Journal of the American Heart Association

ORIGINAL RESEARCH

Trends in Dual Antiplatelet Therapy of Aspirin and Clopidogrel and Outcomes in Ischemic Stroke Patients Noneligible for POINT/CHANCE Trial Treatment

Joon-Tae Kim, MD, PhD; Ji Sung Lee, PhD; Hyunsoo Kim, MD, PhD; Beom Joon Kim, MD, PhD; Keon-Joo Lee, MD, PhD; Jong-Moo Park, MD, PhD; Kyusik Kang, MD, PhD; Soo Joo Lee, MD, PhD; Jae Guk Kim, MD; Jae-Kwan Cha, MD, PhD; Dae-Hyun Kim, MD, PhD; Tai Hwan Park, MD, PhD; Kyungbok Lee, MD, PhD; Jun Lee, MD, PhD; Keun-Sik Hong, MD, PhD; Yong-Jin Cho, MD, PhD; Hong-Kyun Park, MD; Byung-Chul Lee, MD, PhD; Kyung-Ho Yu, MD, PhD; Mi Sun Oh, MD, PhD; Dong-Eog Kim, MD, PhD; Jay Chol Choi, MD, PhD; Jee-Hyun Kwon, MD, PhD; Wook-Joo Kim, MD, PhD; Dong-Ick Shin, MD, PhD; Kyu Sun Yum, MD, PhD; Sung Il Sohn, MD, PhD; Jeong-Ho Hong, MD, PhD; Sang-Hwa Lee, MD, PhD; Man-Seok Park, MD, PhD; Wi-Sun Ryu, MD; Kwang-Yeol Park, MD, PhD; Juneyoung Lee, PhD; Jeffrey L. Saver, MD; Hee-Joon Bae, MD, PhD

BACKGROUND: Recent clinical trials established the benefit of dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) in early-presenting patients with minor ischemic stroke. However, the impact of these trials over time on the use and outcomes of DAPT-AC among the patients with nonminor or late-presenting stroke who do not meet the eligibility criteria of these trials has not been delineated.

METHODS AND RESULTS: In a multicenter stroke registry, this study examined yearly changes from April 2008 to August 2022 in DAPT-AC use for stroke patients ineligible for CHANCE/POINT (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events/Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) clinical trials due to National Institutes of Health Stroke Scale >4 or late arrival beyond 24 hours of onset. A total of 32 118 patients (age, 68.1±13.1 years; male, 58.5%) with National Institutes of Health Stroke Scale of 4 (interquartile range, 1–7) were analyzed. In 2008, DAPT-AC was used in 33.0%, other antiplatelets in 62.7%, and no antiplatelet in 4.3%. The frequency of DAPT-AC was relatively unchanged through 2013, when the CHANCE trial was published, and then increased steadily, reaching 78% in 2022, while other antiplatelets decreased to 17.8% in 2022 (P_{trend}<0.001). From 2011 to 2022, clinical outcomes nonsignificantly improved, with an average relative risk reduction of 2%/y for the composite of stroke, myocardial infarction, and all-cause mortality, both among patients treated with DAPT-AC and patients treated with other antiplatelets.

CONCLUSIONS: Use of DAPT-AC in stroke patients with stroke ineligible for recent DAPT clinical trials increased markedly and steadily after CHANCE publication in 2013, reaching deployment in nearly 4 of every 5 patients by 2022. The secondary prevention in patients with ischemic stroke seems to be gradually improving, possibly due to the enhancement of risk factor control.

Key Words: acute ischemic stroke ■ aspirin ■ clopidogrel ■ dual antiplatelet treatment ■ late-presenting stroke ■ nonminor stroke

Correspondence to: Joon-Tae Kim, MD, PhD, Department of Neurology, Chonnam National University Medical School, Chonnam National University Hospital, 42 Jebongro, Dong-gu, Gwangju 61469, Korea. Email: alldelight2@jnu.ac.kr Hee-Joon Bae, MD, PhD, Department of Neurology, Seoul National University College of Medicine, Cerebrovascular Disease Center, Seoul National University Bundang Hospital, 82, Gumi-ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea. Email: braindoc@snu.ac.kr

This manuscript was sent to Luciano A. Sposato, MD, MBA, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.033611

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The study, conducted in South Korea, found a notable increase in the use of dual antiplatelet therapy with aspirin and clopidogrel from 2013 onwards among >32 000 stroke patients ineligible for recent dual antiplatelet therapy clinical trials, coinciding with the publication of the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial.
- Our results also indicated an increase in annual rates for risk factor control, such as statin and diabetes medication use.
- Slight decreases in the annual risk of early vascular outcomes were observed both in patients treated with dual antiplatelet therapy with aspirin and clopidogrel and patients treated with mono- or other dual antiplatelet regimens.

What Are the Clinical Implications?

- Late-presenting strokes or nonminor strokes in actual clinical practice may signify a substantial gap between evidence and clinical practice, underscoring the need to conduct clinical trials on dual antiplatelet therapy with aspirin and clopidogrel for secondary prevention in nonminor (National Institutes of Health Stroke Scale >4) and nonacute (beyond 24 hours of onset) ischemic stroke patients who were ineligible for recent dual antiplatelet therapy with aspirin and clopidogrel clinical trials.
- The secondary prevention effects in patients with ischemic stroke seem to be gradually improving, possibly due to the enhancement of risk factor control.

Nonstandard Abbreviations and Acronyms

CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
CRCS-K	Clinical Research Center for Stroke-Korea
DAPT-AC	dual antiplatelet therapy with aspirin and clopidogrel
NIHSS	National Institutes of Health Stroke Scale
OE	Other determined etiology
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
THALES	The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UD	undetermined cause

Long-term dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) is not recommended for long-term secondary prevention after ischemic stroke because reduction in recurrent ischemic stroke is counterbalanced by an increase in intracranial and major bleeding.[1] However, short-term DAPT-AC was shown to confer net benefit with greater reductions in recurrent ischemic stroke than increase in bleeding complications, in the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial in 2013 and the POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial in 2018.[2–4] In addition, DAPT-AC is only recommended for very specific patients who have had a recent stroke associated with severe symptomatic intracranial stenosis (ie, 70%–99% stenosis) based on the SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial.[5] Current guidelines, therefore, recommend short-term use of DAPT-AC, for the first 21 days or 90 days poststroke, for early secondary prevention in patients with acute (initiation within 24 hours of onset) minor (National Institutes of Health Stroke Scale [NIHSS] scores of 0–3 or 4) ischemic stroke or high-risk transient ischemic attack.[6,7] For most ischemic stroke patients not meeting these criteria due to more severe neurologic deficit or later time after onset, aspirin monotherapy, clopidogrel monotherapy, or combination of aspirin and extended-release dipyridamole have been primarily considered.[6]

However, recent studies have indicated that in routine clinical practice DAPT-AC is frequently administered to patients who do not meet the inclusion criteria of the CHANCE or POINT clinical trials.[8,9] In the Get With The Guidelines (GWTG)-Stroke registry, >40% of patients with nonminor stroke received DAPT-AC despite lack of randomized trial evidence in this setting.[8] However, these studies did not investigate temporal trends in the use of DAPT-AC in trial-ineligible patients nor variation in use among specific trial-ineligible subsets.

