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Exploring the efficacy and safety of dual antiplatelet therapy in patients with embolic stroke of undetermined source according to stroke risk stratification: Propensity-score matched analysis

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ABSTRACT

Introduction: Dual antiplatelet therapy (DAPT) is widely used for embolic stroke of undetermined source (ESUS) despite limited evidence regarding its efficacy and safety. This study compared DAPT and single antiplatelet therapy (SAPT) in patients with ESUS during hospitalization (first 7 days) and up to 30 days post-stroke, identifying subgroups that benefit most from DAPT.

Methods: We retrospectively analyzed data from 4,505 patients with ESUS enrolled in a multicenter registry from 2014 to 2019. The primary outcome was early neurological deterioration (END) within 7 days of stroke onset, and the secondary outcome was major adverse cardiovascular events (MACE) within 30 days. Propensity score

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matching (1:1) was applied to balance baseline characteristics, and subgroup analysis was conducted based on Essen stroke risk score (ESRS, ≥3 vs. <3).
Results: After matching, 1,835 patients were included in each treatment group for END analysis. In the overall cohort, DAPT did not significantly reduce END compared to SAPT (2.8 % vs. 3.5 %, adjusted OR 0.800; $p = 0.202$). Similarly, there was no significant difference in 30-day MACE (1.3 % vs. 1.4 %, adjusted HR 1.124; $p = 0.512$). However, in patients with ESRS ≥3, DAPT was associated with a statistically significant reduction in the risk of END (2.2 % vs. 5.4 %, PS-adjusted OR 0.563; $p = 0.036$), with no increase in major bleeding.
Conclusion: DAPT did not confer benefit in unselected patients with ESUS but was effective in reducing END in high-risk individuals with ESRS ≥3. These findings support a risk-stratified approach to DAPT use in ESUS.

Introduction

Since the publication of the Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial (2013) and the Platelet-Oriented Inhibition in New Transient ischemic attack (TIA) and Minor Ischemic Stroke (POINT) trial (2018), the effectiveness and safety of dual antiplatelet therapy (DAPT) in patients with minor stroke or TIA during the early high-risk period have been well established.[1,2] A recent randomized clinical trial (RCT) in patients with mild-to-moderate ischemic stroke also demonstrated that DAPT can prevent early neurological deterioration (END).[3] DAPT with aspirin and clopidogrel, works synergistically to inhibit platelet aggregation, thereby lowering the risk of recurrent ischemic events.[4,5] However, its potent antiplatelet effect also increases the risk of bleeding, and its use is warranted only when the reduction in ischemic events outweighs the bleeding risk.[6] Although RCTs have validated DAPT's utility in acute coronary syndromes,[7] atherosclerosis is the primary pathophysiology.[8] However, its role in ischemic stroke is more complex due to diverse underlying mechanisms.

Embolic stroke of undetermined source (ESUS), a widely recognized subtype of ischemic stroke since 2014, representing a significant subset of ischemic stroke cases, in which no definitive cause has been identified after extensive diagnostic examination.[9] This condition is defined as the presence of a non-lacunar brain infarct without proximal arterial stenosis or high-risk cardioembolic sources that can be detected with standard diagnostic testing.[10] The potential etiologies of ESUS include hidden atrial fibrillation, medium cardioembolic risk sources, and non-stenotic atherosclerotic plaques. The effectiveness of secondary prevention strategies in ESUS varies depending on the potential etiology.[10]

The Essen stroke risk score (ESRS) is a clinical tool used to estimate the risk of recurrent stroke and cardiovascular events in patients with a history of ischemic stroke or TIA.[11,12] Several studies have reported that DAPT efficacy was further influenced by the risk profile assessed by the ESRS,[12,13] and these studies classified patients as low (score 0–2) and high risk (score ≥3).[12,13] These findings suggest that ESRS-based risk stratification may help identify ESUS patients most likely to benefit from DAPT.

We hypothesized that DAPT would be effective in a specific group of patients with ESUS who have vascular risk factors. To evaluate this hypothesis, we compared the effectiveness and safety of DAPT versus SAPT in patients with ESUS during hospitalization (within 7 days of stroke) and up to 30 days post-stroke. Additionally, we performed subgroup analyses based on vascular risk factors and ESRS to identify the patient groups in which DAPT is most beneficial for ESUS.

