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Characteristics and causes of recurrent ischemic events in minor ischemic stroke and TIA in the READAPT study

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ABSTRACT

Background and purpose: Understanding the causes of recurrent ischemic events in patients with minor stroke or high-risk TIA is crucial to understand unmet needs in secondary prevention. This study examines the characteristics and causes of recurrences after non-cardioembolic minor stroke/high-risk TIA in patients treated with the best medical care.

Methods: This subgroup analysis from a prospective real-world study (READAPT, NCT05476081) included patients with non-cardioembolic minor ischemic stroke (NIHSS $\leq$5) or TIA (ABCD^2 score $\geq$ 4), receiving short-term DAPT. We described the etiologic distribution according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification of the index and of the recurrent event. We analyzed baseline characteristics of patients with and without a 90-day ischemic recurrence to identify factors linked to recurrence.

Results: Out of 1641 patients, 56 (3.4 %) had a recurrent ischemic event (35 strokes and 21 TIAs). The cause of recurrences was undetermined in 21 (37.5 %), small vessel occlusion in 18 (32.1 %), large artery atherosclerosis in 11 (19.6 %), other determined in 3 (5.4 %), and cardioembolism in 3 (5.4 %). The etiologic distribution of

[1] READAPT study group: group authorship, affiliations, and list of participating centers are reported in the Supplemental table 1.

recurrent events differed from that of the corresponding index events ($p = 0.002$). Non-compliance to DAPT was more prevalent in patients with recurrences compared with those without (8.9 % vs 3.7 %, $p = 0.048$).
Conclusions: Patients with recurrences after a minor stroke or high-risk TIA have a different etiologic distribution compared with their index events. Additionally, a lower compliance to DAPT was observed in those with recurrences, suggesting that adherence to DAPT should be encouraged to optimize the outcome of patients.

1. Introduction

Minor ischemic strokes and high-risk transient ischemic attacks (TIAs) carry up to 5–10 % risk of short-term recurrence even after optimal secondary prevention [1–3]. Short-term (21–90 days) dual antiplatelet therapy (DAPT) has become the mainstay of secondary prevention for those patients with a non-cardioembolic ischemic event –alongside antihypertensive, statins, and management of cardiovascular risk factors – after the publication of randomized clinical trials [4–6] whose results translated into guideline recommendations [7,8]. However, despite adequate preventive therapy, the risk of recurrence remains substantial and further efforts are needed to improve secondary prevention of ischemic stroke. Understanding the mechanisms of recurrence could be helpful in reducing this risk. The etiology of recurrent ischemic events might also be important to evaluate the effectiveness of secondary prevention as it might determine different therapeutic approaches and could influence the risk of subsequent ischemic recurrence [2,9–12]. However, there are scarce data on the etiology of recurrent ischemic events in patients with minor ischemic stroke or high-risk TIA. Observational studies are sometimes limited to counting recurrences as components of the primary outcome [2] while the primary and secondary analyses of main RCTs on DAPT mostly focused on risk factors associated with the outcome event [13,14]. Less is known about differences in efficacy and safety of antiplatelets regimen according to etiology; only an analysis of the CHANCE-2 trial [13] comparing ticagrelor with clopidogrel showed no treatment interactions by stroke etiology.

In this study, we aimed to describe the characteristics of recurrent ischemic events after minor ischemic stroke or high-risk TIA in patients treated with the best medical care, including DAPT, and to explore the factors that may be associated with a recurrent ischemic event.

2. Methods

2.1. Study design and inclusion criteria

The present study was a pre-specified subgroup analysis of the REAl-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack (READAPT) study (NCT05476081), whose methodology was previously detailed elsewhere [15]. READAPT was an observational, prospective, multicenter, real-world study endorsed by the Italian Stroke Association (ISA-AII) and adherent to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [16].

The study was performed from February 2021 to February 2023 in 64 Italian stroke centers and included, with prior informed consent, patients with non-cardioembolic minor ischemic stroke or high-risk TIA, whether hospitalized or not, older than 18 years, receiving short-term DAPT (21–90 days) according to the best clinical practice and guidelines [7,8,17], although without strict clinical or procedural limits (in the absence of rigid entry criteria based on NIHSS or ABCD2, DAPT onset time or loading dose). Key exclusion criteria were DAPT prescription after endovascular stenting procedures and participation to interventional RCTs on stroke prevention. Patients received a 90-day follow-up visit (in-person or remote) to evaluate outcomes and adherence to the therapy. All data were collected in an electronic anonymized database created using the Research Electronic Data Capture software hosted at the University of L'Aquila and accessed through link/password or a quick response (QR) code. The investigators of the leading center—University of L'Aquila—had full access to all the data, that were checked for completeness and consistency and take responsibility for its integrity and data analysis.

