Stroke

ORIGINAL CONTRIBUTION

Timing of Initiation and Efficacy of Dual Antiplatelet Therapy in Minor Stroke or High-Risk TIA

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BACKGROUND: Dual antiplatelet therapy (DAPT) is recommended within 24 hours for patients with minor ischemic stroke or high-risk transient ischemic attack. However, the optimal timing for initiating DAPT remains unclear.

METHODS: From a prospective multicenter cohort involving 20 stroke centers between January 2011 and April 2023, patients with minor noncardioembolic ischemic stroke (National Institutes of Health Stroke Scale score ≤5) or high-risk transient ischemic attack who presented within 7 days of symptom onset were included. We evaluated outcomes based on in-hospital initiation of DAPT versus monotherapy (aspirin or clopidogrel alone). The primary outcome was a composite of recurrent stroke, myocardial infarction, and death within 90 days. Patients were grouped by time from symptom onset to hospital arrival: 0 to 24 hours, 24 to 72 hours, and >72 hours. Time-to-treatment effects were analyzed using Cox proportional hazards models, with inverse probability of treatment weighting based on propensity scores. The adjusted models incorporated demographic factors, baseline clinical characteristics, vascular risk factors, stroke subtype, relevant arterial status, and prior antiplatelet use.

RESULTS: Among the 41 530 patients (mean age, 66.3 years; 25 771 [62%] male), 25 112 (60.5%) received DAPT. The 90-day primary outcome occurred in 2663 (10.7%) of the DAPT group versus 1900 (11.6%) in the monotherapy group (hazard ratio, 0.82 [95% CI, 0.77–0.87]). The benefit of DAPT was most pronounced when initiated within 24 hours (hazard ratio, 0.74 [95% CI, 0.69–0.79]). No significant benefit was observed when DAPT was initiated between 24 and 72 hours (hazard ratio, 1.00 [95% CI, 0.88–1.15]), and a higher risk was suggested for initiation beyond 72 hours (hazard ratio, 1.25 [95% CI, 1.01–1.55]). Time-dependent analysis showed a benefit crossing the null at ≈42 hours.

CONCLUSIONS: Early initiation of DAPT was associated with the greatest clinical benefit, consistent with current guideline recommendations. The therapeutic effect appeared to decline progressively beyond this period, with an estimated threshold around 42 hours.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aspirin ■ clopidogrel ■ ischemic attack, transient ■ ischemic stroke ■ platelet aggregation inhibitors

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.125.053343.
For Sources of Funding and Disclosures, see page XXX.

Stroke is available at www.ahajournals.org/journal/str

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Nonstandard Abbreviations and Acronyms

ATAMIS	Antiplatelet Therapy in Acute Mild to Moderate Ischemic Stroke
CHANCE	Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events
CRCS-K-NIH	Clinical Research Center for Stroke-Korea-National Institutes of Health
DAPT	dual antiplatelet therapy
HR	hazard ratio
INSPIRES	Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis
IPTW	inverse probability of treatment weighting
LAA	large artery atherosclerosis
MAPT	monoantiplatelet therapy
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PS	propensity score
PSM	propensity score matching
THALES	The Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has become a cornerstone of early secondary prevention in patients with minor ischemic stroke or high-risk transient ischemic attack (TIA).[1] Based on the landmark trials, such as the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events), POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke), and the THALES trial (The Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and acetylsalicylic Acid for Prevention of Stroke and Death),[2–4] current guidelines recommend DAPT for patients with minor stroke or high-risk TIA who present within 24 hours of symptom onset.[5]

In real-world clinical settings, delays are common due to late symptom recognition, interhospital transfers, or diagnostic confirmation time.[6] Despite these challenges, DAPT use in acute stroke management has been steadily increasing as clinicians aim to reduce early recurrence risk.[7] However, whether starting DAPT beyond 24 hours still confers a meaningful benefit remains uncertain. Secondary analysis from the POINT and the recent INSPIRES trial (Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis) in China demonstrated that DAPT benefit remains favorable even when it is initiated up to 72 hours after symptom onset.[8,9]

Therefore, we aimed to leverage a nationwide multicenter stroke registry to assess the relationship between the time of DAPT initiation and clinical outcomes in patients with minor ischemic stroke or high-risk TIA. Our objectives were to (1) compare 90-day vascular outcomes between DAPT versus monoantiplatelet therapy (MAPT) across different time-to-arrival intervals, and (2) estimate the time threshold for DAPT efficacy.

METHODS

Study Design

This study analyzed data from the CRCS-K-NIH registry (Clinical Research Center for Stroke-Korea-National Institutes of Health), a multicenter, prospective, web-based registry. The study design was observational and cohort-based, incorporating consecutive patients with acute ischemic stroke or TIA. Detailed descriptions of the CRCS-K-NIH registry have been published previously.[10–12] CRCS-K-NIH registry included patients admitted to 20 academic hospitals across South Korea between January 2011 and April 2023. The study was approved by the institutional review boards of all participating centers. A waiver of informed consent was granted owing to the use of anonymized data and minimal participant risk, with data collected for quality assessment of stroke care. Individual patient-level data are available on reasonable request to the corresponding author, subject to legal and ethical restrictions. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Participants

We identified patients with acute minor ischemic stroke admitted between January 2011 and April 2023, incorporating elements from the landmark minor stroke trials for high-risk TIA.[2–4] Eligible patients were adults (≥18 years) with acute minor ischemic stroke (defined as a National Institutes of Health Stroke Scale score ≤5) or high-risk TIA. High-risk TIA was defined as either the presence of an acute ischemic lesion on diffusion-weighted magnetic resonance imaging[13] or symptomatic intracranial arterial stenosis/occlusion.[14] Patients had to have symptom onset within 7 days before admission and receipt of aspirin or clopidogrel on admission.

We excluded patients with high-risk cardioembolic sources, those receiving acute reperfusion therapies (intravenous thrombolysis or endovascular thrombectomy), or antiplatelet/anticoagulant regimens other than aspirin or clopidogrel.[15]

The final study population was categorized based on the antiplatelet regimen administered on admission: MAPT with aspirin or clopidogrel, or DAPT combining both agents.

Outcome Measures

The primary outcome was a composite of stroke recurrence, myocardial infarction, and all-cause mortality within 90 days.

Secondary outcomes included individual occurrences of recurrent stroke and all-cause mortality. Outcomes were prospectively captured during hospitalization and through structured telephone interviews and outpatient follow-ups.[10] Outcome definitions followed standardized criteria and were consistent with prior landmark trials.[2–4] Specifically, the definition of stroke recurrence also included cases of early neurological deterioration attributable to stroke progression, defined as worsening neurological status due to progressive ischemia, swelling of infarcted tissue, or perilesional edema on follow-up imaging.[16,17] Events that occurred before hospital arrival were not captured and were inherently left-censored according to the study design.

