RATE OF VASCULAR EVENTS AFTER THE FIRST HOSPITALISATION FOR NON-CARDIOEMBOLIC ISCHAEMIC STROKE OR TRANSIENT ISCHAEMIC ATTACK IN REAL-WORLD SETTINGS IN JAPAN: OBSERVATIONS FROM ASTRIS

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Introduction

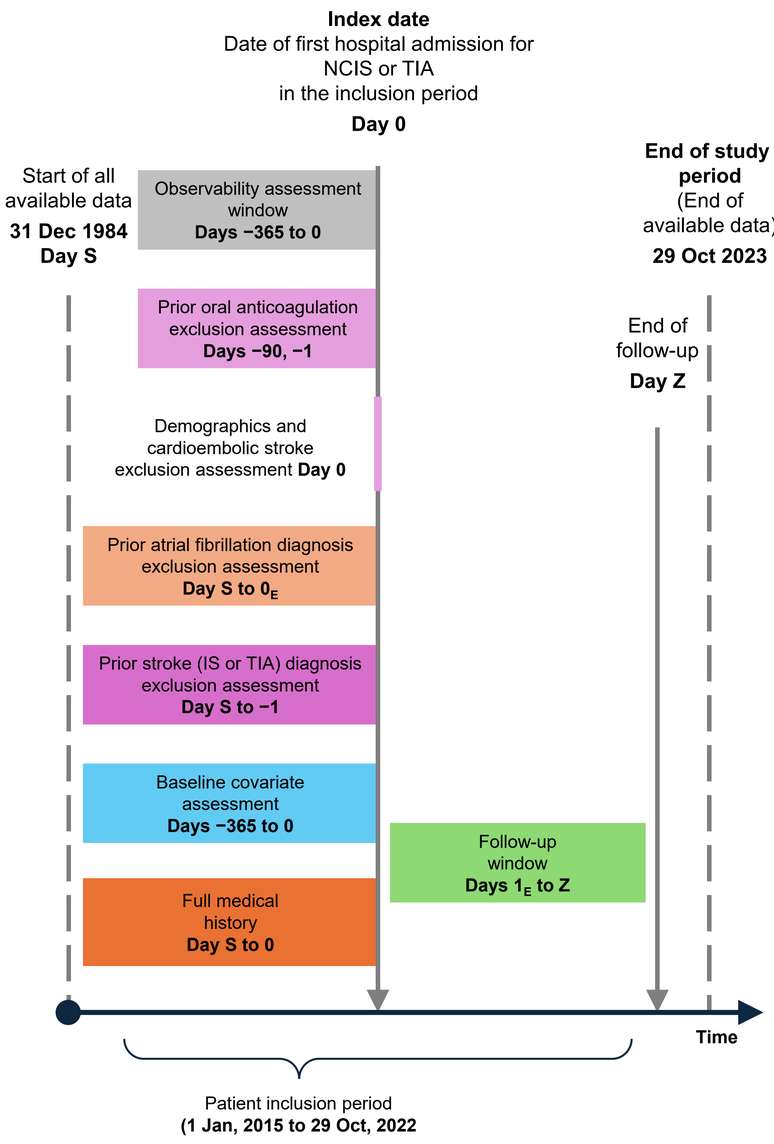
- Worldwide, stroke is the third most common Global Burden of Disease level 3 cause of death, and the fourth most common cause of disability-adjusted life-years.[1]
- In 2021, the global prevalence of stroke was 93.8 million, with 11.9 million incident strokes and 7.3 million deaths.[1]
- Globally, ischaemic stroke (IS) is the most frequent type of stroke, accounting for 65.3% of all incident cases, with global predictions that the incidence rate of IS will increase across all age groups, sexes, and socio-demographic index quintiles between 2020 and 2030.[1,2]
- It is estimated that recurrence rates of IS vary between 5.7–17.7% at year 1 and 14.0–35.3% at year 5.[3]
- In Japan, stroke remains the fourth most common cause of death,[4,5] and stroke incidence in Japan remains higher than in many Western countries.[6]
- The rate of recurrent IS and other clinically relevant events is not fully established among patients with non-cardioembolic IS (NCIS) or transient ischaemic attack (TIA) in contemporary clinical settings in Japan.
- ASTRIS-Japan aims to describe the rate of adverse clinical events in hospitalised patients newly diagnosed with acute NCIS or TIA.