In the present subgroup analysis, we only included patients meeting the criteria for minor ischemic stroke (NIHSS $\leq$5) or high-risk TIA ($ABCD^2$ score $\geq$ 4) according to the major DAPT trials [4–6]. We excluded patients not meeting those NIHSS or $ABCD^2$ threshold to obtain a population at high risk of recurrent events and who is proven to benefit from DAPT in clinical trials. We also excluded patients lost to follow-up, those with a too short follow-up (<80 days) and those who received a diagnosis of atrial fibrillation or any condition requiring anticoagulation during the follow-up.

Strokes were distinguished from TIAs according to the WHO time-based criterion, whereas events were classified as strokes if symptoms lasted >24 h and as TIAs if symptoms lasted $\leq$24 h [18]. The etiology was defined according to the TOAST classification [19], by judgment of the local trained and experienced investigator of the center, in concordance with the findings of instrumental examinations.

The description of recurrent ischemic events included: time from index event, severity at onset quantified via the NIHSS score, causes of recurrent ischemic events, ongoing DAPT at the time of the event, and other concomitant treatments. We also assessed DAPT adherence which was as proper compliance to the prescribed dose and duration during the treatment window, while DAPT discontinuation was described as a permanent and premature discontinuation (before 21 days) of the treatment.

The 90-day follow-up visit assessed adherence to treatment (dose and duration), mRS, adverse events, effectiveness and safety outcomes. For the present study, we considered as primary effectiveness outcome the recurrent cerebral ischemic events (TIAs and ischemic strokes) and their causes. Moreover, the occurrence of any outcome event—whether ischemic or hemorrhagic— ended their follow-up.

2.2. Statistical analysis

Categorical data were reported as numbers and percentages, continuous data as median and interquartile range (IQR). Categorical and continuous data were compared through the Pearson χ^2 and Mann-Whitney U tests, respectively both used to test the significance of differences between two groups. Two-sided statistical significance was set at a $p < 0.05$.

We described the characteristics of recurrent ischemic events and performed a comparison between the baseline characteristics of patients with and without those events. To compare outcomes between patients with and without a recurrence, we calculated the odds ratio (OR) for 90-day ordinal mRS score distribution with 95 % confidence interval, using an ordinal generalized linear model (GLM). The OR was adjusted for confounding factors potentially associated with ischemic stroke prognosis (age, sex, baseline mRS and NIHSS, hypertension, diabetes, DAPT loading dose, duration and compliance).

We also compared the etiology – according to the TOAST definitions – of recurrent ischemic events with those of the corresponding index events. Analyses were performed with R, version 4.4.2, and RStudio, version 2022.12.0 + 353.

3. Results

We included 1641 patients, 1080 of whom (65.8 %) were male; the median age of patients was 72 (IQR 63–79) years. The qualifying index event was a minor stroke in 1183 (72.1 %) cases and a TIA in 458 (27.9 %) cases, according to the time-based definition. Fig. 1 shows the flowchart of the selection of patients.

Overall, the index event was attributable to undetermined cause in 713 (43.4 %) patients, small vessel occlusion (SVO) in 490 (29.9 %), large-artery atherosclerosis (LAA) in 356 (21.7 %), and other determined etiology in 83 (5.1 %).

During the 90-day follow-up, we counted 56 (3.4 %) recurrent ischemic events of which 35 (62.5 %) were ischemic strokes and 21 (37.5 %) TIAs (Table 1). Thirteen events (23.2 %) occurred within 24 h of the index event, while 5 events (8.9 %) occurred between 25 h and 7 days, 10 (17.9 %) between 8 and 30 days from the index event, and 25 (50.0 %) between 31 and 90 days. Thirty-six patients (64.3 %) with a recurrent ischemic event were still on DAPT at the time of the recurrent event. Fig. 2 shows the timing of recurrent ischemic events according to the status of ongoing or discontinued DAPT. Most of the patients with a recurrent event, were taking concomitant antihypertensives (n = 49, 87.5 %), statins (n = 46, 82.1 %), and/or antidiabetic medications (n = 19, 33.9 %) at the time of the recurrence.

