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Lifestyle and secondary prevention for patient with ischemic mild stroke

（軽症脳梗塞のライフスタイルと再発予防に関する研究）

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Ⅰ. Introduction

Morbidity from stroke in the Japanese population is an 8-fold higher than in western populations [1], and results in high rates of sever disability and cognitive dysfunction[1,2]. Among stroke survivors, recurrence is common. Previous studies from stroke registry in western countries have reported 17% to 30% cumulative recurrence rates in the first 5 years after a stroke[3-5]. The Hisayama study [2], the only cohort study that has reported on the recurrence rate of stroke in the Japanese population, showed a slightly higher rate of stroke recurrence: 20% within 2 years and 35% within 5 years in all stroke patients. However, the 5-year stroke recurrence rate increased to 40% when focusing only on ischemic stroke.

According to a major Japanese hospital-based stroke database [6], 70% of ischemic strokes are atherosclerotic (non-cardioembolic) ischemic strokes, including atherothrombotic or atheroembotic infarction, lacunar infarction and branch atheromatous disease. Moreover, the majority of stroke patients are mild stroke. It has been reported that approximately 60% of atherosclerotic ischemic strokehave mild paresis (modified Rankin Scale: mRS $\leq$ 2), and independently walking without any aid. Although in the Japanese database, precise data on the recurrence rate in mild stroke patients is unknown, during the first year after a mild stroke, a high recurrence rate of

10% to 15% has been reported in studies from western countries [7,8].

The majority of recurrence events in stroke survivors is recurrent strokes, at least for the first several years [9], and often results in severe disability. Thus, mild stroke patients have been suggested to be a target population for aggressive secondary prevention.The guideline of management for secondary prevention published by Japan Stroke Society[10], American Stroke Association[11] and European Stroke Organization[12], indicated several recurrent risk factors, such aspathophysiologic factors (e.g. hypertension, hyperlipidemia, diabetes mellitus) and lifestyle factors (e.g. obesity, smoking, alcohol, physical activity), and recommend that we should control or management these risk factors by medication and lifestyle intervention.

Secondary preventionsby medication are already well established in the previous study.PROGRESS trial of antihypertensive treatment showed that bloodpressure-lowering therapy decreased the recurrence offatal and non-fatal stroke by 28% [13], and SPARCL trial of lipid lowering treatment with statin showed 33% risk reduction compared with control group[14]. On the other hand, lifestyle intervention for secondary prevention is strongly recommended by guidelines, but there was no report of randomized controlled trial in lifestyle intervention for secondary prevention. So, further research needs methodological exploration in lifestyle intervention. In case of secondary prevention strategy for coronary heart disease, same pathophysiologic

background as atherosclerotic ischemic stroke, combination therapy of medication and lifestyle modification decreased the risk of all cause mortality by 45% [15]. This suggested that medication and lifestyle intervention is equally beneficial for secondary prevention in atherosclerotic ischemic stroke. However, there was no report of only mild stroke patients, the status of recurrence and recurrent risk factorswere unclear.

Therefore, we performed a survey research to clarify the status of recurrent risk factors in mild stroke patients. Our previous research indicated that 70% of mild stroke patients had several recurrent risk factors at the time of hospitalization, and some of the risk factors did not improve significantly within 6 months after discharge [16].This suggested that insufficient management of recurrent risk factors might contribute to stroke recurrence.

In this study, we aim to verify the lifestyle intervention as a secondary prevention strategy, we performed a follow-up study to investigated the recurrence rate and predictive factors for stroke recurrence in study 1, and performed a preliminary study to design an intervention RCT in study 2.

Ⅱ. Study 1: 3-year cumulative recurrence rates and predictors in mild stroke

Purpose

Study 1 aimed to estimate 3-year cumulative recurrence rates and identify independent predictors, including lifestyle factors, for vascular events in patients with mild stroke.

Materials and Methods

Study area and population

From December 2006 to September 2007, patients with acute ischemic stroke who met criteria for emergent admission to a sophisticated acute hospital in Nagoya City, mRS 0-1, directly returned home after discharge and who had no communication disability were consecutively enrolled in this study within two weeks from the onset. Patients over 80 years old, with cardioembolic stroke, dementia with under 10% tile over 80 yo (Mini-Mental State Examination: MMSE≤ 17)[17,18], past history of psychiatry disorders, or extracorporeal dialysis were excluded. The Research Ethics Committee of Nagoya University School of Health Sciences approved the study and all of the study participants provided written informed consent (Approved No. 6-504).

Study protocol

A baseline examination was conducted while the patients were hospitalized, and again 3 months post-discharge. Then, all patients were prospectively followed for occurrence of primary events. Primary events were defined as recurrence of stroke or other vascular events such as myocardial infarction, angina pectoris and peripheral artery disease. The primary outcome was determined by neurologist using CT scan and MRI for stroke recurrence, and by cardiologist using coronary angiography. Then we ascertained by medical records review, interviews for patient or their relatives by telephone. In case that telephone interviews were refused by patients, we confirmed to the treating physicians.

Stroke subtype

The diagnosis subtypes of stroke in the present study were based on clinical history, neurological examination and all available clinical information including brain CT or MRI. The subtypes of ischemic stroke were classified based on TOAST (trial of Org 10172 in acute stroke treatment)[19]. Patients were divided into two subtypes: large-vessel disease (LVD) and small-vessel disease (SVD). Cardioembolic stroke was diagnosed by using electrocardiogram, 24-48-hour Holter-electrocardiogram

monitoring, echocardiogram and transesophageal echocardiogram. Cardioembolic sources included atrial fibrillation, prosthetic valve, endocarditis, atrial myxoma, atrial mural thrombus, cardiomyopathy, acute myocardial infarction within one week prior to the onset and patent foramen ovale with atrial septal aneurysm.

