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Defining short-term outcomes of minor ischemic stroke due to small artery occlusion in the era of dual antiplatelet treatment: A READAPT study sub-analysis

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ABSTRACT

Background: The outcomes of minor ischemic stroke resulting from small artery occlusion (SAO-MIS) have not yet been characterized after dual antiplatelet treatment (DAPT) has become the standard of care. We provided updated figures on the short-term prognosis of SAO-MIS treated with early short-term DAPT and compared the outcomes of SAO-MIS versus non-SAO-MIS patients.

Methods: This is a prespecified sub-analysis from a prospective multicentric real-world study (READAPT, NCT05476081) including patients with minor (NIHSS≤5) non-cardioembolic ischemic stroke treated with DAPT. The primary outcome was a composite of 90-day symptomatic ischemic stroke or major cardiovascular events. Secondary outcomes were the 90-day ordinal distribution of modified Rankin Scale (mRS) scores, 90-day excellent functional outcome (mRS of 0 to 1), and 24-h early neurological deterioration (END). Safety outcomes were 90-day intracerebral hemorrhage, moderate-to-severe and any bleedings. All outcomes were compared between SAO-MIS and non-SAO-MIS patients.

Results: We included 678 MIS, of whom 253 (37.3 %) were SAO-related. At 90 days, 3 patients with SAO-MIS had primary outcome (1.2 % [95 % CI 0.2 %–3.5 %]), which were all SAO-related ischemic strokes. For the secondary outcomes, most SAO-MIS patients (n = 191, 75.5 %) had 90-day excellent functional outcome and 12 had 24-h END (4.7 % [95 % CI 2.5 %–8.3 %]). Referring to safety outcomes, 90-day intracerebral hemorrhage occurred only in one patient with SAO-MIS (0.4 % [95 % CI 0.0 %- 2.2 %]). Compared to non-SAO-MIS, the 90-day risk of

recurrent vascular events was significantly lower among SAO-MIS (aHR 0.24 [95 % CI 0.08–0.68]; $p = 0.007$), while there were not significant differences in other secondary outcomes, nor in the risk of safety events.
Conclusions: Our findings show overall favorable short-term prognosis after SAO-MIS treated with DAPT. Future studies should investigate factors associated with residual stroke risk and long-term outcomes of SAO-MIS.

1. Introduction

Small artery occlusion (SAO) -related stroke accounts for ~25 % of all ischemic strokes. [1] Although the functional outcome of a single SAO-related stroke is generally good, [2] symptoms may show early progression in up to 30 % of patients, [3,4] increasing the risk of long-term dependency. Additionally, recurrent infarctions may be associated with a more severe clinical presentation and result in more significant disability. [2].

For patients with acute SAO-related minor ischemic stroke (SAO-MIS), short-term dual antiplatelet therapy (DAPT) has become the preferred treatment for antithrombotic-based secondary prevention, [5–8] alongside optimization of treatments for other risk factors. The latest international guidelines recommend early initiation of DAPT as soon as possible after any non-cardioembolic MIS subtype, including those related to SAO. [9–12] The impact in the real-world of this change in the treatment paradigm has not been described. Hence, we aimed to investigate the short-term prognosis of patients with SAO-MIS treated with the current standard of care for secondary stroke prevention and to compare outcomes of SAO-MIS versus non-SAO-MIS patients in the real-world setting.

2. Methods

The Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack (READAPT – NCT05476081) is an observational prospective multicentric real-world study coordinated by the University of L'Aquila and endorsed by the Italian Stroke Association – Associazione Italiana Ictus (ISA-AII). The study was carried out according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. [13] Study procedures have been detailed in a prior publication. [14] Patients' enrollment took place at 64 Italian Stroke centers spanning from February 1st, 2021 to February 28th, 2023.

Patients aged ≥18 years were included if they had an acute non-cardioembolic mild-to-moderate ischemic stroke or high-risk TIA and were treated with a short course of DAPT. The READAPT study did not exclude patients based on strict National Institute of Health Stroke Scale (NIHSS) and ABCD2 cut-off scores, but local investigators were recommended to adhere to guidelines for DAPT prescription. [9–12] Eligible patients were enrolled shortly after the index event. Local investigators were trained to prescribe best medical treatment for cardiovascular comorbidities (i.e., antihypertensives, lipid-lowering drugs and antidiabetics) in accordance with current international guidelines [9–12] via webinars.

An electronic anonymized database was created using Research Electronic Data Capture (REDCap) software. The READAPT database was hosted at the University of L'Aquila and accessed by investigators through link/password or quick response (QR) code. A baseline case report form was implemented to collect patient demographics, cardiovascular risk factors, pre-stroke treatment, stroke severity (NIHSS), pre- and post-stroke modified Rankin scale (mRS) score, neuroimaging findings, presumed cause of the index event, and acute treatment (i.e., intravenous thrombolysis, endovascular thrombectomy, endarterectomy).