Materials and methods

Study design and participants

This study included patients from the real-world study of ESUS (ROS-ESUS) cohort. The ROS-ESUS is a nationwide multicenter cohort study of patients with ischemic stroke that included only those with ESUS. We retrospectively enrolled patients from 19 stroke centers in the Republic of Korea between January 2014 and December 2019. The ROS-ESUS cohort enrolled patients aged ≥20 years with non-lacunar infarction occurring within 7 days, and with undetermined etiology according to the Trial of Org 10172 in Acute Stroke Treatment classification as follows: negative evaluation (or cryptogenic stroke) or cardioembolism, but not high-risk cardioembolic sources.[14] Additionally, the ESUS classification was determined by physicians at each stroke center, and all patients with ESUS were consecutively enrolled in the ROS-ESUS cohort. A total of 4,505 patients were finally included in the analysis of END within 7 days after stroke and 3,589 in the analysis of MACE in the 30 days after stroke. Following 1:1 propensity score matching, 1,835 patients were assigned to each treatment arm for the END analysis, and 1,323 patients to each arm for the MACE analysis (Fig. 1). Written informed consent was obtained from all prospectively enrolled patients or their caregivers. This study was approved by the institutional review board of each participating hospital (approval number, SMC-2022-02-010)

Examination and outcomes

Demographic data, risk factors for cardiovascular disease, medication history prior to the index stroke, blood and urine laboratory examination results, neurological status, including severity, and related imaging findings were investigated for all patients. The ESRS was calculated based on the results of the vascular risk factor data.[11] Stroke severity was defined using the National Institutes of Health Stroke Scale (NIHSS). Clinical outcomes were assessed using the modified Rankin scale (mRS). Cerebral angiography (either CT angiography or MR angiography) was mandatorily performed in all patients. To exclude paroxysmal AF, all patients underwent a 12-lead electrocardiogram and at least 24 hours of cardiac rhythm monitoring. Routine examination for stroke etiology, including laboratory testing, electrocardiography, and cerebral angiography, as well as optional extended evaluations, such as 24-hour Holter monitoring, transthoracic echocardiography (TTE) with or without bubble test, transesophageal echocardiography (TEE) with or without bubble test, implantable loop recorder, and transcranial Doppler with bubble test were performed at the discretion of the treating physicians. The availability of these evaluations was recorded **(Supplemental Table 1)**.

The primary outcome was the occurrence of END, defined as any of the following during hospitalization (within 7 days of the index stroke): an increase in the overall NIHSS score by ≥2, or loss of consciousness or motor impairment with an NIHSS increase of ≥1. END could result from ischemic stroke recurrence (a new ischemic lesion in a different vascular territory), ischemic stroke progression (expansion of the initial lesion, mass effect, or focal cerebral edema), or symptomatic hemorrhagic transformation (NIHSS increase of ≥4).[15-17] Only END cases confirmed by neuroimaging were considered primary outcomes, and neurological deficits attributable to systemic conditions were classified as "other" in the END etiology within this cohort and were excluded from the present study. Additional outcomes included major bleeding within 7 days (hemorrhagic stroke or extracranial hemorrhage) and favorable clinical outcomes at discharge or on day 7 (mRS score 0–2 or NIHSS score 0–5). Participants were further monitored for up to 30 days for recurrent

ischemic stroke, myocardial infarction, and major bleeding, with the composite of these events defined as the secondary outcome, major adverse cardiovascular events (MACE).

Statistical analysis

Continuous and categorical variables were analyzed using the independent t-test or Mann–Whitney U tests and the chi-square or Fisher's exact test, respectively. To reduce confounding in comparing the effectiveness of dual versus single antiplatelet therapy in patients with ESUS, we performed 1:1 propensity score matching using nearest-neighbor matching without replacement, with no caliper applied. The propensity score was estimated using logistic regression including age, sex, hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, previous stroke, previous TIA, and several structural and embolic cardiac sources (e.g., PFO, ASA, heart failure, LV hypokinesia, recent myocardial infarction, and complex aortic atheroma). Standardized mean differences (SMDs) were calculated to assess covariate balance, and values <0.1 were considered indicative of good balance. Given the observational design, balance in unmeasured factors (e.g. medication adherence and frailty) could not be directly assessed. As partial proxies for vulnerability or treatment intensity, we reported balance on variables available in our dataset (e.g. previous mRS, discharge statin use), while acknowledging that these do not fully capture adherence or frailty.