Statistical Analysis

We analyzed the baseline characteristics of the entire patient cohort, regardless of the time window, summarizing continuous variables as mean and SD, categorical variables as frequency and proportion, and ordinal variables as median with interquartile range. Missing data were minimal in this study. The exposure and outcome variables had no missing values. Body mass index, systolic blood pressure, and initial glucose level had <5% missing data, which were imputed using the median of observed values. All other covariates were complete.

Based on current guidelines recommending DAPT initiation within 24 hours of symptom onset[1] and the INSPIRES trial allowing treatment initiation up to 72 hours,[8] we categorized the time from symptom onset to hospital arrival into 3 clinically relevant intervals: within 24 hours (0–24 hours), 24 to 72 hours, and beyond 72 hours (up to 7 days).

To assess the balance between treatment groups, we generated a single propensity score (PS) model, rather than separate models for each of the time interval subgroups, incorporating interaction terms between subgroup indicators and covariates.[18] This approach was adopted to minimize the risk of subgroup inconsistency, reduce comparability, overfitting in small strata, and inadequate confounding adjustment.[18] Using this unified PS model, we applied inverse probability of treatment weighting (IPTW) as the primary method to balance covariates, including in all subgroup analyses. PS matching (PSM) was additionally performed as a secondary analysis to evaluate the robustness of findings. Covariate balance was evaluated using absolute standardized differences before and after IPTW and PSM.

Baseline characteristics with crude, multivariable-adjusted, and PS-adjusted comparisons between the MAPT and DAPT groups were conducted for the overall cohort as well as within each predefined onset-to-treatment interval. For crude analyses, continuous variables were compared using the Student *t* test, categorical variables using the Pearson χ^2 test, and ordinal variables using the Wilcoxon rank-sum test. For IPTW-adjusted analyses, the weighted χ^2 test and weighted Student *t* test were used, whereas PSM-adjusted analyses utilized conditional logistic regression models.

For primary and secondary outcomes, we plotted Kaplan-Meier curves to estimate 90-day cumulative incidence and used the log-rank test to compare DAPT versus MAPT across different time windows. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression under 3 frameworks: multivariable adjustment, IPTW, and PSM. Analyses were performed for the overall cohort and stratified by prespecified onset-to-treatment intervals to assess temporal variations in DAPT efficacy. The same set of covariates—including age, sex, stroke severity (National Institutes of Health Stroke Scale score), body mass index, premorbid modified Rankin Scale score, TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification determined by an magnetic resonance imaging–based algorithm,[15,19] hypertension, diabetes, dyslipidemia, history of coronary artery disease, history of stroke or TIA, smoking status, symptomatic intracranial steno-occlusion, prior antiplatelet use, initial glucose level, and systolic blood pressure were used in both the multivariable Cox model and the PS model. Using this unified PS model, we conducted IPTW-adjusted Cox regression with robust standard errors. In addition, for validation, we performed PSM followed by Cox regression with robust standard errors to account for clustering within matched pairs. In addition, multivariable Cox proportional hazards models were performed with further adjustment for in-hospital antihypertensive, hypoglycemic, and lipid-lowering therapies.

To explore more granular temporal effects within the early treatment window, we further stratified the first 24 hours into 3 narrower intervals (0–6, 6–12, and 12–24 hours) and evaluated the corresponding treatment effects.

As a complementary analysis, we also performed a per-protocol analysis comparing the cumulative incidence between antiplatelet groups, restricted to patients who maintained the initially assigned antiplatelet regimen as a discharge medication, which is typically prescribed for 2 weeks to 1 month until the first outpatient clinic visit.

In addition, we conducted predefined subgroup analyses to examine whether the effect of DAPT varied according to age (<75 versus ≥75 years), sex (female versus male), arrival year (<2019 versus ≥2019, considering the implementation of clinical practice guidelines following the POINT trial), index event severity (National Institutes of Health Stroke Scale score ≤3 versus 4–5), stenosis severity (presence versus absence of symptomatic steno-occlusion), stroke cause (large artery atherosclerosis (LAA), small vessel occlusion, or other causes), history of prior antiplatelet use, and history of coronary heart disease. Interaction tests were performed to assess heterogeneity across subgroups.

To examine the time-dependent effect of DAPT more granularly, we treated time from symptom onset to hospital arrival as a continuous variable. An interaction term between treatment group and time was included in the Cox model to assess time-dependent changes in HRs and identify the optimal window for DAPT. From this model, we identified the time point at which the 95% CI for the HR crossed 1, indicating the loss of a statistically significant benefit of DAPT compared with MAPT. Post hoc analyses, including subgroup analyses based on stroke cause, symptomatic steno-occlusion, and history of antiplatelet were also conducted. To assess the robustness of the estimated threshold, we performed a bootstrap resampling procedure with 1000 iterations to estimate the distribution and 95% CI of the threshold time. We also conducted an exploratory, post hoc sensitivity analysis separating monotherapy into aspirin and clopidogrel to compare each agent with DAPT. Baseline characteristics for these subgroups were compared before and after weighting or matching. The same covariates and unified PS model were applied across multivariable, IPTW,

and PSM frameworks; time windows were identical to the primary analysis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics, Treatment Patterns, and Outcomes

Over the entire study period, a total of 41 530 patients met the eligibility criteria (Figure S1), of whom 25 112 (60.5%) received DAPT, and 16 418 (39.5%) received MAPT on admission. Patients selected for DAPT had more vascular risk factors than those treated with monotherapy (Table 1). The DAPT group was slightly older (67.0 versus 65.2 years) and had higher frequencies of prior stroke/TIA (20.6% versus 14.5%), coronary artery disease (8.2% versus 4.9%), and prior aspirin use (30.7% versus 18.0%). LAA was more prevalent among DAPT patients (48.6% versus 37.2%), as was the presence of symptomatic intracranial stenosis/occlusion of the relevant artery (37.1% versus 29.4%). Baseline characteristics varied according to the time from symptom onset to hospital arrival, with differences observed in stroke mechanism and prior antiplatelet use, specifically showing an increased proportion of patients with LAA and more common prior antiplatelet use among later-arriving patients (Tables S1 through S4).

The adoption of DAPT in clinical practice showed a dramatic temporal evolution across all initiation windows throughout the study period, with prescription rates increasing substantially from approximately one-third of patients in 2011 (34.0%, 36.9%, and 37.2% for 0–24-hour, 24–72-hour, and >72-hour windows, respectively) to nearly 90% by 2023 (88.8%, 85.9%, and 87.8%, respectively; Figure 1). This upward trend was consistent across all time windows, including patients presenting beyond 24 hours after symptom onset.

