INCIDENCE OF ISCHAEMIC STROKE RECURRENCE IN PATIENTS AFTER NON-CARDIOEMBOLIC ISCHAEMIC STROKE IN ENGLAND: OBSERVATIONS FROM ASTRIS

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P989

Introduction

- Globally, stroke is a leading cause of mortality and morbidity, resulting in significant clinical and economic burden.[1]
- In England, ischaemic stroke (IS) accounts for 87% of first-ever strokes.[2]
  - IS accounts for over 62% of all incident strokes globally and 3.3 million people die from IS annually.[3]
- We used real-world data from England to estimate the frequency of recurrent stroke and bleeding events after an initial non-cardioembolic IS (NCIS) to inform secondary stroke prevention strategies.

Methods

Study design

- ASTRIS-UK is a retrospective cohort study that used secondary data from the Clinical Practice Research Datalink-Aurum database and Hospital Episodes Statistics (HES) in England to follow adult patients between 2012 and 2021, after their first (index) NCIS.
- Patients were included in the study if they had no recorded history of atrial fibrillation prior to, or within 15 days post-discharge following their index NCIS and had not received oral anticoagulant therapy within 90 days before the index NCIS unless they had a record of either deep vein thrombosis/pulmonary embolism or hip/knee surgery. These eligibility criteria ensured that the majority of patients with cardioembolic IS were excluded.
- Patient characteristics, IS recurrence, and incidence of major bleeding, intracranial bleeding, and all-cause death were assessed.
- Study events were identified from linked hospitalisations recorded within the HES Admitted Patient Care dataset.
- Major bleeding events were defined as hospitalisations related to intracranial bleeding, gastrointestinal bleeding, or other critical organ and/or other types of major bleeds, identified by primary diagnosis International Classification of Diseases (ICD) codes in patients with a follow-up HES discharge record.
- Intracranial bleeding events were defined as hospitalisations due to intracerebral haemorrhage, subarachnoid haemorrhage, or subdural haematoma as identified by primary diagnosis ICD codes in patients with follow-up HES discharge records.

Statistical analysis

- Incidence rates of IS recurrence and other study endpoints were calculated using the number of incident cases during follow-up as the numerator and total person-years as the denominator, with 95% confidence intervals (CIs) assuming a Poisson distribution. Cumulative risks of study outcomes were estimated by the cumulative hazard function.

Results

Participant characteristics and incidence of recurrent IS

- Between 2012 and 2020, 52,419 people experienced an index NCIS with 41.7% of people >75 years of age at entry stroke (**Table 1**).
- Overall, 7.4% of survivors had a recurrent IS within 1 year with an association with age at entry.
  - The incidence rate of recurrent IS within 1 year for people <65 years of age was 5.9 per 100 person-years while the incidence rate for people >75 years of age was 9.3 per 100 person-years.
- The risk of first-year IS recurrence rates was broadly similar in patients who had their index NCIS in 2012–2014, 2015–2017, and 2018–2020 (**Table 1**).

Table 1. Patient characteristics and incidence of recurrent IS within 12 months since index NCIS†

	Patients, n (%)	Follow-up, P-Y	Events, n	IR per 100 P-Y (95% CI)
All patients	52,419 (100.0)	43,306	3201	7.4 (7.1–7.7)
Sex				
Female	24,546 (46.8)	19,856	1545	7.8 (7.4–8.2)
Male	27,873 (53.2)	23,451	1656	7.1 (6.7–7.4)
Age at entry stroke, years				
<65	16,082 (30.7)	13,621	804	5.9 (5.5–6.3)
65–75	14,458 (27.6)	12,298	782	6.4 (5.9–6.8)
>75	21,879 (41.7)	17,388	1615	9.3 (8.8–9.8)
Calendar years				
2012–2014	17,281 (33.0)	14,279	1103	7.7 (7.3–8.2)
2015–2017	19,516 (37.2)	16,158	1150	7.1 (6.7–7.5)
2018–2020	15,622 (29.8)	12,869	948	7.4 (6.9–7.9)

†An index stroke event was defined as NCIS if the patient had no history of atrial fibrillation prior to, or within 15 days from, hospitalisation for IS and had not received oral anticoagulant therapy within 90 days before hospitalisation for IS unless they had a record of either DVT/PE or hip/knee surgery.
CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; IS, ischaemic stroke; NCIS, non-cardioembolic ischaemic stroke; P-Y, person-years; PE, pulmonary embolism.

Incidence and cumulative risk of recurrent IS by time since index NCIS

- The incidence rate of recurrent IS was highest in the 3 months following the index NCIS at 15.7 per 100 person-years and reduced gradually over time thereafter (**Table 2**).
- Cumulative risks of IS recurrence by the end of years 2 and 5 were 9.9% and 16.5%, respectively (**Table 2**).