Unadjusted and adjusted logistic regression analyses were performed to assess the primary outcomes, and unadjusted and adjusted analyses of 30-day survival were performed to assess the secondary outcomes. In the multivariable analysis, variables were selected using the backward elimination method. Confounders in the adjusted model included age, sex, initial NIHSS, previous mRS, hypertension, diabetes, hyperlipidemia, current smoking status, previous stroke, coronary heart disease, and discharge treatment (statins), which differed significantly between groups (Table 1). The results of the unadjusted and adjusted models are described as odds ratios (ORs), hazard ratios (HRs) and 95 % confidence intervals (CIs). The association of antiplatelet therapy type with END was analyzed in subgroups according to vascular risk factors, NIHSS score (≤ 3 vs. >3), PFO, ESRS, and discharge treatment (statin). The interaction between END and each subgroup was investigated using a two-tailed logistic regression analysis. All *p*-values were calculated using a two-tailed test, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using the open-source statistical software R version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

Results

Study population

Before matching, among the 4,505 patients with ESUS, 2,670 (59.3 %) received DAPT, and 1,835 (40.7 %) received SAPT. Patient demographics, risk factors, and other clinical variables are summarized in Table 1. Significant differences in age, sex, initial NIHSS score, previous stroke, previous coronary heart disease, hypertension, diabetes mellitus, hyperlipidemia, current smoking, and discharge treatment (statin) were observed between the groups. After matching, the baseline characteristics were well balanced between the groups, with all SMDs below 0.1.

Primary and secondary outcomes of patients with ESUS using overall cohort data

In a logistic regression analysis of the primary outcomes at hospitalization (within 7 days) using overall cohort data, END was confirmed in 74 patients (2.8 %) in the DAPT group and in 64 patients (3.5 %) in the SAPT group (adjusted odds ratio [OR], 0.800; 95 % CI, 0.567–1.127; $p = 0.202$). An mRS score of 0–2 at discharge was achieved in 1,975 patients (74.0 %) in the DAPT group and in 1,331 patients (72.5 %) in the SAPT group (adjusted OR, 1.027; 95 % CI, 0.874–1.208; $p = 0.745$). NIHSS scores of 0–5 at discharge were significantly more frequent with DAPT than with SAPT ($p = 0.030$); however, this difference was not significant in the adjusted model (adjusted OR, 0.969; 95 % CI, 0.773–1.215; $p = 0.787$). (Table 2) In the 30-day survival analysis, MACE occurred in 29 patients (1.3 %) in the DAPT group and in 18 patients (1.4 %) in the SAPT group (adjusted HR, 1.124; 95 % CI, 0.612–2.661; $p = 0.512$). Major bleeding occurred in three patients (0.1 %) in the DAPT group and in four patients (0.3 %) in the SAPT group (adjusted HR, 0.222; 95 % CI, 0.023–2.150; $p = 0.194$). This finding remained consistent in the propensity score–adjusted (PS-adjusted) model, with no statistically significant differences in outcomes observed between the single and dual antiplatelet therapy groups (Table 2).

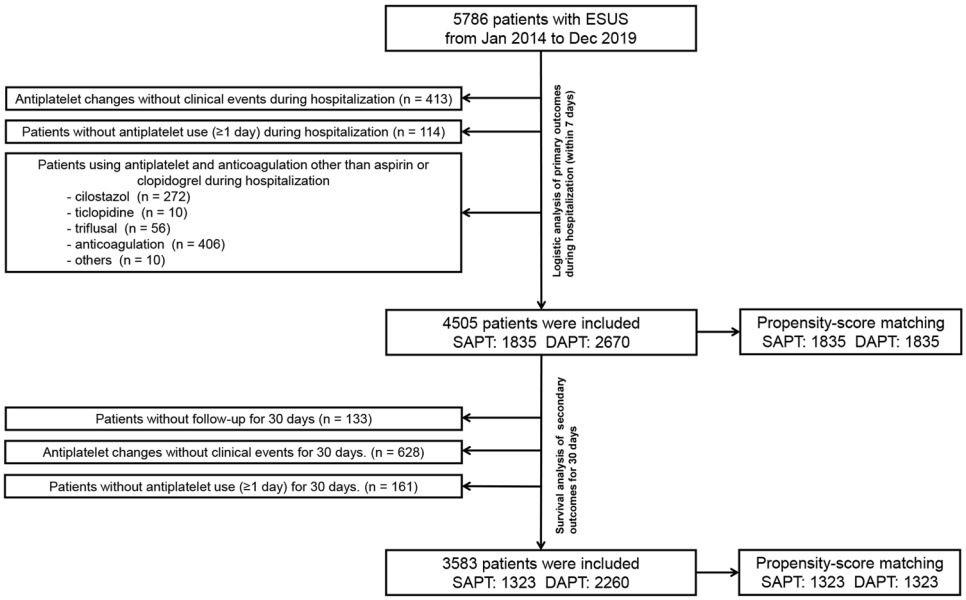

Fig. 1. The patient selection strategy used in this study. ESUS, embolic stroke of undetermined source; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; ESRS, Essen stroke risk score.