The median follow-up duration was 367 days (interquartile range, 353–381), whereas a total of 94.4% of patients were followed up for at least 90 days. During the follow-up period, 6249 patients (15.0%) experienced recurrent stroke, 74 (0.2%) had an acute myocardial infarction, and 2325 (5.6%) died from any cause. Event rates of the primary outcome were slightly lower in the DAPT group (10.7% versus 11.6%, Figure 2A). Recurrent stroke occurred in 10.0% of patients who received DAPT, compared with 11.0% with MAPT (Figure S2A). All-cause mortality by 90 days was low and similar between groups (1.40% DAPT versus 1.44% MAPT, Figure S3A).

Time-Dependent Effect of DAPT Over MAPT

After PS weighting and matching, baseline covariates were well balanced between groups (absolute standardized differences <0.1 for key variables), confirming the effectiveness of adjustment strategies (Tables S1 through S4; Figure S4). DAPT was consistently associated with lower risks of the primary composite outcome and stroke recurrence across all analytic models (multivariable adjustment, IPTW, and PSM). HRs for the primary outcome ranged from 0.82 to 0.85, and for stroke recurrence from 0.80 to 0.83. Mortality rates at 90 days were similar between groups (HRs, 0.90–0.92; Table 2).

Within 24 Hours of Onset

DAPT initiated within 24 hours was associated with significantly lower 90-day event rates compared with monotherapy (11.9% versus 14.5%, Figure 2B), primarily due to reduced stroke recurrence (11.3% versus 14.0%) and a slight reduction in mortality (1.3% versus 1.6%). The benefit was consistent across all models: HR 0.74 (95% CI, 0.69–0.79) by multivariable and IPTW adjustment; HR, 0.77 (95% CI, 0.71–0.83) by PSM (Table 2).

Between 24 and 72 Hours

Event rates were comparable between groups (primary outcome: 9.5% versus 8.3%, Figure 2C; recurrent stroke: 8.6% versus 7.5%, Figure S2C; mortality: 1.5% versus 1.4%, Figure S3C). Adjusted HRs showed no significant difference: HR 1.00 to 1.04 across all models (Table 2).

Between 72 Hours and 7 Days

DAPT was associated with higher event rates than MAPT (primary outcome: 7.2% versus 5.6%, Figure 2D; stroke recurrence: 6.3% versus 5.1%, Figure S2D; mortality: 1.7% versus 1.1%, Figure S3D). HRs indicated a potential excess risk with DAPT: HR, 1.25 (95% CI, 1.01–1.55) in IPTW; similar trends in multivariable (HR, 1.19) and PSM (HR, 1.21) models (Table 2).

Further adjustment for in-hospital therapies did not materially alter the results, with the early benefit of DAPT remaining significant within 24 hours and diminishing thereafter (Table S5 and S6).

In a per-protocol analysis, the results were directionally consistent with the primary findings. Across time windows, crude 90-day event rates for the composite outcome were 13.9% versus 12.0% for the overall cohort, 17.2% versus 13.4% within 24 hours, 9.96% versus 10.7% between 24 to 72 hours, and 6.63% versus 8.12% between 72 hours and 7 days (MAPT versus DAPT, respectively; Figure S5). The majority of events occurred during hospitalization, with crude in-hospital proportions of 98.7% for the composite outcome, 99.3% for stroke recurrence, and 95.0% for all-cause death.

In a more granular analysis within the first 24 hours, the protective effect of DAPT was consistently observed