Therefore, we hypothesized that the secular trends of DAPT-AC use in patients with acute ischemic stroke who do not meet the eligibility criteria of recent DAPT-AC clinical trials might suggest a temporal trend indicative of evolving clinical practices.

METHODS

Subjects

This study was an analysis of a prospective, multicenter, nationwide registry of consecutive patients with acute stroke or transient ischemic attack admitted to 18 academic hospitals in South Korea, the Clinical Research Center for Stroke-Korea (CRCS-K) registry. Detailed methodologic information about the CRCS-K registry has been reported previously.[10,11] Inclusion criteria for this study were as follows: (1) admitted with acute ischemic stroke between April 2008 and August 2022; (2) noncardiogenic stroke mechanism; and (3) NIHSS score >4 or arrival beyond 24 hours of onset. Exclusion criteria were as follows: (1) treated with acute reperfusion therapy or carotid revascularization such as endarterectomy or carotid artery stenting; and (2) treated with anticoagulation.

Data Collection

Demographic, clinical, imaging, and laboratory data were prospectively collected. Ischemic stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, which were refined to incorporate additional information based on modern imaging studies.[12] Antiplatelet regimens were categorized into 4 groups: (1) DAPT-AC; (2) other mono- or dual-antiplatelet treatment (aspirin alone, clopidogrel, cilostazol, ticlopidine, triflusal, ticagrelor alone or in a combination other than aspirin+clopidogrel); (3) triple antiplatelet therapy with aspirin, clopidogrel, and other antiplatelets; and (4) no antiplatelet therapy. Although the 2021 American Heart Association/American Stroke Association (ASA) secondary prevention guidelines issued a new recommendation for ticagrelor plus aspirin for patients with minor to moderate stroke (NIHSS score <5) after the publication of the THALES (The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA [acetylsalicylic acid] for Prevention of Stroke and Death) clinical trial,[6,13] ticagrelor alone and ticagrelor plus aspirin were not commonly used during the study period in South Korea. Therefore, these antiplatelet agents were grouped together in the mono- or other dual antiplatelet regimen category.

Patient Follow-Up and Outcomes

Three months after initial ischemic stroke admission and data collection, patients were followed up by trained research coordinators in face-to-face or telephone interviews based on a standardized interview protocol.[10,11] For the analysis of annual changes in early vascular outcomes, we used data collected after January 2011, which was the point at which the registry began prospectively collecting data on vascular events at 3 months and 1 year. Outcomes analyzed were as follows: (1) the composite of stroke, myocardial infarction, and all-cause mortality, (2) recurrent stroke (either ischemic or hemorrhagic), and (3) all-cause mortality.

Statistical Analysis

Patient baseline characteristics are presented as means and SDs or medians with interquartile ranges for continuous variables and numbers and percentages for categorical variables. Changes in baseline characteristics according to the calendar year were tested for statistical significance using the Cochran–Armitage trend test, Mantel–Haenszel χ^2 test, and a linear contrast test in analysis of variance, as appropriate. Detailed analyses were undertaken comparing the 2 predominant treatment strategies, DAPT-AC versus mono- or other dual antiplatelet regimens, from which patients treated with triple antiplatelet therapy or no antiplatelet therapy were excluded.

Comparisons of baseline characteristics between DAPT-AC users and other antiplatelet regimen users were made using the Student *t* test or Wilcoxon rank sum test for continuous variables and a χ^2 test for categorical variables, as appropriate. The log-rank test for trend and a linear contrasts test in Cox proportional hazards regression were used to evaluate the statistical significance of changes in survival outcomes according to the calendar year.

Additionally, to identify changes in the trend of DAPT-AC proportion and adjusted event rates, joinpoint regression was estimated by using the Joinpoint Regression Program. By fitting segmented linear regression models to the data, joinpoint analysis can identify points where the rate of change in the data significantly deviates. The average annual percent change is then calculated based on these identified joinpoints, providing a comprehensive understanding of the average annual percentage change.[14]

To examine the associations between calendar year and outcomes, marginal Cox model with robust variance estimator was used to account for the center effect.[15] Adjusted variables were considered as clinically relevant variables as follows: age, sex, NIHSS score, arrival within 24 hours, body mass index, history of stroke, history of coronary artery disease, hypertension, diabetes, dyslipidemia, current smoking, prior statin use, large artery steno-occlusion, TOAST, statin, antidiabetes medication, DAPT-AC, and calendar year. All statistical analyses were performed using SAS software (Version 9.4, SAS Institute Inc, Cary, NC) and Joinpoint Regression Program (Version 5.0.2, Statistical Research and Applications Branch, National Cancer Institute).

Ethics Approval

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all the participating centers. A waiver for informed consent was provided because of study subject anonymity and minimal risk to the participants. The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the CRCS-K steering committee.

RESULTS

General Characteristics

A total of 32 118 patients met study selection criteria (patient selection flowchart shown in Figure S1. The mean age was 68.1±13.1 years, men were 58.5%), and median NIHSS score of 4 (interquartile range, 1–7) (Table 1). Trial ineligibility was due to arrival >24 hours alone in 54.0%, NIHSS >4 alone in 28.6%, and both in 17.4%. Among patients with NIHSS >4, median NIHSS was 7 (interquartile range, 5–11). Most patients (71.4%) arrived >24 hours after onset. The stroke subtypes were large artery atherosclerosis, small vessel occlusion (24.8%), other determined etiology (OE, 3.5%), and undetermined cause (UD, 21.9%). At admission, 51.6% of the patients received DAPT-AC, and 45.2% received other antiplatelet regimens; aspirin alone (37.1%), clopidogrel alone (2.9%), or other antiplatelet treatment (5.2%), such as cilostazol, ticlopidine, or triflusal, either alone or in combination with aspirin or clopidogrel.