Table 2. Incidence and cumulative risk of recurrent IS since index NCIS†

Time since index NCIS	Patients, n	Follow-up, P-Y	Events, n	IR per 100 P-Y (95% CI)	Cumulative risk,‡ % (95% CI)
Year 1	52,419	43,306	3201	7.4 (7.1–7.7)	7.0 (6.8–7.3)
<3 months	–	11,676	1828	15.7 (15.0–16.4)	–
3–12 months	–	31,631	1373	4.3 (4.1–4.6)	–
Year 2	39,393	34,634	1002	2.9 (2.7–3.1)	9.9 (9.6–10.2)
Year 3	29,949	26,010	612	2.4 (2.2–2.6)	12.2 (11.9–12.6)
Year 4	22,337	19,150	458	2.4 (2.2–2.6)	14.6 (14.2–15.1)
Year 5	16,154	13,678	260	1.9 (1.7–2.2)	16.5 (16.1–17.0)

Note: There were 324 events that occurred beyond year 5 that do not appear in this table.
†An index stroke event was defined as NCIS if the patient had no history of atrial fibrillation prior to, or within 15 days from, hospitalisation for IS and had not received oral anticoagulant therapy within 90 days before hospitalisation for IS unless they had a record of either DVT/PE or hip/knee surgery.
‡Cumulative hazard rate by the end of each year.
CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; IS, ischaemic stroke; NCIS, non-cardioembolic ischaemic stroke; P-Y, person-years; PE, pulmonary embolism.

Other adverse clinical events during follow-up

- The incidence rate of other adverse clinical events was numerically highest in the first year, and then similar/stable over subsequent years (years 2–5) (**Table 3**).
- By the end of year 5, approximately one-third of patients had died (Table **3**).

Table 3. IRs of major bleeding, intracranial bleeding, and all-cause death per year of entire follow-up of a cohort of patients with NCIS

	Follow-up, P-Y	Events, n	IR per 100 P-Y (95% CI)	Cumulative risk† (95% CI)
Major bleeding				
Year 1	44,386	991	2.2 (2.1–2.4)	2.2 (2.1–2.3)
Year 2	35,900	535	1.5 (1.4–1.6)	3.7 (3.5–3.9)
Year 3	27,092	376	1.4 (1.3–1.5)	5.1 (4.8–5.3)
Year 4	20,057	258	1.3 (1.1–1.5)	6.4 (6.1–6.6)
Year 5	14,378	199	1.4 (1.2–1.6)	7.7 (7.4–8.1)
Intracranial bleeding				
Year 1	44,628	423	1.0 (0.9–1.0)	0.9 (0.8–1.0)
Year 2	36,368	210	0.6 (0.5–0.7)	1.5 (1.4–1.6)
Year 3	27,628	158	0.6 (0.5–0.7)	2.1 (1.9–2.2)
Year 4	20,572	92	0.5 (0.4–0.6)	2.5 (2.4–2.7)
Year 5	14,832	71	0.5 (0.4–0.6)	3.0 (2.8–3.2)
All-cause death				
Year 1	44,763	4671	10.4 (10.1–10.7)	10.1 (9.8–10.4)
Year 2	36,582	2203	6.0 (5.8–6.3)	16.1 (15.8–16.5)
Year 3	27,852	1580	5.7 (5.4–6.0)	21.8 (21.3–22.3)
Year 4	20,772	1253	6.0 (5.7–6.4)	27.8 (27.3–28.4)
Year 5	14,982	850	5.7 (5.3–6.1)	33.5 (32.8–34.2)

Note: There were 253 major bleeding events, 121 intracranial bleeding events, and 1354 deaths that occurred beyond year 5 that do not appear in this table.
†Nelson–Aalen cumulative hazard estimate by the end of each period.
CI, confidence interval; IR, incidence rate; NCIS, non-cardioembolic ischaemic stroke; P-Y, person-years.

Conclusion

- Despite advances in stroke prevention, IS recurrence rates between 2012 and 2021 in England have not changed.
- The cumulative 5-year risk of IS recurrence after NCIS was substantial, at 16.5%.
  - The incidence of recurrent IS was numerically higher during the first year following the index NCIS than during the subsequent years.
- Younger age was associated with lower IS recurrence in the first 12 months following an index NCIS, however, with an incidence rate of recurrent IS of 5.9 per 100 person-years in patients aged <65 years, our data show an unmet need among all age groups.
- The annual incidence rates of major and intracranial bleeding and all-cause mortality were highest the first year after NCIS and were relatively stable thereafter.
- Our results underline the need for improved secondary stroke prevention strategies for survivors of NCIS.

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Conflicts of interest / disclosures

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