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Maximum walking speed at discharge could be a prognostic factor for vascular events in patients with mild stroke: A cohort study

（退院時最大歩行速度は軽症脳梗塞後の血管イベント予測因子となる：コホート研究）

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Abstract

Background: A previous study reported that daily physical activity is one of the independent predictors of vascular events after mild ischemic stroke. This study aimed to identify the prognostic value of physical activity-related factors as well as known vascular risk factors for vascular events in mild ischemic stroke.

Methods: This was a single-center prospective cohort study. Patients with acute ischemic stroke and transient ischemic attack with modified Rankin scale scores ranging from 0 to 2 were consecutively enrolled in this study. Enrolled patients were followed up for composite vascular events as primary outcomes up to three years post discharge. Primary outcomes included stroke and cardiovascular death, hospitalization due to stroke or transient ischemic attack recurrence, cardiovascular disease, and peripheral artery disease. During hospitalization, known vascular risk factors such as age, sex, previous history of vascular events, body mass index, non-dominant mid-upper arm circumference, modified Rankin scale at discharge, stroke subtype, white matter lesions, blood pressure, abnormal ankle-brachial index, comorbidities, laboratory data, prehospital lifestyles and medications. Moreover, at the time of discharge, physical activity-related factors

such as maximum walking speed, handgrip strength, knee extensor isometric muscle strength, anxiety, and depression were assessed as potential predictors. Univariate and multivariate Cox proportional hazards analyses were used to identify independent risk factors for composite vascular events. The cumulative events rate of the patients was evaluated using the Kaplan-Meier method.

Results: A total of 255 patients (175 men, median age 70.0 years) were enrolled in this study. The Kaplan-Meier estimates of cumulative risk of composite vascular events at one-, two-, and three-years were 9.6%, 14.4%, and 15.2%, respectively. After multivariate analysis, cerebral white matter lesions of periventricular hyperintensity (grade=3; hazard ratio: 2.904; 95% confidence interval: 1.160 to 7.266; p=0.023) and maximum walking speed (<1.45m/s; hazard ratio: 2.232; 95% confidence interval: 1.010 to 4.933; p=0.047) were identified as significant independent predictors of composite vascular events.

Conclusions: The results of this study indicate that walking speed could be an independent prognostic factor for composite vascular events in mild ischemic stroke. Walking speed at discharge may stratify the target group for intensive risk reduction after discharge.

要旨

【背景】軽症脳梗塞において身体活動量は血管イベントの独立した予測因子となることが報告されている。本研究では身体活動量関連因子と血管イベントとの関連を明らかにすることを目的とした。

【方法】研究デザインは、単一施設、前向きコホート研究を用いた。対象は急性期病院入院の脳梗塞、一過性脳虚血発作患者、退院時 modified Rankin Scale 0～2 のものとした。入院中に既存の再発予測因子（年齢、性別、血管疾患既往、Body Mass Index、上腕中央周囲長、退院時 modified Rankin Scale、脳梗塞病型、大脳白質病変、血圧、足関節／上腕血圧比、合併症、血液生化学検査、入院前生活習慣、投薬状況）と、退院時に身体活動量関連因子（最大歩行速度、握力、膝伸展筋力、不安・抑うつ）の調査を行い、その後最大 3 年間血管イベント（脳血管疾患、心血管疾患、末梢動脈疾患による死亡、再入院）の発生を追跡調査し、予測因子との関連を解析した。

【結果】255 名（男性 175 名、年齢中央値 70 歳）を対象とした。Kaplan-Meier 法による血管イベント発生率は 1 年 9.6%、2 年 14.4%、3 年 15.2%であった。コックス比例ハザード解析の結果、側脳室周囲白質病変（grade=3; hazard ratio: 2.904; 95% confidence interval: 1.160 to 7.266; p=0.023）、最大歩行速度（<1.45m/s; hazard ratio: 2.232; 95% confidence interval: 1.010 to 4.933; p=0.047）が独立した血管イベント予

測因子として抽出された。

【結論】本研究結果より、軽症脳梗塞において退院時の最大歩行速度が独立した血管イベント予測因子となることが示された。歩行速度がリスク症例の同定に寄与し、リスク軽減を目的とした介入に重要な評価指標になることが示唆された。

Introduction

Although global stroke incidence and associated mortality rates declined over the past decades, stroke remains a leading cause of long-term disability.[1,2] In ischemic stroke, which accounts for over 70% of all types of stroke,[1,2] the most common is a mild ischemic stroke (MIS), which is ranked from 0 to 2 on the modified Rankin scale (mRS).[3] Previous studies reported that patients with MIS were at high risk for stroke recurrence (10-15%) and other cardiovascular events (5%) three years after stroke onset.[4–6] In addition, one-third of the patients with stroke recurrence presented with severe motor paralysis.[7] Therefore, preventive intervention is particularly important, and prognostic risk stratification is essential for clinical management of patients with MIS.

