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**Dual antiplatelet therapy after non-cardioembolic ischemic stroke or transient ischemic attack beyond randomized controlled trials: results from the “REAL-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack”
(READAPT - NCT05476081)**

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*To the Spirit of Curiosity
a relentless light that guided my steps,
inspired my purpose,
and illuminated the darkest days,
with the hope of understanding.*

*To my family and parents,
who taught me to pursue my aims
with ambition, integrity, and determination...*

*To my grandfather Domenico,
who showed me what it means to navigate life
with serenity, strength and dignity...*

*To Maria, my beloved partner;
for her constant presence
and unwavering support
through every moment.*

“[...] Sapere aude! Habe Mut, dich deines eigenen Verstandes zu bedienen!”

(Immanuel Kant, Berlinische Monatsschrift, 1784)

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Abstract

Background and aims. Dual antiplatelet therapy (DAPT) has proven superior to monotherapy in preventing early recurrent events after minor non-cardioembolic ischemic stroke or high-risk transient ischemic attack (TIA) in randomized clinical trials (RCTs). However, the applicability of these results to broader real-world populations remains poorly characterized, particularly for patients with moderate stroke severity, diverse etiologies, acute reperfusion treatments, or complex comorbidities. We aimed to assess the real-world effectiveness and safety of early short-term DAPT in clinical scenarios extending beyond the eligibility criteria of landmark trials.

Methods: The READAPT study is a large, prospective, multicenter, observational cohort study conducted across 64 Italian stroke centers. It enrolled patients with acute non-cardioembolic ischemic stroke or TIA who were treated with short-term DAPT in routine clinical practice, regardless of stroke severity, timing, or treatment protocols. Several pre-specified analyses were performed to evaluate the effectiveness and safety of DAPT in patient populations not represented in RCTs, including individuals with (1) mild-to-moderate ischemic stroke (National Institute of Health Stroke Scale [NIHSS] 4–10), (2) strokes due to small-artery occlusion (SAO) or large-artery atherosclerosis (LAA), (3) those receiving intravenous thrombolysis, and (4) patients with cancer.

Results: In propensity-matched comparisons, DAPT was associated with improved 90-day functional outcomes and greater early neurological improvement compared to single antiplatelet therapy (SAPT) in patients with mild-to-moderate stroke, without increased risk of intracranial hemorrhage. Women with mild-to-moderate stroke, especially at younger age, had a lower 90-day risk of vascular recurrence after DAPT compared to men. Infarct location (anterior vs. posterior circulation) did not significantly influence the safety or effectiveness of DAPT, except for slightly worse 90-day functional outcomes in posterior circulation strokes. In SAO-related stroke, short-term DAPT appeared safe and potentially beneficial. Among patients with LAA, DAPT use beyond trial boundaries was common but linked to higher bleeding risks, highlighting the need for individualized assessment. DAPT following thrombolysis was safe and associated with improved 90-day functional outcomes and fewer ischemic events compared to DAPT alone, whereas in patients with active malignancy, particularly hematological cancer, it was linked to a higher risk of both ischemic and bleeding events at 90 days.

Conclusions: The READAPT study expands current knowledge on DAPT use beyond randomized trial criteria, confirming potential benefits in broader real-world populations while emphasizing the importance of careful patient selection. These findings support a more personalized approach to secondary stroke prevention with DAPT.

1. Introduction

1.1 Minor ischemic stroke and high-risk transient ischemic attack

Patients who experience a non-cardioembolic minor acute ischemic stroke (MIS) or a high-risk transient ischemic attack (TIA) are at substantial risk for early recurrent cerebrovascular events, many of which can lead to lasting disability.¹⁻³ Evidence indicates that the risk of a subsequent stroke within the first 90 days ranges from 5% to 10%, with the highest incidence occurring in the first few weeks following the index event.¹⁻³ This early vulnerability contributes significantly to overall morbidity and mortality, underscoring the need for timely and effective secondary prevention strategies.