Table 1. Baseline Characteristics of Patients by Time Window

	Whole time window			Within 24 h			24 to 72 h			Beyond 72 h		
	Aspirin or clopidogrel	Clopidogrel-aspirin	*P* value*	Aspirin or clopidogrel	Clopidogrel-aspirin	*P* value*	Aspirin or clopidogrel	Clopidogrel-aspirin	*P* value*	Aspirin or clopidogrel	Clopidogrel-aspirin	*P* value*
N	16418	25112		9888	15464		4072	6082		2458	3566	
Age, y	65.2±13.6	67.0±12.8	<0.0001	64.9±13.6	66.9±12.9	<0.0001	65.3±13.7	67.0±12.6	<0.0001	66.2±13.4	67.7±12.8	<0.0001
Male	9878 (60.2)	15893 (63.3)	<0.0001	6015 (60.8)	9870 (63.8)	<0.0001	2422 (59.5)	3810 (62.6)	0.0013	1441 (58.6)	2213 (62.1)	0.0073
BMI	23.9±3.6	24.0±3.7	<0.0001	23.8±3.5	24.0±3.7	0.0023	23.9±3.7	24.1±3.7	0.0298	23.9±3.7	24.1±3.8	0.0428
Initial NIHSS	2 (1–3)	2 (1–3)	<0.0001	2 (1–3)	2 (1–3)	0.0238	2 (1–3)	2 (1–3)	<0.0001	2 (0–3)	2 (1–3)	0.0001
Initial NIHSS score distribution			<0.0001			0.0185			<0.0001			<0.0001
0	3976 (24.2)	5747 (22.9)		2442 (24.7)	3723 (24.1)		883 (21.7)	1188 (19.5)		651 (26.5)	836 (23.4)	
1–3	9256 (56.4)	13921 (55.4)		4420 (55.8)	8504 (55.0)		2355 (57.8)	3436 (56.5)		1381 (56.2)	1981 (55.6)	
4–5	3186 (19.4)	5444 (21.7)		1926 (19.5)	3237 (20.9)		834 (20.5)	1458 (24.0)		426 (17.3)	749 (21.0)	
Medical history												
Previous TIA or stroke	2379 (14.5)	5179 (20.6)	<0.0001	1526 (15.4)	3306 (21.4)	<0.0001	506 (12.4)	1181 (19.4)	<0.0001	347 (14.1)	692 (19.4)	<0.0001
Previous CAD	805 (4.9)	2052 (8.2)	<0.0001	500 (5.1)	1324 (8.6)	<0.0001	196 (4.8)	444 (7.3)	<0.0001	109 (4.4)	284 (8.0)	<0.0001
Hypertension	10312 (62.8)	16891 (67.3)	<0.0001	6135 (62.0)	10325 (66.8)	<0.0001	2592 (63.7)	4079 (67.1)	0.0004	1585 (64.5)	2487 (69.7)	<0.0001
Diabetes	5056 (30.8)	8976 (35.7)	<0.0001	2924 (29.6)	5302 (34.3)	<0.0001	1293 (31.8)	2309 (38.0)	<0.0001	839 (34.1)	1365 (38.3)	0.0010
Dyslipidemia	4860 (29.6)	8888 (35.4)	<0.0001	2882 (29.1)	5565 (36.0)	<0.0001	1177 (28.9)	2111 (34.7)	<0.0001	801 (32.6)	1212 (34.0)	0.2575
Recent smoking	4515 (27.5)	6635 (26.4)	0.0153	2668 (27.0)	4021 (26.0)	0.0842	1173 (28.8)	1672 (27.5)	0.1480	674 (27.4)	942 (26.4)	0.3871
Previous treatment hx of antiplatelet	2956 (18.0)	7719 (30.7)	<0.0001	1769 (17.9)	4658 (30.1)	<0.0001	710 (17.4)	1852 (30.5)	<0.0001	477 (19.4)	1209 (33.9)	<0.0001
Onset-to-arrival time (median, IQR)	1 (0–2)	1 (0–2)	0.0006	0 (0–0)	0 (0–0)	0.1041	2 (1–2)	2 (1–2)	0.2969	4 (3–5)	4 (3–5)	0.5690
Index stroke			<0.0001			0.0001			0.1549			0.2360
Ischemic stroke	15445 (94.1)	23850 (95.0)		9117 (92.2)	14453 (93.5)		3952 (97.1)	5931 (97.5)		2376 (96.7)	3466 (97.2)	
TIA	973 (5.9)	1262 (5.0)		771 (7.8)	1011 (6.5)		120 (2.9)	151 (2.5)		82 (3.3)	100 (2.8)	
Premorbid mRS score			0.0266			0.2438			0.1544			0.7807
0	14018 (85.4)	21491 (85.6)		8428 (85.2)	13254 (85.7)		3496 (85.9)	5238 (86.1)		2094 (85.2)	2999 (84.1)	
1	1109 (6.8)	1793 (7.1)		701 (7.1)	1125 (7.3)		258 (6.3)	419 (6.9)		150 (6.1)	249 (7.0)	
2	598 (3.6)	921 (3.7)		357 (3.6)	547 (3.5)		138 (3.4)	217 (3.6)		103 (4.2)	157 (4.4)	
3	521 (3.2)	691 (2.8)		297 (3.0)	403 (2.6)		139 (3.4)	160 (2.6)		85 (3.5)	128 (3.6)	
4	153 (0.9)	186 (0.7)		96 (1.0)	120 (0.8)		35 (0.9)	39 (0.6)		22 (0.9)	27 (0.8)	
5	19 (0.1)	30 (0.1)		9 (0.1)	15 (0.1)		6 (0.1)	9 (0.1)		4 (0.2)	6 (0.2)	
TOAST			<0.0001			<0.0001			<0.0001			<0.0001
LAA	6106 (37.2)	12196 (48.6)		3596 (36.4)	7219 (46.7)		1516 (37.2)	3011 (49.5)		994 (40.4)	1966 (55.1)	
SVO	5152 (31.4)	6699 (26.7)		3092 (31.3)	4198 (27.1)		1359 (33.4)	1715 (28.2)		701 (28.5)	786 (22.0)	
CE	618 (3.8)	746 (3.0)		379 (3.8)	539 (3.5)		167 (4.1)	127 (2.1)		72 (2.9)	80 (2.2)	
OD	690 (4.2)	849 (3.4)		411 (4.2)	546 (3.5)		159 (3.9)	195 (3.2)		120 (4.9)	108 (3.0)	
UD	3852 (23.5)	4622 (18.4)		2410 (24.4)	2962 (19.2)		871 (21.4)	1034 (17.0)		571 (23.2)	626 (17.6)	
Symptomatic steno-occlusion of relevant a.	4823 (29.4)	9320 (37.1)	<0.0001	2852 (28.8)	5601 (36.2)	<0.0001	1187 (29.2)	2194 (36.1)	<0.0001	784 (31.9)	1525 (42.8)	<0.0001
Laboratory findings												
Initial glucose	141.9±63.1	147.2±66.3	<0.0001	141.4±60.3	146.2±63.6	<0.0001	142.3±65.1	149.7±71.1	<0.0001	143.4±70.5	147.6±69.3	0.0228
SBP	150.1±27.6	151.6±27.7	<0.0001	151.6±28.1	153.0±28.1	<0.0001	148.8±27.2	150.5±27.3	0.0019	146.1±25.5	147.4±26.2	0.0481

BMI indicates body mass index; CAD, coronary artery disease; CE, cardioembolism; IQR, interquartile range; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, other determined cause; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient ischemic attack; and TOAST, Trial of Org 10172 in Acute Stroke Treatment; UD, undetermined cause.

*P value by Pearson χ^2 test, Student *t* test, or Wilcoxon rank-sum test as appropriate.

ORIGINAL CONTRIBUTION

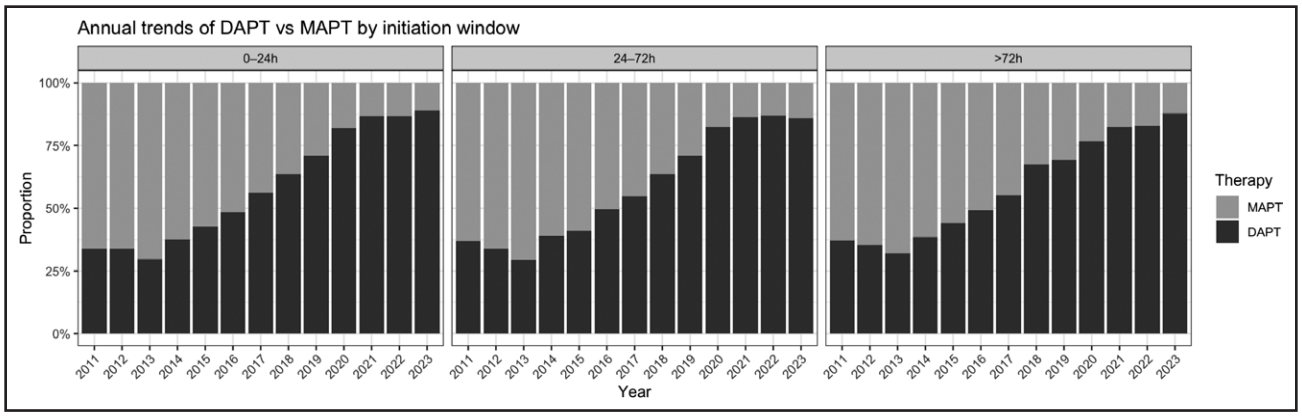

Figure 1. Annual trends in dual antiplatelet therapy (DAPT) vs monoantiplatelet therapy (MAPT) initiation by treatment window (0–24 hours, 24–72 hours, >72 hours) from 2011 to 2023.

across all early subgroups (0–6, 6–12, and 12–24 hours), with HRs ranging from 0.75 to 0.83 (Table S7).