Definition of recurrent risk factors (guidelines)

We selected hypertension, dyslipidemia, diabetes mellitus, obesity, smoking, alcohol intake, physical activity as well known established recurrent risk factors from guideline[10-12)]. At baseline, each participant completed a self-administered questionnaire covering medical history, smoking habits, alcohol intake, and exercise habits. Positive smoking was defined as current smoker. Positive alcohol intake was defined as average alcohol consumption over 30 mg per day. Physical inactivity was defined as subjects who engaged in sports or other forms of leisure time physical activity less than 90 min per week.

Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 min, according to the guideline of Japanese Society of Hypertension 2004[20)]. The mean of the 3 measurements was used for the analysis. Hypertension was defined as blood pressure > 140/90 mmHg and/or current use of antihypertensive agents. Waist circumference was

measured at the umbilical level in a standing position by a trained staff member. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated. Obesity was defined according to the Japanese criteria as BMI ≥ 25 kg/m^2 [21)].

Blood samples were collected after an overnight fast for determination of lipids and glucose levels. Serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations were determined enzymatically. Dyslipidemia was defined according to Japanese criteria[22)] as high-density lipoprotein cholesterol <40mg/dl, low-density lipoprotein cholesterol ≥120 mg/dl, or current use of lipid lowering agents. Fasting blood glucose levels were measured by the glucose oxidase method. The criteria for diabetes were applied from the Evidence-based Practice Guideline for the Treatment of Diabetes in Japan[23)] as fasting blood glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or current use of insulin or oral medication for diabetes.

Other risk factors

・*Ankle-brachial pressure index (ABI)*

ABI is a subclinical marker for lower extremity arterial disease [24)]. Previous study showed that low-ABI is independent predictor of stroke, coronary heart disease in healthy subjects [25)]. Measurements were carried out after a 5-min rest in the supine

position with the upper body as flat as possible. The ABI was calculated as the ratio of the higher of the two systolic pressures (tibial posterior and anterior artery) above the ankle to the average of the right and left brachial artery pressures. If there was a discrepancy of≥10 mmHg in blood pressure values between the two arms, then the higher reading was used for the ABI. Pressures in each leg were measured and ABIs were calculated separately for each leg. Abnormal ABI was defined as ABI≤0.9 or 1.3≤ABI according to the American Heart Association (AHA) guideline[24].

・*Metabolic syndrome (MetS): Japanese criteria*

MetS shows that obesity with visceral fat accumulation and closely associates with first-ever stroke and atherosclerotic vascular events[26], but not well establish as a recurrent risk factor. MetS was defined by using criteria recommended for Japanese population. MetS was defined as the presence of abdominal obesity plus two or more of the following components: elevated blood pressure, hyperlipidemia, low high-density lipoprotein, and elevated blood glucose. Abdominal obesity was defined as a waist circumference ≥ 85 cm in men and ≥ 90 cm in women. Elevated blood pressure was defined as average systolic / diastolic blood pressures ≥ 130/85 mmHg and/or current use of antihypertensive medicine. Hyperlipidemia was defined as serum triglycerides ≥ 150 mg/dl. Low high-density lipoprotein cholesterol levels <40

mg/dland/or current use of lipid-lowering agents. Elevated blood glucose level was defined as fasting blood glucose ≥ 110mg/dl or current use of insulin or oral medication for diabetes.

・*Lifestyle factors: physical activity and salt intake*

AHA scientific statement recommended that we should manage lifestyle factors, such as physical activity, salt intake, fat intake and glucose intake, for secondary prevention in vascular event[27]. In this study, we selected physical activity and salt intake as a lifestyle factor, because others are difficult to assess and the assessment was not established of validity and reliability.

Physical activity and salt intake were assessed at 3 months post-discharge. The mean daily step count was used (total step count over 7 days / 7) for 1 week as an index of patients' physical activity. To estimate daily steps, an electrical pedometer (Kenz Lifecorder, Suzuken, Nagoya, Japan) was chosen because of the reliability and validity of the data output[28,29]. All patients were instructed to put on the pedometer themselves and were instructed to use the pedometer 24 h/day for 1 week, except while bathing and sleeping.

Salt intake was measured daily salt intake by a self-monitoring device (GENEN MONITOR, Kono ME institute, Kawasaki, Japan). The reliability and validity of this

device have been previously reported[30].Before going to bed, the patients were instructed to void completely and discard the urine. Overnight urine was collected in a 1-L urine cup. After waking up, participants voided and placed the urine in the urine cup, adding any urine they had voided overnight. Patients were asked to collect their urine for approximately 8 h and to set the salt monitor and record the display value for consecutive 3 days. Mean daily salt intake (total salt intake over 3 days / 3) was calculated for each patient. Patients were divided into four groups for analysis according to median value of physical activity and salt intake.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Baseline characteristics and risk factor variables were compared among recurrent and survivor groups by the chi-square test, the Kruskal-Wallis U test and by the unpaired t-test. Univariate associations between pathophysiological / lifestyle factors and recurrence were assessed using Kaplan–Meier survival analysis, and significance was determined using the log rank test with continuous variables analyzed as median value. Hazard ratios (HRs) for recurrence were determined by univariate Cox proportional hazards regression analyses and variables with a *P* value of <0.1 at univariate analysis were entered into a multivariate Cox model to determine HRs. All statistical analyses were

performed with the SPSS 16.0 software package (SPSS Japan, Tokyo, Japan), and a *P* value of <0.05 was considered significant.

Results

Study population

A total of 102 patients (78 men and 24 women) were successfully followed for 3 years. The mean follow-up period was 1134±80 d. Baseline patient characteristics are shown in Table 1 and 2. Five out of 102 patients were not prescribed any antiplatelet agent, four patients due to cancer and one patient due to peptic ulcer hemorrhage.

Outcome at 3 years

Figure 1A shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects. The cumulative risk of recurrence for all subjects at 1, 2 and 3 years were 18.6%, 24.5%, and 28.4%, respectively. Twenty-five out of 102 patients (24.5%) had stroke recurrence, 4 (3.9%) had a coronary event, 2 (2%) died due to cancer, and 1 (1%) had no fixed residence. Eight patients of the 25 who had recurrent strokes had a severe stroke (mRS $\geq$ 3). Out of 25 patients who had stroke recurrence, 1 patient was hemorregic stroke defined by CT, and 24 patients were ischemic stroke in white-matter lesion defined by MRI.

