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# Early neurological deterioration in minor stroke caused by small artery occlusion: Incidence, risk factors and treatment impact

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ABSTRACT

*Introduction:* Early neurological deterioration (END) is a forecast factor in poor outcomes in minor strokes. END's prevalence and forecast factors in minor strokes caused by small artery occlusion (SAO) are still unclear.
*Patients and Method:* We retrospectively analyzed 451 patients with minor stroke (NIHSS $\leq$ 5) caused by SAO hospitalized within an initial 24 h at BachMai Hospital's stroke center. END was defined as conditions with an elevated two or more NIHSS points within an initial 72 h. The primary outcome included the determination of the END incidence. The secondary outcome identified forecast factors for END through multivariate logistic regression analyses, and therapeutic impacts of antiplatelet and thrombolytic treatments.
*Results:* END occurred in 9.5 % (43/451) of patients (62.7 % male, mean age 63.8 $\pm$ 11.8 years). Independent forecast included admission SBP $\geq$ 150 mmHg (OR = 1.99; 95 % CI: 1.01 - 3.94; $p = 0.048$), diabetes history (OR = 0.58; 95 % CI: 1.05 - 4.33; $p = 0.036$), admission blood glucose $\geq$ 14mmol/L (OR = 2.99; 95 % CI: 1.05 - 8.54; $p = 0.04$), and internal capsule infarction (OR = 2.23; 95 % CI: 1.01 - 4.92; $p = 0.048$). The patients group admitted within 4.5 h, DAPT has significantly lower END risk compared to SAPT (OR = 0.079; 95 % CI: 0.007 - 0.939; $p = 0.04$) and altepase (OR = 0.013; 95 % CI: 0.01 - 0.12; $p < 0.01$). END risk was similar between SAPT and altepase ($p = 0.074$).
*Discussion and Conclusion:* END is a 9.5 % incidence in minor acute ischemic stroke due to SAO. Independent forecasts are admission SBP and blood glucose, diabetes history, and internal capsule infarction. The DAPT group has significantly lower END risk than the SAPT and alteplase groups.

## Introduction

Minor ischemic stroke, defined by an NIHSS score $\leq$ 5 with zero score on items 1a-1c, may present with mild initial symptoms but carry significant long-term risks.[1–3] Around 28 % of patients are unable to live independently upon hospital release, and another 28 % cannot return home.[4] Stroke recurrence and cardiovascular events occur in 6.2 % within one year, rising to 12.9 % at five years, with all-cause mortality increasing from 1.8 to 10.6 % over the same period.[5,6]

END is characterized by increasing neurological abnormalities beyond baseline severity, serving as an indicator of unfavorable neurological recovery.[7,8] Definition of END varies in literature, ranging from an increase in NIHSS by 1 to 4 points or more. In this work we adopt the END definition of increasing NIHSS by at least 2 points as this provides the best between-study homogeneity, with lowest heterogeneity and greatest precision, as suggested by Werring et al.[9] END prevalence in minor stroke varies between 21 and 46 %, with SAO being a common cause.[10–13] Lacunar ischemic stroke, subtype of SAO, presents

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with lacunar syndromes without cortical dysfunction. Imaging typically reveals small (<1.5 cm), deep lesions in the brainstem or subcortical areas of one hemisphere (including white matter, thalamus, or basal ganglia), with no evidence of cardiac embolism or significant cerebral atherosclerosis (stenosis ≥ 50 %).[14] In patients with lacunar stroke, END rates range from 2.3 to 47.5 %, averaging 23.54 % but heterogeneity was high ($I^2 = 90.29$ %).[9]

The PRISMS trial, which involved patients with non-disabling symptoms, revealed no advantage of alteplase over aspirin for favorable neurological outcomes (mRS = 0-1 at 90 days: 78.2 % for alteplase against 81.5 % for AAS (ARD = 1.1 % (95 % CI: −9.4 to 7.3 %) in minor stroke, including 36.6 % with lacunar ischemic stroke.[15] The ARAMIS trial found DAPT non-inferior to alteplase in SAO (mRS = 0-1 at 90 days: RD = 3.0 %; 95 % CI: −4.3 % to 10.3 %, $p = 0.76$).[16] Additionally, CHANCE, POINT, and THALES trials showed greater efficacy of DAPT over SAPT in non-cardio thrombotic minor stroke for secondary prevention.[17–19] A recent post-hoc ARAMIS analysis suggested that DAPT was likely more effective than alteplase in preventing END in minor stroke without large vessel occlusion.[20] Given DAPT's potential superiority in preventing END in minor strokes caused by SAO, this study aimed to evaluate END rates, identify associated prognostic factors, and compare END incidence among patients admitted within 24 h and treated with DAPT, SAPT and alteplase in acute minor stroke resulting from SAO.