Quality checks were made on a weekly basis and queries were regularly sent to centers investigators to guarantee the completeness and integrity of data entry. Study investigators received specific training before the study was initiated to ensure appropriate completion of the baseline and follow-up case-report forms and the correct adjudication of study outcomes.

2.1. Study population

For the purposes of this analysis, we only selected patients who had optimal use of DAPT according to recommendations from available guidelines. [9] Specifically, we included patients who started DAPT <24-h of stroke onset and who had a National Institute of Stroke Scale (NIHSS) score at presentation ≤5 regardless to symptoms duration. Additionally, we selected only patients with evidence of recent ischemic lesion(s) at neuroimaging (brain non-contrast computed tomography CT – NCCT or magnetic resonance imaging – MRI), to ensure a more accurate definition of stroke/TIA etiology (i.e., patients with TIA without lesion(s) were excluded). Patients with transient symptoms (baseline NIHSS of 0) and neuroimaging evidence of ischemic lesion(s) at brain CT or MRI were considered MIS. Patients who underwent reperfusion therapies (i.e., intravenous thrombolysis, endovascular thrombectomy, carotid endarterectomy) were excluded. This exclusion criterion was implemented to address potential confounding effects on the risk of outcomes in patients treated with acute reperfusion therapies, who were excluded from landmark randomized DAPT trials. [5–8]

Stroke etiology was defined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. [15] Patients with a traditional clinical lacunar syndrome and brainstem or subcortical hemispheric lesion(s) with a diameter ≤ 1.5 cm on CT/MRI were adjudicated as SAO- MIS, while others were adjudicated as non-SAO-MIS. Patients with multiple lesions at neuroimaging fulfilling the SAO-MIS definition were classified as SAO-MIS. The etiological adjudication of each index event was performed by local investigators, who were provided with homogeneous criteria and trained before study initiation. Similarly, local investigators were trained to adjudicate clinical characteristics, cardiovascular risk factors and neuroimaging findings according to pre-specified criteria.

2.2. Follow-up and outcomes

All included patients were followed up for 90 ± 10 days. At the end of the follow-up period local investigators performed a face-to-face or remote visit. The follow-up case report form collected data on performed investigations, compliance to treatments, adverse events, mRS, effectiveness and safety events. Adherence to DAPT and prescribed medications for comorbidities was also assessed at the follow-up visit based on self-report information from patients' interview. Optimal adherence was defined when the patient reported continuous intake for at least 21 days for DAPT and throughout the follow-up period for anti-hypertensives, lipid-lowering drugs, and antidiabetics.

The primary outcome was a composite of new symptomatic ischemic stroke (new and sudden neurological deficit associated with congruous ischemic lesion(s) at neuroimaging regardless of symptoms duration) or other major cardiovascular events (myocardial infarction, death due to vascular causes) at 90 days. Information on recurrent stroke etiology was also collected and defined according to the TOAST classification. [15] Secondary outcomes were the 90-day ordinal distribution of patients' mRS scores, 90-day excellent functional outcome (mRS of 0 to 1) and 24-h early neurological deterioration (END), which was defined as a persistent increase of ≥2 points in the NIHSS score within 24 h of admission but not related to cerebral hemorrhage. [16,17] The safety outcomes were 90-day intracerebral hemorrhage, moderate-to-severe

and any bleeding events. The severity of bleeding events was assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery (GUSTO) trial definitions. [18] All bleeding events were adjudicated as safety outcomes irrespective of whether they were clinically evident, asymptomatic, or incidentally diagnosed. Each local investigator adjudicated outcomes on review of medical charts.

2.3. Statistical analysis

Descriptive statistics were used to report baseline characteristics of SAO-MIS patients. Specifically, categorical variables were reported as absolute numbers with percentages (%), while continuous variables as mean ± standard deviation (SD), or median and interquartile range (IQR), according to their distribution. The baseline characteristics of SAO-MIS and non-SAO-MIS patients were compared using the Wilcoxon test or the Pearson $X2$ test, both used to test the significance of differences between two groups for continuous and categorical variables, respectively. Two-sided statistical significance was set at a $p < 0.05$. Poisson regression analysis was used to assess the incidence of outcomes at 90 days. For all 90-day outcomes, we reported the absolute numbers of events with % occurring among SAO-MIS patients. We also compared outcomes of SAO-MIS patients with those of MIS due to other etiologies. For the primary outcome, the time-to-event 90-day risk of symptomatic stroke and other major vascular events was compared between SAO-MIS and non-SAO-MIS patients using Cox regression. Results were presented as hazard ratio (HR) with 95 % confidence intervals (CIs). For the secondary outcomes, the 90- day ordinal distribution of mRS scores was compared using an ordinal generalized linear model (GLM). The 90-day rate of excellent functional outcome, as well as the 24-h risk of END and of all safety outcomes were compared using a GLM with binomial distribution and log link function to calculate risk ratios [95 % CIs]. Covariate-adjusted analyses were performed for all outcomes, accounting for prespecified demographic and clinical factors that might influence outcome disparities between groups (age, sex, ethnicity, hypertension, diabetes, baseline mRS and NIHSS, DAPT loading dose, adherence to DAPT and other prescribed medications). All statistical analyses were performed using R software, version 4.2.