Several population-based studies have examined the risk of ischemic recurrence following non-cardioembolic MIS or high-risk TIA, providing important insights into both short- and long-term prognosis. The Oxford Vascular Study (OXVASC) showed that the cumulative risk of recurrent ischemic stroke after MIS or TIA reaches approximately 10% at 1 week, 12% at 1 month, and 18% at 3 months, underlining the high early vulnerability of this population.⁴ Long-term follow-up from the same cohort revealed a 5-year recurrence risk exceeding 30%, particularly among individuals with large artery atherosclerosis or multiple vascular comorbidities.⁵ The Northern Manhattan Study (NOMAS)⁶ and the REasons for Geographic And Racial Differences in Stroke (REGARDS)⁷ cohort confirmed that patients with non-cardioembolic MIS or TIA remain at elevated risk even beyond the acute phase, with annual recurrence rates ranging from 2% to 4% depending on vascular risk profiles and adherence to preventive strategies. More recently, Khan et al. conducted a systematic review and meta-analysis to quantify the long-term risk of stroke after a TIA or MIS.⁸ The study included over 170,000 patients from 38 cohort studies and reported a 5-year cumulative incidence of 12.5% and a 10-year incidence of 19.8% for recurrent stroke. The annual risk was highest in the first year (5.94 events per 100 person-years) and remained stable around 1.7–1.8 per 100 person-years from the second through the tenth year of follow-up.⁸

Across all these studies, consistent predictors of ischemic recurrence include older age, hypertension, diabetes mellitus, smoking, dyslipidemia, large artery disease, and intracranial atherosclerosis.^{1-3,9} In patients with TIA, neuroimaging markers, such as acute lesions on diffusion-weighted imaging (DWI) at brain magnetic resonance imaging (MRI), significant arterial stenosis, and white matter hyperintensities (WMHs), further improve risk stratification.¹⁰⁻¹² These imaging features have been incorporated into refined prognostic tools

such as the ABCD²-I score, an extension of the original ABCD² score, which combines clinical and imaging parameters to enhance prediction of early stroke recurrence.¹³ An ABCD² score ≥ 4 or ABCD²-I score ≥ 6 are commonly used as a threshold to identify patients at high risk of early recurrence and guide urgent intervention.¹⁴ Additionally, clinical presentation with recurrent symptoms has been associated with a consistently higher short- and long-term risk ischemic stroke compared to a single TIA episode and may reflect ongoing or unstable cerebrovascular pathology.¹⁵

Recognizing these high-risk features at the time of initial evaluation is essential to tailor the intensity and timing of secondary prevention strategies, particularly during the early period of highest vulnerability. Indeed, as the risk of recurrence is greatest within the first hours to days following a high-risk TIA or minor ischemic stroke MIS, the implementation of early, intensive, and individualized secondary prevention strategies is critically important. The timely initiation of antithrombotic therapy, alongside aggressive control of modifiable vascular risk factors, is essential during this vulnerable window to effectively reduce the burden of recurrent cerebrovascular events and improve long-term clinical outcomes.^{16,17}

1.2 Antiplatelet treatment for long-term stroke prevention

1.2.1 Aspirin and Clopidogrel

Acetylsalicylic acid (ASA, aspirin), commonly known as aspirin, has long represented the cornerstone of secondary prevention after ischemic stroke. In a 2002 meta-analysis by the Antithrombotic Trialists' Collaboration, antiplatelet monotherapy, mainly with aspirin was associated with a 23% reduction in the odds of recurrent stroke in patients with a previous ischemic stroke or TIA.¹⁸ An earlier meta-analysis from 1996 had reported a more modest benefit, showing only a 13% risk reduction.¹⁹

The P2Y₁₂ receptor inhibitor clopidogrel has demonstrated a more favorable gastrointestinal safety profile compared to ASA.²⁰ However, in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, conducted among patients with prior ischemic stroke, myocardial infarction, or peripheral artery disease, clopidogrel did not significantly reduce the composite vascular risk compared to ASA.²⁰ These findings underscored the modest efficacy of antiplatelet monotherapy and stimulated interest in more potent strategies.