## Patients and methods

### *Study design*

This observational, retrospective, longitudinal study included all patients with minor stroke (NIHSS ≤ 5) due to SAO (TOAST classification) admitted within 24 h of symptom onset.[14] The study took place at Bach Mai Hospital's Stroke Center in Hanoi, Vietnam, from December 2023 to December 2024. Exclusion criteria include having pre-stroke mRS ≥ 2, being pregnant or breastfeeding, and having concomitant brain lesions such as traumatic brain injury, intracranial or subarachnoid hemorrhage, or brain tumors (Table 1, Supplement Data).

All stroke patients admitted to our center are treated in the acute stroke unit, undergoing full clinical examination, including NIHSS scoring upon admission and re-evaluation every six hours or when abnormalities are observed. Stroke assessment follows AHA guidelines, including brain parenchymal lesion assessment imaging (MRI or CT), intracranial vascular assessment (MRA or CTA), carotid ultrasound, echocardiography, electrocardiogram and blood tests for ischemic stroke subtype classification using the TOAST criteria.[14]

Antiplatelet therapy adheres to AHA and ESO recommendations: DAPT with aspirin and clopidogrel for NIHSS ≤ 3 within the first 24 h, maintained for 21 days (up to 90 days) before switching to SAPT.[21,22] DAPT with ticagrelor plus aspirin for patient with NIHSS ≤ 5, may be used for up to 30 days, after that switching to SAPT.[19] Minor stroke patients admitted within initial 4.5 h are evaluated for thrombolysis based on disabling neurological deficits by AHA and ESO recommendations; otherwise, optimal medical therapy with SAPT or DAPT is administered.[2,21]

### *Ethical approval*

The ethical committee of Bach Mai Hospital approved the study under decision number 4837/BM-HĐĐĐ,with the council's activity code IRB-VN01019. Written consent was obtained from all patients and their families prior to participation.

### *Sample size calculation*

We calculated the sample size based on the proportion of patients with minor strokes resulting from lacunar stroke, using END as the

**Table 1**
Clinical and paraclinical characteristics in END and No END cohorts (*see Supplement Data*).

| | Total *N* = 451 100 % | END *N* = 43 9.5 % | No-END *N* = 408 90,5 % | p | Note |
|---|---|---|---|---|---|
| *Patient Characteristics* | | | | | |
| Age (IQR) | 63.8 ± 11.8 | 64.63 ±12.74 | 63.68±11.76 | 0.98 | α ¥ |
| Male, n(%) | 283, 62.7 | 26, 60.5 | 257, 63.0 | 0.75 | £ |
| Initial SBP, mmHg, mean ±sd | 153.5 ± 24.0 | 157.26 ±23.67 | 153.09 ±24.02 | 0.28 | α ¥ |
| Initial DBP, mmHg, mean ±sd | 88.4 ± 15.1 | 88.16 ±15.98 | 88.38±15.01 | 0.93 | α ¥ |
| Initial SBP ≥ 150 mmHg n(%) | 238, 52.8 | 29, 67.4 | 209, 51.2 | 0.04 | £ |
| NIHSS Median (IQR) | 2, 2-4 | 3, 2-4 | 2, 2-3 | 0.12 | β € ¤ |
| Disabling n (%) | 187, 41.5 | 20, 46.5 | 167, 40.9 | 0.48 | £ |
| *Risk of stroke* | | | | | |
| Hypertension n(%) | 315, 69.8 | 35, 81.4 | 280, 68.6 | 0.08 | £ |
| Diabetes n(%) | 103, 22.8 | 15, 34.9 | 88, 21.6 | 0.048 | £ |
| High blood cholesterol n(%) | 38, 8.4 | 5, 11.6 | 33, 8.1 | 0.43 | £ |
| Smoking n(%) | 106, 23.5 | 11, 25.6 | 95, 23.3 | 0.74 | £ |
| Overweight/Obese BMI≥25 n (%) | 85, 18.8 | 10, 23.3 | 75, 18.4 | 0.44 | £ |
| *Blood test* | | | | | |
| Platelets mean±sd | 266.6 ± 63.0 | 283.14 ±78.18 | 264.74 ±61.04 | 0.07 | α ¥ |
| INR mean±sd | 0.98 ±0.38 | 0.94±0.1 | 0.99 ±0.40 | 0.043 | α ¥ |
| Cholesterol total mean±sd | 4.99 ±1.23 | 5.31 ±1.43 | 4.96±1.2 | 0.07 | α ¥ |
| HDL-C mean±sd | 1.14 ±0.43 | 1.22 ±0.42 | 1.13 ±0.44 | 0.24 | α ¥ |
| LDL-C mean±sd | 2.77 ±0.95 | 3.05 ±1.19 | 2.74 ±0.91 | 0.11 | α ¥ |
| Urea mean±sd | 5.59 ±3.28 | 5.90 ±5.08 | 5.56 ±3.04 | 0.51 | α ¥ |
| Creatinine mean±sd | 74.94 ±22.65 | 71.86 ±28.87 | 75.26 ±21.90 | 0.35 | α ¥ |
| GOT mean±sd | 25.58 ±15.62 | 23.12 ±11.99 | 25.84 ±15.95 | 0.28 | α ¥ |
| GPT mean ± sd | 25.67 ±24.58 | 22.70 ±12.90 | 25.98 ±25.49 | 0.41 | α ¥ |
| Glucose on admission mean ±sd | 7.80 ±3.26 | 8.71 ±5.06 | 7.71±3.0 | 0.055 | α ¥ |
| Glucose on admission≥14mmol/l n (%) | 26, 5.8 | 6, 14.0 | 20, 4.9 | 0.02 | £ |
| *Cerebral infarction sites* | | | | | |
| Thalamus n(%) | 69, 15.3 | 7, 16.3 | 62, 15.2 | 0.85 | £ |
| Internal capsule n(%) | 64, 14.2 | 10, 23.3 | 54, 13.2 | 0.07 | £ |
| Caudate nucleus n(%) | 12, 2.7 | 0 | 12, 2.9 | 0.25 | £ |
| Lentiform nucleus n(%) | 110, 24.4 | 9, 20.9 | 101, 24.8 | 0.58 | £ |
| Insular n(%) | 9, 2.0 | 1, 2.3 | 8, 2.0 | 0.87 | £ |
| Corona radiata n(%) | 137, 30.4 | 13, 30.2 | 124, 30.4 | 0.98 | £ |
| Temporal lobe n(%) | 16, 3.5 | 0 | 16, 3.9 | 0.38 | £ |
| Frontal lobe n(%) | 14, 3.1 | 2, 4.7 | 12, 2.9 | 0.63 | £ |
| Occipital lobe n(%) | 15, 3.3 | 0 | 15, 3.7 | 0.38 | £ |
| Brainstem n(%) | 94, 20.8 | 7, 16.3 | 87, 21.3 | 0.44 | £ |
| Cerebellum n(%) | 18, 4.0 | 0 | 18, 4.4 | 0.24 | £ |
| Hemorrhagic transformation n (%) | 1, 0.2 | 0 | 1, 0.2 | 1 | £ |