Previous guidelines indicate disease factors, such as hypertension, dyslipidemia, and diabetes mellitus, as well as lifestyle factors, such as obesity, smoking, alcohol, and physical inactivity, to be risk factors for recurrence of MIS.[8] Among lifestyle factors, we previously demonstrated that lower physical activity (PA) three months after discharge is one of the independent predictors of vascular event after adjustment for other vascular risk factors.[5] This implies that PA-related factors measured during hospitalization are likely to predict stroke or

cardiovascular events after MIS and allow us to stratify the patients for secondary prevention program from immediately post discharge. Therefore, this study aimed to identify the prognostic value of PA-related factors as well as known vascular risk factors at hospital discharge for vascular event in patients with MIS.

Methods

Subjects

From November 2011 to April 2016, we prospectively enrolled consecutive patients with acute ischemic stroke and transient ischemic attack (TIA) who admitted to Aichi Medical University Hospital in Aichi, Japan. The eligibility criteria were: age older than 20 years, a mRS from 0 to 2 at discharge, absence of communication disability that defined as inability to respond to self-report questionnaire or telephone interview, directly returned home after discharge, and consent to participation in this study. Patients with severe dementia (Mini-Mental State Examination ≤17), a history of psychiatric disorder, extracorporeal dialysis, blood coagulation disorder, or a plan of long-term hospitalization for treatment of other disease were excluded. The university research ethics committee approved this study; Aichi Medical University (Approval No.11-044) and Nagoya University

Graduate School of Medicine (Approval No.16-507). All participants provided written informed consent.

Study design and protocol

We performed a single-center prospective cohort study. A baseline examination was conducted while the patients were hospitalized. Thereafter, patients were prospectively followed up for primary outcomes up to three years post discharge.

Primary outcome

Primary outcome was a composite of stroke, cardiovascular death, and hospitalization due to vascular events including stroke or TIA recurrence; cardiovascular disease such as myocardial infarction, angina pectoris, and heart failure; and peripheral artery disease, including lower extremities and abdominal aorta. The primary outcome was determined by neurologists, cardiologists, and vascular surgeons at university hospital, and we checked the events by medical records and periodic follow-up telephone calls to patients or their relatives every six months. Regarding patients who developed more than one event, the first event was considered in the analysis.

Known vascular risk factors

In this study, we defined known vascular risk factors as follows: age, sex, previous history of vascular events, body mass index (BMI), non-dominant mid-upper arm circumference, mRS at discharge, stroke subtype, white matter lesions, blood pressure, abnormal ankle-brachial index (≤0.9 or >1.4),[9] comorbidities (hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome), and laboratory data (serum high-density and low-density lipoprotein cholesterol [HDL-C, LDL-C], triglycerides [TG], hemoglobin A1c [HbA1c], albumin), prehospital lifestyles (smoking and alcohol intake), and medications.[8,10]

The stroke subtypes were classified into atherothrombotic, cardioembolic, lacunar, and others.[11] TIA was defined as a transient neurological dysfunction without evidence of infarction on brain imaging.[12] Cerebral white matter lesions of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) were graded according to the Fazekas's grading system based on the magnetic resonance imaging.[13] PVH was graded as 0=absence, 1="caps" or pencil-thin lining, 2=smooth "halo", or 3=irregular PVH extending into the deep white matter. DWMH was graded as 0=absence, 1=punctate foci, 2=beginning

confluence of foci, or 3=large confluent areas. The classification of stroke subtypes and TIA, and grading of cerebral white matter lesions were determined by neurologists and rehabilitation doctors.

Blood pressure was measured by using self-blood pressure measurement method.[14] The semiautomatic digitized sphygmomanometer (UA-782; A and D Company, Tokyo, Japan), which is based on the oscillometric method, was used for all of the participants. The mean of systolic (SBP) and diastolic blood pressure (DBP) during consecutive three days prior to hospital discharge was used for the analysis.

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or current use of antihypertensive agents.[14] Dyslipidemia was defined as HDL-C <40 mg/dl, LDL-C ≥140 mg/dl, TG ≥150 mg/dl, or current use of lipid-lowering agents.[15] Diabetes mellitus was defined as HbA1c ≥6.5 %, fasting blood glucose ≥126 mg/dl or, current use of antidiabetic agents.[16] Metabolic syndrome was defined as the presence of abdominal obesity (waist circumference ≥85 cm in men, ≥90 cm in women) along with two or more of the following three components: (1) TG ≥150 mg/dl and/or HDL-C <40 mg/dl and/or current use of lipid-lowering agents; (2) SBP ≥130 mmHg and/or DBP ≥85 mmHg and/or current use of antihypertensive agents.;

and (3) fasting blood glucose ≥110 mg/dl and/or HbA1C ≥6.0 % and/or current use of antidiabetic agents.[17] Prehospital lifestyle regarding smoking and alcohol intake was assessed by questionnaires and/or interviews.

Medication use was assessed at discharge and three months post discharge to examine medication control for risk factors after discharge.

