3 years, was carried out to establish a stroke data bank as a computerized registry system, and registration was started in 1999. Until 2001, approximately 8,000 acute stroke cases from nationwide 45 stroke center hospitals were accumulated, and their breakdown was then published (4). In this book, various comparisons of the collected data with other epidemiological studies were performed, and the data obtained from this system was a study, although some important problems still exist, such as the accuracy of data that was left to the discretion of each physician. Even under these limitations, the stroke data bank contained enough information about stroke patients with dyslipidemia and so we utilized the data.

Between 1999 and 2002, information on 7,149 patients with acute ischemic stroke was entered into the stroke data bank. We acquired data on 1,487 patients who had first-ever ATI or LI and showed a good functional outcome on discharge, with a modified Rankin scale of 0 to 3 for J-STARS-C.

The clinical subtype of stroke for each patient was determined according to the Classification of Cerebrovascular Disease III of the National Institute of Neurological Disorders and Stroke (5). Patients were designated as HT if they were taking anti-hypertensive agents or had a systolic blood pressure of $\geq$140 mmHg, diastolic blood pressure of $\geq$90 mmHg or both. They were categorized as DM if they were treated with oral hypoglycemic agents or insulin, their serum fasting blood sugar level was $\geq$126 mg/dl or both, and HL was designated if they were taking hypolipidemic drugs, their serum cholesterol level was $\geq$220 mg/dl or triglyceride $\geq$150 mg/dl or both. The Japan Stroke Scale (JSS) (6) and National Institutes of Health Stroke Scale (NIHSS) were used to evaluate the severity of stroke on admission and on discharge, and the patient outcome was assessed using a modified Rankin scale on discharge.

Statistical Analysis

The data was analyzed with Stat View Version 5.0 (SAS Institute Inc., Cary, NC, USA) for Macintosh computers. The values were expressed as means±standard deviation, and the values for the modified Rankin scale were expressed as medians. The association between HL and age was assessed by logistic regression analysis, and the statistical significance for differences between the 2 groups was tested using the Mann-Whitney U test for continuous data or chi square test for frequency data. Values of $p<0.05$ were considered to indicate statistical significance.

Results

The patients were divided into 2 groups according to the presence (n=467) or absence (n=1,020) of HL. The distribution of patients stratified by every 5 years of age and the rate of HL were shown in Fig. 1. The presence of HL was significantly associated with a younger age as seen by logistic regression analysis ($p<0.0001$), for which the odds ratio was 0.975 and the 95% confidence interval ranged from 0.965 to 0.985 for each increase in age of 1 year. In addition, 90.6% of the patients with HL were aged between 45 and 80 years old. The clinical characteristics of the 2 groups were compared in Tables 1 and 2. Patients with HL had a significantly lower average age ($p<0.0001$), higher frequency of HT ($p=0.0002$) and DM ($p<0.0001$) and the both ($p<0.0001$), and lower scores for JSS ($p=0.047$) and NIHSS ($p=0.01$) on admission in comparison to those without HL. The ratio of ATI to LI and the frequency of atrial fibrillation and prior IHD did not differ between the 2 groups.

Among 467 patients with HL, 38.1% were treated with any hypolipidemic drugs, 9.2% with dietary and/or exercise therapy, and the remaining 52.7% did not receive treatment on admission. Also, 31.7% of those with HL had HT and DM.

Referring to these results, it was decided that patients eligible for J-STARS should be men and women aged between 45 and 80 years, then we tried to speculate as to what sort of patients would be enrolled in J-STARS. First, we separated the patients aged between 45 and 80 from the ATI or LI patients with HL (Group A), and next excluded patients with 3 mRs (Group B), and finally excluded the patients given hypolipidemic drug (Group C) (Table 3).

Discussion

In this study, we found that patients with first-ever ATI or LI with HL had a younger age of onset and lower severity of stroke and higher frequency of other lifestyle-related diseases such as HT and DM compared with those without HL, whereas the ratio of ATI to LI and the frequency of prior IHD did not differ between the two groups. This study also showed that only 38.1% of the patients with HL received hypolipidemic drug on admission.

HL is a significant risk factor for the development of IHD, whereas the relationship between HL and stroke remains controversial. Although no association exists between one's