Encouraged by the positive results of dual antiplatelet therapy (DAPT), the combination of aspirin and clopidogrel, in patients with acute coronary syndrome (ACS) or after percutaneous

coronary intervention (PCI),^{21,22} several randomized clinical trials (RCTs) evaluated their role in secondary prevention after cerebrovascular events.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial enrolled 15,603 patients with either established atherosclerotic disease or multiple vascular risk factors.²³ Compared to ASA alone, aspirin plus clopidogrel did not significantly reduce the composite vascular outcome in the overall population (6.8% vs. 7.3%). However, a significant benefit was observed in the symptomatic subgroup, including patients with a history of ischemic stroke (6.9% vs. 7.9%).²³

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial specifically investigated aspirin plus clopidogrel in 3,020 patients with MRI-confirmed lacunar infarcts.²⁴ The study was stopped early, as DAPT failed to significantly reduce the rate of recurrent stroke (2.5% vs. 2.7% per year), while the incidence of major bleeding nearly doubled (2.1% vs. 1.1%).²⁴

The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial evaluated DAPT in 7,599 individuals with a recent non-cardioembolic ischemic stroke or TIA, plus at least one additional vascular risk factor.²⁵ Compared with clopidogrel monotherapy, aspirin plus clopidogrel did not significantly lower the composite vascular endpoint (15.7% vs. 16.7%) but significantly increased the risk of life-threatening bleeding (2.6% vs. 1.3%).²⁵ Notably, most bleeding events occurred after 3 months, suggesting that the risk of hemorrhage increases with prolonged treatment.²⁵ A methodological consideration is that the comparator was clopidogrel rather than ASA, which may have exaggerated the relative bleeding risk of DAPT.²⁵

Altogether, these trials led to the conclusion that long-term DAPT is not recommended for secondary stroke prevention and is contraindicated in patients with small vessel disease, such as those with lacunar infarction. Nevertheless, findings from the MATCH trial suggested that short-term DAPT could be beneficial in selected patients at high early risk of recurrence and low risk of bleeding, such as those with MIS or high-risk TIA.²⁵

DAPT with aspirin plus clopidogrel was also tested in patients with non-valvular atrial fibrillation (NVAf). The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial compared DAPT to warfarin in patients eligible for oral anticoagulation.²⁶ The trial was stopped early due to the clear superiority of warfarin in reducing stroke and systemic embolism.²⁶

The Atrial Fibrillation Clopidogrel Trial with Aspirin for Prevention of Vascular Events (ACTIVE-A) trial enrolled patients with NVAf who were unsuitable for anticoagulation.²⁷ Compared with ASA alone, DAPT significantly reduced the incidence of stroke (2.4% vs. 3.3% per year) and other vascular events, but at the cost of higher major bleeding rates (2.0% vs. 1.3%).²⁷

However, the development of non-vitamin K antagonist oral anticoagulants (NOACs), particularly apixaban, revolutionized stroke prevention in NVAf. In the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial, apixaban significantly reduced the risk of stroke compared to ASA, without increasing the risk of major bleeding, in patients ineligible for warfarin.²⁸

1.2.2 Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor with vasodilatory properties that, when combined with ASA, has shown efficacy in the long-term secondary prevention of non-cardioembolic stroke. However, its use is often limited by side effects such as headache and gastrointestinal discomfort.

The European Stroke Prevention Study (ESPS), a multicenter trial conducted between 1979 and 1985, evaluated the combination of ASA with short-acting dipyridamole 75 mg three times daily, demonstrating a 37.5% relative risk reduction in recurrent stroke compared to placebo.²⁹ Its successor, ESPS-2 (Second European Stroke Prevention Study), compared to aspirin alone, extended-release dipyridamole alone (200 mg twice daily), the combination (aspirin plus dipyridamole), and placebo.³⁰ Both agents reduced stroke risk individually, with additive benefit for the combination, achieving a 23% relative risk reduction versus aspirin monotherapy.³⁰

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), conducted between 1997 and 2005, further confirmed a 20% hazard reduction in the composite outcome of vascular events with long-term aspirin plus dipyridamole compared to aspirin alone, though the benefit became evident only after approximately 2 years of treatment.³¹