Pathophysiological factors predictive for recurrent stroke over 3 years

In univariate analyses in patients with LVD, abnormal ABI and MetS were significantly associated with higher recurrence rates (Table 3). In multivariate Cox regression analyses, LVD, abnormal ABI and MetS were selected as significant independent predictors for stroke recurrence or cardiovascular events. Figure 1, panel B-D, shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for pathophysiological factors.

Lifestyle factors predictive for recurrent stroke over 3 years

In univariate analyses, higher salt intake was associated with higher recurrence and lower physical activity tended to be associated with higher recurrence. When divided into four groups, the poor lifestyle management group was associated with higher stroke recurrence (Table 4). In multivariate Cox regression analyses, the poor lifestyle management group remained associated with recurrence. Kaplan–Meier survival curves for salt intake and lifestyle management are presented in Figure 2.

Discussion

The results of the this study showed that approximately 30% of mild ischemic stroke patients experienced vascular events during the 3 years after onset. To our knowledge, this report is the first study to demonstratethe high recurrence rate in Japanese patients with mild strokes. Moreover, the findings of this study provide several predictive risk factors which include not only pathophysiological factors but lifestyle factors for vascular events. These findings will be of particular significance for the secondary prevention of mild strokes.

Recurrence rates of vascular events in mild stroke

In the present study, the 3-year risk of recurrence after mild stroke was approximately 30%, exceeding the 10% to 20% rates reported in previous community-based studies which included mild to severe stroke[3-5]. Wijk et al.[7], in a study treating the mild stroke during 3-year follow-up, showed a 20% vascular event recurrence and 10% stroke recurrence. In our study showed a 30% vascular event recurrence and 25% stroke recurrence. There might be several reasons for this discrepancy. First, a high proportion of LVD in the present study might have influenced the recurrence rate. It has been suggested that LVD recurs at higher rates

than SVD[1,2,4]. In the present study, the proportion of LVD was 59%, higher than previous research[2,7]. Added to this, the recurrence rate of 39% during 3-year follow-up among LVD in the present study was higher than that in the Hisayama study (25%), the only cohort study of stroke recurrence in Japan. For the background behind this higher recurrence rate, increasing prevalence of recurrent risk factors may raise the rate of recurrence such as dyslipidemia, diabetes and obesity. These risk factors have gradually increased during the past decade in Japanese population[31]. Secondly, race may be a possible reason for high stroke recurrence. Asian populations, including Chinese, Koreans and Japanese, have a higher stroke incidence and stroke recurrence than western populations[11]. High stroke recurrence results in increase of severity of the effects of stroke. Indeed, approximately 30% of cases of stroke recurrence in the present study resulted in severe disability. This indicates that strict control of recurrent risk factors is of particular importance for mild stroke patients.

Pathophysiological factors for recurrent predictors

The results of the present study indicated that abnormal ABI, MetS and LVD were independent predictive factors for 3-year vascular events. This suggests that advances of arthrosclerosis or complexity of traditional risk factors are essential for moderate-term vascular events in mild stroke.

Low ABI, a subclinical marker for lower extremity arterial disease. Previous study showed that ABI is inversely related to traditional risk factors for vascular disease and represents a marker for atherosclerotic changes in other vascular beds [25]. Thus the etiology of abnormal ABI is atherothrombosis. In fact, all of 13 patients with abnormal ABI were classified LVD. Prevalence of abnormal ABI with other atherothorombosis like stroke in this study has reported to result in poor prognosis [32]. The findings of this study are in line with these previous reports, suggesting abnormal ABI can be a powerful prognostic factor for stroke recurrence in mild stroke.

MetS shows that obesity with visceral fat accumulation closely associates with atherosclerotic vascular events [26]. Moreover visceral fat obesity is closely related to adipose tissue. Several studies have demonstrated that adipose tissue actively produces a variety of locally and systemically functioning bioactive molecules, including tumour necrosis factor-α, plasminogen-activator inhibitor type-1 and adipocytokine, that also interact in cardiovascular diseases [33,34]. Especially, decreased adiponectine and increased leptine effect on increase blood pressure, sympathetic nervous system activity, and expressed within atherosclerotic plaques. Considering these effects, the present results may reflect advanced atherosclerosis or the presence of active, unstable plaque in cerebral large vessels.

In the present study, common recurrent risk factors such as hypertension or

dyslipidemia were strong predictors as shown in AHA guideline [11]. Indeed, we also had high prevalence rate in hypertension (78%) and dyslipidemia (70%) in the present study. However, the results in multivariate analysis did not select these factors for recurrence predictors. We think this is probably a mathematical result due to almost equal prevalence rate of those factors between recurrence and survivor group.

In the present study, the medications were checked up to 6 month after discharge and almost same medications were found during that period in each subject. In this study, medication with statins seemed rather low, but this is almost same rate compared with Japanese large sample registry and trials [6,35]. However, the details of the control conditions for risk factors during the rest of follow-up were unknown. Further study will need to clarify risk factor control in consideration with medications that were shown the effects or possible effects on stroke recurrence, eg, angiotensin-converting enzyme inhibitor [13], or statins.

Lifestyle factors for recurrent predictors

High salt intake and lower physical activity were also indicated as independent predictive factors for stroke recurrence. This result highlights that lifestyle modification can help to prevent vascular events. Results from Japanese population-based prospective cohort studies have showed significant associations

between salt intake and stroke incidence[36]. Similarly, a meta-analysis of 11 cohort studies showed that higher salt intake was associated with greater risk of stroke (relative risk ratios: 1.23)[37]. As reported in a previous study, stroke mortality has a strong relationship to dietary salt intake independent of blood pressure[38]. The mechanism responsible for the association between salt intake and strokes is still unknown, but may be related to artery thickness, stiffness and platelet reactivity. In the Japanese population, it is suggest that approximately 40% of Japanese people have high sodium sensitivity[39], so dietary modification is of particular value for prevention of stroke recurrence.