PA-related factors

Physical therapists measured maximum walking speed (MWS),[18,19] handgrip strength,[20] knee extensor isometric muscle strength,[18,20] anxiety, and depression[21] at discharge.

Ten-meter (m) maximum walking time was measured with three meters acceleration line, followed by 10 m line. Before walking, patients were indicated to walk as fast as possible. They were permitted to use a walking aid, such as a cane or a walker, if normally required. Walking time was measured two times, and the shortest value was used to calculate the MWS (m/s).

Handgrip strength was measured by the JAMAR hand dynamometer (Sammons Preston, Illinois, USA). Patients were asked to sit with their wrist in a neutral position and the elbow flexed at 90°. Handgrip strength was measured two

times for each hand, and the highest value was applied for the analysis.

Knee extensor isometric muscle strength was measured using a digital hand-held dynamometer (μ-Tas F1; Anima Corporation, Tokyo, Japan). During testing, the participants dangled their legs off the table, with their arms held on the edge of the table and were then fitted with a hand-held dynamometer on the anterior aspect of the measured ankle, which was fixed to the stem of the table by a vinyl strap. After one or two practice trials, each participant was asked to extend the leg and push as hard as possible, with maximal effort two times per leg. The lever length was also measured from the lateral joint space of the knee to the lateral top of the belt. Knee extensor isometric muscle strength was transformed into Newton meters per body weight (Nm/kg), and the highest value was used for the analysis.

Anxiety and depression were assessed by well validated questionnaires of Hospital Anxiety and Depression scale.[22] This scale is a self-reported questionnaire comprising 14 items (seven items for anxiety and the other seven items for depression) with four-point Likert scale.

Patient education for desirable lifestyle during hospitalization

During hospitalization, all patients received individual education regarding desirable lifestyle to reduce stroke risk, including reduction in fat and salt intake, smoking cessation, alcohol reduction, and promoting PA, which achieves walking activity with fast pace for 30 to 40 minutes per day until the end of three months post discharge.[7,23] No patients received rehabilitation program post discharge that intended to reduce vascular events risk.

Statistical analysis

The continuous variables were expressed as median (inter-quartile range) because almost all the data showed skewed distributions. Categorical variables were expressed as numbers (%). The changes of medication use at discharge and three months post discharge were assessed by chi-square test. Baseline variables of the patient characteristics were compared according to composite vascular events and MWS using the Mann-Whitney U-test, chi-square test, or Fisher's exact test.

Univariate and multivariate Cox proportional hazards analyses were used to identify independent risk factors for composite vascular events. For Cox proportional hazards analysis, the following cutoffs were defined: age ≥65, PVH and DWMH Fazekas's grade =3,[24] SBP ≥140 mmHg,[14] DBP ≥90 mmHg,[14] BMI ≥25,[25]

mid-upper arm circumference <22 cm,[26] HDL-C <40 mg/dl,[15] LDL-C ≥140 mg/dl,[15] TG ≥150 mg/dl,[15] HbA1c ≥6.5 %,[16] Albumin <3.5 g/dl,[27] alcohol intake ≥25 g/day,[25] MWS <1.45 m/s (lowest tertile), handgrip strength ≤28.0 kgf for men and ≤15.0 kgf for women (lowest tertile), knee extensor isometric muscle strength ≤1.27 Nm/kg for men and ≤0.92 Nm/kg for women (lowest tertile), anxiety and depression scores ≥8 in each score.[22] Variables with p <0.1 at univariate analysis were entered into multivariate analysis using stepwise selection. The cumulative events rates were evaluated for each of composite vascular events and stroke or TIA recurrence using the Kaplan-Meier method. Then, the cumulative composite events rate was examined according to tertiles of MWS using the Kaplan-Meier method followed by the log-rank test.

All statistical analyses were performed using SPSS 24.0 software package (IBM Japan, Tokyo, Japan). A p value <0.05 was considered statistically significant.

Results

Patient clinical characteristics and primary outcomes

A total of 255 patients (175 men, median age 70.0 years) were enrolled in this study. During the median 679 (250-1100) days follow-up period, 31 patients (12.2%)

experienced primary outcomes: 22 (8.6%) experienced stroke or TIA recurrence, six (2.4%) experienced cardiovascular disease, and three (1.2%) experienced peripheral artery disease (Figure 1). Besides, six out of the 22 patients (27.3%) who experienced stroke or TIA recurrence had a severe disability (mRS ≥3). Composite vascular event rates according to baseline stroke subtype in atherothrombotic, cardioembolic, lacunar, and others, such as arterial dissection and undetermined etiology, were 12.7%, 7.4%, 12.2% and 20.0%, respectively. In TIA, event rate was 18.8%.

The Kaplan-Meier estimates of cumulative risk of composite vascular events at one-, two-, and three-years were 9.6%, 14.4%, and 15.2%, respectively. Of these, cumulative risk for stroke or TIA recurrence at one-, two-, and three-years were 7.4%, 9.7%, and 10.5%, respectively (Figure 2).