To explore whether the treatment effect of DAPT varied across subgroups, we conducted predefined subgroup analyses (Figure 3). Although DAPT was generally associated with a reduced risk of recurrent vascular events, there was notable heterogeneity across clinical subgroups, particularly among patients who arrived >3 days after symptom onset, in whom the treatment effect reversed, favoring MAPT in those with LAA or prior antiplatelet use.

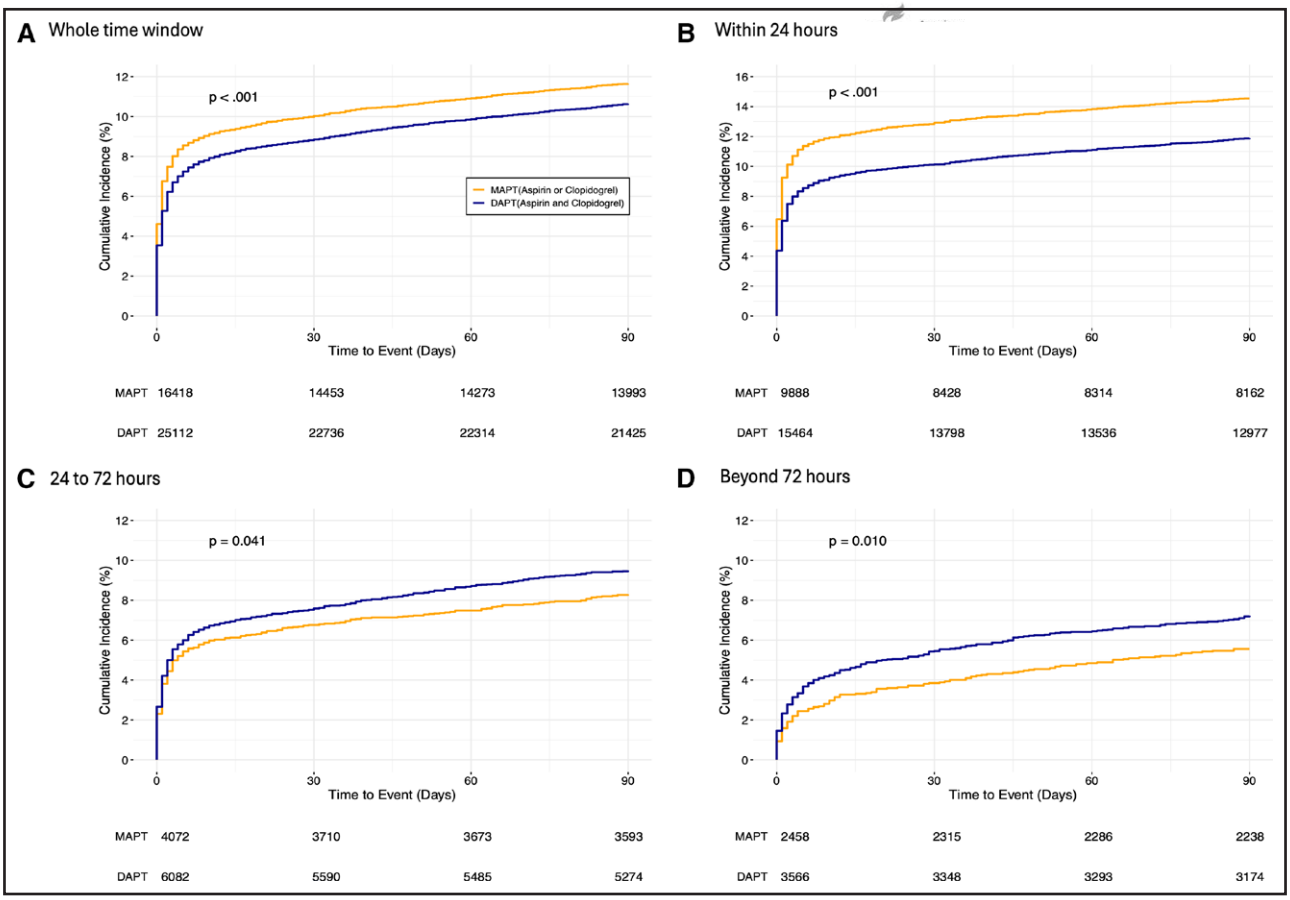

Figure 2. Cumulative incidence of the primary outcome (composite of stroke recurrence, myocardial infarction, and all-cause mortality) up to 3 months after symptom onset by antiplatelet use (aspirin or clopidogrel vs aspirin and clopidogrel) and stratified by 4 time windows.

A, Whole time window (0–90 days). **B**, Within 24 hours (0–1 day). **C**, From 24 to 72 hours (1–3 days). **D**, Beyond 72 hours (3–7 days). The number at risk for each group is displayed below the *x* axis. *P* values were calculated using the log-rank test. DAPT indicates dual antiplatelet therapy; and MAPT, monoantiplatelet therapy.

Table 2. HRs for Primary and Secondary Outcomes by Time Window

Time window	Whole time window		Within 24 h		24 to 72 h		Beyond 72 h		*P* for interaction
Crude analysis	HR (95% CI	*P* value	HR (95% CI	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Primary outcome	0.91 (0.85–0.96)	0.0010	0.80 (0.75–0.86)	<0.0001	1.15 (1.00–1.32)	0.0427	1.31 (1.07–1.62)	0.0106	<0.0001
Secondary outcomes									
Stroke recurrence	0.89 (0.84–0.95)	0.0003	0.79 (0.74–0.85)	<0.0001	1.16 (1.00–1.33)	0.0446	1.26 (1.01–1.57)	0.0388	<0.0001
All-cause death	0.97 (0.82–1.15)	0.7550	0.83 (0.67–1.03)	0.0877	1.08 (0.77–1.52)	0.6561	1.61 (1.02–2.54)	0.0426	0.0291
Multivariable Cox model	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	
Primary outcome	0.82 (0.77–0.87)	<0.0001	0.74 (0.69–0.79)	<0.0001	1.04 (0.91–1.19)	0.5632	1.19 (0.96–1.46)	0.1102	<0.0001
Secondary outcomes									
Stroke recurrence	0.80 (0.75–0.85)	<0.0001	0.73 (0.68–0.78)	<0.0001	1.03 (0.90–1.19)	0.6650	1.13 (0.90–1.40)	0.2945	<0.0001
All-cause death	0.92 (0.77–1.09)	0.3209	0.77 (0.62–0.96)	0.0190	1.04 (0.74–1.46)	0.8360	1.55 (0.97–2.45)	0.0643	0.0190
After IPTW	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Primary outcome	0.82 (0.77–0.87)	<0.0001	0.74 (0.69–0.79)	<0.0001	1.00 (0.88–1.15)	0.9448	1.25 (1.01–1.55)	0.0409	<0.<0.0001
Secondary outcomes									
Stroke recurrence	0.80 (0.75–0.85)	<0.0001	0.72 (0.67–0.78)	<0.0001	1.00 (0.87–1.16)	0.9927	1.17 (0.93–1.46)	0.1793	<0.0001
All-cause death	0.90 (0.75–1.06)	0.2107	0.77 (0.62–0.95)	0.0173	0.95 (0.67–1.35)	0.7827	1.61 (1.00–2.61)	0.051	0.0201
After PSM	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Primary outcome	0.85 (0.79–0.90)	<0.0001	0.77 (0.71–0.83)	<0.0001	1.04 (0.89–1.21)	0.6337	1.21 (0.95–1.52)	0.1184	<0.0001
Secondary outcomes									
Stroke recurrence	0.83 (0.77–0.89)	<0.0001	0.76 (0.70–0.82)	<0.0001	1.03 (0.88–1.21)	0.7316	1.15 (0.90–1.47)	0.2705	<0.0001
All-cause death	0.91 (0.76–1.10)	0.3401	0.80 (0.63–1.01)	0.0653	0.99 (0.67–1.46)	0.9564	1.41 (0.85–2.34)	0.1785	0.1183