Methods

Study design

- ASTRIS-Japan, is a retrospective cohort study based on the secondary use of healthcare data from a Japanese nationwide electronic medical record database maintained by Real-World Data, Co. Ltd.
- Patients aged ≥18 years with a first hospitalisation for NCIS or TIA between 1 January, 2015 and 29 October, 2022 were followed from 1 day after discharge until the end of observation or death (**Figure 1**).
- The study design applied to the overall population from the first hospitalisation for NCIS and TIA (defined as Day 0) is shown in **Figure 1**.
- Patients with prior occurrence of IS or TIA were excluded.
- Rates of adverse clinical events (IS, haemorrhagic stroke, cardiac events, newly diagnosed atrial fibrillation, and all-cause death) were assessed.

Figure 1. Design of the ASTRIS-Japan study for the overall population



Observability assessment window: An observability lookback period of at least 365 days (spanning Day −365 to 0) will be assessed before evaluating patient baseline characteristics.
Day 0_E: Discharge from index hospitalisation. Day S: Start date of all available data.
Day 1_E: Follow-up starts 1 day after discharge from index hospitalisation. Day Z: Patients will be followed until the earliest of death, end of observability, or the end of study period.
Note: additional censoring criteria were applied based on specific analyses.
NCIS, non-cardioembolic ischaemic stroke; TIA, transient ischaemic attack.

Statistical analysis

- Descriptive analyses were conducted using summary statistics for continuous and categorical data with mean, standard deviation, median, and interquartile range reported.
- The incidence rates per 1000 person-years of each adverse clinical event were estimated with 95% confidence intervals (CIs) reported. Analyses were computed using Aetion® Substantiate and R (v4.2).

Results

Participants

- A total of 18,719 patients (comprising 17,869 and 850 patients hospitalised for IS and TIA, respectively) were included in the analysis (**Table 1**).
- The overall mean age (years [standard deviation]) was 74.6 (12.4) and 44.4% were female.
- In the overall population, 13,445 (71.8%) were receiving antiplatelet therapy as assessed during the index hospitalisation.
- In patients with an index IS or TIA event, antiplatelet therapy was used by 12,193 (72.3%) and 532 (62.6%), respectively (**Table 1**).
- Patients were followed for a mean of 2 years (**Table 2**).

Table 1. Clinical characteristics and index event management in patients with first hospitalisation for NCIS or TIA