3. Results

We included 678 patients, of whom 253 (37.3 %) had SAO-MIS, while the remaining 425 (62.7 %) had other etiologies. **(**Fig. 1**)** All patients underwent a brain NCCT within 24 h of admission, while brain MRI was conducted in 546 (80.5 %) patients. Extracranial and intracranial brain vessels were investigated in all cases. Specifically, extracranial vessels study with color Doppler ultrasound was performed in 74.9 % of cases, while transcranial color Doppler was completed in 32.2 % of patients. CT and MR angiography of brain vessels were conducted in 61.4 % and 43.0 % of cases, respectively. As regards cardiological investigations, all patients underwent routine electrocardiography (ECG), while prolonged ECG monitoring (24-h or 48-h Holter ECG) and transthoracic echocardiography were performed in 477 (70.4 %) and 506 (74.6 %) patients, respectively.

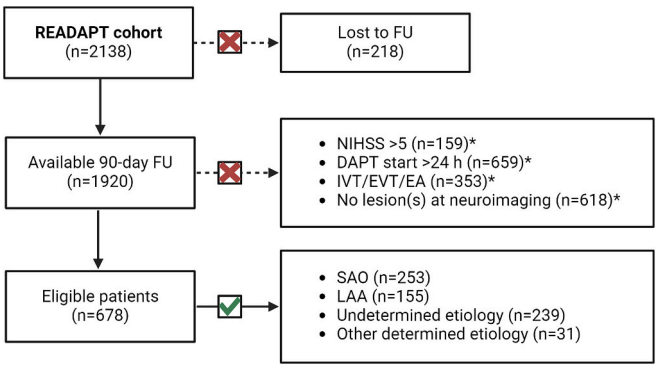

Fig. 1. Study flow-diagram.
DAPT: dual antiplatelet treatment; EA: endarterectomy; EVT: endovascular thrombectomy; FU: follow-up; IVT: intravenous thrombolysis; LAA: large artery atherosclerosis; MIS: minor ischemic stroke; NIHSS: National Institute of Health Stroke Scale; SAO: small artery occlusion; *: patients may have >1 exclusion criteria.

3.1. Baseline characteristics of SAO-MIS patients

Baseline characteristics of the SAO-MIS population are reported in Table 1. SAO-MIS patients were mostly non-Hispanic white (98.0 %) and males (66.0 %). The mean age at SAO-MIS onset was 69.37 ± 10.63 years. Most SAO-MIS patients (79.0 %) had no symptoms (mRS of 0) prior to the index event (79.5 %), while the median NIHSS score at presentation was 2 (IQR 0–3). As regards cardiovascular risk factors, SAO-MIS patients had a high prevalence of hypertension (88.9 %) and dyslipidemia (67.2 %). No cases of atrial fibrillation or other cardioembolic arrhythmias were detected in SAO-MIS patients during follow-up. **(**Table 1**).**

All SAO-MIS patients were treated with clopidogrel plus aspirin for a median time of 21 days (IQR 21–30). Loading dose was prescribed in 62.1 % of SAO-MIS patients. Adherence to DAPT was optimal in most patients (96.4 %). After DAPT was discontinued, most SAO-MIS patients continued aspirin (61.3 %) or clopidogrel (37.5 %) up to the follow-up visit. Reasons for early DAPT discontinuation (<21 days) in SAO- MIS patients were a bleeding event during treatment in 6 out of 9 patients (66.7 %), while the remaining discontinued DAPT for arbitrary choice (33.3 %). When indicated, all SAO-MIS patients received treatment for cardiovascular comorbidities after the index event, with optimal adherence to antihypertensives, lipid-lowering drugs and antidiabetics (>90 % for all prescribed medications). **(**Table 1**).**