Table 1
Characteristics of individuals with embolic stroke of undetermined source (ESUS) receiving single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT).

	Total	Before propensity-score matching		*p-value*	After propensity-score matching		*SMD*
Characteristics		SAPT	DAPT		SAPT	DAPT	
Total ESUS population	4,505	1,835	2,670		1,835	1,835	
Age at ESUS (years), median (IQR)	65.56±13.86	64.58±14.8	66.24±13.14	<0.001	64.58±14.8	65.08±13.71	0.037
Female, n (%)	1,753 (38.9 %)	775 (42.2 %)	979 (36.7 %)	<0.001	775 (42.2 %)	753 (41.04 %)	0.025
Initial NIHSS, median (IQR)	2 (1, 5)	2 (1, 6)	2 (1, 5)	0.026	2 (1, 6)	2 (1, 5)	0.098
Previous mRS	0 (0, 0)	0 (0, 0)	0 (0, 0)	<0.001	0 (0, 0)	0 (0, 0)	0.075
History of comorbidities							
Previous stroke	70 (15.6 %)	220 (12.0 %)	484 (18.1 %)	<0.001	220 (12.0 %)	214 (11.66 %)	0.006
TIA	83 (1.9 %)	28 (1.53 %)	55 (2.1 %)	0.224	28 (1.53 %)	23 (1.25 %)	0.023
Coronary heart disease	437 (9.8 %)	126 (6.9 %)	311 (11.7 %)	<0.001	126 (6.9 %)	133 (7.25 %)	0.014
Hypertension, n (%)	2,759 (61.3 %)	1,064 (58.0 %)	1,695 (63.5 %)	<0.001	1,064 (58.0 %)	1101 (60 %)	0.040
Diabetes, n (%)	1,399 (28.9 %)	449 (24.5 %)	850 (31.8 %)	<0.001	449 (24.5 %)	451 (24.58 %)	0.002
Hyperlipidemia, n (%)	1,789 (39.8 %)	629 (34.3 %)	1,160 (43.5 %)	<0.001	629 (34.3 %)	621 (33.84 %)	0.009
Current smoker, n (%)	1,260 (27.9 %)	464 (25.3 %)	796 (29.8 %)	0.001	464 (25.3 %)	541 (29.48 %)	0.094
Medium cardioembolic risk							
Atrial septal aneurysm	37 (0.82 %)	13 (0.71 %)	24 (0.9 %)	0.596	13 (0.71 %)	8 (0.44 %)	0.036
Patent foramen ovale	845 (18.8 %)	365 (19.8 %)	480 (18.0 %)	0.128	365 (19.8 %)	346 (18.86 %)	0.026
Congestive heart failure	16 (0.4 %)	4 (0.2 %)	12 (0.5 %)	0.480	4 (0.2 %)	5 (0.27 %)	0.011
Left ventricle hypokinesia	54 (1.4 %)	18 (1.0 %)	36 (1.4 %)	0.421	18 (1.0 %)	20 (1.09 %)	0.010
Myocardial infarction (4–6 months)	4 (0.1 %)	1 (0.1 %)	3 (0.1 %)	0.895	1 (0.1 %)	2 (0.11 %)	0.019
Aortic arch atheroma (complex)	43 (3.0 %)	13 (3.6 %)	30 (2.8 %)	0.541	13 (3.6 %)	11 (0.6 %)	0.013
Discharge treatment (statins), n (%)	4,193 (93.1 %)	1,669 (91.0 %)	2,524 (94.5 %)	<0.001	1,669 (91.0 %)	1702 (92.75 %)	0.093

IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; TIA, transient ischemic attack.

Table 2
Primary and secondary outcomes of patients with embolic stroke of undetermined source using overall cohort data.