Physical activity also tended to be associated with stroke recurrence. In a meta-analysis of 18 cohort studies, lower physical activity had a 33% higher risk of stroke incidence or mortality compared with more active individuals[40]. Although the association between physical activity and strokes has not been well established, it has been clearly demonstrated that insulin resistance and HDL-cholesterol, which contribute to prevent the progression of atherosclerosis, are related to higher physical activity[41]. Improvement of endothelial dysfunction by exercise is also other possible mechanism for the prevention of stroke recurrence[42]. Thus, an increase in physical activity should be a candidate for prevention of stroke recurrence, with the expectation that it could generate direct or synergistic effects with other interventions. Indeed, the

poor lifestyle management group (lower physical activity and higher salt intake) in the present study had highest recurrence rate compared to the other three groups.

Study limitations

There are several potential limitations to the findings in study 1. A relatively small sample size might affect the results. Other recurrence correlates, such as carotid artery sclerosis, MRI findings, or malnutrition, may need to be studied to provide more insight into the process of recurrence. Nevertheless, the present study is the first report on the recurrence of vascular events and predictive factors in patients with mild strokes in Japan.

Summary of study 1

Study 1 result clarified high stroke recurrence rate within 3-year, and identified LVD, abnormal ABI, MetS and poor lifestyle management were significant independent predictor of vascular events in patients with mild stroke. The findings of study 1 suggest that the recurrence rate in mild strokes has increased in conjunction with increased prevalence of recurrent risk factors. This result also suggests that risk reduction through a combination of medication and lifestyle intervention may improve this higher recurrence rate.

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Table 1. Demographic and clinical characteristics of patients

	Recurrence(n=29)	Survivor (n=70)
Age (yo)	65.6 (10.0)	63.2 (8.8)
Male gender (%)	75.8	77.4
MRI findings (%)		
white-matter lesion	84.2	72.9
cerebellar infarction	6.9	5.7
brain-stem infarction	6.9	21.4
NIHSS	4.5	4.1
Stroke Subtype (LVD) (%)	79.3	47.8
Abnormal ABI (%)	24.1	8.4
MetS (%)	41.1	26.8
Hypertension (%)	78.6	70.4
Dyslipidemia (%)	50.0	63.4
Diabetes Mellitus (%)	28.6	15.5
Obesity (%)	35.7	31.0
Pre-Smoking (%)	75.0	54.9
Pre-Alcohol intake （%）	21.4	33.8
Pre-Physical inactivity (%)	53.6	67.6
Medication		
Antiplatlet agents (%)	94.8	96.6
Aspirin (%)	76.8	79.2
Cilostazol (%)	7.8	7.4
Clopidogrel (%)	9.2	9.7
ACEi / ARB (%)	66.6	58.3
Statin (%)	22.2	38.3

Age and NIHSS were presented as mean ± standard deviation. Other data presented as number or proportion. LVD; large vessel disease. SVD; small vessel disease. MetS; metabolic syndrome. ABI; ankle-brachial pressure index. HDL; high-density lipoprotein. LDL; low-density lipoprotein. BMI; body mass index. ACEi; angiotensin-converting enzyme inhibitor. ARB; angiotensin II receptor blocker.

Table2. Lifestyle characteristics of patients at 3-month post discharge

	Recurrence (n=29)	Survivor (n=70)	Total (n=99)
Salt intake (g)	11.08±2.75	10.08±2.13	10.38±2.32
Physical activity (steps)	5668±2921	6755±3140	6446±3104

Data was presented as mean ± standard deviation.

Table 3 Results of univariate and multivariate Cox proportional hazards analysis in pathophysiological factors

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	*P* value	Hazard Ratio	*P* value
Stroke subtypes (LVD)	4.18 (1.21-14.3)	0.022	2.81 (1.13-6.96)	0.025
Gender (male)	1.10 (0.36-3.33)	0.855	NE	
Age (yo > 65)	1.87 (0.73-4.75)	0.186	NE	
Abnormal ABI	3.51 (1.33-9.25)	0.011	3.30 (1.33-8.20)	0.009
MetS	3.81 (1.44-10.0)	0.006	2.67 (1.23-5.80)	0.013
Hypertension	1.39 (0.45-4.32)	0.557	NE	
Dyslipidemia	0.65 (0.26-4.76)	0.376	NE	
Diabetes Mellitus	1.69 (0.60-4.76)	0.314	NE	
Obesity	1.47 (0.57-3.81)	0.417	NE	
Smoking	2.26 (0.74-6.89)	0.148	NE	
Alcohol intake	0.66 (0.21-2.01)	0.469	NE	
Physical inactivity	1.14 (0.43-3.05)	0.782	NE	

*Analysis performed on 100 patients. NE; variable not entered into model.

Other abbreviations as in Table 1.