α–mean normally distributed continuous variable, β–mean nonnormally distributed continuous variable; ¥-t-test; €-Kolmogorov-Smirnov test; £-chi-square test; ¤-a variable that satisfies $p < 0.2$.

rtPA–recombinant tissue plasminogen activators; mRS-modified Rankin scale; international normalized ratio; TIA-transient ischaemic attack; SBP–systolic blood pressure; DBP–diastolic blood pressure; NIHSS–National Institute of Health stroke scale; BMI–body mass index; aPTT–activated partial thromboplastin time; HDLC–high-density lipoprotein; LDLC – low-density lipoprotein; GOT–glutamic oxaloacetic transaminase; GPT–glutamic pyruvic transaminase; TOAST–trial of ORG 10172 in acute stroke treatment.

primary criterion. Using a prevalence of END ($p = 0.283$), indicating that 28.3 % of patients had END, from Berberich's 2019 study on mild lacunar strokes (NIHSS $\leq 5$), a relative precision of $d = 0.155$ and a reliability coefficient of $\alpha$=0.05, we estimated the required sample size to be $N = 406$. To account for up to 10 % of missing or incomplete data, we adjusted the target sample size to 447 patients.

### *Statistical analysis*

Patients were categorized into two groups: END and no-END. The diagnostic criteria for END are an increase in NIHSS score of 2 or more points in the first 72 h of illness compared with the initial status on admission. The incidence of END was assessed across the cohort, including those treated with SAPT, DAPT or thrombolysis from onset. Clinical characteristics (age, sex, admission blood pressure, NIHSS score, time window to admission, admission blood glucose levels, risk factors (hypertension, diabetes, obesity, smoking, prior stroke/TIA, pre-stroke mRS), blood test (platelets, INR, fibrinogen, aPTTs, lipid profile, urea, creatinine, GOT, GPT), and brain imaging (location of ischemia and hemorrhagic transformation classified by ECASS) were compared between two groups. Treatment modalities (alteplase, SAPT, or DAPT), hospital stay duration, and outcomes (mRS at discharge, 30 days and 90 days) were also analysed (*definition of variables in Supplement Data*).

Statistical analysis used t-tests for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and $\chi 2$ tests for categorical data. Univariate logistic regression analysis evaluated potential clinical characteristics with prognostic significance between the END and no-END groups, encompassing general characteristics of clinical status, blood tests, cerebral vascular imaging variables, and treatment modalities to discern distinct characteristics. We chose several features with $p < 0.2$ for multivariate logistic regression analysis to uncover variables and propose a predictive model. Analyses were conducted using SPSS 16.0 (IBM, Armonk, NY), with $p < 0.05$ considered statistically significant.

