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Recurrent Stroke Incidence and Etiology in Patients with Embolic Stroke of Undetermined Source and Other Stroke Subtypes

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Aims: This study aimed at clarifying the incidence of recurrent stroke and its etiology in patients with embolic stroke of undetermined source (ESUS) and other stroke subtypes in both the acute and chronic periods.

Methods: A total of 645 patients who were admitted with acute ischemic stroke (IS) between March 2015 and August 2019 were enrolled. Among them, 511 patients with ESUS, cardioembolism (CE), large artery atherosclerosis (LAA), or small vessel disease (SVD) were analyzed in this study. After discharge, 391 patients who visited the outpatient clinic were followed up until August 2020. The outcome was stroke recurrence.

Results: In the acute admission, recurrence rates were 7.6%, 8.1%, 18.8%, and 2.2% in patients with ESUS, CE, LAA, and SVD, respectively, and there were significant differences between the groups. The subtype of recurrence was almost identical to that of the index stroke. In the outpatient clinic, the annual recurrence rates were 4.4%, 4.3%, 6.0%, and 2.9% in ESUS, CE, LAA, and SVD, respectively, and no difference was observed. Subtypes of recurrence in outpatients with ESUS included ESUS, intracerebral hemorrhage (ICH), and SVD. Patients with ESUS and SVD had a higher risk of ICH during follow-up.

Conclusions: Although the risk of recurrence was comparable between patients with ESUS and CE and intermediate between patients with LAA and SVD, in the acute admission unit, the risk in outpatients was similar among all subtypes. ESUS was the most recurrent stroke subtype in outpatients with ESUS. The risk of hemorrhagic stroke was significant in patients with SVD and ESUS.

Key words: ESUS, Stroke subtype, Stroke etiology, Atrial fibrillation, Stroke recurrence

Introduction

The risk of ischemic stroke (IS) recurrence is highest in the acute stage, especially in the first 7 days after onset, and gradually declines with time[1-3]; this is the case for embolic stroke of undetermined source (ESUS)[4]. However, the risk and etiology of recurrent stroke in ESUS, which might differ between acute and chronic stages, needs further investigation because the best medical treatment for preventing stroke recurrence depends on the risk and etiology of recurrent stroke. In the acute stage, usually during the admission period, the risk of recurrent stroke is particularly high in patients with large artery atherosclerosis (LAA)[3]; however, the recurrence risk of other stroke subtypes after the acute period remains controversial[4]. Physicians usually start to see patients in the outpatient clinic within 6 months of their index stroke and administer medical treatments, including appropriate antithrombotic therapy, for patients with cardioembolic (CE) stroke and non-CE stroke to prevent secondary stroke. Both NAVIGATE ESUS[5] and RE-SPECT ESUS[6] studies reported that recurrent stroke incidence in outpatients with ESUS ranged from 4.0% to 5.0% in outpatient clinics, irrespective of the use of direct oral anticoagulant or aspirin. On the basis of nine cohort studies, a systematic review of ESUS also reported an average

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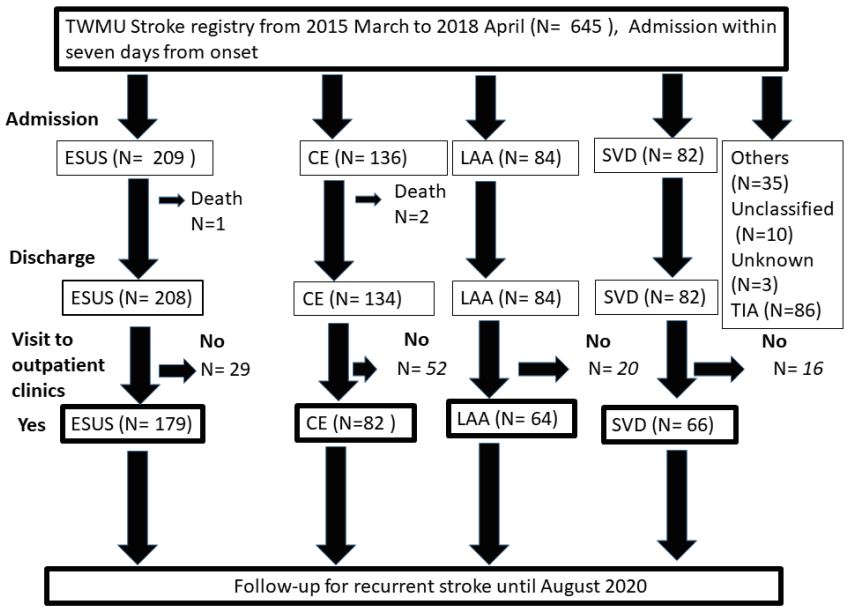

