Real-World Patient Characteristics and Clinical Outcomes Across Stroke TOAST Subtypes: Analysis of a Large Representative US Electronic Health Record Database

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Introduction

- Around 610,000 people in the United States (US) experience a first (incident) stroke each year, with a further 185,000 experiencing a recurrent stroke.[1]
- The majority of strokes in the US (87%) are classified as ischaemic strokes (IS).[1] Approximately 75% of IS are classified as a non-cardioembolic IS (NCIS).[2]
- According to the aetiological 'TOAST' (Trial of Org 10172 in Acute Stroke Treatment) classification, IS can be divided into five subtypes[3]:
  1) Large-artery atherosclerosis (LAA) (embolus/thrombosis).
  2) Cardioembolism (high/medium risk).
  3) Small-vessel occlusion (SVO) (lacune).
  4) Other determined aetiology.
  5) Undetermined/cryptogenic cause (≥2 causes, negative evaluation, incomplete evaluation).
- The risk of recurrent stroke can be mitigated with appropriate secondary stroke prevention, including antiplatelet and antithrombotic therapies.[4,5]
  - However, about one in 10 survivors of stroke will experience a second stroke within 1 year of an index NCIS,[6] and there is an unmet need for better prevention strategies.

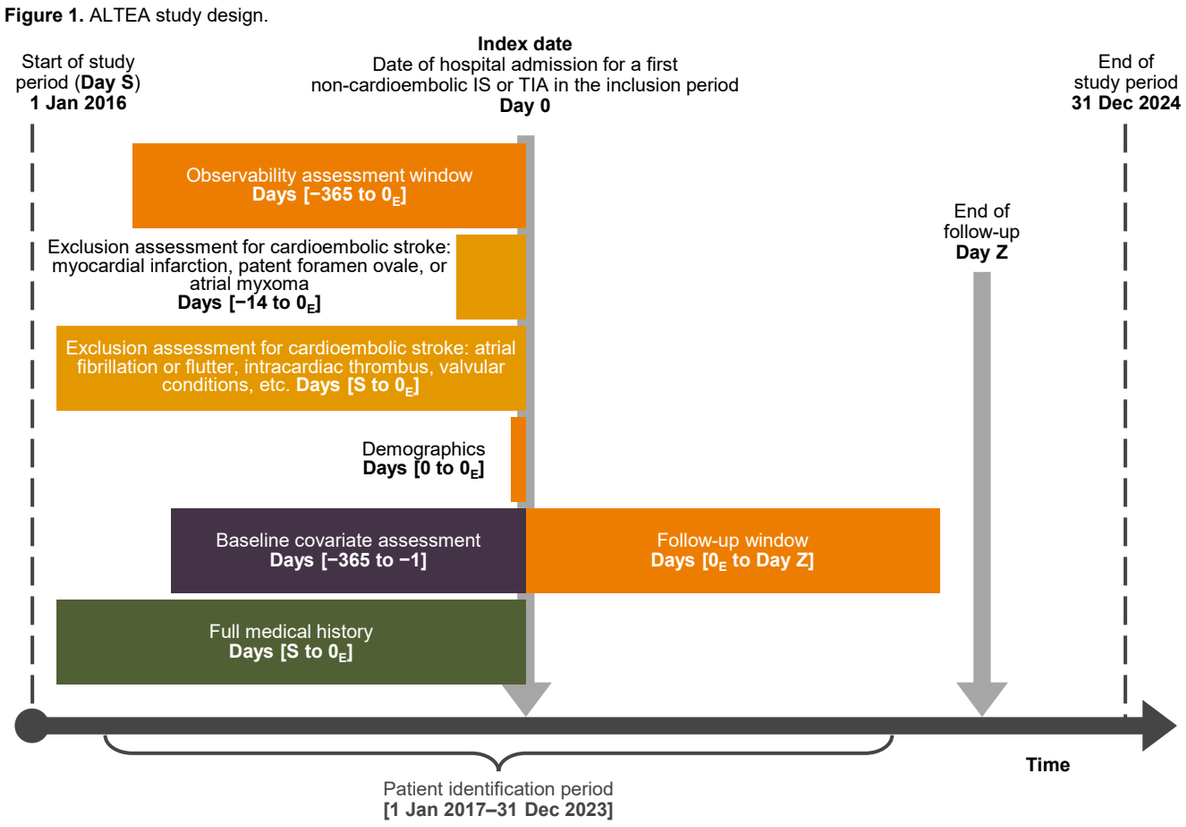
Objectives

- This sub-analysis of the US-based retrospective observational ALTEA study (Analysis of a Large naTionally representative US database on the BurdEn of disease and treatment pAtterns among stroke and TIA patients) assessed real-world patient characteristics, treatment patterns and outcomes according to TOAST subtypes.

Methods

- ALTEA included adults (≥18 years of age) hospitalised for first NCIS or transient ischaemic attack (TIA; based on International Classification of Diseases, 10th Revision, Clinical Modification codes) between January 2017 and December 2023, as recorded in the Truveta electronic health record (EHR) database (**Figure 1**).