### *Primary outcome*

The primary outcome was the incidence of END in patients with minor stroke (NIHSS $\leq 5$) due to SAO, classified by TOAST (Fig. 1).

### *Secondary outcome*

Univariate logistic regression identified variables (clinical, paraclinical, cerebral vascular imaging, and treatment characteristics) differing significantly between the END and no-END groups ($p < 0.2$). The factors were further analyzed using multivariate logistic regression (outcome variable designated as END) to develop a predictive model for END.

END rates were compared across groups administered thrombolytics or antiplatelets (DAPT and SAPT) within 4.5 h of onset to evaluate the most effective preventive approach (Fig. 1).

## Results

The study included 451 patients who had experienced minor stroke as a result of SAO, with a mean age of 63.8 ± 11.8 years and 62.7 %

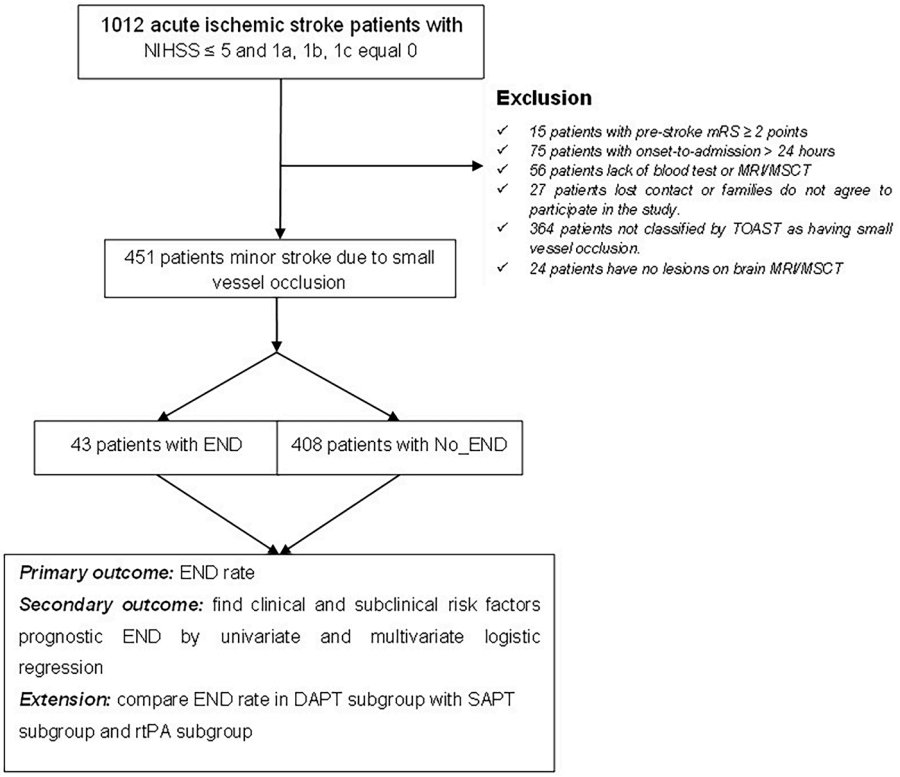


**Fig. 1.** Flow chart. END-early neurological deterioration; mRS-modified Rankin score; NIHSS-national institutes of Health stroke scale; DAPT-dual antiplatelet therapy, SAPT-single antiplatelet therapy, rtPA–alteplase. The DAPT group included patients who received dual antiplatelet therapy from the first day of hospitalization. The SAPT group included patients who received single antiplatelet therapy from the first day of hospitalization. The alteplase group consisted of patients who received thrombolysis after admission within the first 4.5 h.

were male. The overall END rate was 9.5 % (43/451). The END rate decreased over time, where the timing of END occurrence in the first 24 h and 24-48 h was nearly identical, with 39.6 % and 37.2 %, respectively. The 48-72 h window had a rate of 23.3 %. END typically involved a 2-point NIHSS increase (44 %), followed by ≥ 4-point (33 %) and 3-point (23 %) increases (Fig. 2, Fig. 3, Fig. 4, Supplement Data).

END was strongly associated with poor outcomes (mRS = 2-6) at discharge (OR = 17.80; 95 % CI:7.30-43.36; $p < 0.01$), at 30 days (OR = 21.45; 95 % CI: 10.08 - 45.62; $p < 0.01$), and at 90 days (OR = 20.68; 95 % CI: 9.65 - 44.32; $p < 0.01$) (*Tab.4 Supplement Data*).

Of the cohort, 23.7 % (107/451) were admitted within the thrombolysis window (first 4.5 h), while most admissions occurred between 12 and 24 h (41.2 %), followed by 6-12 h (24.8 %) and 4.5-6 h (10.2 %) (Fig. 3, Supplement Data).