Fig. 1. Flowchart of the participants included in the Study

ESUS, embolic stroke of undetermined source; CE, cardioembolism; LAA, large artery atherosclerosis; SVD, small vessel disease; AF, atrial fibrillation

recurrent stroke incidence of 4.5% per year[7]; however, information on the etiology of recurrent stroke is little. Recently, Veltkamp *et al.* conducted a secondary analysis using NAVIGATE ESUS data and reported that the subtype of most recurrent strokes occurring after ESUS was ESUS itself and that CE associated with atrial fibrillation (AF) accounted a minority of cases[8]. In terms of other stroke subtypes, the incidence rates of recurrent stroke in patients with non-CE stroke, including both small vessel disease (SVD) and LAA, were 2.0%–3.0% according to PRATRO-I[9], 2.6%–5.0% according to CSPS.com trial[10], and 2.5% according to J-STARS[11]. In the SPS3 trial, recurrent stroke incidence in patients with SVD was around 2.5%[12]. Several studies showed that recurrent stroke incidence was around 2.0%–3.0% in patients with a history of CE stroke with AF[13, 14]. Contrarily, in outpatients receiving medical treatment in the WASID and SAMMPRIS trials, the risk of LAA with severe vascular lesions was high (around 10% per year)[15, 16]. These findings suggest that recurrence risk may differ between ESUS and LAA, SVD, or CE. Since the concept of ESUS was established, only a few studies have compared the risk and etiology of recurrence between ESUS and other stroke subtypes[4]. Thus, to clarify the clinical characteristics of ESUS in comparison with other stroke subtypes, we prospectively followed the incidence of stroke recurrence and its etiology in both the acute admission and chronic outpatient periods in the same patient population.

Materials and Methods

Patients

We recruited patients from our prospective cohort study, Tokyo Women' Medical University (TWMU) Stroke Registry (https://upload.umin.ac.jp, UMIN000031913), which included those who were admitted to our hospital within 7 days of onset of IS or transient ischemic attack (TIA). Between March 1, 2015, and August 31, 2019, a total of 645 patients in this registry **(Fig. 1)** were enrolled. We defined TIA as tissue-based, without acute infarction[17]. In brief, IS was classified into CE, LAA, SVD, other, and unknown at discharge according to the TOAST classification[18]; this classification was based on findings from routine blood examination, magnetic resonance imaging (MRI) or computed tomography, electrocardiography, carotid ultrasonography, transthoracic echocardiography, and 24-hour Holter electrocardiogram (ECG) in all patients and by additional transesophageal echocardiography and continuous 7-day monitoring of ECG in patients with suspected ESUS. Among the patients in the unknown etiology group, we defined ESUS based on the criteria proposed by Hart *et al.*[19] After excluding patients with other stroke etiologies (n=35) and unclassified because of mixed etiology (n=10), unknown etiology (which did not meet the criteria for ESUS, n=3) and

TIA (n=86), data on 511 patients, including those with ESUS (n=209), CE (n=136), LAA (n=84), and SVD (n=82), were further analyzed in this study. In the ESUS group, none of the patients showed paroxysmal AF (PAF) on 24-hour ECG monitoring or continuous ECG monitoring for at least 7 days. According to the general consensus, intracranial branch atheromatous disease (BAD) is included in ESUS[20]. Among the 209 patients with ESUS, 47 (22.5%) patients met the criteria for BAD. There were three patients who died during admission. Therefore, the subtype diagnoses in 508 patients at discharge were ESUS (n=208), CE (n=134), LAA (n=84), and SVD (n=82). Among these 508 patients, 391 patients visited our outpatient clinic within 6 months after the onset of stroke and were followed up until August 31, 2020. Medical treatment was provided using appropriate antithrombotic agents, and their blood pressure (<140/90 mmHg), low-density lipoprotein (LDL) cholesterol (<120 mg/dL), and hemoglobin A1c (HbA1c; <7.0%) were managed according to the guidelines in our country. These outpatients were followed up for stroke recurrence and its subtype, survival, and new-onset AF **(Fig. 1)**. Outpatients with ESUS underwent ECG exanimation when they complained of pulse deficit, palpitation, and/or chest pain. Otherwise, all patients underwent routine ECG examination at 6-month intervals. All patients provided written informed consent before enrollment in the TWMU STROKE Registry.

