Evaluating Real-World Outcomes of Single Versus Dual Antiplatelet Therapy After an Ischemic Stroke: Mortality and Major Adverse Cardiovascular Events

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Objective

- To describe post-stroke Single (SAPT) and Dual Antiplatelet Therapy (DAPT) use using a novel aspirin ascertainment method informed by electronic health records (EHR) and compare subsequent outcomes in a non-cardioembolic ischemic stroke (IS) cohort in a US based commercially insured population.

Background

- Non-cardioembolic ischemic stroke is a major contributor to cardiovascular morbidity and mortality, and secondary stroke prevention is a core component of post-stroke management.
- Guidelines recommend antiplatelet therapy for secondary stroke prevention (typically aspirin as foundational therapy, with other antiplatelets used in higher-risk patients), alongside risk-factor modification.
- Real-world evaluation of SAPT versus DAPT is limited by treatment identification, particularly because aspirin is frequently obtained over-the-counter and is incompletely captured in claims data.
- This research utilized a novel method to identify SAPT vs DAPT treatment following index non-cardioembolic IS by leveraging detailed EHR information from a large, multi-payer US database.[1]

Methods

- The study population included US adults (18+) in the Healthcare Integrated Research Database (HIRD®) hospitalized with a primary diagnosis of a non-cardioembolic IS from 01 JAN 2016 to 30 JUN 2024 with EHR data, ≥1 year of continuous enrollment pre-index, and ≥1-day post-index follow up. **(Table 1)**
- The HIRD is a US claims database of commercial and Medicare Advantage health plans with research-eligible data use permissions and a population broadly representative of the US Census distribution for age, sex, and region.[2]
- Antiplatelet exposure was defined as any of the following during the exposure window beginning on index stroke date and ending 90 days after discharge:
  1. pharmacy claim for aspirin or P2Y12 inhibitor;
  2. documentation of aspirin in the structured medication section of the EHR; or
  3. identification of aspirin through keyword searches (e.g., aspirin, ASA) in unstructured EHR text.
- Inverse probability of treatment weighting (IPTW) was applied to balance baseline demographic and clinical differences, measured during the 1-year baseline, between SAPT and DAPT groups. Balance was assessed using standardized mean differences. **(Table 2)**
- The effect of SAPT vs DAPT treatment on the cumulative incidence of all-cause mortality and MACE (stroke, MI, and all-cause death) was estimated over a 1-year follow-up period using IPTW survival models.
- Because death is a competing risk for nonfatal outcomes, a total-effect model was used to estimate the effect of treatment on the cumulative incidence of secondary strokes and major bleeding. This accounts for direct effects and pathways mediated by death.[3]

Results

- 14,469 adults with non-cardioembolic IS met the study inclusion criteria and had evidence of SAPT (7,731, 53.4%) or DAPT (6,738, 46.6%) within 90 days post-stroke. **(Table 1)**
- IPTW-adjusted 1-year all-cause death was 3.8% (SAPT) vs 2.3% (DAPT) for an absolute risk difference of −1.5% (95% CI: −2.0 to −0.8). Adjusted 1-year MACE incidence was 9.9% (SAPT) vs 8.7% (DAPT) with an absolute difference of −1.2% (95% CI: −2.0%, 0.1%). **(Figure 1)**
- Secondary strokes were relatively common and serious complications (5.5% in both SAPT and DAPT cohorts), often occurring shortly after the initial event. The total effect of treatment on secondary strokes was negligible (−0.05% difference, 95% CI: −0.83%, 0.73%). **(Figure 1)**
- Patients receiving DAPT had a higher (3.4%, vs 2.8% SAPT), but not statistically different (0.58% risk difference, 95% CI: −0.01%, 1.12%) rate of major bleeding following index IS events. **(Figure 1)**