Recurrent ischemic events were attributable to undetermined cause in 21 (37.5 %) cases, SVO in 18 (32.1 %), LAA in 11 (19.6 %), other determined etiology in 3 (5.4 %), and cardioembolism in 3 (5.4 %).

Patients with and without ischemic recurrence had similar distribution of etiologic categories of index events (p = 0.457, Table 2). In the 56 patients with ischemic recurrences, the distribution of etiologies was different for the recurrent event as compared to the related index event (p for distribution =0.002; Fig. 3). More in detail, among recurrent events there were less strokes attributable to undetermined cause (38 % vs 52 %) and more strokes attributable to SVO (32 % vs 21 %) compared with the related index events, while the proportions of LAA and other causes were similar between the recurrent and related index events. The most frequent etiology shifts were observed from undetermined cause to SVO (n = 8) and LAA (n = 3). Three (5 %) new cardioembolic events were registered in patients who had undetermined cause (n = 2 cases) or to LAA (1 case) at the index event.

Patients who had a recurrent ischemic event, compared with those who did not, had a poorer compliance to DAPT in terms of constant drug intake and duration (8.9 % vs 3.7 %, p = 0.048) (Table 1). Patients with recurrences, compared with those without, had a worse 90-day functional outcome as shown by the ordinal mRS score distribution (OR 2.17 [95 % C.I.1.24–3.81], p = 0.006) (Fig. 4).

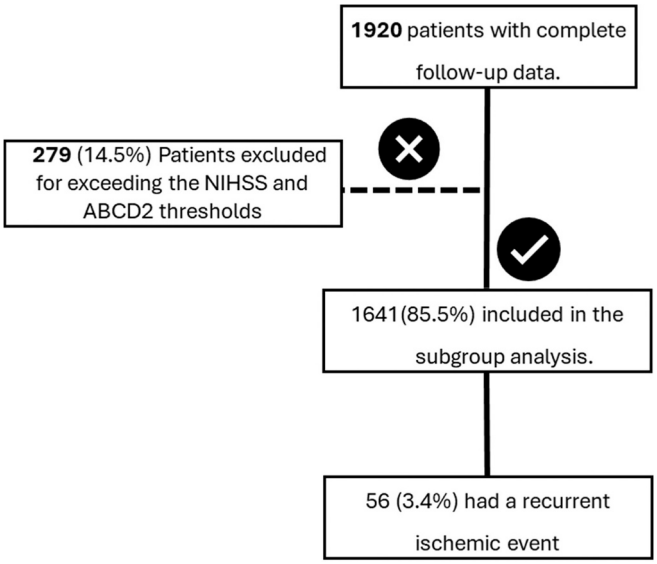

Fig. 1. Flow chart of patients' selection.

Table 1
Characteristics of recurrent ischemic events (n = 56).

Characteristics	N (%)
Symptoms duration	
≥24 h (ischemic stroke)	35 (62.5)
<24 h (TIA)	21 (37.5)
Time to recurrence	
≤24 h	13 (23.2)
25 h-7 days	5 (8.9)
8–30 days	10 (17.9)
31–60 days	16 (28.6)
61–90 days	12 (21.4)
Neuroimaging lesion(s)	
Yes	32 (57.1)
No	24 (42.9)
Symptom location	
Unknown	1 (1.8)
Right hemisphere	20 (35.7)
Left hemisphere	28 (50.0)
Posterior	5 (8.9)
Multiple	2 (3.6)
NIHSS at onset	
NIHSS ≤3	33 (58.9)
NIHSS >3 to ≤5	11 (19.6)
NIHSS>5	12 (21.4)
Cause (TOAST classification)	
LAA	11 (19.6)
SVO	18 (32.1)
Cardioembolic	3(5.4)
Other	3 (5.4)
Undetermined	21 (37.5)
ESUS	16 (28.6)
DAPT ongoing (yes)	**36 (64.0)**
Concomitant drugs	
Antihypertensives	49 (87.5)
Statins	46 (82.1)
Antidiabetics	19 (33.9)
mRS at 90 days	
0	19 (33.9)
1	15 (26.8)
2	6 (10.7)
3	7 (12.5)
4	5 (8.9)
5	3 (5.4)
6	1 (1.8)

Abbreviations. TIA: Transient ischemic attack, NIHSS: National Institutes of Health Stroke Scale, LAA: large artery atherosclerosis, SVO: small vessel occlusion, ESUS: embolic stroke of unknown source, DAPT: dual antiplatelet treatment, mRS: modified Rankin Scale.