Annual Trends of the Use of DAPT-AC

In the first study year, 2008, DAPT-AC was used in 33.0% of patients, while other antiplatelet regimens were used in 62.7%. Use frequencies remained in this range until 2013 and then DAPT-AC use gradually increased to 78% in 2022 (P for trend <0.001) (Table 2, Figure 1). In the Joinpoint analysis of annual percent changes in DAPT-AC use, 2 joinpoints were observed in 2013 and 2020 (Figure S2). The annual changes of patient characteristics are shown in Table S1, with an increase in age, height, weight, and body mass index observed since 2008. The proportion of patients who with arrival beyond 24 hours as their only trial ineligibility feature mildly increased, those with NIHSS >4 mildly decreased, and those with both remain unchanged. During this time period, baseline features of patients prescribed DAPT-AC showed increasing frequencies of prestroke clopidogrel (12% in 2008 to 16.3% in 2022, P_{trend} <0.001) and statin use (10.7%–30.1%, P_{trend} <0.001) and in-hospital antihypertensive treatment (34.2%–50.6%, P_{trend} <0.001), antidiabetic medication

Table 1. General Characteristics of Subjects

	All subjects
N	32 118
Age, mean±SD	68.1±13.1
Male, n (%)	18 799 (58.5)
Height, cm (mean±SD)	161.8±9.0
Weight, kg (mean±SD)	62.5±11.7
BMI (mean±SD)	23.8±3.5
NIHSS score, med (IQR)	4 (1–7)
Reasons for trial ineligibility	
Arrival beyond 24 h only	17 351 (54.0)
NIHSS >4 only	9170 (28.6)
Both	5597 (17.4)
In-hospital antiplatelet treatment	
DAPT-AC	16 569 (51.6)
Other mono/dual antiplatlet regimen	14 503 (45.2)
Triple antiplatlet	284 (0.9)
No antiplatlet	762 (2.4)
TOAST, n (%)	
LAA	16 032 (49.9)
SVO	7950 (24.8)
OE	1115 (3.5)
UD	7021 (21.9)
Medical history, n (%)	
TIA	555 (1.7)
Stroke	6798 (21.2)
PAD	233 (0.7)
CAD	2222 (6.9)
Hypertension	21 878 (68.1)
Diabetes	11 997 (37.4)
Dyslipidemia	10 179 (31.7)
Smoking	
Never	19 985 (62.2)
Current	8492 (26.4)
Ex-smoker	2435 (7.6)
Recently quit	1206 (3.8)
Medication history, n (%)	
Antiplatelet	9290 (28.9)
Prior aspirin	6523 (20.3)
Prior clopidogrel	3884 (12.1)
Antihypertensive	16 220 (50.5)
Statin	6253 (19.5)
Antidiabetics	8883 (27.7)
Large artery steno-occlusion, n (%)	
No	15 425 (48.0)
Mild	3408 (10.6)
Significant	7232 (22.5)
Occlusion	6053 (18.8)
In-hospital treatment, n (%)	
Aspirin	28 999 (90.3)
Clopidogrel	19 361 (60.3)

Continued

Table 1. Continued

	All subjects
Cilostazol	3411 (10.6)
Triflusal	333 (1.0)
Ticlopidine	645 (2.0)
Antidiabetics	9055 (28.2)
Antihypertensive	14 676 (45.7)
Statin	29 409 (91.6)

BMI indicates body mass index; CAD, coronary artery disease; DAPT-AC, dual antiplatelet therapy with aspirin and clopidogrel; IQR, interquartile range; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OE, other determined etiology; PAD, peripheral artery disease; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

(23.5%–28.8%, P_{trend}=0.0002), and statin use (59.9%–96.7%, P_{trend} <0.001).

The annual change in characteristics among patients prescribed DAPT-AC is shown in Table S2 and Figure 2. All TOAST stroke subtypes showed a pattern of relative unchanged DAPT-AC use frequency from 2008 to 2013 followed by steady increases to 2022. Between 2008 and 2022, DAPT-AC use increases were as follows: large artery atherosclerosis 37.7% to 82.5%; small vessel occlusion 23% to 79.7%; UD 35.8% to 68.9%; and OC 13.3% to 66.7% (Figure 2A). Similarly, use of DAPT-AC among all trial ineligibility subgroups showed a pattern of relatively stable use frequency from 2008 to 2013 followed by steady increases to 2022 (Figure 2B). Between 2008 and 2022, DAPT-AC prescription increased among patients with the following: arrival beyond 24 hours alone, 32.7% to 78.6%; NIHSS >4 alone, 29.9% to 80.4%; and both arrival beyond 24 hours and NIHSS >4, 39.0% to 75.0%. Considering degree of stenosis subgroups, a similar pattern of relative stability between 2008 and 2013 and then steady increase to 2022 was seen for all 4 subgroups: no occlusion, mild stenosis, severe stenosis, and occlusion, with a particularly accelerated increase in the no-stenosis group (Figure 2C).

Vascular Event Outcomes Within 3 Months and 1Year

The mean follow-up duration was 338.4±88.6 days, and 97.4% and 89.4% of the study subjects completed 3-month and 1-year of follow-up, respectively. The comparison of vascular outcomes between 2011 and 2022 was conducted in 27 529 patients, among whom 15 260 (55.4%) received DAPT-AC and 12 269 (44.6%) received other mono- or dual antiplatelet regimens. Comparing the baseline features of the 2 groups, DAPT-AC use was associated with older age, male sex, earlier hospital arrival after onset, large artery atherosclerosis stroke subtype, presence of cardiovascular

Table 2. Annual Changes in Use of Antiplatelet Regimens Over Study Years

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	P_{trend}
N	990	1364	1314	1825	1773	2234	2348	2470	2352	2594	2625	2941	2699	2792	1797	<0.001
DAPT-AC	327 (33.0)	479 (35.1)	503 (38.3)	593 (32.5)	600 (33.8)	710 (31.8)	848 (36.1)	972 (39.4)	1108 (47.1)	1342 (51.7)	1608 (61.3)	1949 (66.3)	1955 (72.4)	2165 (77.5)	1410 (78.5)	
Other mono or dual antiplatelet regimen	621 (62.7)	831 (60.9)	782 (59.5)	1125 (61.6)	1136 (64.1)	1478 (66.2)	1403 (59.8)	1379 (55.8)	1160 (49.3)	1180 (45.5)	951 (36.2)	932 (31.7)	663 (24.6)	542 (19.4)	320 (17.8)	
Triple antiplatelet	5 (0.5)	3 (0.2)	12 (0.9)	15 (0.8)	12 (0.7)	9 (0.4)	22 (0.9)	16 (0.6)	22 (0.9)	14 (0.5)	20 (0.8)	31 (1.1)	36 (1.3)	46 (1.6)	21 (1.2)	
No antiplatelet	37 (3.7)	51 (3.7)	17 (1.3)	92 (5.0)	25 (1.4)	37 (1.7)	75 (3.2)	103 (4.2)	62 (2.6)	58 (2.2)	46 (1.8)	29 (1.0)	45 (1.7)	39 (1.4)	46 (2.6)	

P value by Cochran–Mantel–Haenszel test. DAPT-AC indicates dual antiplatelet therapy with aspirin and clopidogrel.