Baseline patient characteristics according to composite vascular events and MWS are shown in Table 1. Patients with vascular events showed higher PVH grade, high prevalence of previous stroke history, and slower MWS. Patients who manifested slower MWS had more known vascular risk factors, such as old age, cerebral white matter lesions, hypertension, and higher HbA1c, than those who did not.

Among medications, percentage of cases using antihypertensive agents increased from 39.6% at discharge to 70.1% at three months after discharge, while such change was not observed regarding other medications (Table 2).

Cox proportional hazards analysis for composite vascular events

In univariate analysis, PVH, SBP, prescription of antiplatelet agents, previous history of stroke, and MWS were shown (p <0.1). Out of these factors, SBP was associated with a lower hazard ratio, and others were associated with a higher hazard ratio. A multivariate analysis performed on 244 complete sets of data with 29 composite vascular events selected PVH and MWS as significant independent predictors (Table 3).

Survival analysis for MWS

The Kaplan-Meier survival curves of composite vascular events according to tertiles of MWS showed a significantly higher event rate in the lowest tertile (p=0.011). Cumulative risk of composite vascular events one-, two-, and three-years post discharge were 15.6%, 22.1%, and 24.0% in the lowest tertile, 6.5%, 10.4%, and 10.4% in the middle to highest tertile, respectively (Figure 3).

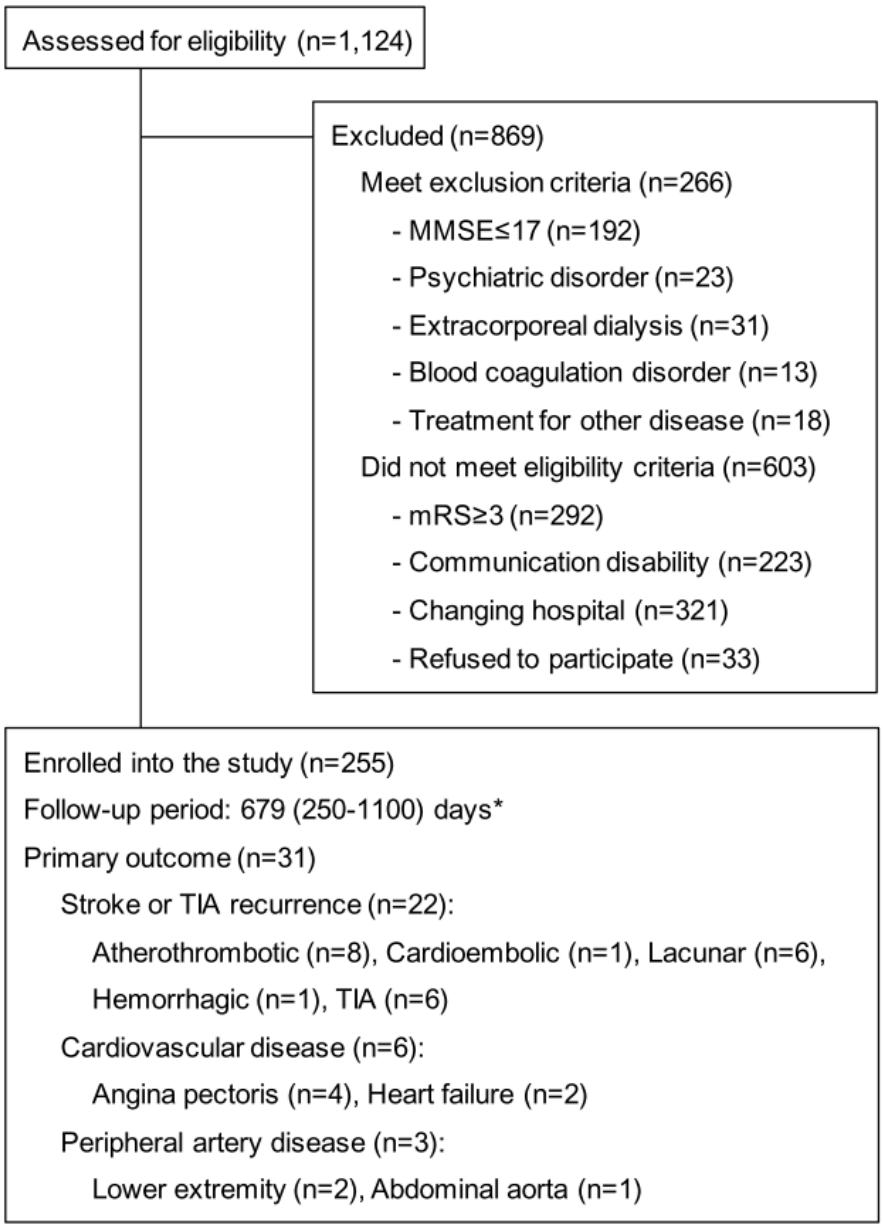


Figure 1. Flow of participants through the study.

*median (inter-quartile range).

MMSE= mini-mental state examination, mRS= modified rankin scale, TIA=transient ischemic attack.