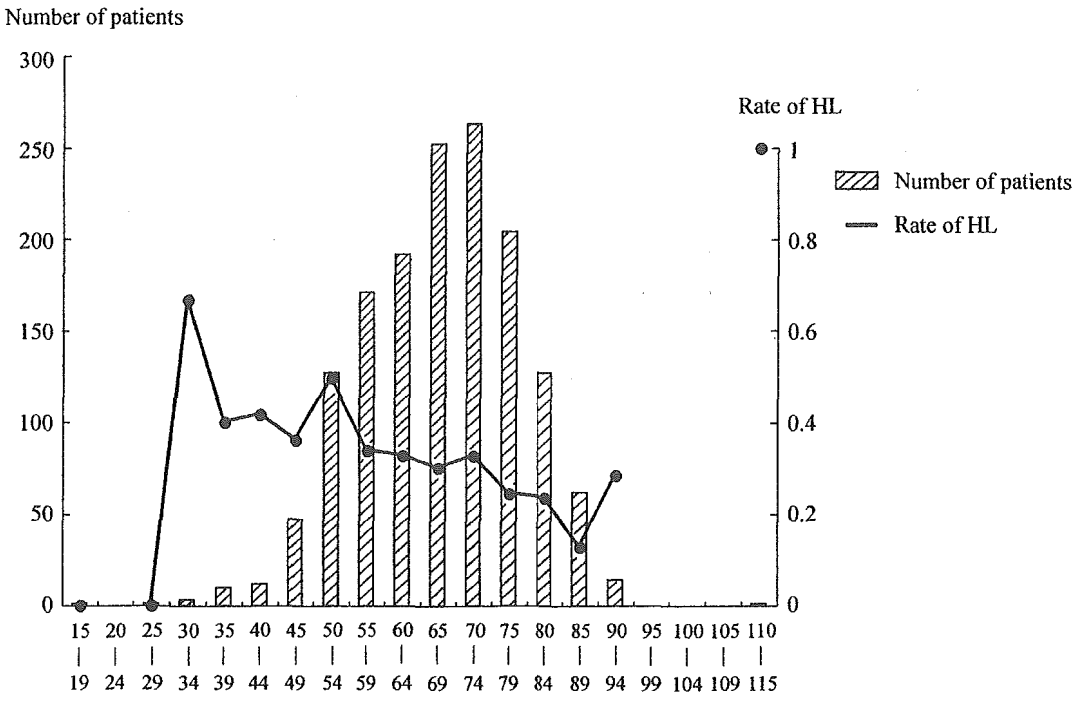

Figure 1. The age distribution of patients stratified by every 5 years and the rate of hyperlipidemia (HL).

serum cholesterol level and strokes over all (7, 8), several studies have found that hemorrhagic and ischemic strokes are related differently to the serum cholesterol level; the association with hemorrhagic strokes is negative, while that for ischemic strokes is positive (9–11). Therefore, an elevated serum cholesterol level is probably linked to an increased risk of ischemic stroke.

In addition to these observations, meta-analysis of coronary prevention and lipid-lowering therapies including statins, resins, fibrates, niacin, surgical intervention, and diet showed a significant risk reduction of 17% for the incidence of stroke (12). When analyzing each subgroup, only the statins exhibited a significant risk reduction at 24%. A more recent meta-analysis of randomized trials published between January 1990 and April 2003, showed that statins significantly reduce the occurrence of strokes by 18% (2). The Heart Protection Study, which was important because it included patients with prior cerebrovascular diseases, found a strong reduction in vascular events with respect to the use of simvastatin compared with a placebo in a mixed population of vascular patients (13). The risk reduction was significant not only for patients with hypercholesterolemia but also for patients with normal or low-normal cholesterol levels. In a subgroup of patients with a history of cerebrovascular disease without coronary heart disease, a 21% relative risk reduction of major vascular events was noted. However, there has been no randomized trial to date focusing on the prevention of recurrent stroke through the use of statins.

J-STARS was designed to investigate the efficacy of preventive treatment using pravastatin against recurrent stroke. The basic enrollment criteria for J-STARS were determined as follows: Patients must be able to travel to an outpatient clinic, must have suffered an ischemic stroke within the past 1 month to 3 years except for a cardioembolic event, and must be clinically diagnosed as HL. Each patient should have had blood samples taken within 1 month before agreeing to participate in J-STARS, and their total cholesterol level was required to be within 180–240 mg/dl. Before starting J-STARS, we needed to be aware of the clinical characteristics of the patients to be enrolled, especially regarding their age distribution, the ratio of ATI to LI, and the frequency of a past history of HT, DM, and IHD. There was no available data regarding these characteristics in Japanese stroke patients, and we performed this study, termed J-STARS-C.

Many of the patients with HL had multiple risk factors, and the observation that 31.7% had all 3 lifestyle-related diseases indicated that the J-STARS probably includes many patients with metabolic syndromes that are important risk factors for a cardiovascular event (14). Referring to these findings, it was decided that patients eligible for J-STARS should be allocated after being stratified by the presence or absence of HT or DM. However, it was the most surprising result of this study that the frequency of prior IHD in patients with HL (10.5%) was not significantly higher than for those without HL (9.4%). There are few previous studies available concerning this matter. One study showed a higher rate of coronary artery disease in patients with higher total choleste-

Table 1. A Comparison of the Clinical Characteristics of Patients with and without HL (I)

	Patients without HL	Patients with HL	p-value
Age (mean±SD)	68.4±10.9	65.3±11.0	<0.0001
Male sex (%)	64.2	60.8	n.s.
Hypertension (%)	61.0	70.9	0.0002
Diabetes mellitus (%)	25.7	42.2	<0.0001
Hypertension and diabetes mellitus (%)	16.4	31.7	<0.0001
Atrial fibrillation (%)	4.6	3.2	n.s.
Ischemic heart disease (%)	9.4	10.5	n.s.
Daily alcohol intake (%)	35.9	32.8	n.s.
Daily smoking (%)	39.5	38.8	n.s.