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial enrolled 20,000+ patients with recent non-cardioembolic ischemic stroke and compared aspirin plus dipyridamole with clopidogrel monotherapy over a mean follow-up of 2.5 years.³² Recurrent stroke rates were virtually identical (~9% vs. ~8.8%), but the combination was associated with

a higher rate of major hemorrhage (4.1% vs. 3.6%) and more frequent treatment discontinuation due to side effects.³²

1.2.3 Cilostazol

Cilostazol, a selective inhibitor of platelet cyclic AMP phosphodiesterase type 3 (PDE3), exerts both antiplatelet and vasodilatory effects and is approved in several East Asian countries for secondary stroke prevention. Compared to ASA, it offers comparable, or slightly superior, efficacy with a significantly lower risk of bleeding, making it a promising option for long-term DAPT. Like dipyridamole, cilostazol is frequently associated with headache, dizziness, and gastrointestinal symptoms. To improve tolerability, gradual dose escalation and symptomatic management of side effects are advised.

In the Add-on Cilostazol vs. Aspirin Alone in Acute Non-cardioembolic Stroke (ADS) trial, conducted in Japan from 2011 to 2017, the early combination of ASA and cilostazol (initiated within 48 hours of stroke onset) did not improve 14-day stroke progression or 3-month functional outcomes compared to ASA alone.³³

In contrast, the Cilostazol Stroke Prevention Study for Combination Therapy (CSPS.com) trial enrolled high-risk patients with MRI-confirmed non-cardioembolic stroke and multiple vascular risk factors or significant ($\geq 50\%$) extra- or intracranial stenosis.³⁴ Participants were randomized to cilostazol added to ASA or CLO, versus monotherapy. Despite early trial termination due to slow enrollment (1884/4000 patients), combination therapy halved the annual risk of ischemic stroke (2.2% vs. 4.5%) without increasing major bleeding.³⁴ However, 10% discontinued treatment due to headache, confirming tolerability as a key limitation.

1.3 Dual antiplatelet therapy for the short-term treatment of non-cardioembolic minor stroke and high-risk TIA

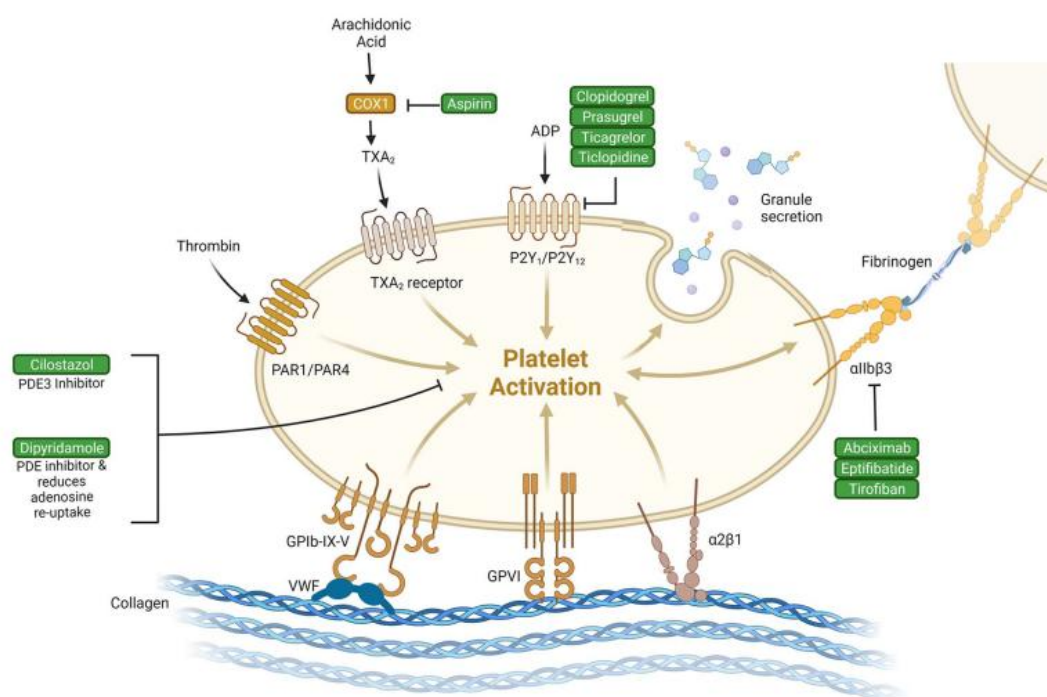
The rationale for the early use of DAPT, specifically aspirin plus clopidogrel, in patients with MIS or high-risk TIA is based on both the clinical urgency of preventing early recurrence and the complementary pharmacodynamic properties of the two agents. **Figure 1**