4. Discussion

In the present subgroup analysis of patients with minor ischemic stroke and high-risk TIA from the READAPT study, we observed that patients with a recurrent ischemic event had a lower compliance to DAPT compared with those without recurrent events, in the absence of any other subgroup differences. Besides, among patients with a recurrence, we found a lack of etiologic concordance between the index event and the related recurrence.

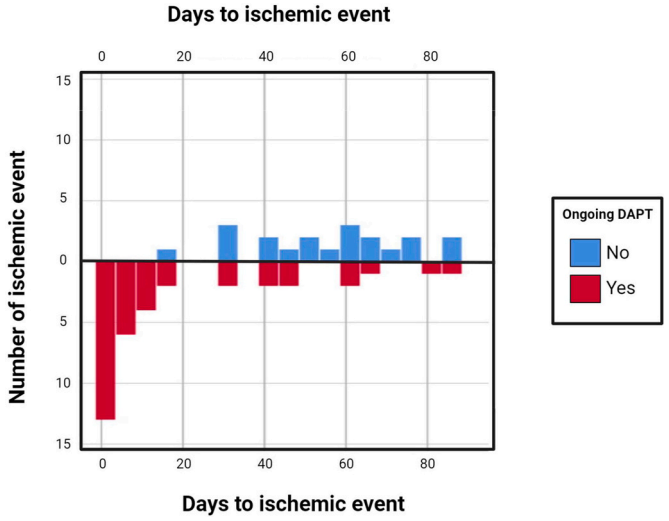

Fig. 2. Time to ischemic recurrence according to ongoing DAPT or SAPT.

Notably, the etiology of the index event did not predict the risk of short-term recurrence in our study. This finding contrasts with those coming from the general population of patients with ischemic stroke, where LAA was the stroke subtype most prone to recurrence [11]. Similarly, observational studies on TIA and minor stroke [2] and a systematic review on general stroke recurrences [10] found that stroke attributable to LAA and to cardioembolism had higher recurrence rates compared to SVO-related stroke. Referring to the population of patients with minor ischemic stroke, the CHANCE-2 study showed that stroke attributable to LAA had a higher risk of recurrence compared with other etiologies [13], while the CHANCE trial [14] showed that stroke attributable to intracranial arterial stenosis – which is LAA-related according to the TOAST classification – had higher rates of recurrences compared to stroke attributable to SVO. The lack of difference in the risk of recurrent ischemic events according to etiology in our population can be explained by the low numbers of outcome events that may preclude statistical significance. Most recurrent ischemic events occurred in almost a third of the cases within the first 7 days and within the first month in half of the cases, while most patients were still taking DAPT regimen at the time of the recurrence. Therefore, the first two weeks were the period with higher rate of recurrences, in line with previous studies on the general population of patients with ischemic stroke [20–22] and with the POINT trial [23]. The lack of DAPT loading dose might partly explain the risk for early ischemic recurrences in our study, even if we did not find differences between patients who received a loading dose of DAPT and those who did not, likely because of low numbers. Moreover, patients with recurrent ischemic events had worse functional outcomes at 90 days compared with those without recurrent ischemic events, confirming the clinical relevance of recurrent ischemic events. These elements highlight the importance of encouraging early and adequate treatment, particularly the loading dose, which is often missing, with DAPT for patients with a minor non-cardioembolic ischemic stroke or with high-risk TIA.

Patients with a recurrent ischemic event showed less adherence to the dose or duration of prescribed DAPT compared to those without recurrent events. Moreover, almost a third of patients had an ischemic recurrent event after switching from DAPT to single antiplatelet, which opens questions about the concept of optimal duration of DAPT. Low adherence to secondary prevention might therefore explain part of the ischemic recurrences in our population, in accordance with previous evidence showing that low adherence to antiplatelets, statins, and antihypertensives worsens stroke prognosis and increases risk of recurrence compared with high adherence [24,25]. However, it is well known in clinical practice that adherence to secondary prevention medication is

Table 2
Comparison of the characteristics of the population of patients with and without a recurrence.