Risk Factors, Laboratory Examination, and MRI Findings during Admission

Hypertension was defined as a casual blood pressure of ≥ 140/90 mmHg or current use of antihypertensive agents. Levels of fasting blood glucose, HbA1c, serum LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and brain natriuretic protein (BNP) were determined from blood samples at admission. Data on the medical history and medication use of patients were obtained from their clinical records. Diabetes mellitus was defined as a fasting blood glucose level of ≥ 126 mg/dL, HbA1c of ≥ 6.2%, or use of glucose-lowering agents. Dyslipidemia was defined as a fasting serum LDL cholesterol level of ≥ 120 mg/dL, triglyceride level of ≥ 150 mg/dL, HDL cholesterol level of <40 mg/dL, or current use of cholesterol-lowering agents. Smoking status was categorically evaluated from self-reports; a smoker was defined as someone who currently smokes or previously smoked more than 10 cigarettes per day for more than 1 year.

Outcome

The primary outcome was recurrent stroke and neurological worsening in the acute period and the first recurrent stroke in outpatient clinics. The secondary outcomes were survival and new-onset AF. As discriminating stroke recurrence from stroke progression when new neurological deficits or worsening develop after enrollment in the acute period is difficult[21], we did not distinguish recurrence from worsening during admission. When a stroke recurred, all patients were admitted to our hospital, and the etiology was again classified according to the TOAST classification[18] and ESUS criteria described by Hart *et al.*[19]

Statistical Analysis

Statistical analysis was performed using JMP Pro ver. 14 SID (SAS Institute Inc. Cary, NC, USA). Proportions of patients were compared between groups using Pearson's χ^2 test. Continuous variables are presented as medians and quartile range and were compared using the Mann–Whitney U test. In all tests, $P<0.05$ was considered significant. The annual rate of stroke recurrence for each stroke subtype was calculated using the Kaplan–Meier method.

Results

Fig. 1 shows a flowchart of the study. During admission, 511 patients were classified as having ESUS (n=209), CE (n=136), LAA (n=84), or SVD (n=82). **Table 1** shows the baseline data of patients. There were seven patients who were first classified as having ESUS but were then reclassified as having CE after detecting PAF during the continuous 7-day monitoring. There were 3 patients who died and 39 patients who had recurrent stroke or neurological deterioration during the median admission period of 14 days. Recurrent stroke incidence during admission was 7.6%, 8.1%, 18.8%, and 2.2% in patients with ESUS, CE, LAA, and SVD, respectively, and there was a significant difference between the groups (χ^2=8.38, P=0.038) **(Fig. 2A)**. The characteristics of the recurrent stroke subtype were almost identical to those of the index stroke **(Table 2)**. In the Kaplan–Meier curve, recurrence risk tended to be high in patients with LAA, followed by those with CE and ESUS, and was low in those with SVD (log rank P=0.061).

Overall, 508 patients were discharged with a diagnosis of ESUS (n=208), CE (n=134), LAA (n=84), or SVD (n=82). Almost all patients (99.6%) received either antiplatelet or antithrombotic therapy, but two patients (0.39%) were discharged without any antithrombotic medication because of gastrointestinal bleeding and severe anemia. Among them, 391