The first hours to days after a non-cardioembolic cerebrovascular event represent a phase of heightened thrombotic risk, characterized by intense platelet activation, inflammation, and endothelial dysfunction.³⁵ Recurrent ischemic events tend to cluster in this early period, making it a critical therapeutic window.¹⁻⁴

From a pharmacodynamic standpoint, ASA and clopidogrel act on distinct but synergistic pathways of platelet aggregation:

- ASA irreversibly inhibits cyclooxygenase-1 (COX-1), blocking the synthesis of thromboxane A₂ (TXA₂), a potent vasoconstrictor and promoter of platelet aggregation.³⁶ Although ASA's antiplatelet effect begins at low doses, maximum inhibition of COX activity typically requires more than 24 hours, particularly in patients with severe endothelial dysfunction, such as those with advanced atherosclerosis.³⁶ In fact, residual TXA₂ activity can be demonstrated in up to 20% of treated individuals.³⁶
- Clopidogrel, a prodrug, requires hepatic activation via cytochrome P450 (CYP450) enzymes to generate its active metabolite, which irreversibly inhibits the P2Y₁₂ ADP receptor on the platelet surface. With standard dosing (75 mg daily), measurable platelet inhibition is usually achieved only after an average of 4 days, with variability extending up to 7 days. However, loading doses can substantially accelerate onset: 300 mg: effect within ~6 hours; 600 mg: onset reduced to ~2 hours.³⁶

Figure 1. Antiplatelet agents and their mechanisms of action on the platelet.



Abbreviations. ADP: adenosine diphosphate; COX: cyclo-oxygenase; TXA₂: thromboxane A₂. This figure highlights how the multiple sites of action may contribute to the increased efficacy when certain antiplatelet agents are combined. (Figure from Kamarova M, et al. Antiplatelet Use in Ischemic Stroke. Ann Pharmacother. 2022;56(10):1159-1173. doi: 10.1177/10600280211073009).

1.3.1 Evidence predating short-term dual antiplatelet therapy landmark trials

The Early use of eXisting Preventive Strategies for Stroke (EXPRESS) study, conducted in Oxford, was a before-and-after observational analysis (2002–2004 vs. 2004–2007) evaluating the effect of implementing a same-day TIA clinic.² Similarly, the Service d'Accueil des Accidents Vasculaires Cérébraux Transitoires (SOS-TIA), assessed outcomes in patients referred to a 24-hour dedicated TIA clinic within the emergency department.³⁷ Both studies demonstrated substantial reductions in 90-day recurrent stroke rates, compared either to historical controls (EXPRESS)² or to predicted risk based on ABCD² scores (SOS-TIA),³⁷ underscoring the benefit of urgent specialist evaluation and early secondary prevention. DAPT with ASA plus clopidogrel may have contributed to the favorable outcomes in these cohorts.

The Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) pilot trial tested the combination of ASA plus clopidogrel versus ASA alone in 392 patients with TIA or MIS.³⁸ While the combination group experienced a non-significant reduction in stroke recurrence at 90 days (7.1% vs. 10.8%), the incidence of symptomatic intracranial hemorrhage was 3%, raising concerns about safety and reinforcing the need for larger, definitive trials.³⁸

1.3.2 Overview of short-term dual antiplatelet therapy landmark trials

➤ Aspirin + Clopidogrel

The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, conducted in China between 2009 and 2012, randomized 5,170 patients who had experienced either a minor ischemic stroke, defined by a National Institutes of Health Stroke Scale (NIHSS) score of 3 or less, or a high-risk TIA (ABCD² score ≥ 4) within 24 hours of symptom onset.³⁹ Participants were assigned to receive DAPT with aspirin plus clopidogrel for the first 21 days followed by clopidogrel monotherapy until day 90, or aspirin monotherapy for 90 days.³⁹ The DAPT regimen resulted in a significant reduction in 90-day stroke recurrence (8.2% vs. 11.7%) with no difference in moderate or severe bleeding or in the rate of hemorrhagic stroke, which remained at 0.3% in both groups.³⁹