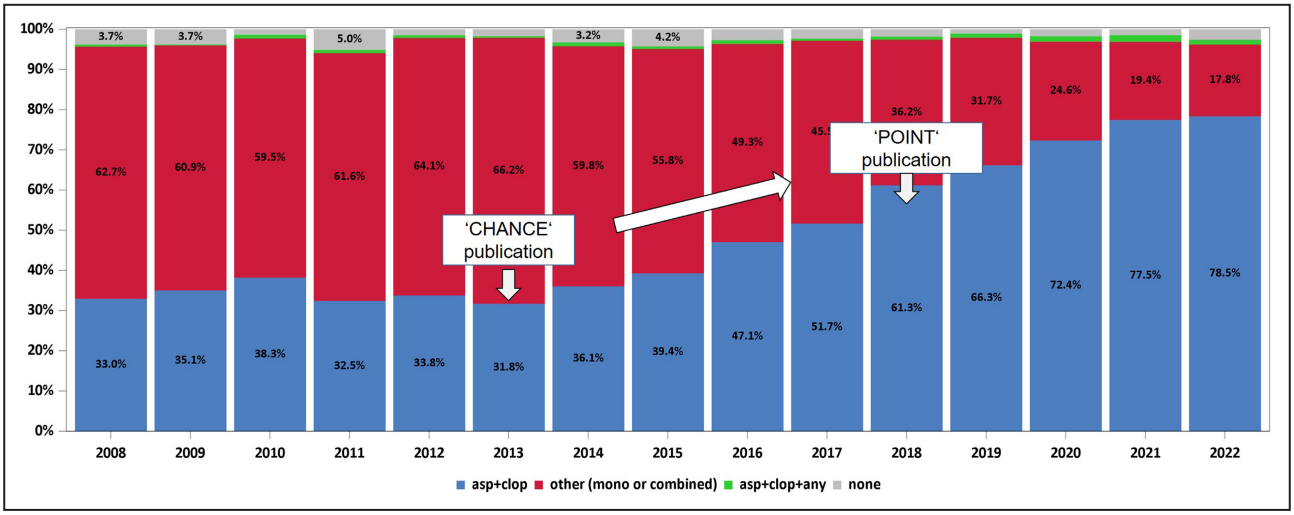

Figure 1. Annual changes of antiplatelet treatments in stroke patients noneligible for recent DAPT-AC clinical trials.
DAPT-AC indicates dual antiplatelet therapy with aspirin (asp) and clopidogrel (clop).

risk factors, and prior antiplatelet, statin, antihypertensive, and antidiabetes medications before index stroke (Table S3).

Among the 27 529 patients, 97% completed a 3-month and 89.5% a 1-year follow-up. The changes in 3-month vascular event rates between 2011 and 2022 are shown in Table 3 and Figure 3. The COVID pandemic appeared to affect events rates with a spike in events during peak pandemic year 2021 and a postpandemic drop in events in 2022. Before the advent of the COVID peak, from 2011 to 2020, in both adjusted and unadjusted analyses, there was a declining trend in each of the outcomes (Table 3, Table S4 and Figure S3). In the adjusted analysis, the composite of stroke, myocardial infarction, and all-cause mortality within 3 months declined from 14.5% to 11.6%, P_{trend} <0.001; and recurrent stroke declined from 12.8% to 9.2%, P_{trend} <0.001, but not in all-cause mortality and hemorrhagic stroke; from 2.7% to 3.1% (P_{trend}=0.16) and from 0.1% to 0.3% (P_{trend}=0.62), respectively (Table 3, Figure 3A). The joinpoint trend analysis revealed a decreasing trend in 3-month recurrent strokes (Figure S4). A similar, though somewhat less pronounced, decline between 2011 and 2022 was also seen at 1-year follow-up in both adjusted and unadjusted analyses for recurrent stroke outcomes, but not in the composite of stroke, myocardial infarction, and all-cause mortality; and all-cause mortality alone (Figure S5, Table S5).

The annual outcome event rates separately in patients prescribed DAPT-AC and patients prescribed other antiplatelet regimens, adjusted and unadjusted, are shown Tables S6 and S7 and Figure 3B and Figure S3B. In general, the absolute declines from 2011 to 2019 were more pronounced, but relative declines were similar in patients prescribed DAPT-AC than in patients prescribed other antiplatelet regimens. For example, in adjusted analysis of 3-month outcomes, for recurrent stroke rates with DAPT-AC declined from 15.8% to 11.8% (absolute risk reduction, ARR 4.0%) while rates with other antiplatelet regimens declined from 13.6% to 11.0% (ARR 2.6%). There were nonsignificant associations of calendar year increase since 2011 with reducing the risk in 3-month composite of stroke, myocardial infarction, and all-cause mortality by relatively 2% (hazard ratio, 0.98 [95% CI, 0.97–1.01]) (Table 4). The proportional assumptions were not met for many of the variables.

For TOAST ischemic subtypes, similar patterns were seen in patients prescribed DAPT-AC and other antiplatelet regimens, except UD ischemic subtype (Tables S8 and S9 and Figure S6). In the UD ischemic subtype, DAPT-AC showed a significant decreasing trend in 3-months vascular events with increasing calendar year (P_{trend} <0.001).

DISCUSSION

Our study, from a large, prospective, multicenter stroke registry collected over >14 years, demonstrates a marked increase in the recent use of DAPT-AC beginning in 2013 among >32 000 stroke patients who were non-eligible for recent DAPT clinical trials. This increase coincided with the publication of the CHANCE trial, though early arriving, minor stroke patients differed from those in this study. Furthermore, we observed a slight decrease in the annual risk of 3-month early vascular outcomes, relative risk reduction 2% per year, both in patients treated with DAPT-AC and patients treated with mono- or other dual antiplatelet regimens. The observations that DAPT-AC is used in ≈70% to 75% of cases in all ischemic stroke subtypes,