3.2. Outcomes of SAO-MIS patients

At 90-day follow-up, 3 patients with SAO-MIS had symptomatic stroke and other major cardiovascular events (1.2 % [95 % CI 0.2 %–3.5 %]). All primary outcomes were recurrent SAO-related strokes occurring in patients with optimal adherence to DAPT. For the secondary outcomes, most SAO-MIS patients ($n = 191$) had excellent functional outcome at 90 days (75.5 %). 24-h END was observed in 12 SAO-MIS patients (4.7 % [95 % CI 2.5 %–8.2 %]). Bleeding events occurred in 8 patients with SAO- MIS (3.2 % [95 % CI 1.4 %–6.2 %]). In particular, only one patient had intracerebral hemorrhage (0.4 % [95 % 0.0 %–2.2 %]). No patient died at 90 days. **(**Fig. 2**).**

3.3. SAO-MIS versus non-SAO-MIS

Baseline characteristics of non-SAO-MIS patients are summarized in Table 1. There were no significant differences in the baseline demographic and clinical characteristics between SAO-MIS and non-SAO-MIS patients, except for a higher prevalence of hypertension (OR 2.67, 95 % CI 1.70–4.19) among SAO-MIS patients. New-onset atrial fibrillation was detected in 3 patients with non-SAO-MIS (0.7 %) during follow-up.

Among non-SAO-MIS related to large artery atherosclerosis ($n = 155$), 21 patients (13.5 %) had ≥50 % extracranial internal carotid artery stenosis, 46 (29.7 %) patients had ≥50 % extracranial vertebral artery stenosis, while symptomatic intracranial arterial stenosis (≥50 %) was found in 88 (56.8 %) cases.

At brain MRI, SAO-MIS patients had a lower number of multiple acute ischemic lesions (median 2, IQR 2–2 versus 2, IQR 2–4; $p < 0.001$), higher periventricular and deep Fazekas scores ($p = 0.039$ and $p = 0.018$, respectively) and more frequent prior lacunar infarcts (56.9 %

Table 1
Baseline characteristics of SAO-MIS and non-SAO-MIS patients.

	SAO-MIS (n = 235)	non-SAO-MIS (n = 425)	P value
Demographic characteristics			
Males, n (%)	167 (66.0)	288 (67.8)	0.699
Age – years, mean ± SD	69 ± 11	69 ± 12	0.784
Ethnicity, n (%)			>0.999
Non-Hispanic White	248 (98.0)	417 (98.1)	
Other	5 (2.0)	8 (1.9)	
Clinical characteristics			
Etiology, n (%)			
SAO	253 (100.0)	–	
LAA	–	155 (36.5)	
Undetermined etiology	–	239 (56.2)	
Other determined etiology	–	31 (7.3)	
Pre-event mRS, n (%)			0.249
0	201 (79.5)	346 (81.4)	
1	34 (13.4)	41 (9.7)	
2	18 (7.1)	38 (8.9)	
Baseline NIHSS, median (IQR)	2 (1–3)	2 (1–3)	0.156
Cardiovascular risk factors, n (%)			
Hypertension[a]	225 (88.9)	319 (75.1)	**<0.001**
Dyslipidemia[b]	170 (67.2)	264 (62.1)	0.212
Diabetes mellitus[c]	67 (26.5)	91 (21.4)	0.157
Current smoking[d]	129 (51.0)	184 (43.3)	0.062
History of TIA/stroke	42 (16.6)	74 (17.4)	0.868
History of myocardial infarction	16 (6.3)	38 (8.9)	0.284
Admission therapy, n (%)			
Antihypertensive drugs	178 (70.4)	270 (63.5)	0.083
Lipid-lowering drugs	83 (32.8)	126 (29.6)	0.438
Antidiabetic drugs	54 (21.3)	78 (18.4)	0.395
Antiplatelet drugs, n (%)			
Aspirin	87 (34.4)	140 (32.9)	0.763
Clopidogrel	13 (5.1)	21 (4.9)	>0.999
Ticagrelor	0 (0.0)	1 (0.2)	>0.999
DAPT information			
Type of DAPT, n (%)			0.459
Aspirin + clopidogrel	253 (100.0)	422 (99.3)	
Aspirin + ticagrelor	0 (0.0)	3 (0.7)	
DAPT duration, days - median (IQR)	21 (21−30)	21 (21–30)	0.231
Loading dose, n (%)	157 (62.1)	262 (61.7)	0.981
Type of antiplatelet continued after DAPT, n (%)			0.200
Aspirin	155 (61.3)	267 (62.8)	
Clopidogrel	95 (37.5)	147 (34.6)	
None	3 (1.2)	14 (3.4)	
Post-discharge therapy, n (%)			
Antihypertensive drugs	243 (96.0)	351 (82.6)	0.402
Lipid-lowering drugs	235 (92.9)	393 (92.5)	0.724
Antidiabetic drugs	77 (30.4)	109 (25.6)	0.207
Adherence (optimal), n (%)			
DAPT	244/253 (96.4)	404/425 (95.1)	0.513
Antihypertensive drugs	234/243 (96.3)	341/351 (97.2)	0.561
Lipid-lowering drugs	230/235 (97.9)	380/393 (96.7)	0.736
Antidiabetic drugs	71/77 (92.2)	102/109 (93.6)	0.718
Reasons for early DAPT discontinuation, n (%)			
Bleeding event during DAPT	6/9 (66.7)	13/21 (61.9)	0.869
Detection of atrial fibrillation	–	3/21 (14.3)	
Arbitrary choice	3/9 (33.3)	5/21 (23.8)	0.928
Neuroimaging findings (brain MRI)			
Number of ischemic lesions, median (IQR)	2 (2–2)	2 (2–4)	**<0.001**
Leukoaraiosis score, n (%)[e]			
Periventricular (grade)			**0.039**
0	37/169 (21.9)	81/272 (29.8)	
1	72/169 (42.6)	121/272 (44.5)	**0.018**
2	38/169 (22.5)	53/272 (19.5)	
3	22/169 (13.0)	17/272 (6.2)	
Deep (grade)			
0	31/167 (18.6)	86/272 (31.6)	
1	87/167 (52.0)	120/272 (44.2)	
2	38/167 (22.8)	56/272 (20.6)	
3	11/167 (6.6)	18/272 (6.6)	
Prior lacunar infarcts, n (%)[f]	144/207 (69.6)	150/339 (44.2)	**<0.001**
White matter hyperintensities, n (%)[f]	152/207 (73.4)	210/339 (61.9)	**0.008**
Perivascular spaces, n (%)[f]	32/207 (15.5)	51/339 (15.0)	0.994
Cerebral microbleeds, n (%)[f]	13/207 (6.3)	17/339 (5.0)	0.663
Cortical superficial siderosis, n (%)[g]	5/207 (2.4)	3/339 (0.9)	0.282