Table 1. Characteristics of Patients during Admission

	Total	Visit in outpatient within 6 months after onset of stroke			ESUS	CE	LAA	SVD
		Yes	No	*P*				
Number	511	391	120		209	136	84	82
Age (years)Median	74	72	80	<0.01	72	79	73	70
IQR	65-81	63-79	70-85		61-79	69-83	67-81	60-77
Men, %	60.5	62.7	53.0	0.06	61.7	55.2	71.4	54.9
Body-mass index	23.2	23.7	22.0	<0.01	23.6	22.0	24.3	24.3
IQR	21-26	21-26	20-24		21-26	21-26	21-26	21-27
NIHSS at admission	2	2	5	<0.01	2	3	3	2
IQR	1-5	1-4	2-11		1-4	1-9	1-5	1-3
mRS at discharge	1	1	3	<0.01	1	2	1	1
IQR	0-3	0-2	1-4		0-1	1-3	0-3	0-1
Admission period, days	18	16	29	<0.01	17	22	20	13
IQR	13-28	12-22	18-44		13-24	14-36	14-29	11-19
All death (%)	3 (0.6)				1 (0.5)	2 (1.5)	0	0
Discharge to home, %	79.1	89.0	34.2	<0.01	83.9	71.6	69.0	86.7
History of hypertension, %	77.5	76.3	81.2	0.27	76.6	72.8	79.5	85.4
Diabetes mellitus, %	40.1	40.3	39.3	0.85	43.5	31.1	45.8	54.9
Dyslipidemia, %	50.3	53.1	41.0	0.02	51.7	39.7	59.8	54.9
CHF, %	10.6	8.9	16.2	0.02	5.3	25.0	8.3	2.4
Ischemic Heart Disease	14.5	14.2	15.4	0.75	10.5	21.3	20.2	7.3
Chronic kidney disease, %	28.2	27.7	29.9	0.65	18.7	41.2	31.3	28.1
Atrial fibrillation	22.8	17.6	40.2	<0.01	0.0	82.4	3.6	0.0
Current Smoking, %	16.1	18.2	9.0	0.02	23.0	4.0	15.7	18.4
eGFR	61.1	61.1	59.8	0.44	64.3	46.6	60.6	64.9
IQR	41-75	42-74	34-77		48-79	32-70	38-70	47-77
LDL cholesterol mg/dl	113	113	111	0.43	112	106	122	122
IQR	89-140	89-142	85-138		90-138	83-130	88-156	99-147
HDL cholesterol mg/dl	53	53	54	0.70	52	56	49	54
IQR	41-66	41-67	41-65		41-68	46-68	39-59	40-69
Triglycerides mg/dl	109	114	97	0.01	113	92	128	128
IQR	77-156	80-167	71-139		81-156	66-138	82-188	77-193
HbA1c (%)	6.1	6.1	6.0	0.59	6.0	6.0	6.4	6.1
IQR	5.7-7.1	5.7-7.2	5.6-7.0		5.7-7.2	5.6-6.7	5.8-7.2	5.7-7.3
Brain Natriuretic Protein, mg/dl	62.6	52.9	166.3	<0.01	46.1	233.1	44.2	41.6
IQR	27-177	25-126	47-366		20-89	102-447	24-150	22-83
Treatment with alteplase, %	6.3	5.1	10.5	0.04	4.8	11.2	8.6	0.0
Endovascular treatment, %	6.8	1.8	6.2	0.01	1.5	6.9	2.5	0.0
Anti-platelet drug at discharge, %	71.3	75.8	56.4	<0.01	83.2	22.2	96.4	96.3
Anti-coagulant at discharge, %	34.2	29.6	49.6	<0.01	16.4	94.0	13.3	2.5
Statin at discharge, %	66.0	70.2	52.1	<0.01	66.5	45.2	90.5	74.1

Data are median and interquartile range (IQR) or number (%). ESUS; embolic stroke of undetermined source, CE; cardioembolism, LAA: large artery atherosclerosis, SVD, small vessel disease, AF; atrial fibrillation. TIA; transient ischemic attack. CHF; congestive heart failure, mRS; modified Rankin scale, NIHSS; national institute of health stroke scale.