Figure 1. ALTEA study design.



Day 0_E, follow-up started from date of discharge from the index hospitalisation; Day S, start of study period; Day Z, the earliest of death, end of follow-up period or up to 365 days following hospitalisation for stroke/TIA.
IS, ischaemic stroke; TIA, transient ischaemic attack.

- To be included, patients had to have ≥12 months' EHR activity prior to the index date and, in the 12 months prior to the index date, to have received care documented in the EHR database from >1 provider. Patients with risk factors associated with cardioembolic stroke were excluded.
- Baseline patient characteristics, treatment patterns and 1-year outcomes were assessed by TOAST subtype (derived from unstructured clinical notes using Truveta's large language model).

Statistical analysis

- Time-to-event methods were used to evaluate all study outcomes. Cumulative risk of study outcomes was estimated using standard Kaplan–Meier methods. Patients were followed from the date of hospital admission until the earliest of death, end of follow-up period or up to 365 days following hospitalisation for IS/TIA.

Results

Study population

- Of 180,021 patients classified as having a NCIS as the index event, 17% (n=29,816) had a documented TOAST subtype (**Table 1**).
- Of these, SVO was the most common (30%), followed by stroke of undetermined aetiology (23%) and LAA (22%).
  - In total, 16% had cardioembolic stroke, with a cardioembolic source that was unknown at the time of admission.
- Median National Institutes of Health Stroke Scale (NIHSS) scores ranged from 2–4. For all TOAST subtypes, most patients had an NIHSS score ≤5. Hypertension, hyperlipidaemia and diabetes were the most common comorbidities across most TOAST subtypes (**Table 1**).

Table 1. Baseline characteristics by TOAST subtype.