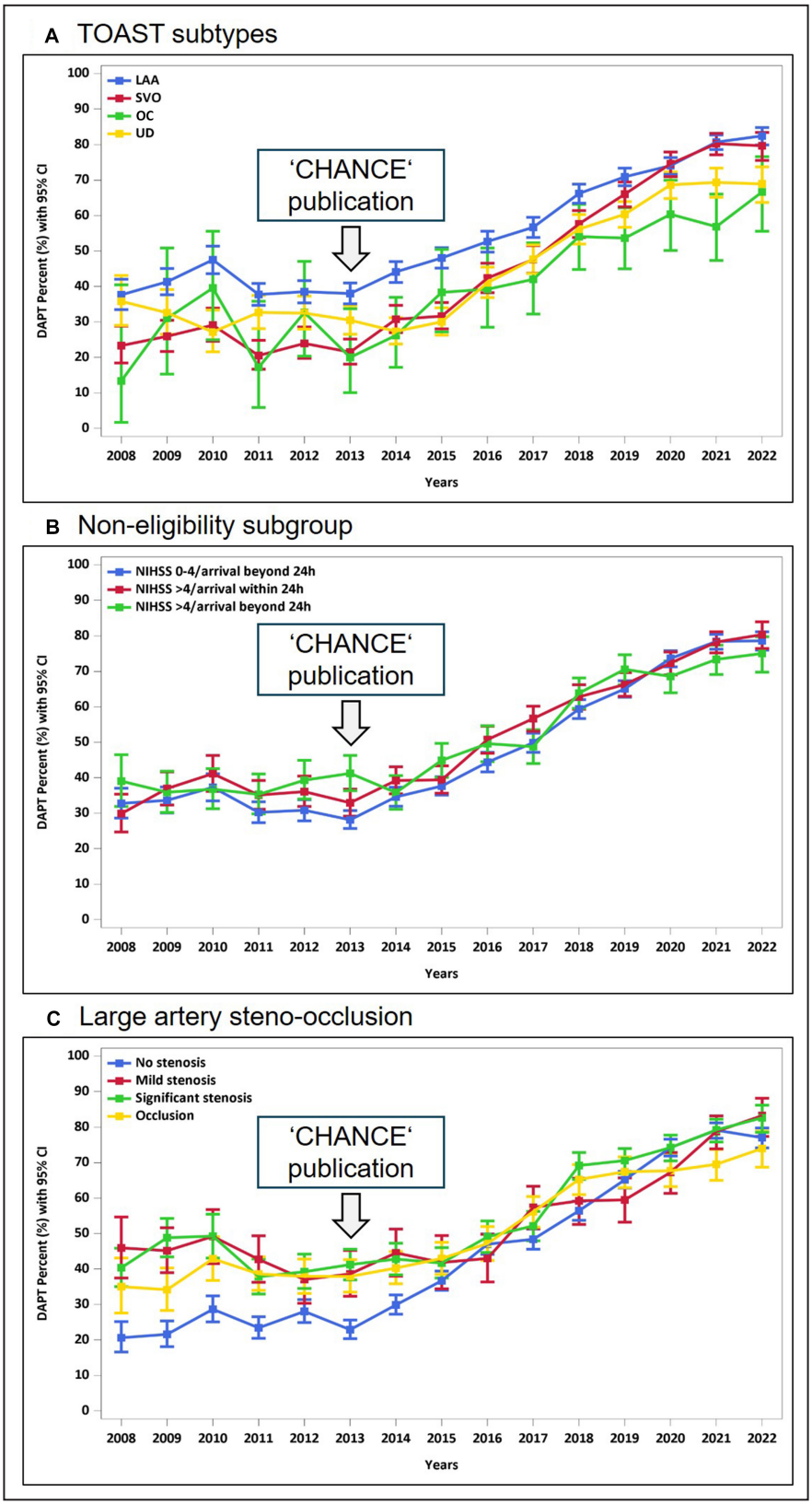

Figure 2. Annual changes of DAPT-AC with aspirin and clopidogrel in TOAST stroke subtypes (A), noneligibility subgroups (B), and large artery steno-occlusion (C).
DAPT-AC indicates dual antiplatelet therapy with aspirin and clopidogrel; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OE, other determined etiology; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

Table 3. Adjusted Annual Vascular Event Rates Within 3-mo in Patients With Ischemic Stroke Noneligible for Recent DAPT Clinical Trials

Adjusted event rate (%, 95% CI)*	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	P_{trend}†
3-mo composite of stroke, myocardial infarction, and all-cause mortality	14.48 (12.91–16.05)	15.55 (13.92–17.18)	13.35 (11.93–14.77)	15.34 (13.92–16.77)	13.95 (12.59–15.31)	13.20 (11.87–14.54)	11.47 (10.29–12.65)	13.26 (12.02–14.51)	12.97 (11.77–14.18)	12.29 (11.10–13.48)	14.27 (13.01–15.53)	11.59 (10.12–13.07)	<0.001
3-mo stroke	12.82 (11.29–14.34)	13.04 (11.49–14.59)	11.13 (9.80–12.46)	13.20 (11.83–14.57)	12.03 (10.73–13.33)	11.60 (10.33–12.87)	10.08 (8.95–11.21)	11.25 (10.08–12.42)	10.98 (9.86–12.10)	10.35 (9.23–11.46)	11.64 (10.48–12.80)	9.15 (7.82–10.47)	<0.001
3-mo all-cause mortality	2.68 (2.00–3.36)	3.53 (2.74–4.33)	3.10 (2.40–3.80)	3.02 (2.40–3.64)	3.10 (2.45–3.76)	2.49 (1.87–3.10)	1.76 (1.30–2.23)	2.57 (2.01–3.13)	2.45 (1.89–3.02)	2.45 (1.90–2.99)	2.78 (2.19–3.37)	3.06 (2.24–3.88)	0.16
3-mo hemorrhagic stroke‡	0.13 (0.00–0.30)	0.13 (0.00–0.31)	0.17 (0.00–0.35)	0.26 (0.03–0.48)	0.05 (0.00–0.14)	0.24 (0.03–0.45)	0.09 (0.00–0.20)	0.22 (0.03–0.40)	0.15 (0.00–0.30)	0.08 (0.00–0.20)	0.20 (0.02–0.38)	0.25 (0.00–0.50)	0.62

Adjusted variables: age, sex, National Institutes of Health Scale (NIHSS) score, arrival within 24 h, body mass index, history of stroke, history of coronary artery disease, hypertension, diabetes, dyslipidemia, current smoking, prior statin use, large artery steno-occlusion (LASO), Trial of Org 10172 in Acute Stroke Treatment, statin, antidiabetes medication, dual antiplatelet therapy with aspirin and clopidogrel, and calendar year.

*Based on the Cox's PH model.

†*P* value by linear contrasts test in Cox's PH model.

‡Because of small event numbers, age, sex, and initial NIHSS scores only were adjusted.

late-presenting stroke, or nonminor stroke in actual clinical practice may indicate a significant evidence-clinical practice gap and highlight the necessity of conducting clinical trials of DAPT-AC for early secondary prevention in nonminor (NIHSS >4) and nonacute (beyond 24 hours of onset) ischemic stroke patients who were ineligible for recent DAPT-AC clinical trials.

As no randomized trials of short-term DAPT-AC versus other antiplatelet regimens in ischemic stroke patients with nonminor presenting deficits (NIHSS >4) or late presentation (beyond 24 hours of onset) exist, it remains unclear whether DAPT-AC is a preferred treatment in this population. Indeed, observational studies from the Korean multicenter stroke registry have suggested that DAPT-AC was not more effective than aspirin monotherapy in nonminor acute ischemic stroke.[9,16] Nonetheless, our study identified a substantial increase in the use of DAPT-AC, from ≈30% in 2008 to >70% in 2022, among stroke patients who did not meet the eligibility of recent DAPT clinical trials. This rise was temporally driven by the reporting of the CHANCE trial in 2013 and continued, though did not accelerate, with the reporting of the POINT trial in 2018.