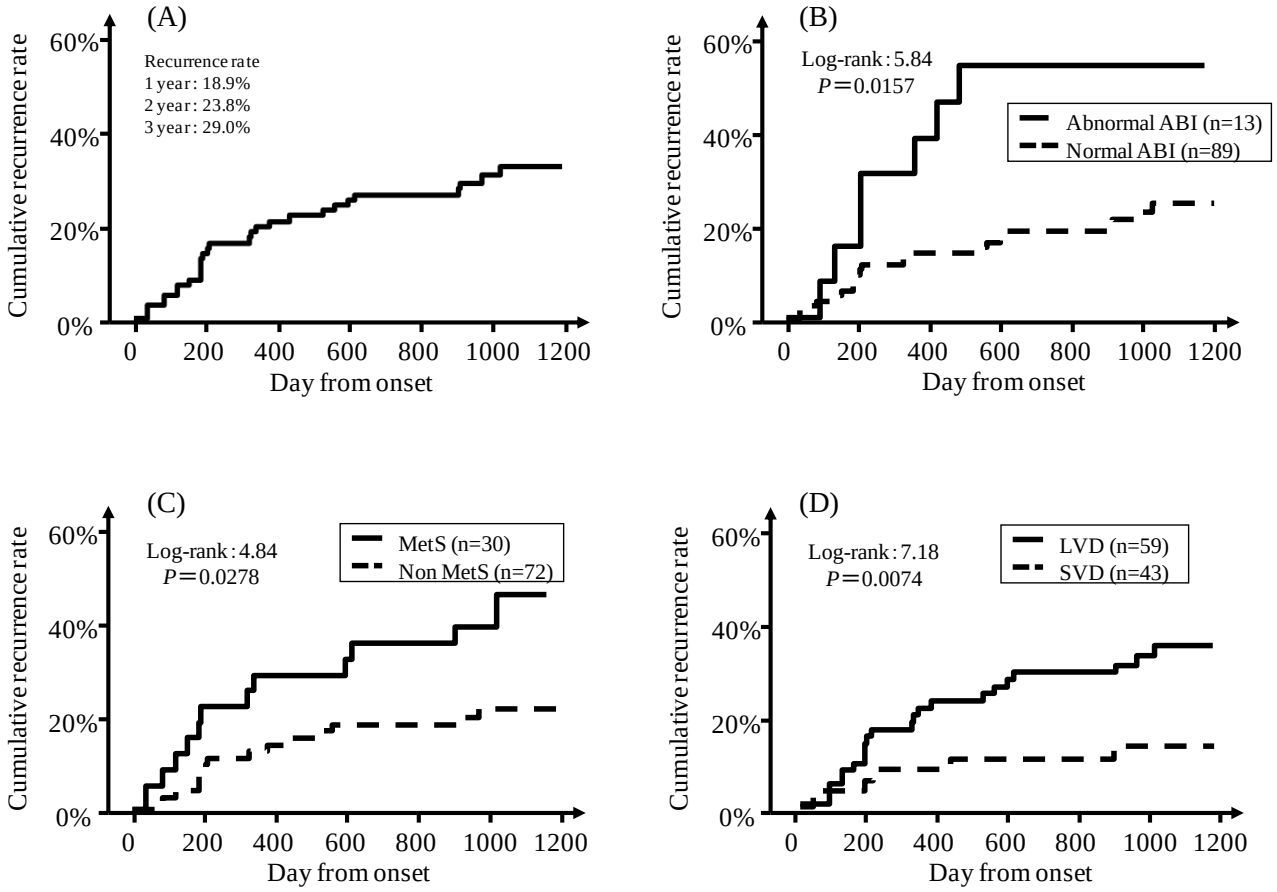

Figure 1.

Kaplan–Meier estimates of cumulative recurrence rates of stroke according to all patients (A), ABI (B), MetS (C) and stroke subtype (D) after adjustment for age, medication. Deaths without stroke recurrence were censored. All abbreviations as in Table 1.

Table 4 Results of univariate and multivariate Cox proportional hazards analysis of lifestyle factors

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	*P* value	Hazard Ratio	*P* value
Salt intake	2.43 (1.04 - 5.68)	0.040	1.98 (1.02 – 4.22)	0.028
Physical actvity	1.10 (0.36 - 3.33)	0.076	NE	

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	*P* value	Hazard Ratio	*P* value
SI＜10.7g, PA≧5800 steps	1		1	
SI≧10.7g, PA≧5800 steps	1.32 (0.64- 2.71)	0.443	NE	
SI＜10.7g, PA＜5800 steps	2.14 (0.51- 8.96)	0.297	NE	
SI≧10.7g, PA＜5800 steps	1.71 (1.11- 2.62)	0.013	1.62 (1.10 -2.39)	0.013

Analysis performed on 89 patients. NE; variable not entered into model. SI; salt intake, PA; physical activity.

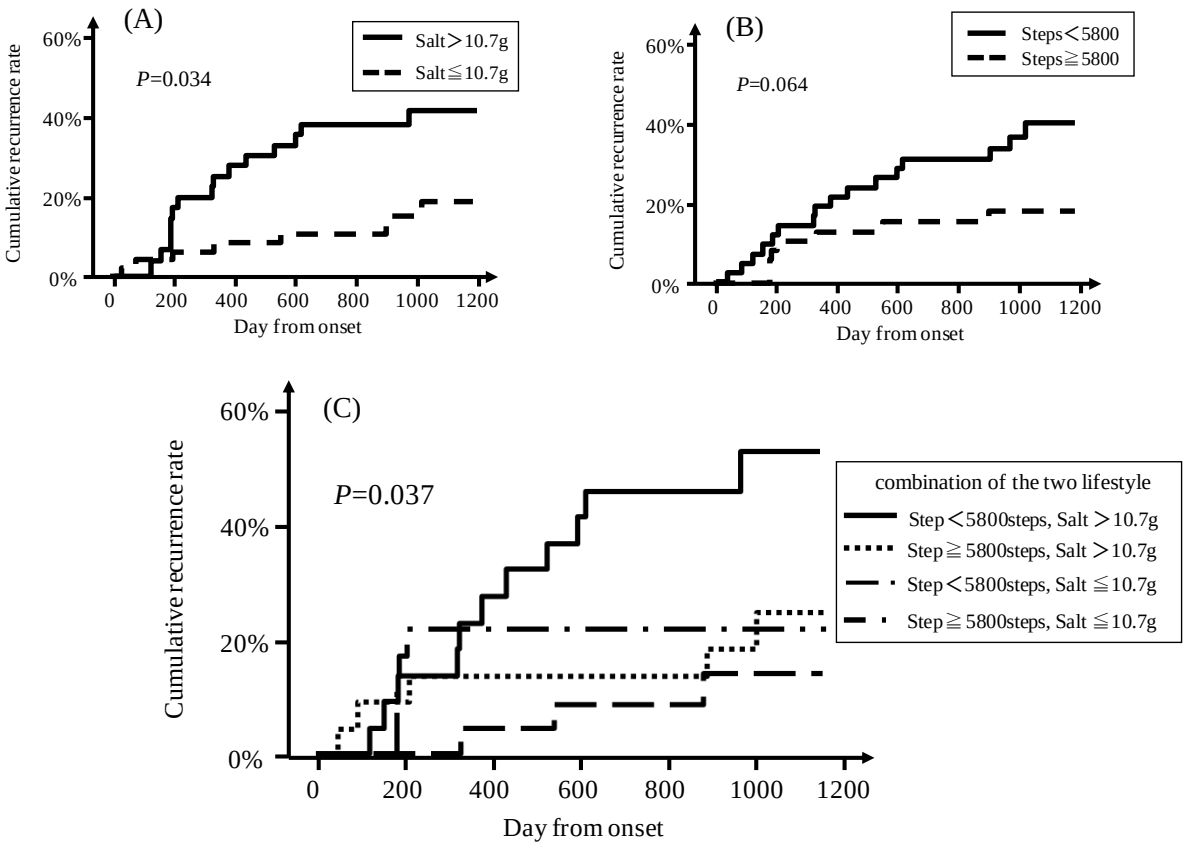

Figure 2.