Primary outcomes (7 days)	No. SAPT (N = 1835)	DAPT (N = 2670)	Unadjusted Odds ratio (95 % CI)	*p-value*	Adjusted Odds ratio (95 % CI)	*p-value*	PS-adjusted Odds ratio (95 % CI)	*p-value*
END	64 (3.5 %)	74 (2.8 %)	0.789 (0.562–1.108)	0.171	0.800 (0.567–1.127)	0.202	0.919 (0.642-1.317)	0.647
- Stroke recurrence	12 (0.7 %)	4 (0.2 %)	N/A	N/A	N/A	N/A	N/A	N/A
- Stroke progression	45 (2.5 %)	67 (2.5 %)	N/A	N/A	N/A	N/A	N/A	N/A
- Symptomatic HT	7 (0.4 %)	3 (0.1 %)	N/A	N/A	N/A	N/A	N/A	N/A
Major bleeding	2 (0.11 %)	2 (0.07 %)	0.687 (0.097-4.882)	0.708	N/A	N/A	N/A	N/A
mRS score of 0 to 2 at discharge	1,331 (72.5 %)	1,975 (74.0 %)	1.076 (0.941–1.231)	0.284	1.027 (0.874–1.208)	0.745	1.109 (0.958-1.285)	0.166
NIHSS score of 0 to 5 at discharge	1,565 (85.3 %)	2,337 (87.5 %)	1.211 (1.019–1.439)	0.030	0.969 (0.773–1.215)	0.787	1.186 (0.982-1.432)	0.076
Secondary outcomes (30 days)	SAPT (N = 1323)	DAPT (N = 2260)	Hazard ratio (95 % CI)	*p-value*	Hazard ratio (95 % CI)	*p-value*	Hazard ratio (95 % CI)	*p-value*
MACE	18 (1.4 %)	29 (1.3 %)	1.007 (0.521–2.142)	0.792	1.124 (0.612–2.661)	0.512	0.998 (0.519-1.917)	0.994
Major bleeding	4 (0.3 %)	3 (0.1 %)	0.197 (0.021–1.896)	0.160	0.222 (0.023–2.150)	0.194	0.500 (0.092-2.727)	0.423
Ischemic stroke	14 (1.1 %)	26 (1.2 %)	1.139 (0.597–2.171)	0.693	1.278 (0.669–2.443)	0.457	1.211 (0.597-2.456)	0.596
Myocardial infarction	1 (0.08 %)	1 (0.04 %)	0.585 (0.037-9.364)	0.705	N/A	N/A	N/A	N/A

SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin scale; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; N/A, not applicable; MACE, major adverse cardiovascular events
Adjusted variables: age, sex, initial NIHSS, previous mRS, hypertension, diabetes, hyperlipidemia, current smoking status, previous stroke, coronary heart disease, and discharge treatment (statins).

When analyzing the primary and secondary outcomes according to ESRS, there was a trend toward increasing frequency of END and major adverse cardiovascular events (MACE) with higher scores; however, this was not statistically significant (**Supplemental Table 2**).

ESRS ≥3 versus <3

In the subgroup of patients with an ESRS ≥3 (p = 0.015), the occurrence of END was significantly lower in the DAPT group (Fig. 2). These results are consistent with previous studies assessing stroke risk with the ESRS,[12] in which DAPT was observed to effectively prevent END at scores ≥ 3. Based on these findings, we divided the overall cohort into two groups: ESRS ≥3 and ESRS <3. Patient demographics and risk factors analyzed according to ESRS category are summarized in **Supplemental Tables 3 and 4**.

Primary and secondary outcomes of patients with ESUS with ESRS ≥3

In the logistic regression analysis of patients with ESUS and an ESRS ≥3, END occurrence was lower in the DAPT group (28 [2.2 %]) than in the SAPT group (37 [5.4 %]) (adjusted OR, 0.410; 95 % CI, 0.248–0.679; p = 0.001; PS-adjusted OR, 0.563; 95 % CI, 0.328–0.964; p = 0.036). NIHSS scores of 0–5 at discharge were significantly more frequent in the DAPT group than in the SAPT group (p = 0.001), although no