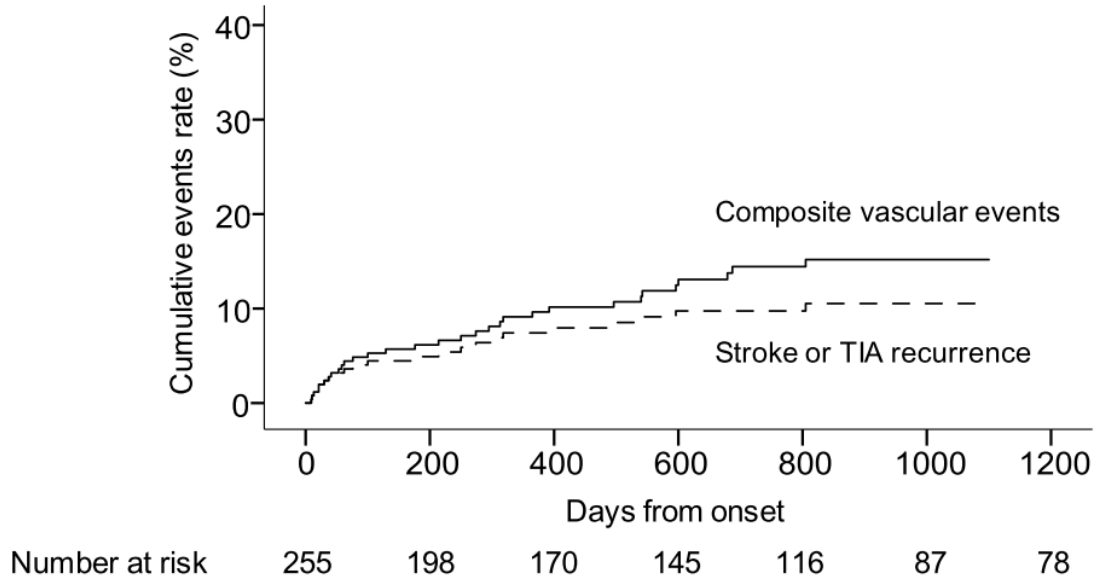
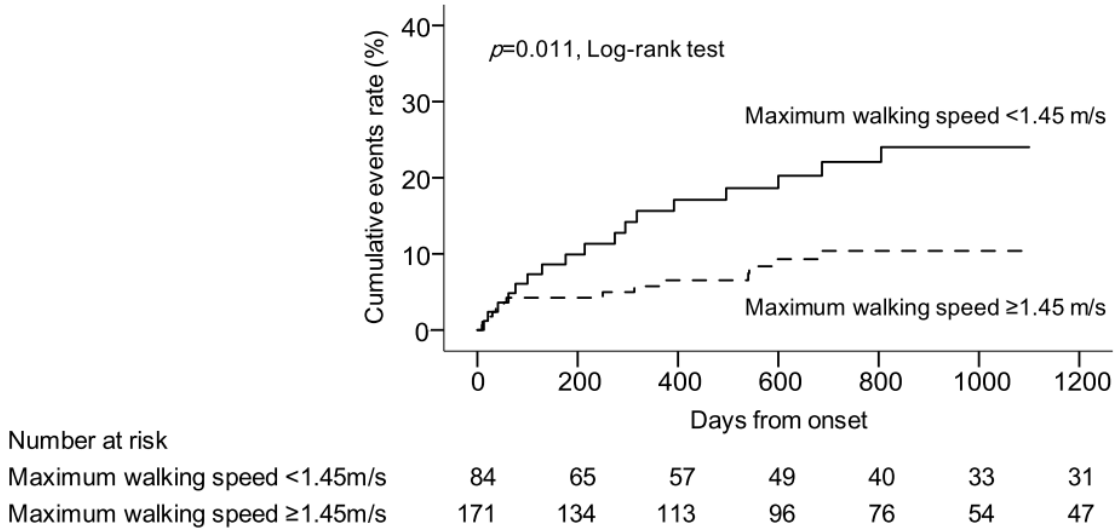


Figure 2. The Kaplan-Meier estimates of cumulative risk of composite vascular events at one-, two-, and three-years were 9.6%, 14.4%, and 15.2%, respectively. For stroke or transient ischemic attack (TIA) recurrence, cumulative risk at one-, two-, and three-years were 7.4%, 9.7%, and 10.5%, respectively.



Number at risk							
Maximum walking speed <1.45m/s	84	65	57	49	40	33	31
Maximum walking speed ≥1.45m/s	171	134	113	96	76	54	47

Figure 3. The Kaplan-Meier estimates of cumulative composite vascular events rate were examined according to tertiles of maximum walking speed: lowest tertile <1.45 m/s, middle to highest tertile ≥1.45 m/s. Cumulative risk of composite vascular events at one-, two-, and three-years were 15.6%, 22.1%, and 24.0% in the lowest tertile, 6.5%, 10.4%, and 10.4% in the middle to highest tertile, respectively.