This study's results in the Korean nationwide stroke registry contrast in several ways with related findings from the US Get With The Guidelines (GWTG)-Stroke nationwide stroke registry.[8] The GWTG-Stroke investigation analyzed only data from 2019 to 2020 so it was not able to evaluate trends over time in DAPT-AC use. Notably, in the comparable 2019 to 2020 time period, the rate of DAPT-AC use in nonminor ischemic stroke patients was substantially higher in the Korean than in the US registry, 66% to 72% versus 44%. Moreover, the DAPT-AC use rate in Korea in nonminor stroke patients was also substantially higher than the use rate in the United States in minor ischemic stroke patients (47%). These findings may reflect that the CHANCE trial, conducted in Asian patients, had a greater impact upon clinicians in Korea, while US physicians awaited the results of the later POINT trial in a Western population and an increase in DAPT-AC was only just beginning in the 2019 to 2020 timeframe.

The high rate of DAPT-AC use in patients ineligible for recent trials likely reflects several factors. In the specific conditions of carotid artery stenting or intracranial large artery atherosclerosis, moderately strong indirect evidence supports DAPT-AC though randomized trials within these populations are lacking. This likely explains the lower rate of DAPT-AC use in nonstenosis compared with any stenosis patients during the first years of the study period. Also, in the setting of breakthrough strokes despite aspirin monotherapy, indirect evidence supports intensifying antithrombotic therapy from aspirin to DAPT-AC.[17,18] These circumstances reflect decision-making by clinicians based

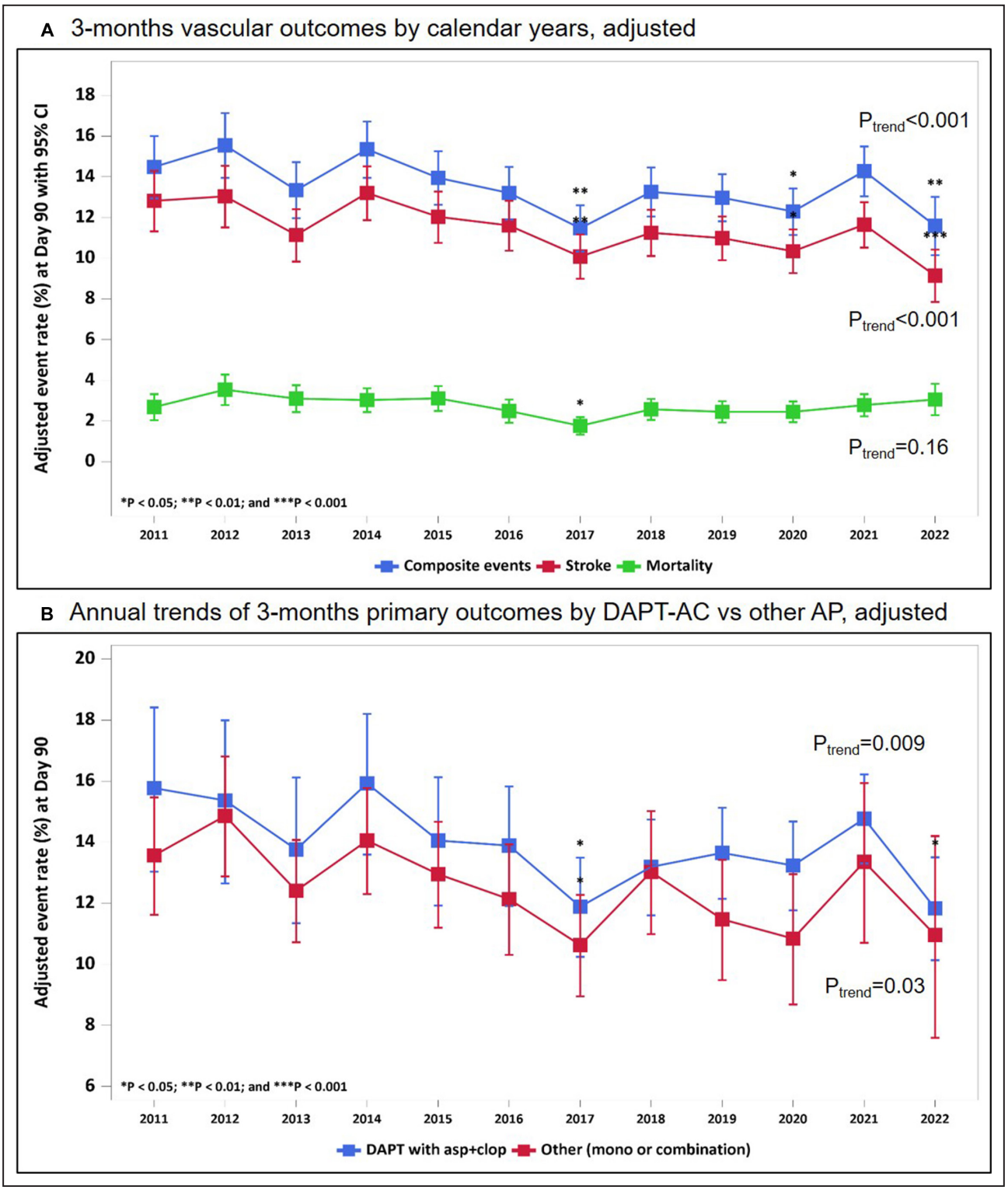

Figure 3. Adjusted vascular outcome events within 3 mo in ischemic stroke patients (A) and by DAPT-AC vs other antiplatelet regimens (B).
AP indicates antiplatelet; DAPT-AC, dual antiplatelet therapy with aspirin (asp) and clopidogrel (clop).

on physiologic reasoning and available data when definitive randomized trial evidence is lacking.[19] These considerations likely also explain the higher DAPT-AC use rate among patients with higher baseline risk for recurrent stroke, in whom clinicians may perceive more intensive preventive therapy is needed.