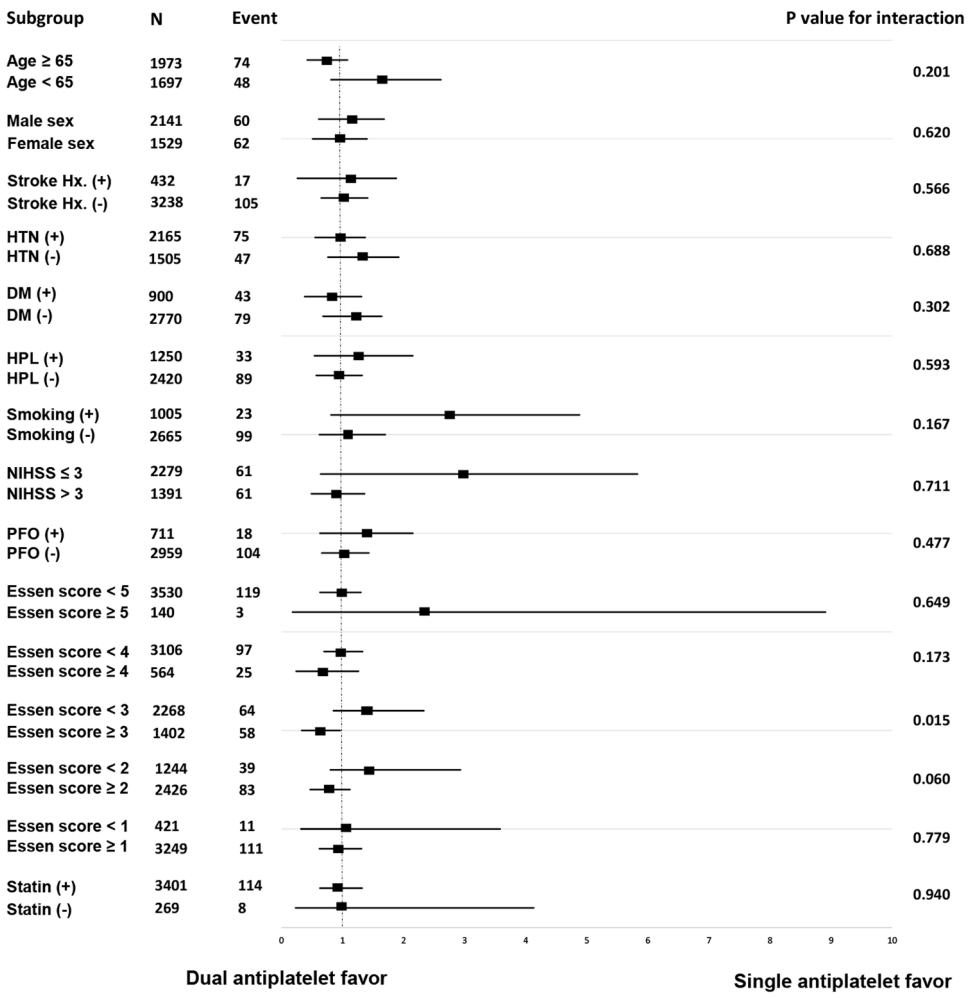

Fig. 2. Forest plots of unadjusted odds ratios for early neurological deterioration after antiplatelet therapy (single vs. dual antiplatelet therapy) in patients with embolic stroke of undetermined source. HTN, hypertension; DM, diabetes mellitus; HPL, hyperlipidemia; NIHSS, National Institutes of Health Stroke Scale; PFO, patent foramen ovale; ESRS, Essen stroke risk score.

significance was observed in the adjusted model (adjusted OR, 0.899; 95 % CI, 0.696–1.161; $p = 0.414$; PS-adjusted OR 1.256; 95 % CI, 0.959–1.645; $p = 0.098$) (Table 3). In an analysis of patients with ESUS with ESRS <3, no significant difference in END occurrences was observed between SAPT and DAPT groups. (adjusted OR, 1.458; 95 % CI, 0.896–2.371; $p = 0.129$; PS-adjusted OR 1.411; 95 % CI, 0.853–2.333; $p = 0.180$) (**Supplemental Table 5**).

In the 30-day survival analysis, MACE occurred in 16 patients (1.5 %) in the DAPT group and in 7 patients (1.5 %) in the SAPT group (adjusted HR, 1.121; 95 % CI, 0.608–2.621; $p = 0.661$; PS-adjusted HR, 1.263; 95 % CI, 0.470-3.391; $p = 0.644$) (Table 3).

Discussion

In this large cohort of patients with ESUS, DAPT was not associated with a significant reduction in END or MACE compared with SAPT in the overall matched population. However, in patients with higher vascular risk (Essen score ≥3), DAPT was associated with a lower risk of END, while overall outcomes remained comparable between the two treatment strategies.