Table 1. Clinical characteristics of patients according to composite vascular events and maximum walking speed

	Composite vascular events			Maximum walking speed		
	With events (n=31)	Without events (n=224)	*p*	<1.45 m/s (n=84)	≥1.45 m/s (n=171)	*p*
Age (yo)	72.0 (62.0-77.0)	69.5 (63.0-76.0)	0.529	76.0 (69.0-79.0)	67.0 (60.0-73.0)	<0.001
Sex (male), n (%)	21 (67.7)	154 (68.8)	0.910	51 (60.7)	124 (72.5)	0.056
mRS (grade 0/1/2), n (%)	10/12/9 (32.3/38.7/29.0)	73/108/43 (32.6/48.2/19.2)	0.403	15/40/29 (17.9/47.6/34.5)	68/80/23 (39.8/46.8/13.5)	<0.001
Stroke subtype and TIA, n (%)			0.546			0.024
Atherothrombotic	16 (51.6)	110 (49.1)		51 (60.7)	75 (43.9)	
Cardioembolic	4 (12.9)	50 (22.3)		11 (13.1)	43 (25.1)	
Lacunar	6 (19.4)	43 (19.2)		18 (21.4)	31 (18.1)	
Others	2 (6.5)	8 (3.6)		1 (1.2)	9 (5.3)	
TIA	3 (9.7)	13 (5.8)		3 (3.6)	13 (7.6)	
PVH (grade 0/1/2/3), n (%)	5/11/6/7 (17.2/37.9/20.7/24.1) (n=29)	44/82/79/15 (20.0/37.3/35.9/6.8) (n=220)	0.014	10/25/31/17 (12.0/30.1/37.3/20.5) (n=83)	39/68/54/5 (23.5/41.0/32.5/3.0) (n=166)	<0.001
DWMH (grade 0/1/2/3), n (%)	1/6/14/8 (3.4/20.7/48.3/27.6) (n=29)	29/52/96/43 (13.2/23.6/43.6/19.5) (n=220)	0.385	4/14/34/31 (4.8/16.9/41.0/37.3) (n=83)	26/44/76/20 (15.7/26.5/45.8/12.0) (n=166)	<0.001
SBP (mmHg)	126.9 (116.4-135.5) (n=30)	132.7 (120.5-147.8) (n=219)	0.142	132.2 (124.8-149.7) (n=80)	130.5 (118.5-146.9) (n=169)	0.140
DBP (mmHg)	78.0 (70.9-85.8) (n=30)	82.3 (74.7-90.3) (n=219)	0.125	80.8 (72.6-86.9) (n=80)	82.5 (74.8-91.8) (n=169)	0.279
Abnormal ABI, n (%)	2 (7.7) (n=26)	26 (12.2) (n=213)	0.748	12 (15.2) (n=79)	16 (10.0) (n=160)	0.241
Nutrition						
BMI (kg/m^2)	22.5 (21.3-24.8)	23.0 (21.4-25.4)	0.499	22.9 (21.3-25.4)	22.9 (21.4-25.3)	0.528
Mid-arm circumference (cm)	27.5 (26.0-29.5)	27.5 (26.0-29.5)	0.793	27.0 (25.0-28.5)	27.5 (26.0-30.0)	0.002
Albumin (g/dl)	4.0 (3.8-4.3)	4.0 (3.8-4.3)	0.969	4.0 (3.7-4.2)	4.1 (3.8-4.3)	0.023
Comorbidity						
Hypertension, n (%)	22 (71.0)	157 (70.1)	0.920	67 (79.8)	112 (65.5)	0.019
Dyslipidemia, n (%)	23 (74.2)	144 (64.3)	0.277	56 (66.7)	111 (64.9)	0.782
HDL-C (mg/dl)	45.0 (38.0-54.0)	47.0 (42.0-57.0) (n=221)	0.347	46.0 (39.0-56.0) (n=83)	48.0 (41.0-57.0) (n=169)	0.305
LDL-C (mg/dl)	106.0 (86.0-140.0)	115.0 (94.0-140.0) (n=221)	0.233	114.5 (90.0-138.0)	114.5 (94.3-140.8) (n=168)	0.538
TG (mg/dl)	111.0 (79.3-142.3) (n=30)	109.5 (80.0-153.0) (n=220)	0.953	111.0 (75.0-150.0) (n=83)	109.0 (81.0-156.0) (n=167)	0.540
Diabetes mellitus, n (%)	10 (32.3)	75 (33.5)	0.892	34 (40.5)	51 (29.8)	0.090
HbA1c (%)	5.9 (5.6-6.7)	6.0 (5.7-6.6) (n=217)	0.380	6.2 (5.7-6.8) (n=82)	5.9 (5.6-6.5) (n=166)	0.043
Metabolic syndrome, n (%)	15 (48.4)	110 (49.1)	0.940	42 (50.0)	83 (48.5)	0.826
Medications, n (%)						
Antiplatelet agents	27 (87.1)	167 (74.6)	0.125	72 (85.7)	122 (71.3)	0.011
Anticoagulant agents	7 (22.6)	54 (24.1)	0.852	14 (16.7)	47 (27.5)	0.057
Statins	17 (54.8)	99 (44.2)	0.265	34 (40.5)	82 (48.0)	0.260
Antihypertensive agents	11 (35.5)	90 (40.2)	0.616	36 (42.9)	65 (38.0)	0.457
Antidiabetic agents	3 (9.7)	43 (19.2)	0.196	21 (25.0)	25 (14.6)	0.043
Prehospital life style						
Current smoking, n (%)	8 (25.8)	54 (24.1)	0.836	18 (21.4)	44 (25.7)	0.452
Alcohol intake (g/day)	0.0 (0.0-14.0)	0.2 (0.0-22.6)	0.218	0.0 (0.0-13.0)	6.0 (0.0-30.0)	<0.001
Previous history, n (%)						
Stroke	11 (35.5)	33 (14.7)	0.004	19 (22.6)	25 (14.6)	0.112
CVD	6 (19.4)	42 (18.8)	0.936	17 (20.2)	31 (18.1)	0.685
PAD	1 (3.2)	2 (0.9)	0.323	1 (1.2)	2 (1.2)	1.000
Physical function						
Maximum walking speed (m/s)	1.43 (1.26-1.67)	1.63 (1.39-1.82)	0.021	1.22 (0.99-1.36)	1.72 (1.61-1.89)	<0.001
Handgrip strength (kgf)	24.0 (16.0-36.0)	28.0 (20.0-34.8)	0.294	21.3 (16.0-26.0)	31.0 (23.0-37.0)	<0.001
KEIMS (Nm/kg)	1.2 (1.0-1.5)	1.4 (1.1-1.7)	0.264	1.1 (0.9-1.3)	1.5 (1.2-1.9)	<0.001
Psychological status						
Anxiety (score)	5.0 (3.0-8.0)	5.0 (3.0-7.0)	0.467	5.0 (3.0-7.0)	5.0 (2.0-7.0)	0.093
Depression (score)	5.0 (2.0-8.0)	4.0 (2.0-8.0)	0.435	6.0 (3.0-8.8)	4.0 (2.0-7.0)	0.002