SD indicates standard deviation, HL: hyperlipidemia.

Table 2. A Comparion of the Clinical Characteristics of Patients with and without HL (II)

	Patients without HL	Patients with HL	p-value
Frequency of ATI (%)	46.4	42.8	n.s.
JSS on admission (mean±SD)	2.0±3.4	1.5±2.7	0.047
JSS on discharge (mean±SD)	0.6±2.0	0.4±1.6	n.s.
NIHSS on admission (mean±SD)	3.5±3.3	3.0±2.3	0.01
NIHSS on discharge (mean±SD)	1.3±1.8	1.3±1.7	n.s.
Modified Rankin scale on discharge (median)	1	1	n.s.
Days of treatment (mean±SD)	28.2±30.3	25.1±23.3	n.s.

SD indicates standard deviation, HL: hyperlipidemia, ATI: atherothrombotic infarction, JSS: Japan Stroke Scale, NIHSS: National Institutes of Health Stroke Scale.

Table 3. Expected Clinical Characteristics of Patients Enrolled in J-STARS

	A	B	C
Number of patients	423	388	242
Age (mean±SD)	64.4±8.9	64.0±8.9	62.5±8.9
Male sex (%)	61.2	61.1	63.6
Hypertension (%)	71.6	70.4	70.2
Diabetes mellitus (%)	44.0	44.8	45.9
Hypertension and diabetes mellitus (%)	32.9	33.0	34.7
Atrial fibrillation (%)	3.3	3.4	3.3
Ischemic heart disease (%)	10.9	11.3	6.6
Frequency of ATI (%)	42.1	41.0	38.8
Daily alcohol intake (%)	33.8	34.5	37.6
Daily smoking (%)	40.0	41.0	45.9

SD indicates standard deviation, ATI: atherothrombotic infarction. Group A: 0–3 mRs at discharge and past history of HL and age between 45 and 80. Group B: 0–2 mRs at discharge and past history of HL and age between 45 and 80. Group C: 0–2 mRs at discharge and past history of HL but not given hypolipidemic drug and age between 45 and 80.

rol levels (more than 6.5 nmol/*l*), although the difference was relatively small (24.0% vs 20.5%) (15). However, a recent study demonstrated that the rate of coronary heart disease in patients with ischemic stroke did not significantly differ among 3 divided groups according to their total cholesterol levels (16). We hypothesized that exclusion of ATI patients with a poor outcome of 4 or 5 on the modified Rankin scale who probably had HL and other atherosclerotic diseases including IHD influenced the result.

In this study, the severity of stroke was lower in patients

with HL than in those without HL, although there was no significant difference in the ratio of ATI to LI between the two groups. This is consistent with the result of a recent study that demonstrated the association between lower triglyceride or cholesterol levels and increased stroke severity (17). The authors indicated that neuroprotective properties of cholesterol should be considered, however, the exact mechanism involved in this phenomenon is uncertain.

This study showed that more than half of the patients (53%) with HL did not receive treatment on admission. Unfortunately, it was uncertain how many of them were treated with statins on discharge. Recently, Lalouschek et al reported on the determination of lipid profiles and use of statins for patients who suffered an ischemic stroke (18). They noted that 68% with clinically relevant atherosclerosis and a total cholesterol level >200 mg/dl were not treated with statins at the hospital on discharge. Furthermore, for patients with clinically relevant atherosclerosis and a total cholesterol level ≦240 mg/dl, 76% were not treated with statins. We believe that statins are also underused in Japan, and many patients can meet the inclusion criteria of J-STARS. We tried to determine the clinical characteristics of patients enrolled in J-STARS under various conditions, although this patient group might not correspond with actual clinical populations, because some patients with not only severe but also moderate HL could not participate in J-STARS. Additionally, patients with better activities of daily living than we expected might be selected. Consequently, more LI patients with mild HL than our expectations will probably be enrolled in J-STARS. It would be of interest to investigate whether or not statins can reduce the recurrence of strokes in a subgroup analysis of LI patients.

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Plasma total homocysteine levels are associated with advanced leukoaraiosis but not with asymptomatic microbleeds on T2*-weighted MRI in patients with stroke

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Both leukoaraiosis and asymptomatic microbleeds are associated with small-artery diseases. Although an association between hyperhomocysteinemia and leukoaraiosis has been reported, no studies have evaluated the association between total homocysteine (tHcy) level and presence of microbleeds in stroke patients. We evaluated the association between tHcy level and leukoaraiosis or microbleeds in stroke patients. In 102 patients with stroke (69.5 ± 10.3 years old, 54 men and 48 women), microbleeds on T2*-weighted MR images were counted, leukoaraiosis on T2-weighted images was graded and fasting plasma tHcy concentrations were measured. Plasma tHcy level was significantly higher in patients with advanced leukoaraiosis than in those without advanced leukoaraiosis (13.9 ± 4.6 μmol/l vs. 10.2 ± 3.4 μmol/l, $P < 0.0001$). Plasma tHcy level was not significantly different in patients with microbleeds and those without microbleeds (11.3 ± 4.1 μmol/l vs. 11.4 ± 4.3 μmol/l, $P = 0.9441$). Elevated tHcy level is significantly and independently associated with advanced leukoaraiosis [odds ratio (OR), 1.330; 95% CI, 1.130–1.565] but not with the presence of microbleeds. Elevated tHcy level appears to be associated with ischemic small-artery disease rather than with bleeding-prone small-artery disease.