HRs were derived from Cox proportional hazards regression models. Adjusted analyses included the following variables: age, sex, initial National Institutes of Health Stroke Scale score, body mass index, premorbid modified Rankin Scale score, Trial of Org 10172 in Acute Stroke Treatment classification, hypertension, diabetes, dyslipidemia, history of coronary artery disease, history of stroke or transient ischemic attack, smoking status, symptomatic intracranial steno-occlusion, prior antiplatelet use, initial glucose level, and systolic blood pressure. The same covariates were used in the propensity score model. In the IPTW analysis, a weighted Cox model with robust standard errors was used. In the PSM analysis, robust standard errors were used to account for clustering within matched pairs. The PSM cohorts comprised 15 774 matched pairs for the whole time window analysis, and 9607, 3861, and 2306 matched pairs for the within 24 h, 24 to 72 h, and beyond 72 h groups, respectively. HR indicates hazard ratio; PSM, propensity score matching; and IPTW, inverse probability of treatment weighting.

In analyses treating time to treatment as a continuous variable, we estimated the threshold beyond which DAPT no longer conferred a statistically significant benefit compared with MAPT. The estimated thresholds were ≈42 hours for the primary composite outcome, 45 hours for stroke recurrence, and 17 hours for all-cause mortality (Figure 4). To further assess robustness, bootstrap analysis yielded 95% CIs of 33 to 55.5 hours for the primary composite outcome, 34 to 59 hours for stroke recurrence, and 0 to 42 hours for all-cause death, encompassing the initially estimated thresholds of 42, 45, and 17 hours, respectively (Figure S6).

Post hoc subgroup analyses revealed variations in the estimated optimal timing: 16 hours for small vessel occlusion, 39 hours for cardioembolism/other determined cause/undermined cause, and 41 hours for LAA (Figure S7). The thresholds were also shorter among patients without symptomatic steno-occlusion (37 versus 44 hours; Figure S8) and those with prior antiplatelet use (37 versus 41 hours; Figure S9).

In an exploratory drug-specific sensitivity analysis separating aspirin and clopidogrel monotherapy, baseline characteristics are summarized in Tables S8 and S9. Outcome comparisons are presented in Tables S10 and S11, which, consistent with the main findings in Table 2, confirmed the