BMI: body mass index; DAPT: dual antiplatelet therapy; IQR: interquartile range; LAA: large artery atherosclerosis; MIS: minor ischemic stroke; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SAO: small artery occlusion; SD: standard deviation; Statistically significant P values (<0.05) are reported in bold.

[a] : Arterial hypertension was defined as a history of blood pressure > 140/90 mmHg and/or current use of antihypertensive medications.

[b] : Dyslipidemia was defined as history of total blood cholesterol levels > 220 mg/dL and/or total triglycerides levels > 130 mg/dL and/or current use of lipid-lowering drugs.

[c] : Diabetes mellitus was defined as history of fasting glucose > 126 mg/dL or current use of hypoglycemic medications.

[d] : Current smoking was defined as the consumption of ≥ 1 cigarette per day over the last year.

[e] : Leukoaraiosis at brain MRI was scored according to the classification system by Fazekas et al. [31].

[f] : Brain MRI markers of small vessel disease were defined according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1) criteria. [32].

[g] : Cortical superficial siderosis was defined according to the definition by Charidimou et al. [33].

versus 35.5 %: p < 0.001) compared to non-SAO-MIS. (Table 1).

Patients with SAO-MIS showed a significantly lower risk of primary outcome compared to other etiologies (adjusted HR 0.24 [95 % CI 0.08–0.69]; $p = 0.007$). Conversely, we found no differences in the 90-day ordinal distribution of mRS scores (adjusted OR 0.99 [95 % CI 0.85–1.16]; $p = 0.896$), as well as in the risk of 24-h END (adjusted risk ratio 2.07 [95 % CI 0.89–4.97]; $p = 0.090$). (Table 2).

For the safety outcomes, there were no significant differences in the 90-day risk of intracerebral hemorrhage (adjusted risk ratio 0.42 [95 % CI 0.02–2.86]; $p = 0.423$), moderate-to-severe (adjusted risk ratio 0.26 [95 % CI 0.01–1.56]; $p = 0.175$) and any bleedings (adjusted risk ratio 0.75 [95 % CI 0.31–1.64]; $p = 0.454$. (Table 2).

4. Discussion

This analysis of the prospective multicentric study READAPT provides updated figures on the short- term prognosis of patients with SAO-MIS after early short-term DAPT has become the standard of care in the real-life practice. We recorded a low short-term risk of new symptomatic stroke or other vascular events with excellent 90-day functional outcome in most SAO-MIS patients. Additionally, the incidence of 24-h END was very low, and no safety concerns emerged for DAPT within this specific population, as 90-day bleedings were extremely rare and comparable to other etiologies.

The available information on the prognosis of SAO-MIS after the introduction of short-term DAPT as the standard of care is rather limited.