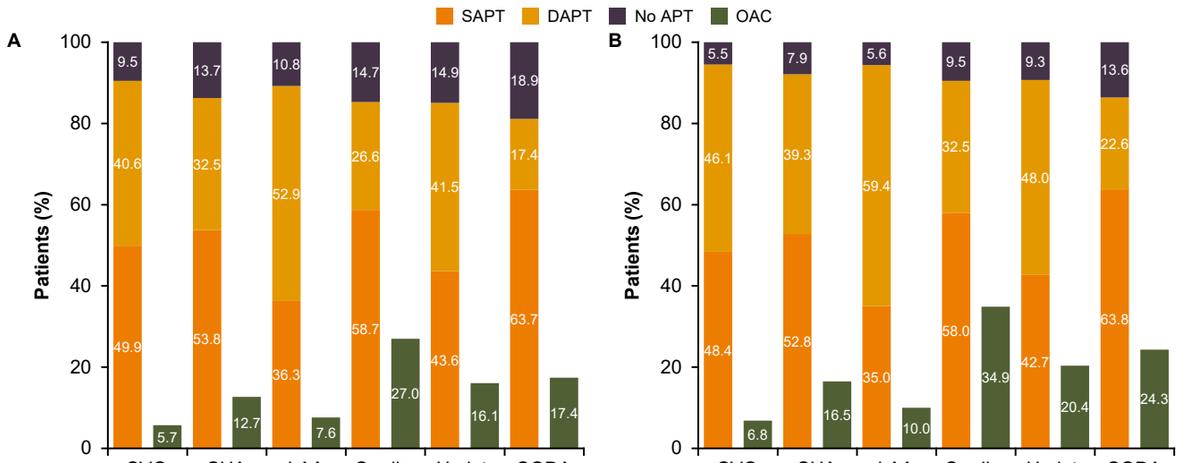
Characteristic	Small-vessel occlusion (n=8990)	Stroke of undetermined aetiology (n=6846)	Large-artery atherosclerosis (n=6473)	Undetermined-combination (n=2021)	Cardio-embolism† (n=4641)	Stroke of other determined aetiology (n=845)
Age, mean (SD), years	67.4 (13.2)	64.7 (15.6)	67.8 (13.1)	69.5 (13.0)	68.3 (14.6)	60.0 (16.4)
Sex, n (%)						
Female	4274 (47.5)	3341 (48.8)	2772 (42.8)	901 (44.6)	2258 (48.7)	410 (48.5)
Male	4613 (51.3)	3380 (49.4)	3581 (55.3)	1078 (53.3)	2277 (49.1)	413 (48.9)
Other or unknown	103 (1.1)	125 (1.8)	120 (1.9)	42 (2.1)	106 (2.3)	22 (2.6)
Comorbidities‡, n (%)						
Hypertension	6372 (70.9)	4517 (66.0)	4222 (65.2)	1366 (67.6)	3092 (66.6)	612 (72.4)
Hyperlipidaemia	3516 (39.1)	2251 (32.9)	2345 (36.2)	764 (37.8)	1721 (37.1)	276 (32.7)
Diabetes	2545 (28.3)	1413 (20.6)	1545 (23.9)	527 (26.1)	980 (21.1)	173 (20.5)
Malignancy	1003 (11.2)	809 (11.8)	675 (10.4)	251 (12.4)	589 (12.7)	200 (23.7)
Coronary artery disease	1265 (14.1)	983 (14.4)	1022 (15.8)	352 (17.4)	787 (17.0)	93 (11.0)
Cerebrovascular disease	1510 (16.8)	1173 (17.1)	1119 (17.3)	337 (16.7)	720 (15.5)	142 (16.8)
Obesity	1343 (14.9)	975 (14.2)	877 (13.5)	286 (14.2)	642 (13.8)	140 (16.6)
Chronic kidney disease	1482 (16.5)	914 (13.4)	808 (12.5)	288 (14.3)	589 (12.7)	114 (13.5)
Anaemia	881 (9.8)	807 (11.8)	521 (8.0)	195 (9.6)	538 (11.6)	163 (19.3)
Prior stroke	1049 (11.7)	835 (12.2)	764 (11.8)	236 (11.7)	522 (11.2)	102 (12.1)
NIHSS score, n (%)						
Median (IQR)	2 (0–4)	2 (0–6)	3 (1–8)	4 (1–12)	2 (0–9)	2 (0–7)
≤5: minor	6612 (83.5)	4623 (71.8)	4223 (67.8)	1153 (58.7)	2945 (67.3)	560 (69.7)
6–15: minor to moderate	1101 (13.9)	1092 (17.0)	1207 (19.4)	466 (23.7)	766 (17.5)	141 (17.5)
>15: moderate to severe	210 (2.7)	721 (11.2)	795 (12.8)	344 (17.5)	664 (15.2)	103 (12.8)
Unknown	1067 (11.9)	410 (6.0)	248 (3.8)	58 (2.9)	266 (5.7)	41 (4.9)

†Patients found to have a cardioembolic source that was unknown at time of admission.
‡The 10 most common comorbidities across all TOAST subtypes are reported, ordered by average percentage per comorbidity.
IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Treatment patterns

- Single antiplatelet therapy (SAPT) use (most often aspirin) was similar during index hospitalisation and at discharge for each TOAST subtype (**Figure 2**).
  - The highest SAPT use was in patients with 'stroke of other determined aetiology' (64% during index hospitalisation and at discharge; **Figure 2**).
- Dual antiplatelet therapy (DAPT) use (most often aspirin + clopidogrel) was higher in all TOAST subtypes at discharge than during index hospitalisation (**Figure 2**).
  - The highest DAPT use was in the LAA subtype (53% during index hospitalisation and 59% at discharge; **Figure 2**).