Comparison of clinical and paraclinical characteristics between the END and No-END groups revealed that the END group exhibited a higher proportion of patients with admission systolic blood pressure (SBP) ≥ 150 mmHg, admission blood glucose ≥ 14mmol/L, diabetes history, and elevated INR levels ($p < 0.05$; Tab.1). To enhance the capacity to discern prognostic factors for END, we conducted a logistic regression analysis on variables exhibiting differences between the END and no-END groups with $p < 0.2$, including admission SBP ≥ 150 mmHg, admission NIHSS score, hypertension and diabetes history, platelet count, INR, cholesterol total, LDL-C, admission blood glucose, proportion of patients with admission blood glucose ≥ 14mmol/L, and internal capsule ischemia. Multivariate analysis identified SBP ≥ 150 mmHg, a history of diabetes, admission glucose ≥ 14mmol/L, and internal capsule ischemia are independent prognostic factors for END in minor strokes caused by lacunar ischemic stroke (Fig. 2).

The mRS scores at discharge, 30 days, and 90 days were significantly better in the no-END group compared to the END group, with a higher proportion achieving mRS 0-1 (Fig. 3 and Supplement Data).

Overall, 96.23 % (434/451) of patients received antiplatelet therapy. Patients on DAPT had a lower risk of END compared to those on SAPT (OR = 0.24; 95 %CI: 0.12 - 0.49; $p < 0.01$) (Fig. 4).

Among patients admitted within the first 4.5 h (23.7 %, 107/451), 77 (71.96 %) patients received DAPT, 16 (14.94 %) patients received alteplase, and 14 (13.1 %) were treated with SAPT. DAPT was associated with a significantly reduced risk of END compared to SAPT (OR = 0.079; 95 % CI: 0.007 - 0.939; $p = 0.04$) and alteplase (OR = 0.013; 95 % CI: 0.01 - 0.12; $p < 0.01$). However, the END risk did not significantly differ in the SAPT and alteplase groups, $p = 0.051$ (Fig. 4, Fig. 5).

## Discussion

Minor strokes account for 30-50 % of the overall ischemic stroke population, with lacunar strokes comprising 25 % globally and 30-42.3 % in Vietnam.[3,23–26] Our study focused on minor stroke caused by SAO, the most common type. The END rate in our cohort was 9.5 %, consistent with Werring et al's meta-analysis (2.3 - 47.5 %, mean 23.54 %; 95 % CI: 21.02 - 26.05).[9] While Werring's study included all END definitions and stroke severities, we focused exclusively on minor strokes (NIHSS ≤ 5) and used an NIHSS increase of ≥ 2 points to define END, a criterion shown to provide better consistency.[7,9,20,27]

In our study, we found that the following were prognostic factors for END in the population of patients with minor stroke due to SAO: admission blood glucose (OR = 2.99; 95 % CI: 1.05 - 8.54, $p = 0.04$), a history of diabetes (OR = 2.13; 95 % CI: 1.05 - 4.33, $p = 0.036$), and infarct lesions at the internal capsule (OR = 2.23; 95 % CI: 1.01 - 4.92, $p = 0.048$). These can be explained as follows: Elevated blood glucose levels and a history of diabetes are significant risk factors for atherosclerosis, including that affecting cerebral arterioles, which may occur in proximal or distal segments, at branching points, or extending from branching segments to distal segments of cerebral arterioles.[9,24,26] Elevated blood glucose levels are frequently observed in individuals with ischemic stroke, affecting up to 40 % of cases.[28] Hyperglycemia amplifies the extent of necrotic regions in the infarct, consequently exacerbating the patient's clinical manifestations.[28–30]

High admission SBP was associated with END (OR = 1.99; 95 % CI: 1.01 - 3.93; $p = 0.048$) in our study. Hypertension affects cerebral perfusion, and fluctuations in SBP are strongly linked to an increased risk of END in patients with lacunar ischemic stroke.[9,31] Nonetheless, the underlying mechanisms remain unclear.[24,26] The internal capsule, a compact region containing dense motor pathways, is particularly vulnerable to ischemic damage. Stroke in this area significantly increases the risk of progressive paralysis, leading to neurological