[#]Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

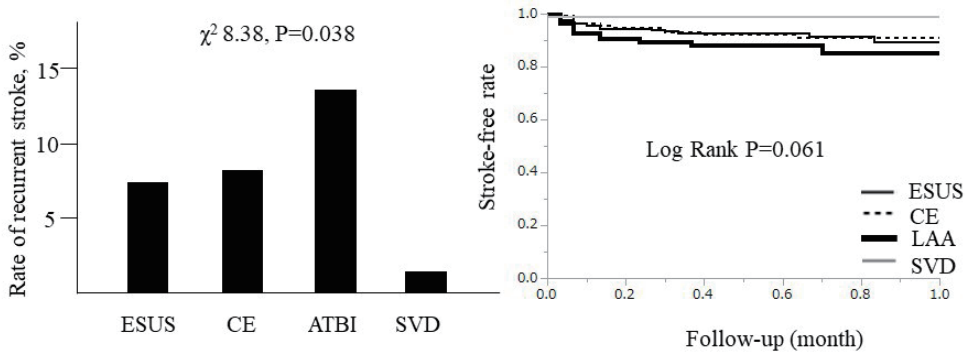

Fig. 2. Stroke recurrence in the acute admission unit

(A) Rate of recurrent stroke during the acute admission period in patients with stroke subtype
(B) Cumulative incidence of recurrent stroke during the acute period by stroke subtype
Recurrent stroke includes both recurrence and neurological worsening

Table 2. Recurrent stroke, neurological worsening, survival and new onset of atrial fibrillation during admission period of acute stage in each stroke subtype

		Total	ESUS	CE	LAA	SVD
Number		511	209	136	84	82
Follow-up period, months, Median (IQR)		0.53 (0.40-0.83)	0.53 (0.40-0.73)	0.62 (0.40-1.00)	0.56 (0.40-0.83)	0.43 (0.36-0.62)
Recurrent stroke,	*N*	39	16	11	11	1
Subtype	ESUS	15	15	0	0	0
	CE	10	0	10	0	0
	LAA	12	0	1	11	0
	SVD	1	0	0	0	1
	Others/Unknown	0	0	0	0	0
	Intracerebral hemorrhage	1	1	0	0	0
Monthly rate, %/month		9.7	9.2	8.9	18.8	2.2
All death		3	1	2	0	0
Incidence of new onset of atrial fibrillation		6	6	-	0	0

patients (78.3%), including 179 (86.1%) of the 208 with ESUS, 35 with BAD, 82 (61.1%) of the 134 with CE, 64 (76.1%) of the 84 with LAA, and 66 (80.4%) of the 82 with SVD **(Fig. 1, Table 3)**, visited our outpatient clinic within 6 months after stroke onset. Patients who could not visit the outpatient clinic were older and had higher NIHSS scores at admission, higher mRS scores at discharge, lesser frequency of being discharged to home, higher incidence of a history of congestive heart failure and AF, higher BNP values, greater prevalence of anticoagulant use, and lesser prevalence of antiplatelet and statin use than those who visited the outpatient clinic **(Table 1)**. Among the 391 outpatients, only 31 patients (7.9%) were lost to follow-up because of personal reasons; however, the follow-up time for each patient was included in the analysis.

During the median follow-up period of 2.2 years in the outpatient clinic, recurrent stroke occurred in 39 patients (annual rate, 4.3%), including 8 patients with intracerebral hemorrhage (ICH) **(Table 3)**. The Kaplan–Meier curve showed a similar recurrence rate among the four stroke subtypes **(Fig. 3A)**. The annual incidence rates of stroke recurrence were 4.4%, 4.3%, 6.0%, and 2.9% in patients with ESUS, CE, LAA, and SVD, respectively. The incidence of stroke recurrence in patients with ESUS was similar to that in the other three groups. The etiology of recurrent stroke was identical to the index stroke in CE and LAA; however, among the 19 patients who recurred after ESUS, ESUS was the most recurrent stroke subtype (n=11). Two and six patients had SVD and ICH, respectively, while none had CE. Among the 179 outpatients with ESUS, 1 patient in 35 BAD cases and 5 patients in 144 non-BAD cases had ICH. In SVD, five patients had recurrent stroke; among

Table 3. Follow-up of outpatients in each stroke subtype

		Total	ESUS	CE	LAA	SVD
Number		391	179	82	64	66
Follow-up period, yr, Median (IQR)		2.2 (1.3-3.4)	2.5 (1.4-3.5)	1.7 (1.3-3.0)	2.1 (1.3-2.9)	3.0 (1.6-3.5)
Recurrent stroke,	*N*	39	19	7	8	5
Subtype	ESUS	12	11	0	0	1
	CE	7	0	7	0	0
	LAA	8	0	0	8	0
	SVD	4	2	0	0	2
	Others/Unknown	0	0	0	0	0
	Intracerebral hemorrhage	8	6	0	0	2
Annual rate, %/yr		4.3	4.4	4.3	6.0	2.9
All death		42	18	13	6	5
Annual rate, %/yr		4.4	4.0	7.7	4.1	2.7
Incidence of new onset of atrial fibrillation		5	4	-	0	1
Annual rate, %/yr		-	0.9	-	0	0.5