ORIGINAL CONTRIBUTION

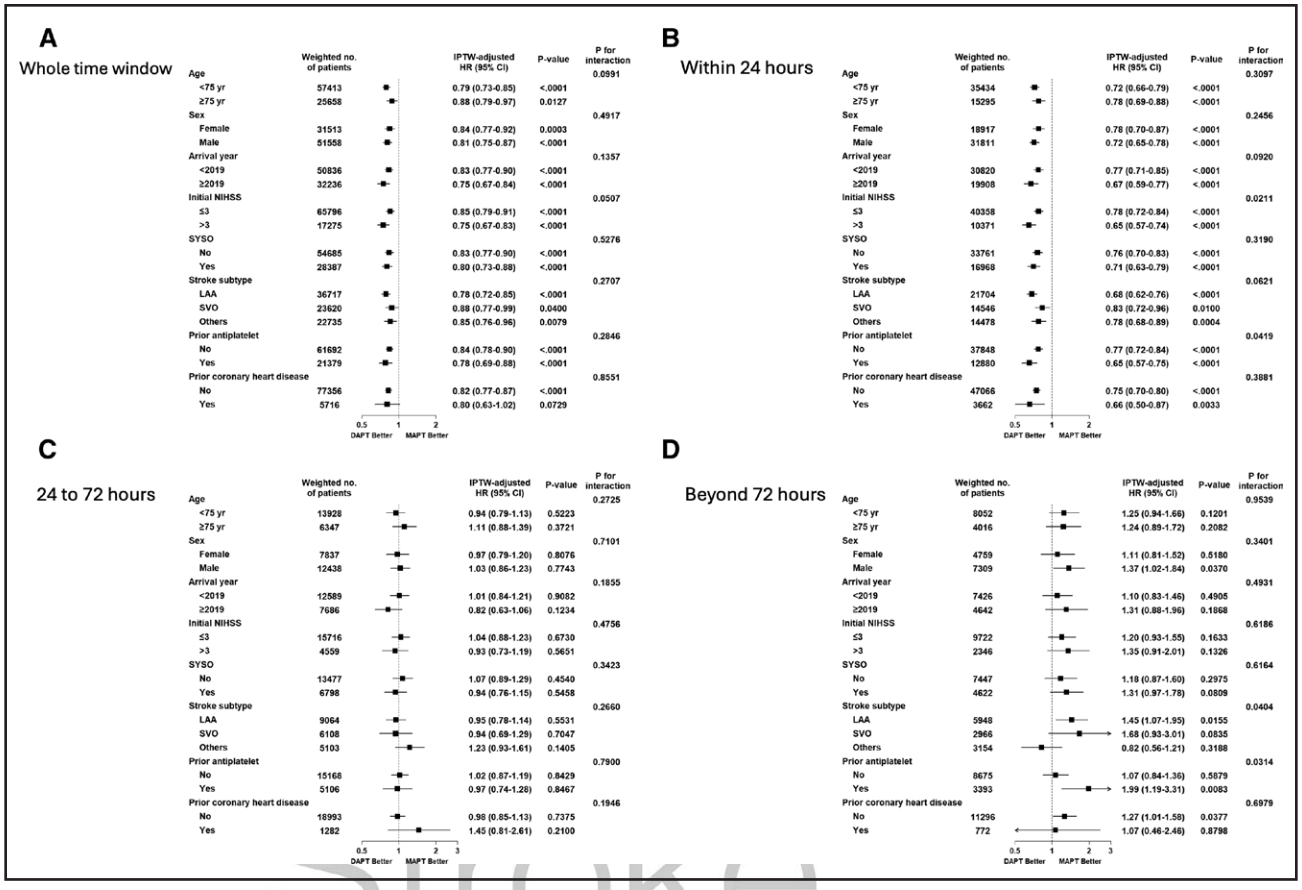

Figure 3. Hazard ratios (HRs) for the primary efficacy outcome across prespecified subgroups.
A, Whole time window (0–90 days). **B**, Within 24 hours (0–1 day). **C**, From 24 to 72 hours (1–3 days). **D**, Beyond 72 hours (3–7 days). The weighted number of patients in each subgroup is presented. *P* values indicate interaction effects between treatment and subgroup characteristics. DAPT indicates dual antiplatelet therapy; IPTW, inverse probability of treatment weighting; LAA, large artery atherosclerosis; MAPT, monoantiplatelet therapy; NIHSS, National Institutes of Health Stroke Scale; SVO, small vessel occlusion; and SYSO, symptomatic steno-occlusion of the relevant artery.

early protective effect of DAPT within 24 hours across all analytic frameworks. The HR curves for the primary outcome also demonstrated a time-dependent attenuation pattern similar to that observed in the overall MAPT versus DAPT comparison. However, the estimated thresholds for loss of DAPT benefit differed between the 2 agents: ≈35

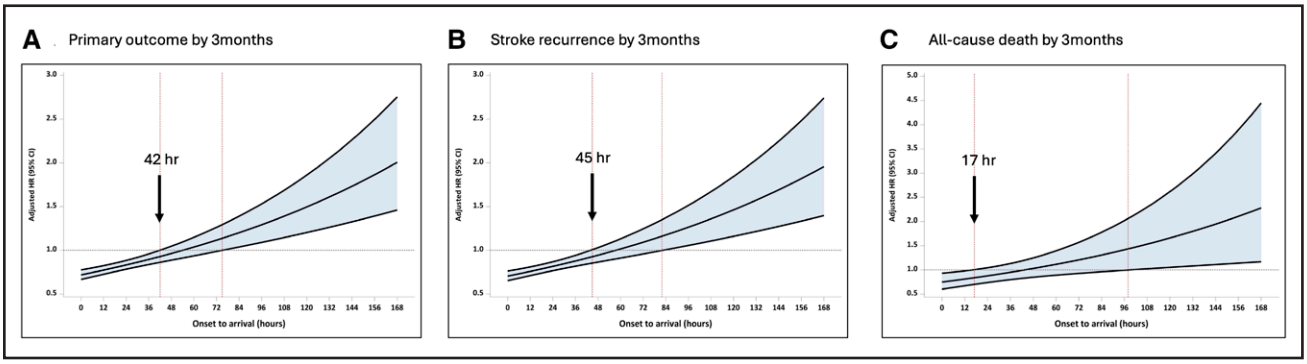

Figure 4. Adjusted hazard ratios (HRs) for the outcomes over time. Adjusted HR curves estimated using a multivariable Cox proportional hazards model, with time from symptom onset to hospital arrival modeled as a continuous variable.
The adjusted model included the following covariates: age, sex, initial National Institutes of Health Stroke Scale score, body mass index, premorbid modified Rankin Scale score, Trial of Org 10172 in Acute Stroke Treatment classification, hypertension, diabetes, dyslipidemia, history of coronary artery disease, history of stroke or transient ischemia attack, smoking status, symptomatic intracranial steno-occlusion, prior antiplatelet use, initial glucose level, and systolic blood pressure. The black line represents the HR, and the shaded area indicates the 95% CI. Black arrows indicate the upper bound of the 95% CI at the estimated time points where the HR crosses 1.0, suggesting potential changes in risk. **A**, Primary outcome at 3 months. **B**, Stroke recurrence at 3 months. **C**, All-cause mortality at 3 months.

hours for aspirin versus DAPT and 64 hours for clopidogrel versus DAPT (Figures S10 and S11).

DISCUSSION

In this nationally representative, real-world cohort of patients with minor stroke or high-risk TIA, DAPT adoption has steadily increased across all time windows from 2011 to 2023, including patients presenting beyond 24 hours. This reflects evolving real-world practice in Korea as clinicians increasingly prescribe DAPT beyond the time window recommended by the current guideline. In our analysis, early DAPT initiation—especially within the first 24 hours—was consistently associated with improved outcomes in reducing recurrent ischemic events, reinforcing the urgency emphasized in clinical guidelines.[5] However, beyond this period, the benefit became less clear. Time-continuous Cox analyses suggested that the therapeutic window for DAPT may extend up to ≈42 to 45 hours, supporting the notion that DAPT may be most effective during the early phase when unstable thrombi or active plaques are biologically active.[20]

These findings extend prior trial evidence and offer insight into the optimal therapeutic window for DAPT. All 3 trials—CHANCE, POINT, and THALES trials—emphasized treatment initiation within 12 to 24 hours of symptom onset, aligning with our observed benefit in the 0 to 24-hour window.[2–4] In patients treated within 24 hours, DAPT conferred a 2.6% absolute stroke risk reduction, closely aligning with CHANCE (3.5%) and POINT (1.5%).[3,4] THALES further validated the early treatment principle (although using ticagrelor instead of clopidogrel) by showing a 17% relative risk reduction in stroke at 30 days.[2] In line with these trials, our study's results reinforce the critical importance of early initiation – the sooner, the better.

A key novel contribution of our analysis is the estimation of a real-world threshold—≈42 hours after symptom onset—beyond which the benefit of DAPT diminished. Although the greatest benefit was seen with initiation within the first 24 hours, our findings suggest that the therapeutic window may extend beyond this period. A post hoc analysis of the POINT trial demonstrated that the benefit of DAPT remained favorable when initiated up to 72 hours after symptom onset, with the 95% CI for major ischemic events crossing above 1 at around 48 hours—aligning with our findings of diminishing benefit beyond this timeframe.[9] ATAMIS trial (Antiplatelet Therapy in Acute Mild to Moderate Ischemic Stroke) also showed DAPT reduced early neurological deterioration within 48 hours of symptom onset.[21]