Introduction

Asymptomatic microbleeds detected by gradient-echo T2*-weighted MRI, which are shown as signal loss, represent hemosiderin deposit [1,2]. Association between presence of microbleeds and severity of leukoaraiosis has been revealed in many previous studies [3–8]. Although both leukoaraiosis and microbleeds are associated with small-artery diseases, leukoaraiosis has been reported to be a risk factor for ischemic stroke [9–12] and microbleeds have been reported to be a risk factor for mainly intracerebral hemorrhage [6–8,13–20]. Both leukoaraiosis and microbleeds are associated with common risk factors, the main one being hypertension, but the risk factors for one of the two but not for the other still remain to be revealed.

Hyperhomocysteinemia has been suggested to be not only an independent risk factor for silent brain infarction [21–24] but also associated with leukoaraiosis [22,24]. However, there have been no studies in which the association between plasma total homocysteine (tHcy) level and presence of microbleeds in stroke patients has been evaluated. The present study was performed to determine whether elevated tHcy level is also associated with presence of microbleeds.

Subjects and methods

Subjects for the present study were enrolled from outpatients of our hospital who had acute stroke treated at our hospital and who agreed to participate in the study. Diagnosis of acute stroke was made on the basis of neurological signs and symptoms and on the basis of results of neuroradiological examinations. Stroke was classified into ischemic stroke and intracerebral hemorrhage, and ischemic stroke was further classified according to the criteria of the National Institute of Neurological Disorders and Stroke as atherothrombotic infarction, cardioembolic infarction, and lacunar infarction (Special Report from the Ref. [25]). Amongst patients with ischemic stroke, those with lacunar infarction and atherothrombotic infarction were included and cases of cardioembolic infarction or undetermined classification were excluded from this study. Acute ischemic stroke was confirmed by

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diffusion-weighted imaging and apparent diffusion coefficient maps. Intracerebral hemorrhage was diagnosed by the use of CT, and cases in which hematoma was not caused by spontaneous intracerebral hemorrhage (e.g. caused by vascular malformation, trauma, cavernous angioma, or brain tumor) were excluded from this study. Written informed consent was obtained from each subject. Hypertension was defined as systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or currently undergoing medical treatment for hypertension. Diabetes mellitus was defined as a glycosylated hemoglobin A1c concentration of >5.8% or current use of hypoglycemic agents. Hyperlipidemia was defined as a total cholesterol level of ≥220 mg/dl or currently undergoing cholesterol-lowering therapy.

In all patients, fasting blood was taken at least 2 months after the last clinical stroke event because depression of tHcy levels in the acute phase of stroke [26,27] and gradual increase of tHcy levels within a few weeks after the acute period of stroke [28] have been reported. After an overnight fast, tHcy level was measured. The blood was immediately centrifuged and stored at −35°C, and plasma tHcy level was determined by high-performance liquid chromatography with fluorescence detection [29].

All of the patients were examined using a 1.0-T clinical MR unit (Siemens, Magneton Harmony, Erlangen, Germany), and the whole brain was scanned with a slice thickness of 5 mm and a 1.5-mm interslice gap. The imaging protocol consisted of axial T2-weighted spin-echo sequences [repetition time (TR)/echo time (TE) = 4500/112; field of view, 201 × 230; matrix, 225 × 512] and axial T2*-weighted gradient-echo sequences (TR/TE = 800/26; flip angle, 20°; field of view, 230 × 230; matrix, 192 × 256). Patients who were unable to be evaluated by MR images because of artifacts were excluded. Microbleeds were defined as homogeneous round signal loss lesions on T2*-weighted MR images excluding lesions in the globus pallidus and in the subarachnoid space, which are probably to represent calcification and adjacent pial blood vessels, respectively. Intracerebral lesions with a hemorrhagic component were also excluded. Leukoaraiosis on T2-weighted images was graded using the scoring system of Fazekas et al into four grades: grade 0 = absent, 1 = punctate, 2 = early confluent, and 3 = confluent [30]. Leukoaraiosis of grade 2 or 3 was regarded as advanced leukoaraiosis. MR images were evaluated by two of the authors (H.N., E.N.) separately without knowledge of the patients' clinical profiles, and the number of microbleeds and the grading scores of leukoaraiosis were determined by consensus.