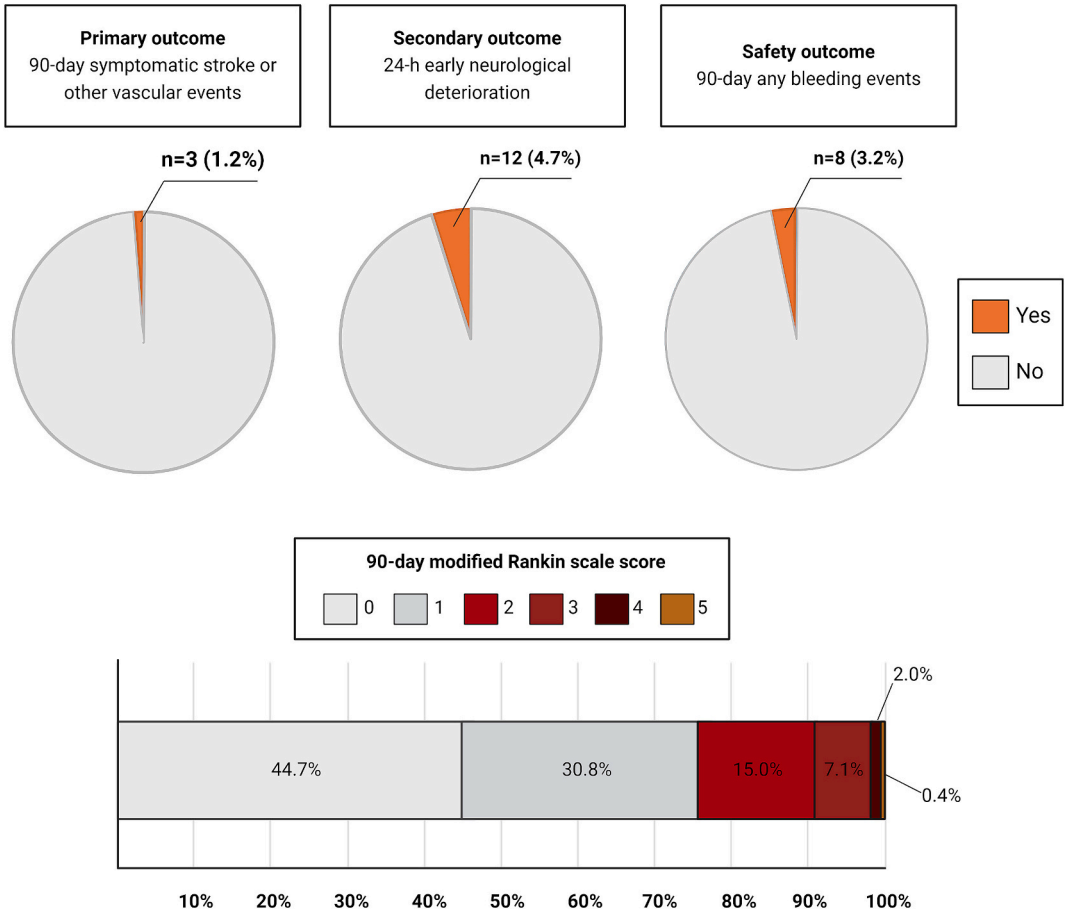

Fig. 2. Outcomes of SAO-MIS patients.
MIS: minor ischemic stroke; SAO: small artery occlusion.

Table 2
Outcomes comparison: SAO-MIS versus non-SAO-MIS patients.

	SAO-MIS (*n* = 253)	non-SAO-MIS (n = 425)	Statistical metric	Unadjusted difference [95 % CI]	P value	Adjusted difference[a] [95 % CI]	P value
Primary outcome							
90-day symptomatic stroke and other cardiovascular events, n (%)	3 (1.2)	21 (4.9)	**Hazard ratio**	0.25 [0.07–0.79]	**0.006**	0.24 [0.08–0.69]	**0.007**
Secondary outcomes							
90-day mRS score distribution, n (%)							
0	113 (44.7)	219 (51.5)					
1	78 (30.8)	114 (26.8)					
2	38 (15.0)	51 (12.0)					
3	18 (7.1)	27 (6.4)	**Odds ratio**	1.07 [0.90–1.28]	0.437	0.99 [0.85–1.16]	0.896
4	5 (2.0)	9 (2.1)					
5	1 (0.4)	1 (0.2)					
6	0 (0.0)	4 (0.9)					
90-day excellent functional outcome (mRS of 0 to 1), n (%)	191 (75.5)	333 (78.4)	**Risk ratio**	0.96 [0.88–1.05]	0.390	0.98 [0.84–1.09]	0.621
24-h early neurological deterioration	12 (4.7)	10 (2.4)	**Risk ratio**	2.01 [0.88–4.60]	0.090	2.07 [0.89–4.97]	0.090
Safety outcomes							
90-day intracerebral hemorrhage, n (%)	1 (0.4)	4 (0.9)	**Risk ratio**	0.42 [0.05–3.74]	0.422	0.42 [0.02–2.86]	0.423
90-day moderate-to-severe bleeding, n (%)	1 (0.4)	6 (1.4)	**Risk ratio**	0.28 [0.03–2.31]	0.206	0.26 [0.01–1.56]	0.175
90-day any bleeding, n (%)	8 (3.2)	18 (4.2)	**Risk ratio**	0.74 [0.32–1.69]	0.482	0.75 [0.31–1.64]	0.464