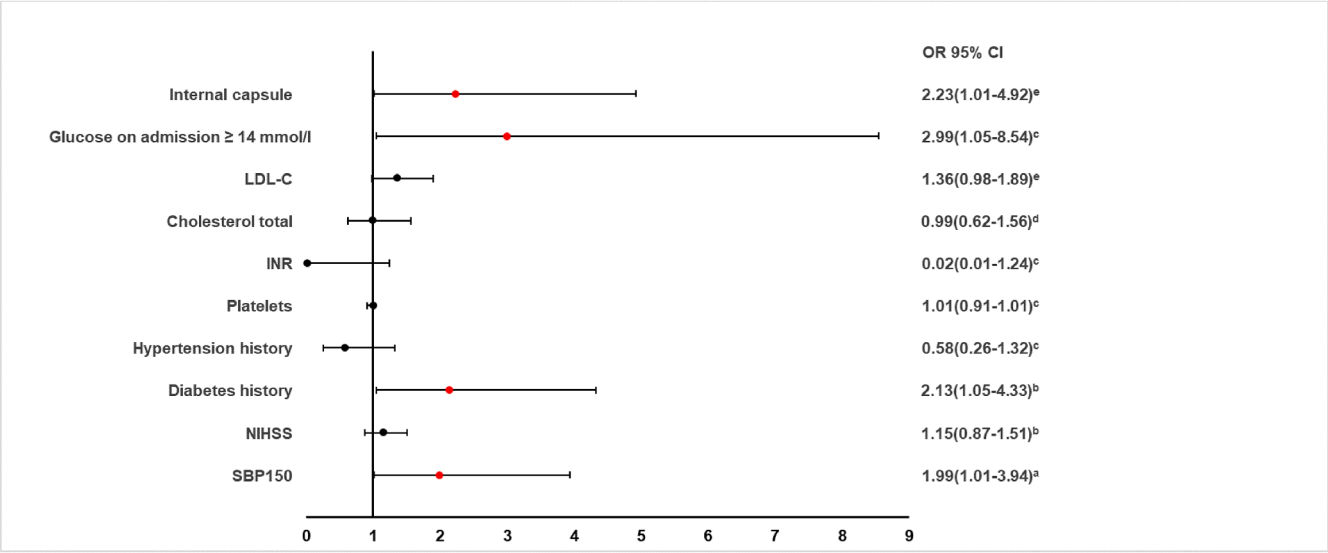


**Fig. 2.** Multivariate logistic regression analysis of some prognostic factors for END. a. Adjusted for SBP150, diabetes history, INR, glucose on admission ≥ 14mmol/l. b. Adjusted for SBP150, NIHSS, diabetes history, internal capsule, hypertension history, platelets, and LDLC. c. Adjusted for SBP150, hypertension history, platelets, INR, glucose on admission ≥ 14mmol/l, internal capsule. d. Adjusted for SBP150, NIHSS, diabetes history, hypertension history, platelets, INR, cholesterol total, LDLC, and internal capsule. e. Adjusted for diabetes history, glucose on admission ≥ 14mmol/l, LDLC, platelets, internal capsule. SBP150–admission systolic blood pressure ≥ 150 mmHg; international normalized ratio; NIHSS-national Institutes of Health Stroke Scale; LDLC–low-density lipoprotein cholesterol; TIA-transient ischemic attack; rtPA-recombinant tissue plasminogen activator. END–early neurological deterioration.

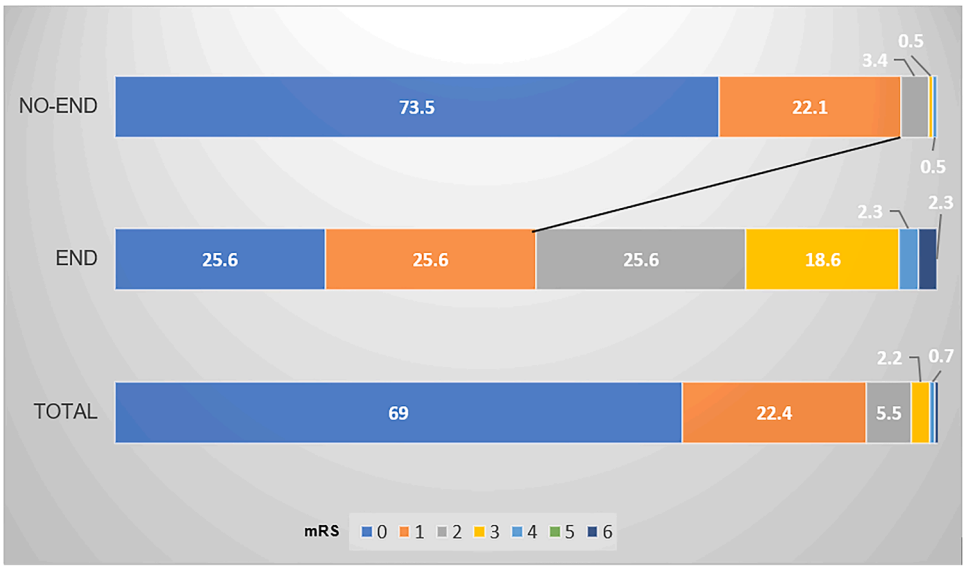


**Fig. 3.** mRS score distribution on the 90th day of END and no-END group. END-early neurological deterioration; mRS-modified Rankin score.