Table 1: Study population and SAPT or DAPT assignment

Step	Criteria	N	% from previous step
1	Patients with primary diagnosis of IS in IP setting during the intake period.†	115,551	-
2	Patient is ≥18 years of age at the time of the index start date and has ≥365 days of continuous enrolment prior to the index event.	79,753	69.0%
3	Patients without evidence (≥1 encounter, any position) of non-cardioembolic IS or TIA diagnosis at any time prior to the index start date (as far back as 2006 as enrolment allows).	57,976	72.7%
4	Patients without evidence (≥2 encounters on different days) of left ventricular thrombus, mechanical valve or atrial flutter during the 365 days prior to and inclusive of the index end date.	56,344	97.2%
5	Patients without evidence (≥2 encounters on different days) of atrial fibrillation during the 365 days prior to and through 30 days following the index end date.	46,038	81.7%
6	Patients without evidence (≥1 encounter) for any oral anticoagulants during the 90 days prior to and inclusive of the index start date, with no evidence (≥2 encounters of same condition on different days) of a pulmonary embolism, deep vein thrombosis, hip surgery or knee surgery during the 365 days prior to and inclusive of the index end date.	45,655	99.2%
7	Patient has ≥1 day of continuous enrolment following the index end date.	44,145	96.7%
Treatment assignment during the index event through 90 days following:			
1	Patients with EHR or claim for aspirin	15,269	34.6%
2	Patients with evidence of SAPT or DAPT‡	14,469	94.8%
2a	Patients with SAPT	7,731	53.4%
2b	Patients with DAPT	6,738	46.6%

†Study period: 01 June 2014–30 September 2024; Intake period: 01 January 2016–30 June 2024.
‡SAPT: aspirin, cilostazol, clopidogrel, prasugrel, ticagrelor or switch between two P1Y12s; DAPT: aspirin + cilostazol, clopidogrel, dipyridamole, prasugrel or ticagrelor.
Abbreviations: DAPT, dual antiplatelet therapy; EHR, electronic health record; IP, inpatient; IS, ischemic stroke; SAPT, single antiplatelet therapy; TIA transient ischemic attack.

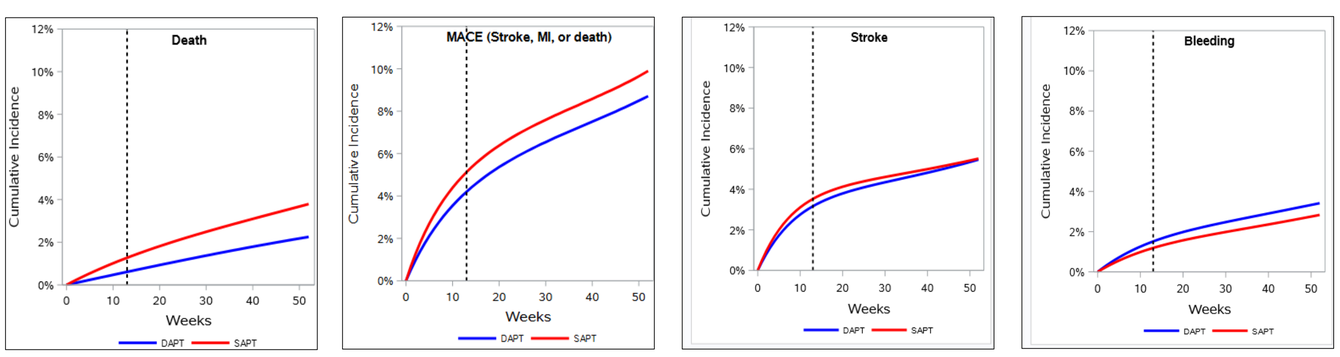
Table 2: Standardized mean differences of baseline variables before and after inverse probability of treatment weighting