[a] : adjusted for age, sex, ethnicity, hypertension, diabetes, baseline NIHSS, baseline mRS, DAPT loading dose, adherence to DAPT and other prescribed medications.
MIS: minor ischemic stroke; mRS: modified Rankin Scale; SAO: small artery occlusion. Statistically significant P values (<0.05) are reported in bold.

To the best of our knowledge there is no data available derived from real-world studies and also limited information coming from landmark randomized clinical trials addressing short- term DAPT. [5–8] To date, the only available trial specifically designed to assess the effect of DAPT in patients with neuroimaging evidence of subcortical lacunes remains the Secondary Prevention of Small Subcortical Strokes (SPS3) study,

which showed similar rates of stroke recurrence but excess bleeding risk in patients treated with DAPT versus aspirin alone. [19] However, the SPS3 trial included SAO-related strokes of any severity treated with late timing initiation (≥14 days from the index event) and long-lasting (mean of 3.5 years) DAPT regimen. Recently, a prespecified sub-analysis of the Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) 2 trial demonstrated a 33 % relative risk reduction for 90-day recurrent stroke with combined ticagrelor plus aspirin treatment compared to aspirin alone in participants with SAO-related MIS (3.6 % versus 7.0 %; HR 0.51 [95 % CI, 0.33–0.79]). [20] No specific sub-analyses of DAPT landmark randomized trials are currently available.

In the present study, the incidence of new symptomatic stroke or other major ischemic events was remarkably low among patients with SAO-MIS (1.2 % [95 % CI 0.2 %–3.5 %]). This figure appears consistently lower compared to the one reported by real-word prospective studies dating back before the widespread adoption of DAPT as the standard of care, which quantified an overall short-term risk of recurrent vascular events after SAO-related stroke ranging from 7.4 % to 13.7 % [21,22]. All recurrent ischemic events among SAO-MIS patients were SAO-related strokes, confirming observations from prior studies wherein most of the short-term recurrencies after a SAO-related stroke were new infarcts stemming from the same etiology. [23,24] Notably, all SAO-MIS patients included in our analysis received not only DAPT but overall secondary prevention with optimal adherence in most cases. Furthermore, we also estimated a significantly lower risk of stroke and other major ischemic events in SAO-MIS patients compared to other etiologies. It is important to note that our study design does not allow to determine whether this lower incidence might reflect the intrinsically low risk of stroke recurrence which is typical of SAO-related strokes, [25,26] rather than resulting from enhanced effectiveness of early DAPT.

As regards the secondary outcomes, we found excellent 90-day functional outcome (mRS of 0 to 1) in the majority of SAO-MIS patients (75.5 %). Although patients with SAO-related stroke generally have favorable 90-day functional outcome, up to one third may experience progressive SAO-related symptoms (END) which is usually related to branch atheromatous thrombosis. [1–3] END has been identified as a strong predictor of short-term unfavorable functional outcome. [17] The incidence of 24-h END observed among SAO-MIS patients in our study (4.7 % [95 % CI 2.5 %–8.2 %]) was consistently lower compared to a recent prospective study wherein most patients were treated with antiplatelet monotherapy (16.7 %). [20] This finding may suggest that more intensive platelet inhibition through DAPT holds the potential to halt further stroke progression in SAO-MIS patients, thereby reducing the risk of early clinical worsening. Additionally, the lack of difference in the 90-day ordinal distribution of mRS scores between SAO-MIS patients and other MIS subtypes could indicate the lack of a discernible differential benefit from DAPT on functional outcome with regard to the stroke etiology.

Regarding safety outcomes, the risk of moderate-to-severe bleedings was very low (0.4 % [95 % CI 0.0 %–2.2 %]) among SAO-MIS patients and a single patient had intracerebral hemorrhage during DAPT. Cerebral small vessel disease has been associated with a higher risk of intracranial bleedings, especially in patients with posterior leukoaraiosis and multiple SAO-related infarcts. [27] Additionally, patients with diffuse brain small vessel-related changes often also exhibit a higher burden of cerebral microbleeds, [28] which could further enhance the risk of bleeding events, especially in the context of antithrombotics intake [29,30]. Despite SAO-MIS patients showed a higher degree of leukoaraiosis and had more frequently prior lacunar infarcts at brain MRI compared to non-SAO-MIS, the rate of major bleedings was very low within our cohort and similar between the two groups. However, it is important to note that the prevalence of microbleeds at brain MRI was similarly low in both our SAO-MIS and non-SAO-MIS cohort (6.3 % and 5.0 %, respectively). Overall, these observations may offer reassurance regarding the safety profile of DAPT in SAO-related strokes.