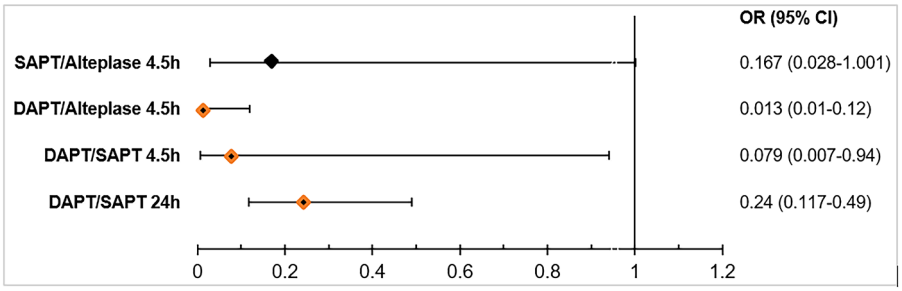


**Fig. 4.** END risk of DAPT, SAPT, Alteplase group. SAPT/Alteplase 4.5h- Patients admitted within the first 4.5h of receiving SAPT versus Alteplase. DAPT/Alteplase 4.5h- Patients admitted within the first 4.5 h of receiving DAPT versus Alteplase. DAPT/SAPT 4.5h- Patients admitted within the first 4.5 h of receiving DAPT versus SAPT. DAPT/SAPT 24h- Patients admitted within the first 24 h of receiving DAPT versus SAPT. DAPT-dual antiplatelet therapy, SAPT-single antiplatelet therapy; END–early neurological deterioration.

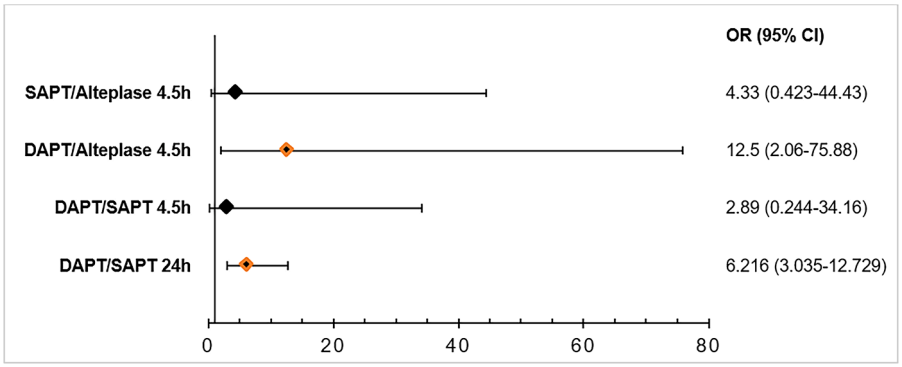


**Fig. 5.** mRS 0-1 on the 90th day of DAPT, SAPT, Alteplase group. SAPT/Alteplase 4.5h- Patients admitted within the first 4.5 h of receiving SAPT versus Alteplase. DAPT/Alteplase 4.5h- Patients admitted within the first 4.5 h of receiving DAPT versus Alteplase. DAPT/SAPT 4.5h- Patients admitted within the first 4.5 h of receiving DAPT versus SAPT. DAPT/SAPT 24h- Patients admitted within the first 24 h of receiving DAPT versus SAPT. mRS-modified Rankin score; DAPT-dual antiplatelet therapy, SAPT-single antiplatelet therapy.

disability. Our findings identified internal capsule ischemia as a prognostic factor for END (OR = 2.23; 95 % CI: 1.01 - 4.92;$p = 0.048$). These results are consistent with prior studies by Takase et al. and Ohara et al., which highlighted lacunar ischemia at the lenticulostriate artery's perfusion location as a predictor of progressive motor paralysis.[32,33]

The pathophysiology of lacunar ischemic stroke can be explained by four mechanisms: (1) Atherosclerotic plaque in the parent vessel entirely obstructs the bifurcation that supplies the infarcted region, (2) atherosclerotic plaque at the confluence of the parent vessel and the small vessel branch that supplies the infarcted area progressively advances, resulting in vascular occlusion, (3) thrombus fragments from disparate sites migrate to occlude the small vessel, and (4) arteriolosclerosis in the distal segment of the relevant small vessel branch advances, leading to gradual constriction and blockage.[9,26] From the above analysis, we see

that the atherosclerotic mechanism is still the main one. Therefore, it seems that the role of antiplatelet aggregation is very important for patients with cerebral infarction due to SAO.

Our study focused on patients with lacunar ischemic stroke admitted within the initial 24 h, a critical window for interventions like DAPT or early thrombolysis, both shown to improve neurological recovery.[9] Recent guidelines suggest that DAPT is superior to SAPT in reducing recurrence rates and enhancing recovery of neurological function in patients with minor ischemic strokes of non-cardio thrombotic etiology.[34] The American Stroke Association and European Stroke Associations recommend thrombolysis for minor strokes (NIHSS = 0-5) with significant neurological deficits within a 4.5-hour window to increase the likelihood of favorable neurological recovery.[2,21] In cases of minor stroke with non-disabling symptoms, a meta-analysis by Lun et al. involving 5,897 individuals found that DAPT was the most effective treatment for improving recovery, followed by aspirin and then alteplase.[35] This raises a key question: does DAPT further reduce the incidence of END compared to SAPT or altepase in SAO minor strokes admitted within the first 24 h?