Data are expressed as median (inter-quartile range) or number of patients (%). mRS=modified rankin scale, TIA=transient ischemic attack, PVH=periventricular hyperintensity, DWMH=deep white matter hyperintensity, SBP=systolic blood pressure, DBP=diastolic blood pressure, ABI=ankle-brachial index, BMI=body mass index, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides, HbA1c=hemoglobin A1c, CVD=cardiovascular disease, PAD=peripheral artery disease, KEIMS=knee extensor isometric muscle strength.

Table 2. Medications at discharge and three months post discharge

	At discharge (N=255)	At three-month (N=231)	*p*
Medications, n (%)			
Antiplatelet agents	194 (76.1)	171 (74.0)	0.601
Anticoagulant agents	61 (23.9)	60 (26.0)	0.601
Statins	116 (45.5)	117 (50.6)	0.256
Strong statins*	103 (40.4)	104 (45.0)	0.303
Antihypertensive agents	101 (39.6)	162 (70.1)	<0.001
ACE / ARB	62 (24.3)	115 (49.8)	<0.001
Calcium channel blocker	57 (22.4)	106 (45.9)	<0.001
Beta blocker	19 (7.5)	26 (11.3)	0.148
Diuretic	17 (6.7)	28 (12.1)	0.038
Number of classes			
1	60 (23.5)	78 (33.8)	<0.001
2	24 (9.4)	53 (22.9)	
≥3	17 (6.7)	31 (13.4)	
Antidiabetic agents	46 (18.0)	47 (20.3)	0.518

*Include atorvastatin, pitavastatin and rosuvastatin.

ACE=angiotensin-converting enzyme inhibitor, ARB=angiotensin II receptor blocker.

Table 3. Results of univariate and multivariate Cox proportional hazards analysis for composite vascular events

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
PVH (grade=3)	4.240	1.802-9.979	0.001	2.904	1.160-7.266	0.023
SBP (≥140mmHg)	0.454	0.186-1.111	0.084	NE		
Prescription of antiplatelet agents	2.476	0.866-7.079	0.091	NE		
Previous history of stroke	2.717	1.301-5.672	0.008	NE		
Maximum walking speed (<1.45m/s)	2.423	1.194-4.916	0.014	2.232	1.010-4.933	0.047

PVH=periventricular hyperintensity, SBP=systolic blood pressure, HR=hazard ratio, CI=confidence interval, NE=not entered into this model.

Discussion

The findings of this study demonstrate that MWS at discharge may predict future vascular events in MIS. Since prevention of vascular events is a main issue of clinical consideration, MWS at discharge could provide the strategy of early risk stratification, which is essential to achieve individualized medical care.