Characteristics	Recurrent Ischemic Event		*p*-value
	Yes (n = 56)	No (*n* = 1585)	
Demographics			
Age, years, median (IQR)	73 (66–81.8)	72 (63–79)	0.206
Female, N (%)	13 (23.2)	548 (34.6)	0.078
BMI, kg/m^2, median (IQR)	26 (23–28)	26 (24–28)	0.727
Medical history			
Smoking (current), N (%)	14 (25.0)	401 (25.3)	0.638
Hypertension, N (%)	50 (89.3)	1284 (81.0)	0.119
Diabetes mellitus, N (%)	18 (32.1)	451 (28.4)	0.548
Hypercholesterolemia, N (%)	32 (57.1)	959 (60.5)	0.613
Hypertriglyceridemia, N (%)	14 (25.0)	324 (20.4)	0.407
Cancer (history or current), N (%)	7 (12.5)	200 (12.6)	0.785
Previous stroke (any), N (%)	11 (19.6)	309 (19.3)	0.959
Ischemic	11 (19.6)	297 (18.7)	0.865
Hemorragic	0 (0.0)	12 (0.8)	0.513
Previous myocardial infarction, N (%)	7 (12.5)	150 (9.5)	0.448
Use of antiplatelet prior to the index event, N (%)	30 (53.5)	659 (41.6)	0.074
Use of statins prior to index event, N (%)	20 (35.7)	506 (31.9)	0.550
Use of antihypertensives prior to index event, N (%)	44 (78.6)	1052 (66.4)	0.057
Use of antidiabetics prior to index event, N (%)	15 (26.8)	373 (23.5)	0.573
Clinical data			
Symptom duration, N (%)			0.849
≥24 h (ischemic stroke)	41 (73.2)	1142 (72.0)	
<24 h (TIA)	15 (26.8)	443 (27.9)	
Hospitalization N (%)	49 (87.5)	1464 (92.4)	0.182
Time to DAPT start, N (%)			0.121
≤24 h	43 (76.7)	1060 (66.8)	
≥25h	13 (23.2)	525 (33.1)	
DAPT loading dose, N (%)	32 (57.1)	858 (54.1)	0.657
IVT/EVT, N (%)	5 (8.9)	219 (13.8)	0.295
ABCD^2, index event median (IQR)*[1] in TIA	5 (4–5)	5 (4–6)	0.842
NIHSS index event, median (IQR)*[2] in ischemic stroke	2 (1–3.7)	2 (1–3)	0.687
Cause of the event (TOAST classification), N (%)			0.457
LAA	13 (23.2)	343 (21.6)	
SVO	12 (21.4)	478 (30.2)	
Other	2 (3.6)	80 (5.1)	
Undetermined	29 (51.8)	684 (43.1)	
Other - specified, N (%):			0.826
Dissection	1 (1.8)	18 (1.1)	
Vasculitis	0 (0.0)	2 (0.1)	
Hypercoagulable state	0 (0.0)	4 (0.3)	
Other	1 (1.8)	56 (3.5)	
Undetermined due to, N (%):			0.923
More than one cause	6 (20.7)	122 (17.8)	
Negative evaluation	10 (34.4)	249 (36.4)	
Incomplete evaluation	13 (44.8)	313 (45.7)	
Symptoms at onset, N (%)			
Motor weakness	30 (53.6)	859 (54.2)	0.516
Aphasia	6 (10.7)	192 (12.1)	0.752
Dysarthria	15 (26.8)	432 (27.2)	0.538
Sensory	10 (17.8)	300 (18.9)	0.503
Visual	4 (7.1)	73 (4.6)	0.266
Diplopia	0 (0.0)	53 (3.3)	0.154
Vertigo	3 (5.3)	93 (5.8)	0.583
Loss of balance	4 (7.1)	183 (11.5)	0.216
Monocular vision loss	0 (0.0)	10 (0.6)	0.706
ESUS*[3], N (%)	8 (14.2)	217 (13.6)	0.458
mRS score at baseline, N (%)			0.561
0	46 (82.1)	1242 (78.3)	
1	7 (12.5)	193 (12.1)	
2	0 (0.0)	81 (5.1)	
3	2 (3.6)	55 (3.5)	

(*continued on next page*)

Table 2 (*continued*)