Figure 2. Treatment patterns by drug category (A) during index hospitalisation and (B) at hospital discharge.

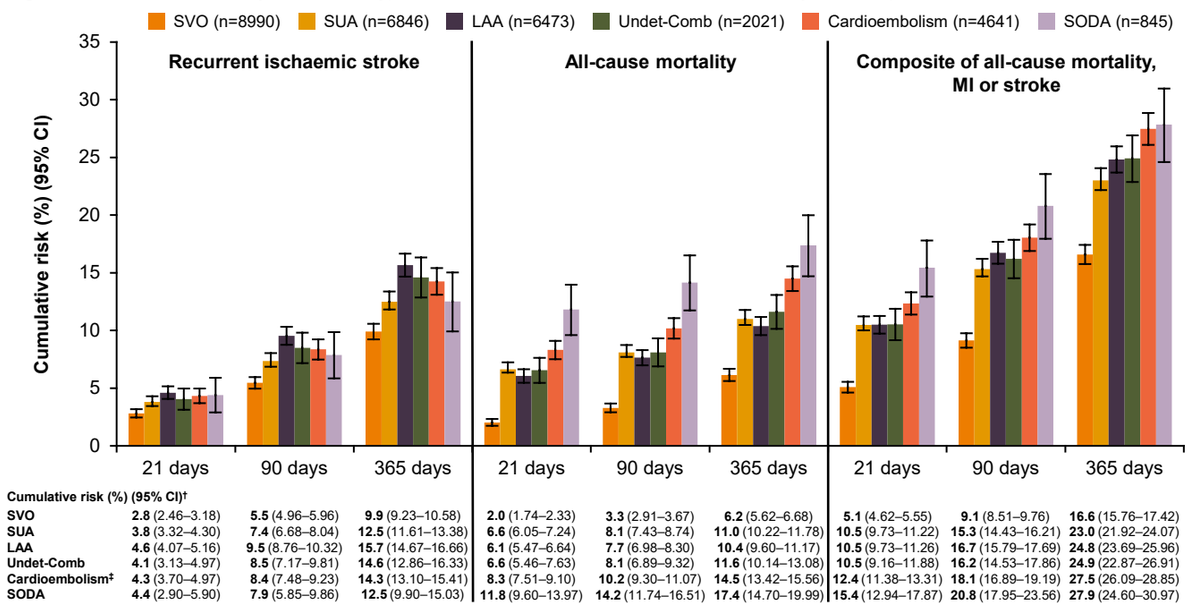


APT, antiplatelet therapy; DAPT, dual antiplatelet therapy; LAA, large-artery atherosclerosis; OAC, oral anticoagulant; SAPT, single antiplatelet therapy; SODA, stroke of other determined aetiology; SUA, stroke of undetermined aetiology; SVO, small-vessel occlusion; Undet-Comb, undetermined-combination.

Clinical outcomes

- The cumulative risk for recurrent IS at 1 year was lowest for SVO (10%) and ranged from 13% to 16% for the other TOAST subtypes (**Figure 3**).
- All-cause mortality and composite outcome (all-cause mortality, myocardial infarction or stroke) increased over 1 year in all TOAST subtypes (**Figure 3**).
  - Cumulative risk at 1 year for both all-cause mortality (6%) and the composite outcome (17%) was lowest following an SVO and was highest among those with stroke of other determined aetiology (all-cause mortality, 17%; composite outcome, 28%; **Figure 3**). However, it should be noted that this stroke subtype had the highest percentage of patients with a malignancy at baseline (24%).

Figure 3. Clinical outcomes by TOAST subtype: recurrent ischaemic stroke, all-cause mortality and composite outcome.