Kaplan–Meier estimates of cumulative recurrence rates of stroke according to salt intake (A), physical activity (B) and combination of the two lifestyle (C) after adjustment for age, medication. Deaths without stroke recurrence were censored.

Ⅲ. Study2：Preliminary study for randomized controlled trial

Introduction and purpose

The result of study 1 identified lifestyle management is one of the independent predictors for stroke recurrence. To confirm cause-effect relationship, we need to clarify the effects of lifestyle intervention on vascular events. However, long term period and large sample seize are necessary to demonstrate the effect of lifestyle intervention on stroke recurrence. So, as a next step, we examine the effect of lifestyle intervention for surrogate markers such as blood pressure, LDL-choresterol, HbA1c and high sensitivity C-reactive protein (hs-CRP) [43] on vascular events. Before starting the randomized controlled trial (RCT), we need to estimate sample size because there was no report about the effect of lifestyle intervention for surrogate makers in mild stroke patients. Therefore, study 2 aimed to perform a preliminary study todesign an intervention RCT.

Materials and Methods

Study population and Randomization

This study was a randomized control-group study. We enrolled 40 patients with acute ischemic stroke who met criteria for emergent admission to a sophisticated acute hospital in Nagoya City, mRS 0-1, directly returned home after discharge and who had no communication disability were consecutively enrolled in this study within two weeks from the onset. Patients with cardioembolic stroke, dementia (MMSE $\leq$ 17), past history of psychiatry disorders, or extracorporeal dialysis were excluded.

At randomization, patients were stratified by abnormal ABI and MetS, and then patients were randomly assigned by using a computer-generated random number sequence to either an advice only group or a lifestyle intervention group. The Research Ethics Committee of Nagoya University Graduate school of Medicine approved the study (Approved No. 645) and all of the study participants provided written informed consent.

Study protocol

The study protocol was registered and officially entered in the UMIN Clinical Trials Registry (UMIN-CTR) system (http://www.umin.ac.jp, No. UMIN000001865)

before the start of the study. We evaluated ABI and MetS before random assignment. We selected surrogate makers for vascular events as primary variables, such as systolic blood pressure, LDL-choresterol, HbA1c and hs-CRP. We assessed at baseline assessment and after finished intervention period (6-month assessment). HDL-choresterol, daily physical activity and daily salt intake were also evaluated both baseline and 6-month assessment.

Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 min, according to the guideline of Japanese Society of Hypertension 2009[39]. The mean of the 3 measurements was used for the analysis. Blood samples were collected after an overnight fast for determination of lipids and glucose levels. Serum HDL cholesterol, LDL cholesterol, HbA1c and hs-CRP were determined enzymatically. Daily physical activity and salt intake were measured by same protocol as previous shown in study 1.

Lifestyle Interventions

A health care professional interventionist provided some advice and counseling about lifestyle modification (weight reduction, sodium intake, physical activity) in both groups at baseline and 6 month. This advice was provided in a single 30-40 minute individual session. Counseling on behavior change was also provided. Then

advice only group had no further contact with the interventionist occurred until after 6 months.

Intervention group was performed lifestyle modification program developed in our laboratory. Lifestyle intervention was composed by exercise and salt reduction, and led by a physical therapist once or twice a week, for 6 months in Nagoya University Fitness Research Center. Exercise program was included counseling or instruction about daily physical activity and exercise training. Exercise training was composed aerobic and resistance training.

Aerobic exercise was performed by cycle ergometer included 3 to 5 minutes of warm-up at 20W, and 20 to 30 minutes of steady-state exercise at target heart rate 100 to 110 beat per minute. Resistance training consisted of 5 resistance exercise (1) chest press, (2) push up and pull down, (3) leg extension, (4) knee extensor and flexor muscle, and (5) abdominal muscle. Intensity was set according to AHA scientific statement published in 2007 [44)], and 10 to 12 repetition per session. Salt reduction intervention was composed counseling, instruction about the relationship between salt intake and stroke recurrence, and monitoring salt intake every 6 weeks.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Baseline

characteristics and risk factor variables were compared among intervention and control groups by the chi-square test, the Kruskal-Wallis U test and by the unpaired t-test.

Primary analyses of blood pressure, LDL-choresterol, HbA1c and hs-CRP change are based on intention to treat. In 6-month assessment, variables were compared among two groups by unpaired t-test. For individuals without these parameters at the 6-month assessment, baseline measurements were carried forward. All statistical analyses were performed with the SPSS 16.0 software package (SPSS Japan, Tokyo, Japan), and a *p* value of <0.05 was considered significant.

Results

Study population

A total of 40 patients (27 men and 13 women) were enrolled in the trial (Figure 1). Baseline characteristics were similar in the randomized groups (Table 1). Then two patients in intervention group were dropped out due to death or removed, and one patient in control groups had recurrent stroke. We successfully followed 37 patients 6-month follow-up period.

Effects of lifestyle intervention

Table 2 shows the changes in the surrogate makers and lifestyle variables during the 6-month intervention period. Daily physical activity and salt intake were significantly improved only in the intervention group.