The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, conducted internationally from 2010 to 2018, evaluated a similar strategy in 4,881 patients with minor stroke or high-risk TIA, but within a shorter window of 12 hours from symptom onset.⁴⁰ Patients were randomized to receive either aspirin plus clopidogrel or aspirin alone for 90 days.⁴⁰ The DAPT group experienced significant reductions in both the composite vascular

endpoint (5.0% vs. 6.5%) and stroke recurrence (4.8% vs. 6.4%) at 90 days.⁴⁰ However, these benefits were accompanied by a higher rate of major bleeding in the DAPT arm (0.9% vs. 0.4%).⁴⁰

➤ *Aspirin + Ticagrelor*

Ticagrelor, a potent and direct-acting P2Y₁₂ receptor antagonist, offers faster and more consistent platelet inhibition compared to clopidogrel, which requires metabolic activation via hepatic enzymes. The efficacy of ticagrelor was evaluated in the Study of Ticagrelor versus Aspirin in Acute Stroke or TIA (SOCRATES) trial, which enrolled patients within 24 hours of symptom onset after a MIS (NIHSS ≤5) or high-risk TIA (ABCD² ≥4 or symptomatic extracranial/intracranial stenosis).⁴¹ Participants were randomized to receive either ticagrelor or aspirin monotherapy for 90 days.⁴¹ Although the trial did not meet its primary endpoint, non-significant reductions were observed in both the composite vascular outcome (6.7% vs. 7.5%) and the rate of ischemic stroke (5.8% vs. 6.7%).⁴¹ Notably, a prespecified subgroup analysis revealed a more pronounced benefit in patients who were already on aspirin prior to enrollment (6.5% vs. 8.4%), suggesting that DAPT with aspirin plus ticagrelor may offer enhanced efficacy in selected populations.⁴²

This hypothesis was further tested in the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial, which randomized 11,016 patients with minor stroke (NIHSS ≤5) or high-risk TIA (ABCD² ≥6 or symptomatic extra/intracranial stenosis) to receive either aspirin plus ticagrelor or aspirin alone for 30 days.⁴³ DAPT significantly reduced the composite risk of stroke or death at 30 days (5.5% vs. 6.6%) but was also associated with a higher rate of severe bleeding (0.5% vs. 0.1%).⁴³ A subgroup analysis focusing on patients with ipsilateral large artery atherosclerosis (LAA), defined as stenosis ≥30%, identified this population as being at higher baseline risk for recurrence.⁴⁴ In this group, DAPT yielded a greater reduction in stroke or death (8.1% vs. 10.9%), although no statistically significant interaction between treatment effect and LAA status was found.⁴⁴

➤ *Aspirin + Ticagrelor in individuals carrying loss-of-function alleles in the CYP2C19 gene*

Given that clopidogrel is a prodrug that requires hepatic bioactivation by CYP enzymes, particularly CYP2C19, to exert its antiplatelet effects, individuals carrying loss-of-function (LOF) alleles in the CYP2C19 gene exhibit impaired metabolic activation of clopidogrel, which

may lead to reduced efficacy of clopidogrel-based antiplatelet therapy. This pharmacogenetic interaction was explored in a genetic substudy of the CHANCE trial, in which 2,933 Chinese patients were genotyped: 58.8% were identified as LOF allele carriers.⁴⁵ In this subgroup, DAPT with aspirin and clopidogrel did not significantly reduce the rate of recurrent stroke compared to aspirin monotherapy (9.4% vs. 10.8%). Conversely, non-carriers experienced a significant benefit from DAPT (6.7% vs. 12.4%).⁴⁵