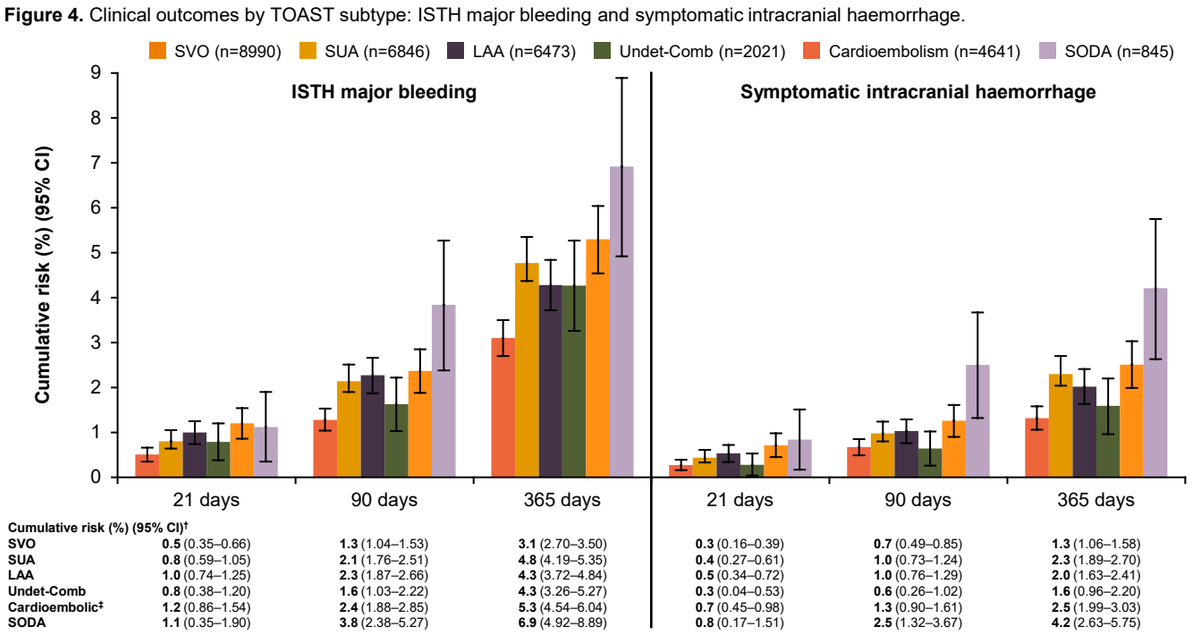


Cumulative risk (%) (95% CI)†	Recurrent ischaemic stroke			All-cause mortality			Composite of all-cause mortality, MI or stroke		
	21 days	90 days	365 days	21 days	90 days	365 days	21 days	90 days	365 days
SVO	**2.8** (2.46–3.18)	**5.5** (4.96–5.96)	**9.9** (9.23–10.58)	**2.0** (1.74–2.33)	**3.3** (2.91–3.67)	**6.2** (5.62–6.68)	**5.1** (4.62–5.55)	**9.1** (8.51–9.76)	**16.6** (15.76–17.42)
SUA	**3.8** (3.32–4.30)	**7.4** (6.68–8.04)	**12.5** (11.61–13.38)	**6.6** (6.05–7.24)	**8.1** (7.43–8.74)	**11.0** (10.22–11.78)	**10.5** (9.73–11.22)	**15.3** (14.43–16.21)	**23.0** (21.92–24.07)
LAA	**4.6** (4.07–5.16)	**9.5** (8.76–10.32)	**15.7** (14.67–16.66)	**6.1** (5.47–6.64)	**7.7** (6.98–8.30)	**10.4** (9.60–11.17)	**10.5** (9.73–11.26)	**16.7** (15.79–17.69)	**24.8** (23.69–25.96)
Undet-Comb	**4.1** (3.13–4.97)	**8.5** (7.17–9.81)	**14.6** (12.86–16.33)	**6.6** (5.46–7.63)	**8.1** (6.89–9.32)	**11.6** (10.14–13.08)	**10.5** (9.16–11.88)	**16.2** (14.53–17.86)	**24.9** (22.87–26.91)
Cardioembolism‡	**4.3** (3.70–4.97)	**8.4** (7.48–9.23)	**14.3** (13.10–15.41)	**8.3** (7.51–9.10)	**10.2** (9.30–11.07)	**14.5** (13.42–15.56)	**12.4** (11.38–13.31)	**18.1** (16.89–19.19)	**27.5** (26.09–28.85)
SODA	**4.4** (2.90–5.90)	**7.9** (5.85–9.86)	**12.5** (9.90–15.03)	**11.8** (9.60–13.97)	**14.2** (11.74–16.51)	**17.4** (14.70–19.99)	**15.4** (12.94–17.87)	**20.8** (17.95–23.56)	**27.9** (24.60–30.97)