Mean (standard deviation) reductions in systolic blood pressure was 11.6 (19.2) mmHg in the intervention group, 7.9 (26.3) mmHg in the control group. Corresponding HbA1c reductions were 0.58 (0.70) %, 0.21 (1.26) %, LDL-choresterol reductions were 3.57 (36.8) mg/dl, 10.4 (27.9) mg/dl, hs-CRP reductions were 1737 (4286) pg/ml, 8.39 (2315) pg/ml, respectively. Systolic blood pressure and HbA1c were significantly improved from baseline to 6-month. LDL-choresterol and hs-CRP had tended to

improvement but not significantly changed in 6-month. On the other hand, there were no changes in variables from baseline to 6-month in the control group.

Sample-size calculation

Sample size was calculated by systolic blood pressure and HbA1c. Consider the data in Table 2, we examined the changes of surrogate makers with and without lifestyle intervention in a sample of 40 patients. To determine α level of 0.05 (Zα: 1.96) and a power of 0.8 (Zβ: 0.84), sample-size for each group was calculated by below equation.

$$\text{Sample size} = 2(Z\alpha + Z\beta)^2/(|\mu 1 - \mu 2|/\sigma)^2 + Z\alpha^2/4$$

μ1: mean value of intervention group, μ2: mean value of control group, σ: standard deviation

・Systolic blood pressure

$$\text{Sample size} = 2(1.96 + 0.84)^2/ (|(-11.64) – 7.9| / 26.3)^2 + 1.96^2/4 = 30$$

・HbA1c

$$\text{Sample size} = 2(1.96 + 0.84)^2 / (|(-0.58) – (-0.21)| / 0.70)^2 + 1.96^2/4 = 58$$

Sample-size calculations indicated that 116 participants (58 in each group) were

needed to show an improvement in systolic blood pressure and HbA1c. Allowing 20% loss to follow-up, the recruitment target size was 145 participants.

Discussion

The results of this study indicate that lifestyle intervention, which combines exercise and salt reduction, has the effect for systolic blood pressure and HbA1c. This suggests that lifestyle intervention might be a useful strategy for secondary prevention in patient with mild stroke.

Our lifestyle intervention indicated significantly improvement in systolic blood pressure and HbA1c level. In previous report showed that lifestyle modification produce beneficial changes in blood pressure, glucose tolerance [45,46)], and the result of this study supported the previous research. However, there was a little effect for LDL-cholesterol and hs-CRP. There might be several reasons for this result. A meta-analysis of 5 RCTs showed that there was non-significant reduction in LDL cholesterol level only exercise intervention[47)]. However, results were statistically significantwhen the one study was deleted from the model. The characteristics of one study were small sample size 52 subjects (other study were over 100 subjects), short follow up periods 24 weeks (others were 24 to 72 weeks) and performed only exercise intervention (others provided dietary advice). This study was preliminary study, so we need to consider about intervention period and dietary advice in following RCT. On the other hand, hs-CRP is hypersensitive maker to subject condition. Indeed, a subject

have slightly fever or injury, hs-CRP undergo significant fluctuation. So, we need to consider whether hs-CRP is suitableas a primary outcome or not in following RCT.

Summary of study 2

The results of study 2 indicated that lifestyle interventionis beneficial for improvement of systolic blood pressure and glucose metabolism. This suggests that lifestyle intervention isappropriate strategy for secondary prevention in patient with mild stroke. From sample size calculation, the target recruitment sample size needs 145 participants for following RCT.