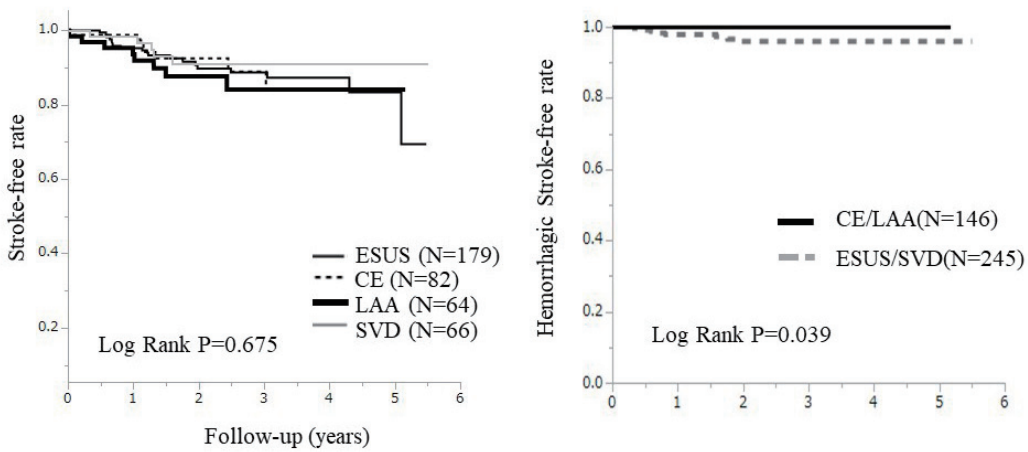

Fig. 3. Stroke recurrence and risk of hemorrhagic stroke in the outpatient clinic

(A) Cumulative recurrent stroke incidence in outpatient clinic by stroke subtype
(B) Cumulative rate of hemorrhagic stroke in outpatient clinic by ESUS/SVD and CE/LAA groups

them, two patients had ICH. The annual incidence rates of ICH were 1.3% and 1.2% in ESUS and SVD, respectively. The Kaplan–Meier curve showed a higher rate of ICH in patients with ESUS and SVD than in those with CE and LAA **(Fig. 3B)**. The ESUS, LAA, and SVD groups were examined for signs of new-onset AF. Four cases of PAF among the patients with ESUS and one among those with SVD were found during follow-up. Therefore, the annual incidence rate of new-onset AF in outpatients with ESUS was 0.9% **(Table 3)**.

Discussion

Our study demonstrated that, under appropriate medical treatment, the risk of stroke recurrence in patients with ESUS was approximately 8% per month in the acute admission period, which is similar to that observed in patients with CE, lower than that in patients with LAA, and higher than that in patients with SVD. In the chronic outpatient clinic, it is 4% per year; this is similar to that for other stroke subtypes. Previous studies showed that the risk of stroke recurrence in patients with LAA is more than 10% within the first month[22], that in patients with CE is 2.3%–4.9% within 14 days[23, 24], and that in patients with ESUS is 4.0%–5.0% within the first month[24]. The highest incidence rates of stroke recurrence in patients with LAA and ESUS in this study were similar to those reported in previous

studies[22, 25]. The high recurrence risk in patients with CE in our study might be partly due to the inclusion of patients with an artificial valve and valvular disease. However, it is worth noting that the characteristics of the recurrent stroke subtype were almost identical to those of the index stroke during the acute period.