Variable	Before weighting			After weighting[1]		
	SAPT	DAPT	SMD	SAPT	DAPT	SMD
Age, mean in years	58.9	59.5	-0.05	59.3	59.4	-0.01
Female, %	44.6	40.0	0.09	42.7	42.8	0.00
White race, %	70.6	73.1	-0.05	71.9	72.0	0.00
Urban, %	54.3	55.2	-0.02	54.1	55.4	-0.02
Commercially insured, %	83.5	84.6	-0.03	83.7	83.6	0.00
SES index score	2.5	2.5	0.00	2.5	2.5	0.00
Measured during 1 year baseline						
Quan-Charlson comorbidity index (mean)	0.8	0.8	0.03	0.8	0.8	0.03
Kim Index score (mean)	0.2	0.2	0.06	0.2	0.2	-0.01
Atherosclerosis, %	3.9	4.5	-0.03	4.1	4.6	-0.02
Chronic kidney disease, %	8.3	8.9	-0.02	8.5	8.7	0.00
Congestive heart failure, %	4.1	4.4	-0.01	4.4	4.2	0.01
Coronary artery disease, %	9.6	12.8	-0.10	11.3	11.3	0.00
Diabetes, %	24.2	29.4	-0.12	26.8	27.0	0.00
Hyperlipidemia, %	39.6	45.4	-0.12	42.5	42.6	0.00
Hypertension, %	51.8	55.8	-0.08	53.9	54.1	0.00
Ischemic heart disease, %	14.3	17.4	-0.09	16.0	16.2	-0.01
Major bleeding events excl. intracranial, %	7.9	6.4	0.06	7.2	7.2	0.00
Obstructive sleep apnea, %	7.2	7.7	-0.02	7.6	7.4	0.01
Peripheral artery disease, %	8.6	10.0	-0.05	9.4	9.4	0.00
Smoking, %	14.8	16.1	-0.04	15.1	16.0	-0.02
Measured during the index event						
Aphagia or dysphagia, %	13.5	12.2	0.04	12.9	13.2	-0.01
Length of stay (days), %						
1	1.1	1.2	-0.02	1.2	1.1	0.00
2-3	40.2	41.8	-0.03	41.0	40.0	0.01
4-7	31.6	32.1	-0.01	31.5	32.5	-0.02
8-30	21.7	21.1	0.01	21.3	21.8	-0.01
31+	5.5	3.7	0.09	5.0	4.5	0.02
Hemiplegia, %	42.7	42.9	0.00	42.9	43.2	0.00
Intensive care unit encounter, %	50.7	46.4	0.09	48.9	49.1	0.00
Cerebral edema, %	6.9	4.4	0.11	6.1	5.5	0.02

Abbreviations: SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; SMD, standard mean difference
[1] Variables also included in weighting and with a SMD<0.03: Presence during the baseline; Anemia, cancer, dementia, intracranial bleeding, myocardial infraction, venous thromboembolism. Measured during the index event; mechanical ventilation, placement of nasogastric feeding tube. Measured on index date; year of index, continuous.

Figure 1. Cumulative incidence of adverse events by SAPT vs DAPT treatment during the 1 year following index event

	Death	MACE	Stroke Total Effect	Bleeding Total Effect
Number of events	387	1,206	741	395
SAPT, cumulative incidence at 52 weeks	3.8%	9.9%	5.5%	2.8%
DAPT, cumulative incidence at 52 weeks	2.3%	8.7%	5.5%	3.4%
Risk difference, DAPT/SAPT	−1.54% (−2.04%, −0.83%)	−1.19% (−2.03%, 0.08%)	-0.05% (-0.83%. 0.73%)	0.58% (-0.01%, 1.12%)
Risk ratio, DAPT/SAPT	0.59 (0.50, 0.76)	0.88 (0.80, 1.01)	0.99 (0.86, 1.14)	1.21 (0.97, 1.45)



Abbreviations: SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events (stroke, myocardial infarction, or death from any cause).
Dashed reference line at approximately 90 days (antiplatelet assessment period); SAPT/DAPT treatment for the remainder of the follow-up period was not assessed.

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Conclusion

In this real-world cohort of patients with non-cardioembolic IS, a novel aspirin identification method was implemented, allowing for the characterization and assessment of outcomes by treatment type. Patients receiving DAPT had a lower incidence of all-cause death and MACE, but increased bleeding events compared with those receiving SAPT.

Limitations

- Administrative claims are collected for the purposes of payment and may not reflect accurate diagnoses and treatment as coding issues may occur and medications may not be taken as prescribed. Pharmacy fills indicate dispensing rather than confirmed ingestion, adherence, or clinical indication, and antiplatelets may be prescribed for multiple reasons.
- Some factors influencing treatment selection and prognosis (e.g., provider preference, benefit design, social risk factors, and family history) were not captured, so residual confounding is possible.
- The cohort was commercially insured or Medicare Advantage, which may limit generalizability to uninsured, Medicaid, and non-US populations.
- Aspirin exposure may still be underestimated if over-the-counter use was not documented in the available EHR data.

References

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