Walking speed, which is becoming a popular index of health status,[28] may also serve as a prognostic factor for vascular events in MIS. Walking speed has been demonstrated to be closely related to PA,[18,19] which has been recommended as one of the main components for preventing stroke recurrence and other vascular disease.[8,29] Our previous findings also indicate that PA may be a causal factor of vascular events,[5,7] since lifestyle modification, including promoting PA, reduces the incidence of vascular events after MIS onset.[30] The underlying mechanisms of the slowness, which leads to vascular events, may be speculated based on multidimensional aspects. For instance, walking speed has been reported to be associated with vascular risk factors, such as inflammatory markers,[31] HDL-C,[32] LDL-C,[33] homocysteine,[34] hypertension,[35] diabetes mellitus,[36] carotid artery intima-media thickness and plaques,[33,37] and white matter lesions.[38] The results of this study also demonstrate associations of slowness and some of these known risk

factors, suggesting that in this study, patients with slowness were at risk for vascular disease. For other potential mechanisms, skeletal muscle mass and intramuscular fat which are associated with walking speed.[39,40] In the previous reports, lower skeletal muscle mass and greater intramuscular fat have been identified as a risk factor for insulin resistance[41,42] and in turn cardiovascular disease including stroke.[43,44] Slowness has also been reported to be associated with cardiovascular events in patients with myocardial infarction[45] and in those with heart failure with ischemic etiology.[46] The findings of this study are in line with these results. Thus, slowness at discharge may serve to predict patients' risk of future vascular events.

PVH, another predictor selected for composite vascular events in this study, has been reported to be associated with increased risk of first-ever stroke[47] and stoke recurrence.[48,49] High grade PVH indicates arteriosclerotic diseases and ischemic tissue damage.[50] In addition, it has been considered that white matter lesions negatively affect the brain's capacity to tolerate an ischemic insult and capacity to compensate for the lost function and consequently facilitate conversion of asymptomatic infarcts into symptomatic infarcts.[48] Regarding atherosclerotic disease, white matter lesions are also influenced by common vascular risk factors

such as aging, diabetes, and hypertension.[51] Thus, we suppose that PVH is not a mere marker of high risk of stroke or TIA recurrence, but a predictor for advanced systemic atherosclerotic disease, including coronary or peripheral artery disease.[52]

SBP was selected as a candidate predictor by univariate Cox proportional hazards analysis. Since hypertension is the major risk factor for stroke recurrence, blood pressure management is a key component for recurrence prevention.[8] However, in this study, higher SBP at discharge tended to be associated with lower incidence of vascular events, while the level was not statistically significant suggesting that those with higher SBP at discharge had been managed by restricting antihypertensive medications during follow-up period. In fact, the proportion of patients using antihypertensive agents increased from 39.6% to 70.1% during three months post discharge, which was approximately the same as the prevalence of hypertension at baseline.

In this study, cumulative recurrence rates of stroke or TIA were 7.4% at one year and 10.5% at three years. These rates were lower than that of previous report, where 12.0% rate of stroke or TIA recurrence at one year was reported.[6] Other vascular events rate, including cardiovascular and peripheral artery diseases, was similar with previous reports, which was approximately 5% during three years.[4–6]

One possible reason for lower recurrence rate of stroke or TIA in this study may be attributed to prescribed medications. Our cohort consisted of approximately 50% atherothrombotic stroke and 20% cardioembolic and 20% lacunar cases (Table 1). Of those with atherothrombotic stroke, 90% were on strong statin medication, which was demonstrated to reduce stroke recurrence and cardiovascular events after stroke or TIA.[53] Added to this, as noted above, antihypertensive agents were precisely prescribed to patients with hypertension. Factors for patient exclusion may also be related with lower recurrence rate in this study. Among exclusion criteria, lower Mini-Mental State Examination score was related with vascular events.[54] In other factors, communication disability of eligibility criteria is likely to involve impairment of language, memory and executive function. These factors can cause vascular events through luck of precise disease management.[54]

Study Limitations

We must consider several limitations of this study. Firstly, the enrollment of MIS in this study was less than 30% of the total patients' population (Figure 1). It has been reported that approximately two-thirds of ischemic stroke patients were MIS,[3] suggesting our results may have a selection bias. This can be due to a result that we

excluded patients with dementia and communication disability, presumably at high risk for vascular events.[54] Therefore, the results of our study may have a limited generalization for MIS. Secondly, recurrence risk factors between caridoembolic and non-cardioembolic stroke are likely to be different; however, the small number of patients in this study did not allow us to perform a subgroup analysis. Further study based on stoke type will be needed to clarify the association between MWS and events rates. The causal effects of slowness on vascular events could also be a next concern of clinical study. Thus, this study may be a preliminary study to propose the impact of MWS as a prognostic indicator in MIS. Nevertheless, this study is the first report to demonstrate the possibility that MWS at discharge could be a prognostic factor for composite vascular events in MIS.

Conclusions

The results of this study indicate that MWS at discharge may stratify the target group for intensive risk reduction after discharge. Further study will need to clarify the cut-off value of MWS on vascular events in MIS.

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