There have been no randomized trials assessing interventions to mitigate END in the literature, and the data is confined to a few observational studies or subgroup analyses from trials.[9,26] The DAPT group (included 351 patients) exhibited a reduced incidence of END with an OR = 0.24; 95 % CI: 0.12 - 0.49; $p < 0.01$ and increased rate of favorable neurological outcome (mRS = 0-1) with OR = 6.216; 95 % CI: 3.035 - 12.729; $p < 0.01$) compared to the SAPT group (Figs. 4 and 5). We analyzed the END rate of patients admitted within the first 4.5 h based on various treatment options. We discovered that the DAPT group exhibited a reduced END rate compared to the SAPT and alteplase groups. The END and favorable neurological outcome rates in the SAPT and alteplase cohorts were not statistically significant. Kimura et al. demonstrated that among a cohort of 144 patients with lacunar ischemic stroke, the DAPT group had a reduced incidence of END compared to the SAPT group, with rates of 9.7 % versus 33.8 %, respectively.[36] Research conducted by Nishi et al., including 54 patients with SAO minor stroke, showed that the cohort of 28 patients receiving dual antiplatelet medication with clopidogrel outperformed the control group.[37] Recently, author Cui et al. conducted a posthoc analysis of the ARAMIS study, revealing that patients with minor ischemic stroke without large vessel occlusion, admitted within the initial 4.5 h of DAPT treatment, exhibited a lower rate of END compared to the alteplase group, at 0.5 % versus 5.7 %, respectively (aRD = −4.8 %; 95% CI:−6.9 to 2.6 %; $p < 0.001$).[20] In Cui et al's research population, the incidence of minor stroke (NIHSS ≤ 5) attributed to SAO was 37.2 % (165/444) patients. In our study, there is a larger cohort of 451 SAO minor stroke patients.[20] The research above indicates the possible efficacy of DAPT in mitigating the risk of END in patients with SAO minor strokes.

Our study has several limitations: 1) An observational research with probable selection bias. 2) A single-center research may not be typical of the population. 3) The subgroups were not balanced enough to provide statistical power when compared to the DAPT, SAPT, and alteplase groups. Our study showed that in patients hospitalized within 4.5 h, the END rate in the DAPT group was lower than that of the SAPT and alteplase groups. Still, the favorable neurological outcome (mRS 0-1) after 90 days did not differ between the DAPT and SAPT groups. 4) The efficacy of DAPT in lowering the risk of END in the SAO minor stroke population was evaluated exclusively by comparing the END rate of the subgroups without considering the characteristics of the subgroups. 5) The study evaluated the impact of DAPT and SAPT on END and mRS at 90 days but did not evaluate treatment adherence, which is also a significant limitation. 6) The study only assessed mRS up to day 90 and did not address the long-term effects of END, such as dementia or quality of life. 7) History of diabetes and blood glucose level at admission are recognized prognostic factors for END. However, the HbA1c level, an important marker in the management of diabetic patients, was not considered in our analysis. 8) Our study results showed that DAPT reduced the risk of END compared with SAPT, but there was no association with treatment outcome at 90 days of disease. 9) Our study did not clearly address which patients used DAPT with ticagrelor or clopidogrel, thus not clarifying the specific role of each different DAPT regimen. The study did not show patients using clopidogrel but carrying CYP2C19 loss-of-function alleles. 10) Our study did not address the pathogenesis of END in the study group, whether it was related to hemorrhagic transformation, progressive cerebral infarction core, or another factor.

## Conclusion

Our study findings revealed that the incidence of END in the SAO minor stroke cohort was 9.5 %. Prognostic indicators for END in this cohort were elevated admission systolic blood pressure, elevated blood glucose levels, a history of diabetes, and ischemic in the internal capsule location. DAPT may significantly impact mitigating END risk in this cohort, necessitating more research to validate these findings.

## Statement of no AI use

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

## Informed consent

Written informed consent was obtained from all subjects before the study.

## Ethical approval and informed consent statements

Following Decision No 4837/BM-HDDD, the Ethics Committee of Bach Mai Hospital approved the study procedure for this paper. Before participation, all patients and their families received a comprehensive explanation of the study and provided their informed consent.

## CRediT authorship contribution statement

**Dung Tien Nguyen:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Duy Ton Mai:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Hung Tran Ha:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Phuong Viet Dao:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Minh Cong Tran:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Huan Xuan Nguyen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition.

## Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Not applicable

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108331.

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