Characteristics	Recurrent Ischemic Event		*p*-value
	Yes (n = 56)	No (*n* = 1585)	
4	1 (1.8)	11 (0.7)	
5	0 (0.0)	2 (0.1)	
Follow-up data			
DAPT compliance to prescribed dose and duration, N (%)	51 (91.1)	1526 (96.3)	**0.048**
Yes	5 (8.9)	59 (3.7)	
No			
DAPT early discontinuation (<21 days), N (%)	4 (7.1)	68 (4.3)	0.306
Cause of DAPT discontinuation, N (%)			0.456
Adverse event	0 (0.0)	18 (1.1)	
Lack of compliance	1 (1.8)	9 (0.6)	
Other	3 (5.3)	41 (2.6)	
Adverse events leading to DAPT discontinuation	0 (0.0)	5 (27.7)	
Allergic reaction	0 (0.0)	13 (72.3)	
Bleeding			
Antiplatelet prescribed after DAPT, N (%)			
ASA	28 (50.0)	993 (62.6)	0.058
Clopidogrel	25 (44.6)	561 (35.4)	
None	3 (5.3)	31 (1.9)	
DAPT >21 days, N (%)	28 (50.0)	640 (40.4)	0.150
DAPT duration – days, median (IQR)	23 (21.0–72.7)	21 (21.0–35.5)	0.385

*1: Only in patients with TIA (overall 458, respectively 15 and 443 in the two groups); *2: Only in patients with ischemic stroke (overall 1183, respectively 41 + 1142 in the two groups); *3: only in the subgroup of undetermined cause (overall 713, respectively 29 + 684).

Abbreviations. IQR: interquartile range, BMI: body mass index, TIA: transient ischemic attack, DAPT: dual antiplatelet treatment, IVT: intravenous thrombolysis, EVT: endovascular thrombectomy, NIHSS: National Institutes of Health Stroke Scale, LAA: large artery atherosclerosis, SVO: small vessel occlusion, ESUS: embolic stroke of unknown source, ASA: acetylsalicylic acid, mRS: modified Rankin Scale.

sometimes suboptimal due to missing doses and early discontinuation without medical advice [26].

A further remarkable finding of our study was a significant shift of the proportion of etiologies between the index event and the related recurrence (Fig. 3). Three of the 56 recurrent ischemic events were cardioembolic as attributable to atrial fibrillation detected during the follow-up, while the most frequent transition was from the undetermined category to SVO. Our finding highlights the possibility that etiologies of recurrent ischemic events can be different from those of index events, with consequent impact on secondary prevention strategies. Currently, however, there are no differentiated secondary prevention treatment approaches for non-cardioembolic strokes according to their etiology. Changes in etiology could be attributable not only to different pathophysiological mechanisms, but also to co-occurrence of multiple causes or to repeated or new diagnostic investigations.

We collected data from a nationwide prospective design in which treatments were prescribed according to clinical practice, which ensured the applicability of our findings to common clinical settings. However, our study also has some limitations. First, we included a relatively low number of recurrent ischemic events, potentially limiting the statistical power of our analyses, even if the overall proportion of those events was low after minor strokes or TIAs, as shown in the main analysis of the READAPT study [27]. Although the small sample size was influenced by the more stringent patient selection criteria compared with the total study cohort, we also chose to include patients undergoing acute revascularization because they had shown comparable or even better efficacy results in a previous analysis [28]. Second, some events that might have been recurrences at the time of presentation might have been coded as index events, thereby underestimating recurrent events. Third, we included almost only Caucasian patients, which limits generalizability to diverse populations. Fourth, the follow-up was limited to 90 days, therefore not capturing the risk of recurrent ischemic events in the long term. Fifth, the attribution to etiological categories was based upon the judgment and experience of local physicians participating in the READAPT study without an external validation, even if a coherence check on data was performed by the promoting center. Lastly, due to the design of the study we did not collect details on why some patients used DAPT for more than 21 days. Additionally,