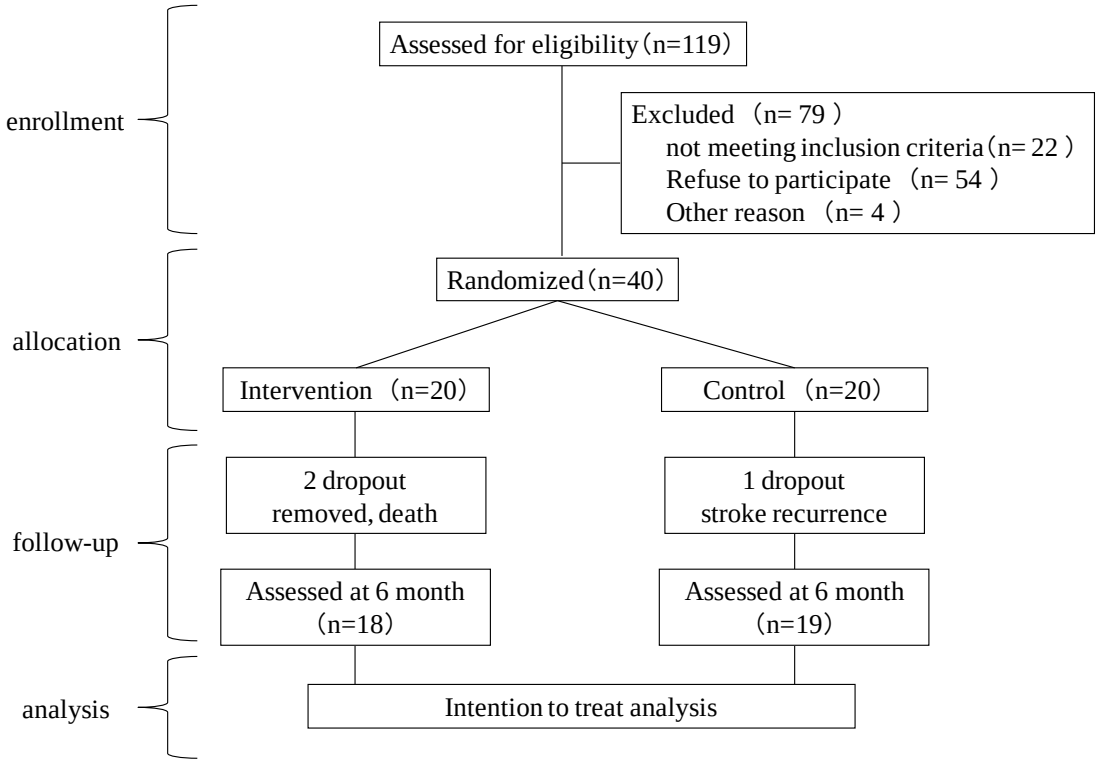

Figure 1. Participant flow of study sample

Table 1. Baseline Characteristics by Randomized Groups

	Intervention (n=20)	Control (n=20)	*P*
age (yo)	63.5±7.0	63.4±11.4	0.985
Male gender (%)	60.0	80.0	0.534
LVD (%)	53.3	46.6	0.876
Abnormal ABI (%)	5	5	1.000
MetS(%)	20	20	1.000
SBP (mmHg)	134.4±19.6	135.2± 25.8	0.929
HbA1c (%)	6.07±1.05	6.02±1.27	0.304
LDL-choresterol (mg/dl)	101.0±33.0	100.5±27.0	0.958
hs-CRP (pg/ml)	2386± 4881	935±950	0.253
HDL-choresterol (mg/dl)	52.7±14.5	54.4±15.2	0.754
BMI (kg/m^2)	23.0±2.19	23.9±4.84	0.533
Smoking (%)	5	5	1.000
Alcohol (%)	0	5	0.882
Salt intake (g)	10.1±1.67	10.7±6.40	0.383
Physical activity (steps)	7440±2138	6549±3138	0.201
Medication (%)			
Antiplatelet agent	94.8	96.6	0.889
ACEi / ARB	66.6	58.3	0.686
statin	22.2	28.6	0.702
oral diabetes agent	35.2	31.6	0.775

Data were presented as mean ± standard deviation or proportion.

LVD; large vessel disease. MetS; metabolic syndrome. ABI; ankle-brachial pressure index. SBP; systolic blood pressure. LDL; low-density lipoprotein. hs-CRP; high sensitivity C-reactive protein. HDL; high-density lipoprotein. BMI; body mass index. ACEi; angiotensin-converting enzyme inhibitor. ARB; angiotensin II receptor blocker.

Table 2. Intervention Outcomes at Baseline and at 6 Months by Randomized Group

Intervention (n=20)	Baseline	6-month	Effect size	*P*
SBP	134.4 (10.6)	122.7 (15.9)	-11.64 (19.18)	0.029
HbA1c (%)	6.07 (1.05)	5.49 (0.46)	-0.58 (0.74)	0.011
LDL choresterol (mg/dl)	101.0 (33.0)	97.5(24.8)	-3.57 (36.8)	0.429
hs-CRP(pg/ml)	2386 (4881)	648 (650)	-1737 (4286)	0.207
HDL choresterol (mg/dl)	52.7 (14.5)	67.3(27.2)	14.6 (25.3)	0.049
Physical activity (steps)	7550 (2234)	9069 (3360)	1519 (2116)	0.018
Salt intake (g)	10.1 (1.7)	8.9 1(0.8)	-1.25 (1.5)	0.013

Control (n=20)	baseline	6-month	Effect size	*P*
SBP	131.9 (14.2)	139.8 (23.8)	7.9 (26.3)	0.342
HbA1c (%)	6.02 (1.41)	5.80 (0.71)	-0.21 (1.63)	0.657
LDL choresterol (mg/dl)	100.45 (30.4)	90.0 (20.8)	-10.4 (27.9)	0.243
hs-CRP(pg/ml)	1139 (1085)	1148 (1902)	8.39 (2315)	0.990
HDL choresterol (mg/dl)	58.0 (16.2)	58.9 (15.5)	0.91 (10.4)	0.779
Physical activity (steps)	5316 (2349)	6830 (41366)	1514 (3154)	0.142
Salt intake (g)	11.0 (2.47)	10.9 (1.87)	-0.05 (2.56)	0.947

Data were presented as mean ± standard deviation.

SBP; systolic blood pressure. LDL; low-density lipoprotein. hs-CRP; high sensitivity C-reactive protein. HDL; high-density lipoprotein.

General discussion

In thesestudies, we identified recurrence risk factors for mild stroke and indicated that lifestyle intervention was useful for secondary prevention in patients with mild stroke. The results of these studies provided new framework of rehabilitation medicine for patients with mild stroke.

In the past, the main aim of stroke rehabilitation was improving sever paresis or improving activity of daily living, so mild stroke patients was not indicated to rehabilitation because they had no disability and short term admission in hospital. However, the results of study 1 indicated that high recurrence rate in early phase, and indicated the importance of secondary prevention for patients with mild stroke. Moreover, we identified the recurrent predictive factors and the effect of lifestyle intervention to surrogate maker provided methodology of strategy for secondary prevention. This proposed new framework of stroke rehabilitation medicine. Exercise therapy is a main part of lifestyle intervention, and exercise is a specific area of expertise for physical therapist. And the subject was stroke patient which mean high risk population for recurrent vascular event. To perform lifestyle intervention as a physical therapy strategy is highly significant from the perspective of rehabilitation medicine.

Indeed, some previous reports in coronary heart diseasedemonstrated that cardiac rehabilitation including lifestyle intervention cardiac rehabilitation has effect both secondary prevention[15)] and cost-effective [48)]. Thus, the same flame work as cardiac rehabilitation may be applied for mild stroke patients. However, we have several problems to in mild stroke patients. For example, lack of medical system for healthcare in outpatients clinic, and healthcare resources in Japan.

Conclusion

In this thesis, we performed prospective cohort study in mild stroke patients, and identified abnormal ABI, MetS, LVD and poor lifestyle managements were independent predictors for stroke recurrence. Clinical management of recurrent risk factors including lifestyle, such as physical activity and salt intake, has focused on reducing new vascular event, because the recurrence rate of Japanese mild stroke patients was so high, and getting sever paresis. Our finding of this results that the patient with LVD, abnormal ABI and MetS was a high risk patient for recurrent vascular event, and lifestyle may be an intervention strategy for secondary prevention particularly in patients with mild stroke. Because they have no sever paresis and no disability in activities of daily living. The results of study 2 suggested that lifestyle intervention may have a possibility for improving recurrent risk factors and secondary prevention. Lifestyle management as well as medication control should recognize as an interventional strategy for secondary prevention. Our future RCT will accurate the cause-effects relationship between lifestyle intervention and stroke recurrence.

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