Table 4. Associations of Calendar Year, DAPT-AC, and Composite of Stroke, MI, and All-Cause Mortality Within 3 mo (Since 2011, n=27 529)

	Unadjusted HR (95% CI)	*P* value	*P* for PH assumption	*P* for non-linear effect	Adjusted HR (95% CI)	*P* value	*P* for PH assumption
Age (per 10-y increase)	1.21 (1.16–1.26)	<0.001	<0.001	0.003	1.12 (1.07–1.17)	<0.001	<0.001
Sex (male)	0.85 (0.82–0.88)	<0.001	0.816		0.96 (0.92–1.01)	0.113	<0.001
NIHSS scores	1.08 (1.07–1.08)	<0.001	0.267	<0.001	1.03 (1.02–1.04)	<0.001	<0.001
Arrival within 24 h	2.66 (2.45–2.88)	<0.001	<0.001		1.98 (1.80–2.17)	<0.001	<0.001
BMI	0.95 (0.94–0.96)	<0.001	<0.001	0.096	0.98 (0.97–0.99)	<0.001	0.022
TOAST							
LAA	1 (Ref)				1 (Ref)		
SVO	0.52 (0.45–0.60)	<0.001	<0.001		0.68 (0.58–0.80)	<0.001	0.084
OE	0.97 (0.81–1.16)	0.725	<0.001		1.33 (1.16–1.52)	<0.001	<0.001
UD	0.92 (0.83–1.02)	0.127	0.003		0.88 (0.79–0.99)	0.027	<0.001
Large artery steno-occlusion							
No stenosis	1 (Ref)				1 (Ref)		
Mild stenosis (<50%)	1.29 (1.11–1.49)	<0.001	0.878		1.04 (0.89–1.21)	0.635	0.995
Significant stenosis	1.29 (1.12–1.49)	<0.001	<0.001		0.99 (0.82–1.19)	0.898	0.001
Occlusion	2.05 (1.84–2.29)	<0.001	0.009		1.39 (1.24–1.57)	<0.001	0.027
Prior stroke	1.20 (1.12–1.29)	<0.001	<0.001		1.01 (0.94–1.09)	0.723	<0.001
Prior CAD	1.25 (1.11–1.41)	<0.001	<0.001		1.10 (0.98–1.24)	0.091	0.013
Hypertension	1.21 (1.14–1.28)	<0.001	0.001		1.10 (1.03–1.18)	0.005	0.241
Diabetes	1.19 (1.13–1.26)	<0.001	<0.001		1.16 (1.04–1.30)	0.007	0.032
Dyslipidemia	1.04 (0.95–1.14)	0.376	0.167		1.09 (1.00–1.19)	0.062	0.617
Prior statin treatment	0.96 (0.88–1.06)	0.443	<0.001		0.87 (0.76–1.00)	0.045	0.571
Current smoking	0.82 (0.76–0.89)	<0.001	<0.001		0.97 (0.89–1.06)	0.497	0.002
Antidiabetes medication	1.13 (1.07–1.20)	<0.001	<0.001		1.03 (0.92–1.16)	0.616	0.356
Statin treatment	0.93 (0.78–1.11)	0.436	<0.001		1.01 (0.86–1.18)	0.902	0.026
DAPT-AC	1.09 (0.96–1.25)	0.193	<0.001		1.10 (0.98–1.24)	0.090	<0.001
Calendar year since 2011	0.98 (0.96–1.01)	0.167	0.922	0.187	0.98 (0.96–1.01)	0.166	0.140

Marginal Cox model with robust variance estimator to account for the center effect. The proportional assumptions were not met for many of the variables. BMI indicates body mass index; CAD, coronary artery disease; DAPT-AC indicates dual antiplatelet therapy with aspirin and clopidogrel; HR, hazard ratio; LAA, large artery atherosclerosis; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OE, other determined etiology; PH,proportional hazard; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

Our study also found a yearly 2% relative risk reduction in 3-month composite vascular outcomes and recurrent stroke, although not statistically significant in the Cox regression analysis. These improvements were observed in both DAPT-AC treated and other mono- or dual antiplatelet treated–patients, suggesting advances in risk factor management over the study period rather than exclusive reliance on DAPT-AC. Our results also indicated an increase in annual rates for risk factor control, such as statin and diabetes medication use. Trends in secondary stroke prevention within this population likely involve factors beyond the comparison of DAPT-AC versus other mono or dual antiplatelet therapy. But the paradoxical "Will Rogers effect" may also be contributing and masking an added benefit of DAPT-AC over other antiplatelet regimens.[20] Migration of higher risk patients from the other antiplatelet regimen group to the DAPT-AC group would cause the event rate to drop in the other antiplatelet as only lower risk patients remain.

Despite this, in the UD subtype, a significant reduction in 3-month composite events with DAPT-AC was observed, suggesting a potential benefit of using DAPT-AC in the noneligibility subgroup, particularly in the UD subgroup, though further study would be warranted. This indicates that the UD subgroup might be a potential target population for future randomized clinical trials for DAPT-AC.

There were several limitations of the study. First, we lacked information on the duration of DAPT-AC use and on the use of other medications and risk factor control. However, we considered that the most important results would stem from the short-term use of poststroke DAPT-AC in these patients as similar to the POINT/CHANCE population. Thus, we considered the primary outcome of the annual changes of outcome observation as a composite of events within 3 months. Second, despite conducting detailed multivariate modeling to evaluate differences in vascular outcomes

between DAPT-AC and other antiplatelet regimens, the retrospective nature of the study made it challenging to avoid unmeasured confounders. Consequently, our findings suggest a potential 15% higher risk of events in the DAPT-AC group compared with the mono- or dual-antiplatelet group. Third, patients who underwent reperfusion therapy were excluded from the study, even though there might be a potential benefit from using DAPT-AC after 24 hours of postreperfusion care. However, some of these patients might not use DAPT-AC due to hemorrhagic transformation or bleeding, which could introduce bias, so they were excluded from this study. Moreover, our study, focused on DAPT-AC, has a limitation because we did not collect safety outcomes related to bleeding. Although we collected and analyzed data on hemorrhagic strokes, not analyzing the annual trend of major bleeding constitutes a limitation. Fourth, this study has inherent limitations because it is a registry-based retrospective study. Additionally, it is limited to the Korean population, and other countries may exhibit different patterns, thus restricting generalization. Moreover, several hospitals have been added to the CRCS-K registry since 2011, and the impact of these additions cannot be excluded. Although we analyzed the secular trend of outcomes from 2011 onwards by prospectively collecting data, the relatively stable nature of DAPT-AC between 2008 and 2011 may not have significantly influenced the analysis of the secular trend in outcomes. Instead, it is noteworthy that this study is the first to analyze time trends and outcomes in large stroke populations not included in recent antiplatelet clinical trials, making the results deserving of attention.

In conclusion, our study, based on a large stroke population from a multicenter stroke registry, demonstrated a marked increase in the use of DAPT-AC among stroke patients who are ineligible for DAPT clinical trials, coinciding at the time of publication of the CHANCE trial in 2013 and continuing to the present. The secondary prevention effects in patients with ischemic stroke seem to be gradually improving, possibly due to the enhancement of risk factor control. Further research is needed to investigate whether the DAPT-AC use is associated with an incremental improvement in risk-adjusted annual rates of early vascular events in patients with nonminor stroke and patients with presentation beyond 24 hours.

ARTICLE INFORMATION

Received January 12, 2024; accepted April 15, 2024.