All values are expressed as mean ± SD. Amongst two groups, the chi-square test for independence was used for comparison of sex ratio, stroke subtype ratio, antiplatelet or anticoagulant therapy, hypertension, diabetes mellitus and hyperlipidemia, and Student's *t*-test for age and tHcy level was also used. Correlations between number of microbleeds and degree of leukoaraiosis and between tHcy levels and degree of leukoaraiosis or number of microbleeds were examined using Spearman's rank correlation test. Logistic regression analysis was used to assess the relationships of advanced leukoaraiosis or the presence of microbleeds with the following variables: tHcy level, age, sex, hypertension, diabetes mellitus, hyperlipidemia, advanced leukoaraiosis, and microbleeds.

Results

The population in this study consisted of 102 patients (69.5 ± 10.3 years old, 54 men and 48 women) with a history of stroke. The background of patients with and without advanced leukoaraiosis and that of patients with and without microbleeds are summarized in Tables 1 and 2, respectively. There were no statistical differences in sex ratio, stroke subtype ratio, prevalences of undertaking antiplatelet or anticoagulant therapy, diabetes mellitus, and hyperlipidemia between the two groups. Age was significantly older and prevalence of hypertension was significantly higher in patients with advanced leukoaraiosis than in patients without advanced leukoaraiosis and in patients with

Table 1 Background of patients with and without advanced leukoaraiosis

	Patients with advanced leukoaraiosis	Patients without advanced leukoaraiosis	*P*-value
Patients [*n* (male/female)]	33 (18/15)	69 (36/33)	0.9900
Age [year, mean (SD)]	75.1 (8.7)	66.8 (10.0)	<0.0001
Stroke subtypes [*n* (ischemic/hemorrhagic)]	24/9	54/15	0.7137
Antiplatelet/anticoagulant therapy [*n* (%)]	5 (15.2)	4 (5.8)	0.2360
Hypertension [*n* (%)]	29 (87.9)	46 (66.7)	0.0422
Diabetes mellitus [*n* (%)]	8 (24.2)	17 (24.6)	>0.9999
Hyperlipidemia [*n* (%)]	16 (48.5)	32 (46.4)	>0.9999
Homocysteine [μmol/l (SD)]	13.9 (4.6)	10.2 (3.4)	<0.0001

Table 2 Background of patients with and without microbleeds

	Patients with microbleeds	Patients without microbleeds	*P*-value
Patients [*n* (male/female)]	40 (20/20)	62 (34/28)	0.7834
Age [year, mean (SD)]	72.2 (8.1)	67.7 (11.2)	0.0330
Stroke subtypes [*n* (ischemic/hemorrhagic)]	29/11	49/13	0.6029
Antiplatelet/anticoagulant therapy [*n* (%)]	4 (10.0)	5 (8.1)	> 0.9999
Hypertension [*n* (%)]	37 (92.5)	38 (61.3)	0.0011
Diabetes mellitus [*n* (%)]	8 (20.0)	17 (27.4)	0.5387
Hyperlipidemia [*n* (%)]	17 (42.5)	31 (50.0)	0.5907
Homocysteine [μmol/l (SD)]	11.3 (4.1)	11.4 (4.3)	0.9441

microbleeds than in those without microbleeds. Plasma tHcy level was significantly higher in patients with advanced leukoaraiosis than in those without advanced leukoaraiosis (13.9 ± 4.6 μmol/l vs. 10.2 ± 3.4 μmol/l, $P < 0.0001$), and a significant positive correlation of tHcy level with degree of leukoaraiosis was found ($r = 0.338$, $P < 0.0001$). In contrast, plasma tHcy level was not significantly different amongst patients with microbleeds and those without microbleeds (11.3 ± 4.1 μmol/l vs. 11.4 ± 4.3 μmol/l, $P = 0.9441$), and there was no significant correlation of tHcy level with number of microbleeds ($r = 0.036$, $P = 0.8039$). There was a significant correlation between number of microbleeds and severity of leukoaraiosis ($r = 0.327$, $P = 0.0001$).

The results of logistic regression analysis showed that elevated tHcy level is significantly and independently associated with advanced leukoaraiosis independent of the presence of microbleeds and independent of age (OR, 1.330; 95% CI, 1.130–1.565; Table 3). In contrast, tHcy level was not significantly associated with the presence of microbleeds (Table 4).

Discussion

In the present study, we evaluated the association of tHcy level with leukoaraiosis and its association with microbleeds. The following results were obtained: (i) tHcy level was significantly higher in patients with advanced leukoaraiosis than in those without advanced leukoaraiosis, and a positive correlation of tHcy level with severity of leukoaraiosis was found; (ii) tHcy level was not significantly different amongst patients with microbleeds and those without microbleeds; and (iii) elevated tHcy level is significantly and independently associated with advanced leukoaraiosis but not with the presence of microbleeds.