	Overall (N=18,719)	NCIS (n=17,869)	TIA (n=850)
Age, years			
Mean age (SD)	74.6 (12.4)	74.6 (12.3)	74.0 (13.6)
Median age (Q1, Q3)	77 (68, 84)	77 (68, 84)	76 (67, 84)
Sex, female, n (%)	8307 (44.4)	7888 (44.1)	419 (49.3)
Smoker, n (%)	4678 (25.0)	4509 (25.2)	169 (19.9)
Japan coma scale at admission, n (%)			
0 – alert	9854 (52.6)	9354 (52.3)	500 (58.8)
I – awake without stimuli	4655 (24.9)	4514 (25.3)	141 (16.6)
II – arousable with some stimuli	674 (3.6)	653 (3.7)	21 (2.5)
III – unarousable by any forceful stimuli	358 (1.9)	350 (2.0)	8 (0.9)
Missing	3178 (17.0)	2998 (16.8)	180 (21.2)
Comorbidities, n (%)			
Hypertension	12,750 (68.1)	12,193 (68.2)	557 (65.5)
Chronic kidney disease	5815 (31.1)	5571 (31.2)	244 (28.7)
Diabetes	5137 (27.4)	4935 (27.6)	202 (23.8)
CAD	4192 (22.4)	3995 (22.4)	197 (23.2)
Heart failure	3813 (20.4)	3649 (20.4)	164 (19.3)
Cancer	3649 (19.5)	3506 (19.6)	143 (16.8)
Dementia	2616 (14.0)	2510 (14.0)	106 (12.5)
Dysphagia	2247 (12.0)	2211 (12.4)	36 (4.2)
Anaemia	2193 (11.7)	2103 (11.8)	90 (10.6)
Carotid stenosis or previous carotid revascularisation	1282 (6.8)	1226 (6.9)	56 (6.6)
Myocardial infarction	782 (4.2)	753 (4.2)	29 (3.4)
PAD	485 (2.6)	466 (2.6)	19 (2.2)
Baseline medications, n (%)			
Antihypertensives	6385 (34.1)	6107 (34.2)	278 (32.7)
Lipid-lowering drugs	3708 (19.8)	3534 (19.8)	174 (20.5)
Statins	3308 (17.7)	3153 (17.6)	155 (18.2)
Anti-diabetic medications	2563 (13.7)	2462 (13.8)	101 (11.9)
Index event management,† n (%)			
Argatroban	3420 (18.3)	3365 (18.8)	55 (6.5)
Ozagrel	3393 (18.1)	3325 (18.6)	68 (8.0)
Heparin/low molecular weight heparin	6154 (32.9)	6015 (33.7)	139 (16.4)
APT within 2 days from admission	8928 (47.7)	8512 (47.6)	416 (48.9)
Edaravone	5407 (28.9)	5372 (30.1)	35 (4.1)
Osmotherapy	548 (2.9)	545 (3.0)	3 (0.4)
Mechanical thrombectomy	153 (0.8)	153 (0.9)	0 (0)
Intra-artery stenting/angioplasty	217 (1.2)	216 (1.2)	1 (0.1)
rt-PA	437 (2.3)	436 (2.4)	1 (0.1)
Rehabilitation therapy	9546 (51.0)	9464 (53.0)	82 (9.6)
In-hospital antithrombotic medication,† **n (%)**			
Any APT	13,445 (71.8)	12,193 (72.3)	532 (62.6)
Single APT	11,477 (61.3)	11,012 (61.6)	465 (54.7)
Aspirin	6270 (33.5)	5902 (33.0)	368 (43.3)
Clopidogrel	3763 (20.1)	3687 (20.6)	76 (8.9)
Prasugrel	41 (0.2)	40 (0.2)	1 (0.1)
Cilostazol	2058 (11.0)	2026 (11.3)	32 (3.8)
Dual APT	4428 (23.7)	4319 (24.2)	109 (12.8)
Aspirin + clopidogrel	3130 (16.7)	3054 (17.1)	76 (8.9)
Aspirin + prasugrel	192 (1.0)	186 (1.0)	6 (0.7)
Aspirin + cilostazol	794 (4.2)	774 (4.3)	20 (2.4)
Clopidogrel + cilostazol	487 (2.6)	477 (2.7)	10 (1.2)
Prasugrel + cilostazol	10 (0.1)	10 (0.1)	0 (0)
Triple APT	195 (1.0)	193 (1.1)	2 (0.2)
Aspirin + clopidogrel + cilostazol	188 (1.0)	187 (1.0)	1 (0.1)
Aspirin + prasugrel + cilostazol	7 (0)	6 (0)	1 (0.1)
Apixaban	272 (1.5)	270 (1.5)	2 (0.2)
Dabigatran	20 (0.1)	19 (0.1)	1 (0.1)
Edoxaban	445 (2.4)	434 (2.4)	11 (0.1)
Rivaroxaban	146 (0.8)	144 (0.8)	2 (0.2)
Warfarin	549 (2.9)	534 (3.0)	15 (1.8)

†Assessed during the index hospitalisation.
APT, antiplatelet therapy; CAD, coronary artery disease; NCIS, non-cardioembolic ischaemic stroke; PAD, peripheral artery disease; Q, quartile; rt-PA, recombinant tissue-type plasminogen activator; SD, standard deviation; TIA, transient ischaemic attack.