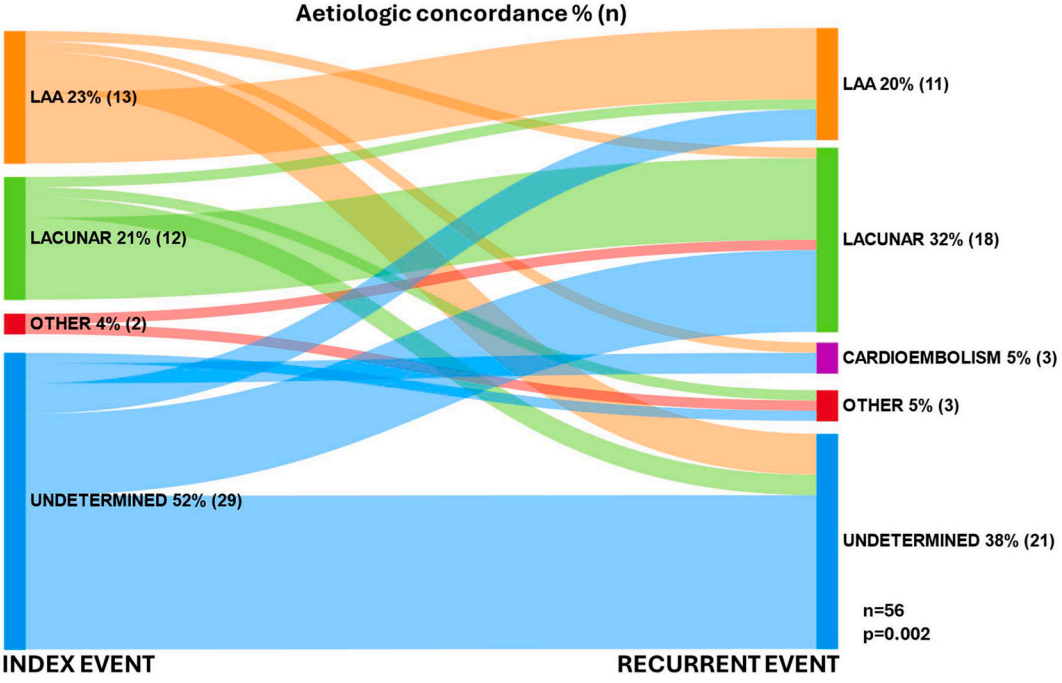

Fig. 3. Sankey diagram of the changes in etiology between the index event and the recurrent event in the 56 patients with recurrence.

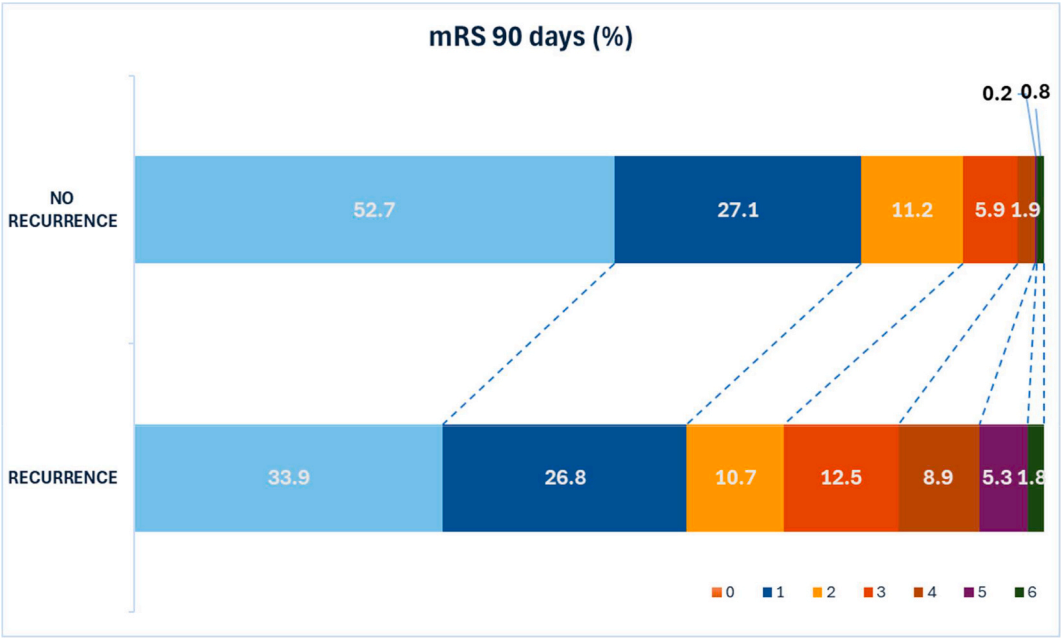

Fig. 4. Unadjusted and adjusted 90-day common OR for mRS ordinal distribution in patients with ischemic recurrence versus those without.
OR unadjusted : 2.17 [95% CI 1.24-3.81] p= 0.006.
OR adjusted*: 2.25 [95% CI 1.25-4.06] p= 0.007 *: adjusted for age, sex, baseline, mRS (modified Rankin Scale) and NIHSS (National Institutes of Health Stroke Scale), hypertension, diabetes, DAPT loading dose, duration and compliance.

patient censoring at the first outcome event may have caused an underestimation of multiple outcome events during the 90-day observation period.