Although both leukoaraiosis and microbleeds are associated with small-artery disease, respective features are different: leukoaraiosis is reported to be a risk factor for ischemic stroke [9–12], and presence of microbleeds represents the progression of bleeding-prone small-artery disease [6–8,13–20]. The neuropathological appearance corresponding to leukoaraiosis is neuronal loss, ischemic demyelination and gliosis [10], and leukoaraiosis has been reported to be commonly associated with ishchemic stroke [9,11,12]. In contrast, presence of microbleeds is associated with symptomatic intracerebral hemorrhage [6–8,13–20]. Recently, the first cohort study has shown that the presence of microbleeds is a risk factor for subsequent intracerebral hemorrhage amongst patients with ischemic stroke [18]. Although a possible association between advanced leukoaraiosis and intracerebral hemorrhage has also been reported, considering the close association between leukoaraiosis and microbleeds [3–8], considerable number of cases with advanced leukoaraiosis probably had co-existence of microbleeds and therefore resulted in intracerebral hemorrhage not restricted to ischemic stroke.

Table 3 Logistic regression analysis for predicting advanced leukoaraiosis

Variable	OR	95% CI	*P*-value
Increased age	1.078	1.015–1.144	0.0138
Male sex	0.932	0.313–2.776	0.8987
Hypertension	3.174	0.696–14.473	0.1358
Diabetes mellitus	1.812	0.550–5.974	0.3287
Hyperlipidemia	0.965	0.336–2.773	0.9474
Microbleeds	3.251	1.053–10.037	0.0404
Homocysteine (μmol/l)	1.330	1.130–1.565	0.0006

Table 4 Logistic regression analysis for predicting microbleeds

Variable	OR	95% CI	*P*-value
Increased age	1.026	0.978–1.077	0.2937
Male sex	1.066	0.420–2.707	0.8929
Hypertension	5.754	1.525–21.704	0.0098
Diabetes mellitus	0.650	0.220–1.918	0.4354
Hyperlipidemia	0.652	0.266–1.598	0.3496
Advanced leukoaraiosis	2.728	0.902–8.253	0.0756
Homocysteine (μmol/l)	0.933	0.820–1.062	0.2921

In the present study, we found a positive correlation of tHcy level with severity of leukoaraiosis but not with presence of microbleeds. Although both leukoaraiosis and microbleeds have common risk factors such as hypertension, the risk factors for one of the two but not for the other still remain to be revealed. This is the first study to reveal no association between tHcy level and presence of microbleeds in stroke patients. Hyperhomocysteinemia has been suggested to be positively associated with ischemic stroke in most previous studies [31–33]. Hyperhomocysteinemia is not only an independent risk factor for silent brain infarction [21–24] but also associated with leukoaraiosis [22,24] as was also shown in the present study. The results of the present study further confirmed the association between hyperhomocysteinemia and ischemic small-artery disease. The reason for no association of tHcy level with presence of microbleeds remains to be revealed. At some point of the progression of small-artery disease, the pathways of damage may differ despite the commonly associated risk factors. Homocysteine may favor thrombosis (and so occlusion and leukoaraiosis) over the process that weakens vessel walls. As homocysteine is associated with both endotherial damage and increased coagulation, homocysteine may make small-artery disease worse but prevent hemorrhage through increased thrombosis.

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脳卒中慢性期の治療
脳卒中の予防にスタチンは有効か

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POINT ポイント

- スタチンの投与が脳卒中の一次予防に有効であることは，多くのRCTやそのメタアナリシスによりほぼ確立された．
- スタチンの投与は，高コレステロール血症，冠動脈疾患の有無を問わず有効である可能性が高い．
- 脳卒中発症抑制効果は，主にスタチンのLDLコレステロール低下作用により発揮されていると考えられる．
- 脳卒中の二次予防に対するスタチンの効果については，今のところ不明であるが，SPARCL，J-STARSといったRCTが進行中である．

スタチンによる脳卒中の一次予防のエビデンス

高コレステロール血症が脳卒中の危険因子であるか否かについては，いまだ明確な結論が得られていない．その一方で，数多くの大規模なRCT（randomized controlled trial）により，スタチンによる脳卒中の発症抑制効果が以下のように明らかにされている．

スタチンによる脳卒中の発症抑制効果が有意であったRCT

プラバスタチンを用いたCARE（Cholesterol and Recurrent Events）[1]では心筋梗塞の患者，LIPID（Long-Term Intervention with Pravastatin in Ischaemic Disease）[2]では高コレステロール血症を有する虚血性心疾患患者において，脳卒中発症に対する抑制効果が示された．また，シンバスタチンを用いたSSSS（Scandinavian Simvastatin Survival Study）[3,4]では高コレステロール血症を有する虚血性心疾患患者，HPS（Heart Protection Study）[5]では冠動脈疾患，冠動脈疾患以外の閉塞性動脈疾患，糖尿病あるいは高血圧のうち少なくとも一つを有する患者において同様の結果が得られている．一方，アトルバスタチンを用いたRCTにおいて，GREACE（Greek Atorvastatin and Coronary-heart-disease Evaluation）では冠動脈疾患患者[6]，ASCOT-LLA（Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm）では，高血圧とそれ以外に3つ以上の心血管リスクファクター（55歳以上，喫煙者，糖尿病，脳卒中の既往など）を有する血中総コレステロールが250 mg/dl以下の患者[7]，CARDS（Collaborative Atorvastatin Diabetes Study）ではII型糖尿病患者[8]，MIRACL（Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering）では，不安定狭心症あるいは非Q波心筋梗塞発症から3日以内の患者[9]といった多彩な背景の患者で脳卒中の発症抑制効果が示されている．