Mortality and clinical events

- A recurrent IS occurred in 3362 (18.0%) patients in the overall population (incidence rate per 1000 person-years [95% CI]: 103.5 [100.0–107.0]; **Table 2**).
- Approximately 18% (n=3292) of patients in the IS subgroup experienced a recurrent IS (incidence rate per 1000 person-years [95% CI]: 107.2 [103.5–110.8]) and approximately 8% (n=70) experienced a first IS in the TIA subgroup (incidence rate per 1000 person-years [95% CI]: 39.8 [30.5–49.1]) across all follow-up (**Table 2**).

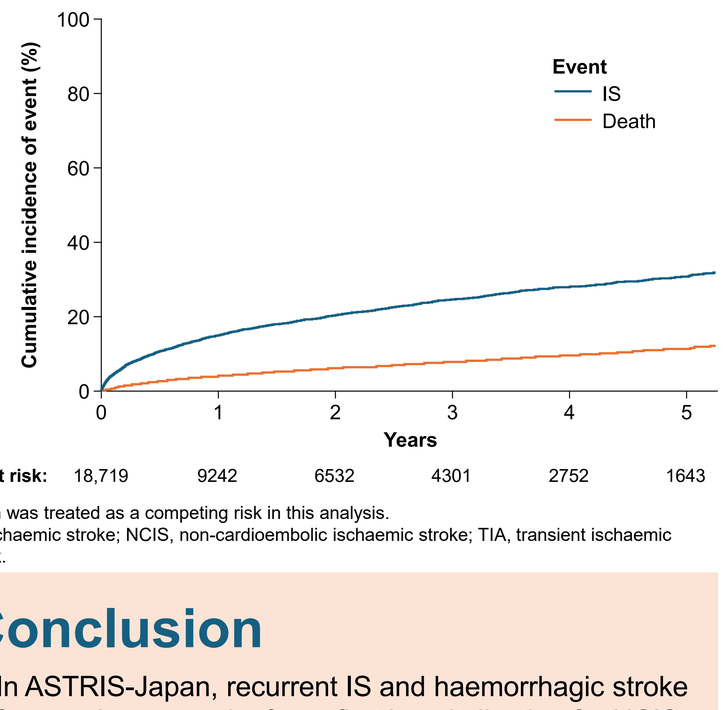
Table 2. Mortality and clinical events across follow-up in patients hospitalised for a first NCIS† or TIA

	Overall N=18,719	NCIS† n=17,869	TIA n=850
Follow-up time, days			
Mean (SD)	756.3 (765.8)	754.0 (765.4)	803.8 (772.7)
Median (Q1, Q3)	520 (66.0, 1245.0)	517 (64.0, 1241.5)	603 (116.0, 1274.8)
IS			
Patients with event,‡ n (%)	3362 (18.0)	3292 (18.4)	70 (8.2)
Up to 12 months, n (%)	2100 (11.2)	2064 (11.6)	36 (4.2)
Incidence rate§ per 1000 P-Y (95% CI) – overall follow-up	103.5 (100.0–107.0)	107.2 (103.5–110.8)	39.8 (30.5–49.1)
Incidence rate§ per 1000 P-Y (95% CI) – up to 12 months	181.3 (173.6–189.1)	187.9 (179.8–196.0)	60.4 (40.6–80.1)
Haemorrhagic stroke			
Patients with event,‡ n (%)	406 (2.2)	384 (2.1)	22 (2.6)
Up to 12 months, n (%)	177 (0.9)	166 (0.9)	11 (1.3)
Incidence rate§ per 1000 P-Y (95% CI) – overall follow-up	10.6 (9.6–11.7)	10.6 (9.5–11.6)	12.0 (7.0–17.0)
Incidence rate§ per 1000 P-Y (95% CI) – up to 12 months	14.1 (12.0–16.1)	13.9 (11.7–16.0)	18.1 (7.4–28.8)
Cardiac event‖			
Patients with event,‡ n (%)	802 (4.3)	758 (4.2)	44 (5.2)
Up to 12 months, n (%)	529 (2.8)	501 (2.8)	28 (3.3)
Incidence rate§ per 1000 P-Y (95% CI) – overall follow-up	21.7 (20.2–23.2)	21.6 (20.0–23.1)	25.0 (17.6–32.4)
Incidence rate§ per 1000 P-Y (95% CI) – up to 12 months	42.9 (39.2–46.5)	42.7 (38.9–46.4)	47.0 (29.6–64.3)
Newly diagnosed atrial fibrillation			
Patients with event,‡ n (%)	851 (4.5)	822 (4.6)	29 (3.4)
Up to 12 months, n (%)	415 (2.2)	404 (2.3)	11 (1.3)
Incidence rate§ per 1000 P-Y (95% CI) – overall follow-up	22.9 (21.3–24.4)	23.2 (21.7–24.8)	15.9 (10.1–21.7)
Incidence rate§ per 1000 P-Y (95% CI) – up to 12 months	33.3 (30.1–36.5)	34.1 (30.8–37.4)	18.1 (7.4–28.8)
All-cause death¶			
Patients with event,† n (%)	1779 (9.5)	1696 (9.5)	83 (9.8)
Up to 12 months, n (%)	819 (4.4)	786 (4.4)	33 (3.9)
Incidence rate§ per 1000 P-Y (95% CI) – overall follow-up	45.9 (43.8–48.1)	46.0 (43.8–48.2)	44.4 (34.8–54.0)
Incidence rate§ per 1000 P-Y (95% CI) – up to 12 months	64.7 (60.2–69.1)	65.2 (60.7–69.8)	53.9 (35.5–72.3)