Strengths of our study include the multicenter prospective design and the adoption of rigorous procedures to improve the accuracy and quality of collected data, as guaranteed by regular quality check of the READAPT electronic database. Additionally, the exclusion of patients without ischemic lesion(s) at brain neuroimaging ensured more accurate definition of stroke subtypes. Conversely, the study bears some relevant limitations. Firstly, brain MRI was performed in approximately 80 % of both SAO-MIS and non-SAO-MIS patients. The remaining cases were categorized based on brain NCCT, which is less sensitive in defining stroke etiology. In particular, information on lesion(s) location was not systematically collected. Therefore, we could not evaluate whether the low rate of END observed among SAO-MIS within our cohort was influenced by a lower prevalence of capsular or subtentorial MIS, which are known to have an increased risk of early worsening. [16,17] Secondly, the appropriateness of outcome adjudication was upon local investigators and the core clinical staff did not have direct access to patient medical records. Furthermore, the primary outcome included only 90-day symptomatic vascular events, thus we cannot exclude underestimation of the overall incidence of new ischemic events (i.e., silent brain infarcts). Similarly, although brain vessels were examined in all cases, CTA/MRA were not systematically performed. Thirdly, the low number of recurrent vascular events, as well as of safety outcomes, did not allow us to identify factors associated with an increased risk of primary outcome or moderate-to-severe bleedings within our cohort. Consequently, we could not assess the impact of baseline characteristics, including brain MRI parameters, on the observed rate of these outcomes. Fourthly, patients included in our study were selected based on the therapeutic decisions made by treating physicians, which were recommended to adhere to current guidelines for secondary stroke prevention following MIS. However, we cannot rule out the possibility that some patients were not treated with DAPT when actually indicated. Moreover, this approach likely resulted in the exclusion of patients with moderate-to-severe SAO-related strokes. Fifthly, we cannot exclude that some patients started DAPT after a very early stroke recurrence which was coded in READAPT as index event; this might have reduced the number of outcome events. Sixthly, adherence to DAPT and other prescribed medications for cardiovascular comorbidities was adjudicated by local investigators relying on patients' self-reporting. As a consequence, in certain cases, this method may have not accurately reflected the actual intake of prescribed medications. Lastly, the imbalance towards the non-Hispanic white population (>95 % of our cohort) might have affected our estimates and limit the generalizability of our findings to different ethnicities.

In conclusion, our results show overall favorable short-term prognosis after SAO-MIS treated with the optimized current standard of care for secondary stroke prevention. As the vast majority of our patients received best medical care with optimal adherence, these findings may offer real-life evidence in support of current guidelines advocating for the prompt initiation of DAPT and optimization of concomitant cardiovascular treatments in all MIS patients. [9–12] Future studies should identify factors associated with the low short-term residual risk of recurrent ischemic events and investigate the long-term prognosis of patients with SAO-MIS.

Ethics

The READAPT study was approved by the Internal Review Board of the University of L'Aquila in February 2021 with the code 03/2021 and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent.

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Declaration of competing interest

Andrea Zini reports compensation from Angels Initiative, Boehringer-Ingelheim, Daiichi Sankyo for consultant services; from Angels Initiative, Boehringer-Ingelheim, CSL Behring for speaking honoraria or other education services; from Daiichi Sankyo for meeting; from Bayer, and Astra Zeneca for participation on a Data Safety, Monitoring Board or Advisory Board; and he is member of ESO guidelines, ISA-AII guidelines, and IRETAS steering committee. Raffaele Ornello reports grants from Novartis and Allergan; compensation from Teva Pharmaceutical Industries, Eli Lilly and Company, and Novartis for other services; and travel support from Teva Pharmaceutical Industries. Simona Sacco reports compensation from Novartis, NovoNordisk, Allergan, AstraZeneca, Pfizer Canada, Inc., Eli Lilly and Company, Teva Pharmaceutical Industries, H. Lundbeck A/S, and Abbott Canada for consultant services; employment by University of L'Aquila; and compensation from Novartis for other services. Maurizio Paciaroni reports compensation from Daiichi Sankyo Company, Bristol Myers Squibb, Bayer, and Pfizer Canada, Inc., for consultant services. Danilo Toni reports compensation from Alexion, Astra Zeneca, Medtronic, and Pfizer for consultant services and participation on a Data Safety, Monitoring Board or Advisory Board. The other authors report no conflicts.

Data availability

The complete dataset used for this study will be shared upon any reasonable request to the corresponding author.

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