In the chronic outpatient clinic, recurrent stroke incidence in patients with ESUS (4.4% per year) was similar to that in the other groups, which ranges from 2.9% per year in the SVD group to 6.0% per year in the LAA group **(Table 3)**. The incidence of recurrent stroke in outpatients with ESUS in our study was similar to that reported in the NAVIGATE ESUS[5] and RE-SPECT ESUS trials[6]. The subtype of recurrent stroke that commonly occurred among outpatients with ESUS was ESUS, while ICH was also often observed in our study. In the secondary analysis of the NAVIGATE ESUS study, 58% of recurrent IS was ESUS and 10%–15% were LAA, CE, or SVD[8]. During the follow-up period, none of the outpatients with ESUS developed CE in this study. The annual hemorrhagic stroke incidence in patients with ESUS (1.3%) in this study is higher than that for those assigned to aspirin treatment in the NAVIGATE ESUS (0.1%) and RE-SPECT ESUS (0.2%) studies. However, in East Asian participants in the NAVIGATE ESUS study, the annual hemorrhagic stroke rate was 0.67%; this is similar to that observed in our study and much higher than that observed in other regions (0.11%)[26]. Our study enrolled aged participants (71 years old) in comparison to the NAVIGATE ESUS (67 years old) and RE-SPECT ESUS (64 years old) studies, and this may have contributed to a higher rate of hemorrhagic stroke. The inclusion of BAD in ESUS might contribute to high risk of hemorrhagic stroke in ESUS in this study, although our study could not show the difference in the rate of ICH between BAD and non-BAD cases of ESUS. The annual incidence rate of hemorrhagic stroke in patients with SVD (1.2%) in this study was similar to that of Japanese patients with SVD who received aspirin treatment in the CSPS2 study (1.20%)[27]. Our results would suggest the importance of preventing hemorrhagic stroke in outpatients with ESUS and SVD. Since we recently reported the use of aggressive lowering of blood pressure level for preventing secondary stroke, especially for preventing hemorrhagic stroke[28], intensive control of blood pressure level together with appropriate use of antithrombotic agents would be beneficial for outpatients with ESUS.

We tried to detect PAF using routine clinical practice in outpatients with ESUS. However, the PAF detection rate was extremely low (1.5% per year). Furthermore, no patient with new-onset PAF developed recurrent stroke. Several studies have reported that new-onset PAF was detected in 30% of patients with cryptogenic stroke after 3 years using an insertable device[29-31]. However, the causal relationship between index stroke and new-onset PAF over a longer follow-up period remains unclear[32].

The strengths of this study are as follows. We could investigate the etiology of all recurrent strokes using exactly the same criteria because patients were managed in our outpatient clinic and were readmitted to our hospital during stroke recurrence. The findings that the characteristics of most recurrent stroke subtypes were identical to those of the index stroke are in line with those of the Oxford Vascular Study[33].

This study has several limitations. First, there were a small number of patients who experienced recurrent stroke. Besides the limited number of patients enrolled, the current management, which involved the use of antithrombotic agents and identification of the medical risk factors, would make the rate of recurrence lower than it has been reported in previous studies[33, 34]. Second, mortality in the outpatient clinic was high (4.4% per year), suggesting that the follow-up for a stroke-free period was incomplete. In previous randomized controlled trials, patients whose systemic condition was fair were usually selected. However, in our study, eligible patients were enrolled without considering their age or systemic condition; thus, the number of patients who died because of malignant neoplasm, bacterial infection, and cardiovascular events was higher. The mortality rate of ESUS was reported to be 1.0%–1.5% per year in the NAVIGATE ESUS[5] and RE-SPECT ESUS[6] trials. However, these were reported to be 4.4% per year for patients with ESUS in this study, 3.9% in a recent meta-analysis[7], and 6.0% in the Oxford Vascular Study[33]. Third, as shown in **Table 1**, the background between patients during acute admission and those in chronic period differs; thus, it is possible that outpatients in the chronic follow-up study do not represent all patients with stroke. Lastly, only 84 and 31 among 209 patients with ESUS received transesophageal echocardiography and continuous 7-day ECG monitoring during acute admission, respectively; thus, we could not extensively examine stroke etiology in all patients with ESUS

Conclusion

The risk of recurrent stroke in patients with ESUS during the acute admission period was similar to that in patients with CE, which tended to be lower than that in patients with LAA but higher than that in

patients with SVD. Furthermore, recurrent stroke incidence in patients with ESUS was similar to that for other stroke subtypes in the outpatient clinic. ESUS was the most common etiology of recurrent stroke in outpatients with ESUS, but ICH was also often observed. CE is unlikely to be the etiology of recurrent stroke in patients with ESUS.

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Author Contributions

ST and KK organized the study group, designed the study protocol, and drafted the manuscript. YS, KI, MK MS EH recruited the patients and collected the clinical information. EH and TH performed the statistical analysis and revised the manuscript.

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