スタチンによる脳卒中の発症抑制効果が有意ではなかったRCT

このような結果の一方で，脳卒中発症抑制効果の示されなかった大規模臨床試験もいくつか存在する．高コレステロール血症患者を対象としたWOSCOPS（West of Scotland Coronary Prevention

Study)[10]，70歳以上の心血管系疾患の既往を有するか，喫煙・高血圧・糖尿病などのハイリスク患者を対象としたPROSPER（Prospective Study of Pravastatin in the Elderly at Risk)[11]，高血圧と1つ以上の心血管危険因子を有する患者を対象としたALLHAT-LLT（Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Treatment)[12] はいずれもプラバスタチンを使用したRCTであるが，有意な脳卒中発症抑制効果はみられていない．PROSPERについては，3年という試験期間は脳卒中の発症について検証するには短すぎたという意見があり，一方，ALLHAT-LLTについては，従来治療群で結果的にスタチンを含む脂質降下薬を服用した患者が少なくなく，スタチン群と従来治療群の間でコレステロールの差が比較的少なかったことなどが有意差のみられなかった原因ではないかとの意見が出されている．

わが国で行われたRCT

一方，わが国においては，RCTとしては，高コレステロール血症の男性患者を対象とし，プラバスタチン群と従来治療群を比較したKLIS（Kyushu Lipid Intervention Study)[13]，60歳以上の高コレステロール血症の患者を対象とし，低用量と常用量のプラバスタチンの効果を比較したPATE (Pravastatin Anti-atherosclerosis Trial in the Elderly)[14] がある．KLISではスタチン群で，PATEでは常用量で脳卒中の発症が少なかったものの，統計学的な有意差は認めなかった．KLISは残念ながら無作為割付に不均衡が生じたRCTであるが，コレステロールを下げるほど脳梗塞の発症が抑制されるという興味深い結果が最近報告されている[15]．

以上の結果から，少なくとも虚血性心疾患の既往を有する患者においては，高コレステロール血症の有無を問わず，スタチン投与により脳血管障害の発症が予防されることはほぼ確立されたと思われる．糖尿病や高血圧症，高齢者という因子のみを有する患者に，脳卒中発症予防のためにスタチンを投与すべきか否かについては，現時点では一致した結論が得られていない．

スタチンによる脳卒中の発症抑制効果を検証したメタアナリシス

以上のようなスタチンの脳卒中発症抑制効果に関するデータを含んだRCTのメタアナリシスも数多く行われている．Brielらは，スタチンの投与により，脳卒中の発症は18％減少し，さらに冠動脈疾患の有無で分けて検討すると，冠動脈疾患あり群で25％，なし群で23％と，ともに有意に脳卒中が減少したと報告している[16]．Amarencoらは，スタチンの投与により，脳卒中の発症は21％減少し，その効果はLDLの低下と密接に関連しており，LDLが10％低下すると脳卒中の発症が15.6％減少すると報告している[17]．Cheungらは，スタチンにより脳卒中の発症は18％減少するが，プラバスタチンでは有意ではあるものの脳卒中は12％しか減少せず，ほかのスタチンに比べ有意に効果が少なかったと述べている[18]．この理由として，スタチンのコレステロール低下作用に差があることが考えられる．実際，プラバスタチンはほかのスタチンに比べ，LDLコレステロールの減少が少ないというメタアナリシスの結果も示されている[19]．

そのほかにも，スタチンにより脳卒中を24％[20]，23％[21] 減らすとしたメタアナリシスがあり，スタチンの投与により脳卒中の発症は20％程度減少すると考えておいてよいと思われる．

スタチンによる脳卒中の二次予防のエビデンスは？

以上のようなスタチンの効果は主に脳卒中の一次予防に関していえることであり，二次予防に関してはエビデンスがほとんどないのが現状である．前述のHPSは脳卒中の既往を有する患者が3,280名と多く含まれていたため，これらの患者においてスタチ

ンが脳卒中を含む心血管イベントを減少させるかについてサブ解析が行われた[22]．それによると，スタチンにより全心血管イベントは有意に20％減少するものの，脳卒中の再発に関してはプラセボ群とほとんど差を認めなかった．スタチンの投与により全心血管イベントを有意に減少させることができれば，それだけで脳卒中の既往のある患者にスタチンを投与することは正当化されると思われるが，やはり脳卒中の再発をprimary endpointとした脳卒中の既往がある患者を対象としたRCTが行われることが望ましい．現在欧米においては，アトルバスタチンを用いたRCTであるSPARCL（Stroke Prevention by Aggressive Reduction in Cholesterol Levels）が進行中である[23]．