†An index stroke event was defined as NCIS if the patient had no history of atrial fibrillation prior to, or within, hospitalisation for IS, had no cardioembolic stroke within hospitalisation for IS, and had not received oral anticoagulant therapy within 90 days before hospitalisation for IS. ‡Number of patients with an event across the total follow-up period, starting from the day after discharge until death, end of observability, or end of data (i.e., 29 October, 2023). For incidence rate, follow-up time was censored upon the earliest of event occurrence, death, end of observability, end of the assessment period (365 days after discharge – applicable only for up to 12-month estimates), or end of data (29 October, 2023). §Incidence rates reflect the first event occurring during follow-up and not necessarily the first ever event in the patient's medical history, except for newly diagnosed atrial fibrillation and haemorrhagic stroke. ‖Includes myocardial infarction and unstable angina pectoris. ¶Includes inpatient deaths; outpatient deaths are only recorded if reported in the EMR. The all-cause mortality rate may be underestimated.
EMR, electronic medical record; IS, ischaemic stroke; NCIS, non-cardioembolic ischaemic stroke; P-Y, person-years; Q, quartile; SD, standard deviation; TIA, transient ischaemic attack.

- The cumulative incidence of IS in the overall population is shown in **Figure 2.**

Figure 2. Cumulative incidence of IS and death in patients with a first hospitalisation for NCIS or TIA



Death was treated as a competing risk in this analysis.
IS, ischaemic stroke; NCIS, non-cardioembolic ischaemic stroke; TIA, transient ischaemic attack.

Conclusion

- In ASTRIS-Japan, recurrent IS and haemorrhagic stroke frequently occurred, after a first hospitalisation for NCIS or TIA, suggesting that their risk (recurrent or subsequent to TIA) remains high in contemporary settings. Improvements in secondary prevention are required.

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Conflicts of interest / Disclosures

TH has received honoraria from Bayer, Daiichi Sankyo, and Pfizer. RM declares no conflict of interest. SO is an employee of Bayer Yakuhin and may own shares or share options in the company. CL is an employee of Aetion Inc and holds options in the company. CC was an employee of Aetion Iberia at the time of the study and holds options in the company. DY is an employee of Aetion Iberia. LB is an employee of Bayer AG and may own shares or share options in the company. JX is an employee of Bayer Inc., and may own shares or share options in the company. KK is an employee of Bayer Hispania, S.L.U. and may own shares or share options in the company. MS has received research funding and consulted for Bayer, Janssen, BMS, AstraZeneca, Novartis, and Alexion.

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