5. Conclusion

In patients with minor ischemic stroke or TIA, recurrent events have a different distribution of etiologies compared with the first event, with the most evident shift from undetermined cause to SVO and LAA. Low compliance to DAPT is associated with higher risk of recurrent events. To optimize prevention of recurrent events management should not only be focused on the prescription of best medical treatment at the right loading and maintenance dose and proper duration, but also on strategies to maximize adherence to prescribed treatment in real-life settings.

Guarantor statement

Professor Simona Sacco, MD, serves as the guarantor for this manuscript. As such, she accepts full responsibility for the integrity of the work, including the data and the accuracy of its analysis, and ensures that all aspects of the manuscript adhere to the highest standards of scientific rigor and ethical conduct.

CRediT authorship contribution statement

Federico De Santis: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matteo Foschi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Michele Romoli:** Writing – review & editing, Visualization, Validation, Investigation. **Tiziana Tassinari:** Visualization, Validation, Investigation, Data curation. **Valentina Saia:** Visualization, Validation, Investigation, Data curation. **Silvia Cenciarelli:** Visualization, Validation, Investigation, Data curation. **Chiara Bedetti:** Validation, Supervision, Investigation, Data curation. **Chiara Padiglioni:** Visualization, Validation, Investigation, Data curation. **Bruno Censori:** Visualization, Validation, Investigation, Data curation. **Valentina Puglisi:** Visualization, Validation, Investigation, Data curation. **Luisa Vinciguerra:** Visualization, Validation, Investigation, Data curation. **Maria Guarino:** Visualization, Validation, Investigation, Data curation. **Valentina Barone:** Visualization, Validation, Investigation, Data curation. **Maria Luisa Zedde:** Visualization, Validation, Investigation, Data curation. **Ilaria Grisendi:** Visualization, Validation, Investigation, Data curation. **Marina Diomedi:** Visualization, Validation, Investigation, Data curation. **Maria Rosaria Bagnato:** Visualization, Validation, Investigation, Data curation. **Marco Petruzzellis:** Visualization, Validation, Investigation, Data curation. **Domenico Maria Mezzapesa:** Visualization, Validation, Investigation, Data curation. **Pietro Di Viesti:** Visualization, Validation, Investigation, Data curation. **Vincenzo Inchingolo:** Visualization, Validation, Investigation, Data curation. **Manuel Cappellari:** Visualization, Validation, Investigation, Data curation. **Mara Zenorini:** Visualization, Validation, Investigation, Data curation. **Paolo Candelaresi:** Visualization, Validation, Investigation, Data curation. **Vincenzo Andreone:** Visualization, Validation, Investigation, Data curation. **Giuseppe Rinaldi:** Visualization, Validation, Investigation, Data curation. **Alessandra Bavaro:** Visualization, Validation, Investigation, Data curation. **Anna Cavallini:** Visualization, Validation, Investigation, Data curation. **Stefan Moraru:** Visualization, Validation, Investigation, Data curation. **Pietro Querzani:** Visualization, Validation, Investigation, Data curation. **Maria Grazia Piscaglia:** Visualization, Validation, Investigation, Data curation. **Valeria Terruso:** Visualization, Validation, Investigation, Data curation. **Marina Mannino:** Visualization, Validation, Investigation, Data curation. **Umberto Scoditti:** Visualization, Validation, Investigation, Data curation. **Alessandro Pezzini:** Visualization, Validation, Investigation, Data curation. **Giovanni Frisullo:** Visualization, Validation, Investigation, Data curation. **Francesco Muscia:** Visualization, Validation, Investigation, Data curation. **Maurizio Paciaroni:** Visualization, Validation, Investigation, Data curation. **Maria Giulia Mosconi:** Visualization, Validation, Investigation, Data curation. **Andrea Zini:** Visualization, Validation, Investigation, Data curation. **Ruggiero Leone:** Visualization, Validation, Investigation, Data curation. **Carmela Palmieri:** Visualization, Validation, Investigation, Data curation. **Letizia Maria Cupini:**

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Consent to participate

All participants gave written informed consent to be enrolled in the study according to the Declaration of Helsinki.

Ethical considerations

The READAPT study received approval from the Internal Review Board of the University of L'Aquila in February 2021 (code 03/2021).

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123641.

Data availability

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

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