❶ スタチンによる脳卒中発症抑制効果について検討した（あるいはその予定の）主なrandomized controlled trial（RCT）

臨床試験名	デザイン	エビデンスレベル	症例数	主な選択基準	使用したスタチン
脳卒中の有意な抑制効果が示された臨床試験					
SSSS[3,4]	RCT, blinded study	Level 1	4,444	虚血性心疾患 高コレステロール血症	シンバスタチン
HPS[5]	RCT, blinded study	Level 1	20,536	冠動脈疾患，冠動脈疾患以外の閉塞性動脈疾患，糖尿病，高血圧のうち少なくとも1つを有する	シンバスタチン
CARE[1]	RCT, blinded study	Level 1	4,159	心筋梗塞	プラバスタチン
LIPID[2]	RCT, blinded study	Level 1	9,014	虚血性心疾患 高コレステロール血症	プラバスタチン
GREACE[6]	RCT, open-label study	Level 1	1,600	冠動脈疾患	アトルバスタチン
ASCOT-LLA[7]	RCT, blinded study	Level 1	10,305	高脂血症のない高血圧患者で，ほかに3つ以上の心血管危険因子を有する	アトルバスタチン
CARDS[8]	RCT, blinded study	Level 1	2,838	Ⅱ型糖尿病	アトルバスタチン
MIRACL[9]	RCT, blinded study	Level 1	3,086	不安定狭心症または非Q波心筋梗塞1～3日以内 総コレステロール値270 mg/dl以下	アトルバスタチン
脳卒中の有意な抑制効果が示されなかった臨床試験					
WOSCOPS[10]	RCT, blinded study	Level 1	6,595	高コレステロール血症	プラバスタチン
PROSPER[11]	RCT, blinded study	Level 1	5,804	70歳以上の心血管系疾患既往歴あるいは喫煙・高血圧・糖尿病などのハイリスク患者	プラバスタチン
ALLHAT-LLT[12]	RCT, open-label study	Level 1	10,355	高血圧と1つ以上の心血管危険因子を有し，LDLコレステロール120～189 mg/dlかつ中性脂肪350 mg/dl未満	プラバスタチン
国内の臨床試験					
KLIS[13]	RCT, open-label study	Level 2	5,640	総コレステロール220 mg/dl以上	プラバスタチン
PATE[14]	RCT, open-label study	Level 1	665	総コレステロール220～280 mg/dl	プラバスタチン
脳卒中の再発をprimary endpointとして進行中の臨床試験					
SPARCL[23]	RCT, blinded study		4,732	脳卒中あるいはTIAの既往を有し，LDLコレステロール100～190 mg/dl	アトルバスタチン
J-STARS[24,25]	RCT, open-label study			心原性脳塞栓症以外の虚血性脳卒中 総コレステロール180～240 mg/dl	プラバスタチン

一方，わが国では，厚生労働科学研究費補助金により，虚血性脳血管障害の既往のある患者を対象として，スタチンの脳卒中再発予防効果を検証するRCTであるJ-STARS（Japan Statin Treatment Against Recurrent Stroke）が実施されている（主任研究者：松本昌泰）[24,25]．対象となる患者の年齢が45歳以上80歳以下と比較的高く，プラバスタチンを使用し，オープン試験であるということを特徴としているため，前述のPROSPERやALLHAT-LLTの結果を踏まえ，追跡期間は平均で5年を予定し，総コレステロール値が180～240 mg/dlという比較的軽度のコレステロール患者を対象とし，的確な割付，追跡，エンドポイントの評価が行えるよう工夫している．試験デザインはPROBE（Prospective Randomized Open Blinded-Endpoint）を採用し，全国135の施設で3,000例の症例登録を目標としている．試験の概要，進捗状況はホームページで公開されている（http://jstars.umin.ne.jp）．このSPARCLとJ-STARSにより，脳卒中の二次予防にスタチンが有効か否かについての回答が得られると思われ，成果が期待される．

対照薬	脳卒中に対する効果
プラセボ	脳卒中28%減少
プラセボ	脳卒中25%減少 虚血性脳卒中30%減少
プラセボ	脳卒中32%減少
プラセボ	脳卒中19%減少 虚血性脳卒中23%減少
従来治療群	脳卒中47%減少
プラセボ	脳卒中27%減少
プラセボ	脳卒中48%減少
プラセボ	脳卒中50%減少
プラセボ	脳卒中11%減少（有意差なし）
プラセボ	脳卒中3%増加（有意差なし）
従来治療群	脳卒中9%減少（有意差なし）
従来治療群	脳梗塞22%減少（有意差なし）
（低用量vs常用量）	低用量に比べ，常用量で脳卒中の発生率が少ない（有意差なし）
プラセボ	
従来治療群	

まとめ

いままでのコホート研究からは，高コレステロール血症は脳卒中の強力な危険因子とはいえない．一方で，多くのRCTやそのメタアナリシスはスタチンが脳卒中の発症を抑制することを証明している．その主なメカニズムは，LDLコレステロールの低下によるものと推定されているが，それ以外のスタチンの多面的な薬理作用にも注目する必要がある．ただし，スタチンによる脳卒中の二次予防についてはエビデンスが不足しており，現在進行中のRCTの結果が待たれる．❶にスタチンによる脳卒中発症予防効果を検証した（あるいはその予定の）RCTをまとめて示したので参照して頂ければ幸いである．EBM

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