†Cumulative risk (%) and 95% confidence intervals were estimated using time-to-event methods, accounting for censoring. Reported cumulative risks represent the probability of experiencing the outcome by the end of the specified time point, regardless of interval-specific event counts.
‡Patients who were found to have a cardioembolic source that was unknown at time of admission.
CI, confidence interval; LAA, large-artery atherosclerosis; MI, myocardial infarction; SODA, stoke of other determined aetiology; SUA, stroke of undetermined aetiology; SVO, small-vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; Undet-Comb, undetermined-combination.

- At 1 year, stroke of other determined aetiology and cardioembolic strokes had the highest rates of major bleeding (7% and 5%, respectively) and symptomatic intracranial haemorrhage (4% and 3%, respectively; **Figure 4**).

Figure 4. Clinical outcomes by TOAST subtype: ISTH major bleeding and symptomatic intracranial haemorrhage.



Cumulative risk (%) (95% CI)†	ISTH major bleeding			Symptomatic intracranial haemorrhage		
	21 days	90 days	365 days	21 days	90 days	365 days
SVO	**0.5** (0.35–0.66)	**1.3** (1.04–1.53)	**3.1** (2.70–3.50)	**0.3** (0.16–0.39)	**0.7** (0.49–0.85)	**1.3** (1.06–1.58)
SUA	**0.8** (0.59–1.05)	**2.1** (1.76–2.51)	**4.8** (4.19–5.35)	**0.4** (0.27–0.61)	**1.0** (0.73–1.24)	**2.3** (1.89–2.70)
LAA	**1.0** (0.74–1.25)	**2.3** (1.87–2.66)	**4.3** (3.72–4.84)	**0.5** (0.34–0.72)	**1.0** (0.76–1.29)	**2.0** (1.63–2.41)
Undet-Comb	**0.8** (0.38–1.20)	**1.6** (1.03–2.22)	**4.3** (3.26–5.27)	**0.3** (0.04–0.53)	**0.6** (0.26–1.02)	**1.6** (0.96–2.20)
Cardioembolic‡	**1.2** (0.86–1.54)	**2.4** (1.88–2.85)	**5.3** (4.54–6.04)	**0.7** (0.45–0.98)	**1.3** (0.90–1.61)	**2.5** (1.99–3.03)
SODA	**1.1** (0.35–1.90)	**3.8** (2.38–5.27)	**6.9** (4.92–8.89)	**0.8** (0.17–1.51)	**2.5** (1.32–3.67)	**4.2** (2.63–5.75)

†Cumulative risk (%) and 95% confidence intervals were estimated using time-to-event methods, accounting for censoring. Reported cumulative risks represent the probability of experiencing the outcome by the end of the specified time point, regardless of interval-specific event counts.
‡Patients who were found to have a cardioembolic source that was unknown at time of admission.
CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis; LAA, large-artery atherosclerosis; SODA, stoke of other determined aetiology; SUA, stroke of undetermined aetiology; SVO, small-vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; Undet-Comb, undetermined-combination.

Conclusions

- These real-world data from the US indicate that the cumulative risk of several clinical outcomes following a recurrent IS was generally consistent across most TOAST subtypes at all time points.
- Risk was generally lower following an SVO, despite a numerically larger proportion of patients in this category who had a history of atherosclerotic disease risk factors, such as hypertension, diabetes and hyperlipidaemia,[7] versus most other subtypes.
- Patients with stroke of other determined aetiology were at higher cumulative risk of all-cause mortality and bleeding than patients with other TOAST subtypes.

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