Patients with ESUS represent a heterogeneous group with diverse potential etiologies, including hidden atrial fibrillation, PFO, non-stenotic atherosclerosis, and cancer-related thromboembolism.[9] RCTs comparing DOACs to aspirin in this population have shown no differences in efficacy and safety outcomes.[18-20] Consequently, most stroke centers follow the CHANCE and POINT trial protocols, treating patients with ESUS using DAPT for 21 days when the initial NIHSS is low.[1,2] The cohort data from this study indicate a rise in DAPT use for patients with ESUS from the mid-to-late 2010s, possibly influenced by findings from these two key RCTs **(Supplemental Table 6)**.[1,2] Despite this trend, research on the optimal use of DAPT for secondary prevention in patients with ESUS remains limited.[21]

DAPT carries an increased risk of intracranial and extracranial bleeding compared with SAPT, with the risk rising progressively with prolonged use.[2] Therefore, DAPT should only be considered in the early stages of ischemic stroke when its benefits outweigh the bleeding risk, depending on the stroke etiology.[22] Successful RCTs have shown that limiting DAPT to the initial period after minor stroke provides benefits, particularly in atherosclerotic stroke subtypes such as acute coronary syndrome, intracranial atherosclerosis, and carotid atherosclerosis.[7,23-25] However, DAPT's effectiveness in patients with moderate cardioembolic risk or cancer-related thromboembolism remains uncertain. Thus, identifying potential ESUS etiologies more closely linked to non-stenotic atherosclerosis rather than cardioembolic or hypercoagulable conditions is crucial for assessing the utility of DAPT.

Vascular risk factors for atherosclerosis include age, hypertension, diabetes, hyperlipidemia, and smoking.[26] The ESRS is derived from these vascular risk factors and cardiovascular history, and previous studies have reported an annual recurrence risk of >4 % at a score of ≥3.[11] Recent studies have suggested that DAPT is particularly

Table 3
Primary and secondary outcomes of patients with embolic stroke of undetermined source with Essen stroke risk score ≥3.

Primary outcomes (7 days)	No. SAPT (n = 690)	DAPT (n = 1273)	Unadjusted Odds ratio (95 % CI)	*p-value*	Adjusted Odds ratio (95 % CI)	*p-value*	PS-adjusted Odds ratio (95 % CI)	*p-value*
END	37 (5.4 %)	28 (2.2 %)	0.397 (0.241–0.654)	<0.001	0.410 (0.248–0.679)	0.001	0.563 (0.328-0.964)	0.036
- Stroke recurrence	9 (1.3 %)	3 (0.2 %)	N/A	N/A	N/A	N/A	N/A	N/A
- Stroke progression	27 (3.9 %)	23 (1.8 %)	N/A	N/A	N/A	N/A	N/A	N/A
- Symptomatic HT	1 (0.1 %)	2 (0.2 %)	N/A	N/A	N/A	N/A	N/A	N/A
Major bleeding	1 (0.14 %)	1 (0.08 %)	0.542 (0.034-8.673)	0.665	N/A	N/A	N/A	N/A
mRS score of 0 to 2 at discharge	420 (60.87 %)	836 (65.67 %)	1.230 (1.015–1.490)	0.034	1.121 (0.920–1.365)	0.259	1.084 (0.874-1.345)	0.461
NIHSS score of 0 to 5 at discharge	550 (79.71 %)	1,078 (84.68 %)	1.227 (1.011–1.489)	0.038	0.899 (0.696–1.161)	0.414	1.256 (0.959-1.645)	0.098
Secondary outcomes (30 days)	SAPT (N = 467)	DAPT (N = 1064)	Hazard ratio (95 % CI)	*p-value*	Hazard ratio (95 % CI)	*p-value*	Hazard ratio (95 % CI)	*p-value*
MACE	7 (1.5 %)	16 (1.5 %)	1.011 (0.532–2.454)	0.761	1.121 (0.608–2.621)	0.661	1.263 (0.470-3.391)	0.644
Major bleeding*	1 (0.2 %)	1 (0.1 %)	0.438 (0.027-7.022)	0.560	N/A	N/A	N/A	N/A
Ischemic stroke	5 (1.1 %)	15 (1.4 %)	1.206 (0.555–2.619)	0.636	1.467 (0.672–3.201)	0.336	1.767 (0.592-5.273)	0.307
Myocardial infarction	1 (0.2 %)	0 (0 %)	N/A	N/A	N/A	N/A	N/A	N/A

SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; CI, confidence interval; END, early neurological deterioration; mRS, modified Rankin scale; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; N/A, not applicable; MACE, major adverse cardiovascular events
Adjusted variables: age, sex, initial NIHSS, previous mRS, hypertension, diabetes, hyperlipidemia, current smoking status, previous stroke, coronary heart disease, and discharge treatment (statins).

beneficial in high-risk patients as assessed by ESRS, compared with SAPT.[12,13] As previous studies have shown that DAPT is effective in patients with a high atherosclerosis burden,[7,24] it may also be effective in reducing END occurrence in this study in patients with ESRS ≥3. Patients in the ESRS ≥3 group are older and have more vascular risk factors (hypertension, diabetes, and hyperlipidemia). Conversely, in the ESRS <3 group, no significant difference in END prevention was observed between DAPT and SAPT groups. On the other hand, no difference in bleeding events was observed between antiplatelet therapies in either the ESRS ≥3 and ESRS <3 group at 30 days of observation, which is likely due to the short follow-up period, as previous RCTs have shown that the difference in bleeding events between DAPT and SAPT becomes increasingly significant with use over 30 days.[2]

Our study has several important limitations. First, the ROS-ESUS cohort consecutively included patients with ESUS who were retrospectively evaluated. This retrospective, non-randomized design precludes establishing causal relationships and may introduce selection bias. Although propensity score matching was used to mitigate this limitation, the registry did not collect data on unmeasured confounders such as medication adherence and frailty; therefore, the balance of all potential confounding factors could not be directly assessed, and the possibility of residual confounding remains. Second, the cohort consisted exclusively of Korean patients, which may limit the generalizability of our findings to other populations with different genetic, environmental, or healthcare system backgrounds. Third, the follow-up period was relatively short (30 days), which may be insufficient to fully evaluate the long-term efficacy and safety of antiplatelet therapy, particularly with respect to bleeding risk and recurrent vascular events. Although prior randomized trials have demonstrated short-term benefits of DAPT in patients with minor ischemic stroke, our analysis may not capture delayed adverse events or sustained protective effects beyond the acute phase. The findings should therefore be interpreted with caution and considered hypothesis-generating rather than definitive evidence for secondary prevention strategies in ESUS. Fourth, in several outcomes—particularly major bleeding and myocardial infarction—the confidence intervals were wide, reflecting the small number of events and limiting statistical precision. This imprecision reduces the certainty of the effect estimates, and these results should be interpreted cautiously. Finally, the dataset lacked information on acute treatments such as intra-arterial thrombectomy or intravenous thrombolysis. These interventions could be associated with END; however, given the low median NIHSS score of 2 in our cohort, the proportion of patients undergoing such treatments was likely minimal.

Conclusion

Although the overall incidence of END did not differ significantly between dual and single antiplatelet therapy in patients with ESUS, stratified analysis by ESRS revealed a differential effect. In patients with an ESRS ≥3, DAPT was associated with a reduced risk of END without an increase in safety concerns, whereas no such benefit was observed in those with an ESRS <3. These findings suggest that DAPT may provide clinical benefit in selected high-risk subgroups, while the overall efficacy and safety profiles of DAPT and SAPT remain comparable in the broader ESUS population.

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CRediT authorship contribution statement

Hyung Jun Kim: Writing – review & editing, Writing – original draft. **Woo-Keun Seo:** Writing – review & editing, Supervision, Conceptualization. **Jong-Won Chung:** Writing – review & editing, Writing – original draft. **Hyun Kyung Kim:** Data curation. **Jang-Hyun Baek:** Data curation. **Hahn Young Kim:** Data curation. **Yang-Ha Hwang:** Data curation. **Sung Hyuk Heo:** Data curation. **Ho Geol Woo:** Data curation. **Hyungjong Park:** Data curation. **Sung-Il Sohn:** Data curation. **Chi Kyung Kim:** Data curation. **Jin-Man Jung:** Data curation. **Sang-Hun Lee:** Data curation. **Jae-Kwan Cha:** Data curation. **Hee-Joon Bae:** Data curation. **Beom Joon Kim:** Data curation. **Bum Joon Kim:** Data curation. **Ji Sung Lee:** Data curation. **Hyo Suk Nam:** Data curation. **Jee-Hyun Kwon:** Data curation. **Wook-Ju Kim:** Data curation. **Hee-Kwon Park:** Data curation. **Man-Seok Park:** Data curation. **Kang-**

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

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None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108438.

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