Affiliations

Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea (J-T.K., H.K., M-S.P.); Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea (J.S.L.); Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea (B.J.K., H-J.B.); Department of Neurology, Korea University Guro Hospital, Seoul, Korea (K-J.L.); Department of Neurology, Uijeongbu Eulji Medical Center (J-M.P.) and , Department of Neurology, Nowon Eulji Medical Center (K.K.), Eulji University School of Medicine, Seoul, Korea, Department of Neurology, Eulji University Hospital, Eulji University, Daejeon, Korea (S.J.L., J.G.K.); Department of Neurology, Dong-A University Hospital, Busan, Korea (J-K.C., D-H.K.); Department of Neurology, Seoul Medical Center, Seoul, Korea (T.H.P.); Department of Neurology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea (K.L.); Department of Neurology, Yeungnam University Hospital, Daegu, Korea (J.L.); Department of Neurology, Ilsan Paik Hospital, Inje University, Goyang, Korea (K-S.H., Y-J.C., H-K.P.); Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Korea (B-C.L., K-H.Y., M.S.O.); Department of Neurology, Dongguk University Ilsan Hospital, Goyang, Korea (D-E.K.); Department of Neurology, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea (J.C.C.); Department of Neurology, Ulsan University College of Medicine, Ulsan, Korea (J-H.K., W-J.K.); Department of Neurology, Chungbuk National University Hospital, Cheongju, Korea (D-I.S., K.S.Y.); Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, Korea (S.I.S., J-H.H.); Department of Neurology, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon-si, Gangwon-do, Korea (S-H.L.); Artificial Intelligence Research Center, JLK Inc., Seoul, Korea (W-S.R.); Department of Neurology, Chung-Ang University College of Medicine, Chung-Ang University Hospital, Seoul, Korea (K-Y.P.); Department of Biostatistics, Korea University College of Medicine, Seoul, Korea (J.L.); and Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, University of California, Los Angeles, CA (J.L.S.).

Acknowledgments

Study concept and design: J.T.K., H.J.B.; Acquisition of data: J.T.K., H.K., M.S.P., B.J.K., K.J.L., J.M.P., K.K., S.J.L., J.G.K., J.K.C., D.H.K., T.H.P., K.B.L., J.L., K.S.H., Y.J.C., H.K. P., B.C.L., K.Y.Y., M.S.O., D.E.K., W.S.R., J.C.C., J.H.K., W.J.K., S.H.L., D.I.S., K.S.Y., S.I.S., J.H.H., J.S.L., J.L., K.Y.P., H.J.B.; Analysis and interpretation of data: J.T.K., H.J.B., J.S.L.; Drafting of the manuscript: J.T.K., H.J.B.. All authors read and approved the final manuscript.

Sources of Funding

This research was supported by funding (2023-ER-1006-01) from Research of Korea Centers for Disease Control and Prevention. This study was supported by a grant (BCRI24042) of Chonnam National University Hospital Biomedical Research Institute.

Disclosures

None.

Supplemental Material

Tables S1–S9
Figures S1–S6

REFERENCES

1. Kheiri B, Osman M, Abdalla A, Haykal T, Swaid B, Ahmed S, Chahine A, Hassan M, Bachuwa G, Al Qasmi M, et al. Clopidogrel and aspirin after ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized clinical trials. *J Thromb Thrombolysis*. 2019;47:233–247. doi: 10.1007/s11239-018-1786-z
2. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
3. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration NETTN, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
4. Pan Y, Elm JJ, Li H, Easton JD, Wang Y, Farrant M, Meng X, Kim AS, Zhao X, Meurer WJ, et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) and platelet-oriented inhibition in new TIA and

minor ischemic stroke (POINT) trials. *JAMA Neurol*. 2019;76:1466–1473. doi: 10.1001/jamaneurol.2019.2531
5. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365:993–1003. doi: 10.1056/NEJMoa1105335
6. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467. doi: 10.1161/STR.0000000000000375
7. Dawson J, Merwick A, Webb A, Dennis M, Ferrari J, Fonseca AC, European SO. European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA. *Eur Stroke J*. 2021;6:CLXXXVII–CLXXCXCI. doi: 10.1177/23969873211000877
8. Xian Y, Xu H, Matsouaka R, Laskowitz DT, Maisch L, Hannah D, Smith EE, Fonarow GC, Bhatt DL, Schwamm LH, et al. Analysis of prescriptions for dual antiplatelet therapy after acute ischemic stroke. *JAMA Netw Open*. 2022;5:e2224157. doi: 10.1001/jamanetworkopen.2022.24157
9. Kim JT, Park MS, Choi KH, Cho KH, Kim BJ, Park JM, Kang K, Lee SJ, Kim JG, Cha JK, et al. Comparative effectiveness of dual antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy in acute, nonminor stroke: a nationwide, multicenter registry-based study. *Stroke*. 2019;50:3147–3155. doi: 10.1161/STROKEAHA.119.026044
10. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, Cha JK, Kim DH, Nah HW, Han MK, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke*. 2015;17:38–53. doi: 10.5853/jos.2015.17.1.38
11. Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, Yu KH, Cha JK, Kim DH, Lee J, et al. Current status of acute stroke management in Korea: a report on a multicenter, comprehensive acute stroke registry. *Int J Stroke*. 2014;9:514–518. doi: 10.1111/ijs.12199
12. Ko Y, Lee S, Chung JW, Han MK, Park JM, Kang K, Park TH, Park SS, Cho YJ, Hong KS, et al. MRI-based algorithm for acute ischemic stroke subtype classification. *J Stroke*. 2014;16:161–172. doi: 10.5853/jos.2014.16.3.161
13. Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, Li H, Bath PM, Dong Q, Xu A, et al. Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *N Engl J Med*. 2021;385:2520–2530. doi: 10.1056/NEJMoa2111749
14. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med*. 2009;28:3670–3682. doi: 10.1002/sim.3733
15. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. 1994;13:2233–2247. doi: 10.1002/sim.4780132105
16. Lee HL, Kim JT, Lee JS, Park MS, Choi KH, Cho KH, Kim BJ, Park JM, Kang K, Lee SJ, et al. Comparative effectiveness of dual antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy in mild-to-moderate acute ischemic stroke according to the risk of recurrent stroke: an analysis of 15 000 patients from a nationwide, multicenter registry. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006474. doi: 10.1161/CIRCOUTCOMES.119.006474
17. Kim JT, Park MS, Choi KH, Cho KH, Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al. Different antiplatelet strategies in patients with new ischemic stroke while taking aspirin. *Stroke*. 2016;47:128–134. doi: 10.1161/STROKEAHA.115.011595
18. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Antiplatelet regimen for patients with breakthrough strokes while on aspirin: a systematic review and meta-analysis. *Stroke*. 2017;48:2610–2613. doi: 10.1161/STROKEAHA.117.017895
19. Caplan LR. Evidence based medicine: concerns of a clinical neurologist. *J Neurol Neurosurg Psychiatry*. 2001;71:569–574. doi: 10.1136/jnnp.71.5.569
20. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312:1604–1608. doi: 10.1056/NEJM198506203122504