Plaque instability peaks within the first 24 hours, but residual platelet activation and thromboinflammatory activity persist into next 1 to 2 days.[22] In our Korean real-world registry, most early neurological deterioration occurred within the first 72 hours,[16] supporting that thromboinflammatory processes remain active for several days after stroke onset, during which DAPT may still confer benefit. Thereafter, DAPT efficacy appeared to gradually decline over time, with the benefit reversing beyond 72 hours, particularly in patients with LAA or prior antiplatelet use. Once the acute phase of plaque instability subsides, vascular mechanisms, such as persistent endothelial activation, ongoing vascular inflammation, and thrombus formation on complex or ulcerated plaques, may be less responsive to intensified platelet inhibition,[23] leading to attenuation of benefit. The observed higher event rate in DAPT-treated patients beyond 72 hours was not explained by hemorrhagic complications, as symptomatic hemorrhagic transformation occurred in only 1 patient (0.03%) among 3566 patients in the >72-hour DAPT group. In addition, part of this reversal may reflect residual confounding despite PS adjustment. Patients with a heavier atherosclerotic burden or those with prior antiplatelet exposure are intrinsically at higher risk of recurrence and are more likely to be preferentially selected for DAPT in clinical practice.[24,25]

A recent trial, INSPIRES, which focused on symptomatic intracranial or extracranial atherosclerosis and those with multiple acute infarctions, found that initiating DAPT up to 72 hours after stroke onset reduced 90-day stroke risk compared with aspirin alone (1.9% absolute risk reduction), without excess severe bleeding.[8] Our findings are generally consistent with this result but suggest a somewhat narrower therapeutic window. Specifically, in patients with LAA stroke, the estimated threshold for DAPT benefit appeared to be around 42 hours after symptom onset. Several factors may explain this shorter optimal window compared with INSPIRES. Patients enrolled in clinical trials are typically selected based on strict inclusion criteria, tend to be healthier, more homogeneous, and more adherent to treatment protocols.[26] In contrast, real-world populations are more heterogeneous, with greater variability in comorbidities, treatment adherence, and stroke mechanisms, which may have led to an earlier attenuation of DAPT benefit in our study.

In our study, time-to-treatment was defined as the interval from symptom onset to hospital arrival, serving as a pragmatic proxy for DAPT initiation in actual clinical workflows, where delays from triage, imaging, and consent are common.[27] In contrast, prior randomized trials used symptom onset to randomization as the inclusion window, which inherently includes delays for diagnostic evaluations, consent, and randomization procedures.[2–4,8] For example, the INSPIRES trial allowed enrollment up to 72 hours postonset, with medications administered within 1 hour after randomization.[8] Notably, the median onset-to-randomization time in INSPIRES was around 46 hours, suggesting that treatment often began later in the course of stroke evolution.[28] Although direct comparisons are limited due to differing definitions and study designs, the estimated 42-hour threshold observed in our study may reflect a broadly similar therapeutic window, highlighting the need for further research to refine optimal timing for DAPT initiation in real-world clinical practice.

One characteristic of East Asian populations is the higher prevalence of CYP2C19 loss-of-function alleles, which significantly reduce clopidogrel responsiveness compared with Western populations.[29] Suggesting this pharmacogenetic feature, our exploratory analysis showed that the attenuation threshold was longer for clopidogrel monotherapy versus DAPT (≈64 hours) than for aspirin versus DAPT (≈35 hours; Figures S10 and S11). In the recent PLATELET trial (Korean Cytochrome P450 2C19 Genotypes and Clopidogrel in Patients With Ischemic Stroke), carriers of these alleles had higher risks of recurrent stroke and cardiovascular events despite clopidogrel therapy, underscoring the clinical impact of this genetic background.[30] Likewise, the INSPIRES genetic substudy demonstrated that CYP2C19 loss-of-function noncarriers still benefited from clopidogrel-aspirin even when treatment was initiated between 24 and 72 hours, suggesting preserved efficacy in patients with efficient clopidogrel metabolism.[31] Given this pharmacogenetic background, our study identified a 42-hour therapeutic window in Korean patients, suggesting that the optimal timing for DAPT may be population-specific and potentially longer in populations with more favorable clopidogrel metabolism. These findings highlight the need for international studies to determine whether genetic differences influence the optimal timing of DAPT initiation.

Several limitations of this study should be acknowledged. First, as a secondary analysis of a multicenter, prospective cohort study, baseline differences existed between treatment groups. Although we adjusted for known confounders using propensity methods, unmeasured factors—such as clinicians' judgment of plaque instability or patient frailty—could have influenced both treatment timing and outcomes. Second, major bleeding events were not systematically captured in our registry. However, prior major trials of early DAPT (CHANCE, POINT, THALES, INSPIRES) consistently reported low rates of severe bleeding (≈0.3% to 0.9%), supporting the overall safety of short-term DAPT in this setting.[2–4,8] Third, data on antiplatelet dosing and loading protocols were not standardized in our registry. This limitation, also noted in prior real-world studies, reflects the variability in physician-driven treatment decisions.[32] However, most of the participating centers were academic hospitals that follow guideline-based practice, and the usual practice is to administer loading doses of antiplatelet agents at initiation, except for patients who were already on antiplatelet therapy before the index event. Fourth, most participating centers were academic hospitals, which may limit generalizability. Nevertheless, the alignment of our results with national stroke audit data suggests broader applicability.[33] Finally, the study was conducted in South Korea, with a predominantly East Asian population and healthcare system, which may limit generalizability to non–East Asian populations or health systems. However, the consistency of these results with randomized trials strengthens their external validity.[2–4,8]

CONCLUSIONS

This study provides real-world evidence that DAPT initiated within 24 hours after a minor ischemic stroke or high-risk TIA confers significant clinical benefit, consistent with findings from CHANCE, POINT, and THALES trials. Importantly, our data suggest that therapeutic benefit may extend up to ≈42 hours, potentially offering an extended window for intervention in patients unable to receive immediate treatment. Prospective studies are warranted to validate these observations and to inform guidelines on optimal DAPT initiation timing for secondary stroke prevention.

ARTICLE INFORMATION

Received August 9, 2025; final revision received December 1, 2025; accepted December 8, 2025.

Presented in part at the XXVII World Congress of Neurology, Seoul, South Korea, October 12–15, 2025.

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Sources of Funding

This research was supported by the Korea National Institutes of Health research project (project No. 2023-ER-1006-02) and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI23C0359). The funding sources did not participate in any part of the study, from conception to article preparation.

Disclosures

Dr Bae reports grants from Amgen Korea Inc, Bayer Korea, Bristol Myers Squibb Korea, Celltrion, Dong-A ST, Otsuka Korea, Samjin Pharm, and Takeda Pharmaceuticals Korea Co, Ltd; and personal fees from Amgen Korea, Bayer, Daewoong

Pharmaceutical Co, Ltd, Daiichi Sankyo, Esai Korea Inc, JW Pharmaceutical, and SK chemicals, outside the submitted work.

Supplemental Material

Tables S1–S11
Figures S1–S11
STROBE Checklist

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