Building on these findings, the Platelet Reactivity in CYP2C19 LOF Carriers and Non-Carriers (PRINCE) trial, a phase II study conducted in China from 2015 to 2017, assessed whether ticagrelor could offer superior platelet inhibition in comparison to clopidogrel in patients with MIS or TIA.⁴⁶ A total of 650 patients were enrolled within 24 hours of symptom onset, with both treatment arms receiving aspirin for the first 21 days.⁴⁶ Overall, high on-treatment platelet reactivity at 90 days was observed significantly less frequently in patients treated with ticagrelor (12.5%) than in those treated with clopidogrel (29.7%).⁴⁶ Among CYP2C19 LOF allele carriers, this difference was even more pronounced (10.8% vs. 35.4%), suggesting that ticagrelor may overcome the metabolic limitations of clopidogrel in this population.⁴⁶

These observations laid the groundwork for CHANCE-2, a multicenter randomized trial conducted from 2019 to 2021, which directly compared DAPT with ticagrelor versus clopidogrel in CYP2C19 LOF allele carriers.⁴⁷ Following screening of 11,255 Chinese patients with minor stroke (NIHSS ≤ 3) or high-risk TIA (ABCD² ≥ 4), a total of 6,412 genetically confirmed carriers were enrolled. Participants received a 21-day course of DAPT (aspirin plus either ticagrelor or clopidogrel), followed by monotherapy with the same P2Y₁₂ inhibitor through day 90.⁴⁷ Genotyping was performed rapidly at the point of care, with a median turnaround time of 85 minutes, allowing for timely therapeutic decisions.⁴⁷ The trial demonstrated a significant reduction in 90-day stroke recurrence in the ticagrelor group (6.0% vs. 7.6%), with no difference in the rate of moderate or severe bleeding (0.3% in both arms), supporting the role of ticagrelor as a more effective alternative in genetically at-risk individuals.⁴⁷

1.3.3 Dual antiplatelet therapy duration: the 3-week rule

The duration of DAPT with aspirin and clopidogrel was 21 days in the CHANCE trial³⁹ and 90 days in the POINT trial.⁴⁰ However, the benefit of DAPT over aspirin monotherapy varied over time. A meta-analysis of the FASTER,³⁸ CHANCE,³⁹ and POINT⁴⁰ trials demonstrated that most of the protective effect of DAPT occurred within the first 10 days after randomization.⁴⁸

A patient-level meta-analysis of CHANCE³⁹ and POINT⁴⁰ further confirmed that the greatest benefit was observed within the initial 21 days.⁴⁹

A detailed time-course analysis showed that during the first 21 days—when both CHANCE³⁹ and POINT⁴⁰ prescribed clopidogrel plus aspirin in the DAPT arm—DAPT significantly reduced the risk of major ischemic events compared to aspirin alone (5.2% vs 7.8%; adjusted HR 0.66, 95% CI 0.56–0.77; $p < 0.001$).⁴⁹ Notably, most of this benefit was concentrated in the first 10 days.⁴⁹ In contrast, from day 22 to day 90, when CHANCE³⁹ continued with clopidogrel alone and POINT⁴⁰ maintained DAPT, no significant difference in ischemic event rates was found between the groups (1.4% vs 1.5%; adjusted HR 0.94, 95% CI 0.67–1.32; $p = 0.72$), suggesting a diminishing marginal benefit of prolonged DAPT beyond the first few weeks.⁴⁹

Further meta-analyses that included short-term trials (e.g., CHANCE,³⁹ POINT⁴⁰) and long-term trials (e.g., SPS3,²⁴ CHARISMA²³) revealed that short-term DAPT (up to 1 month) was associated with significant reductions in ischemic stroke and vascular events.⁵⁰ Intermediate-term DAPT (up to 3 months) maintained this benefit. In contrast, long-term DAPT (>3 months) was associated with increased risks of major bleeding and mortality without significant benefit in preventing ischemic events.⁵⁰

Based on these findings, current international guidelines generally recommend a 3-week course of DAPT with aspirin and clopidogrel for eligible patients (quality of evidence: GRADE $\oplus\oplus\oplus\oplus$, strength of recommendation: $\uparrow\uparrow$).^{16,17} In selected cases, such as those with progressive or recurrent stroke/TIA or symptomatic severe intracranial stenosis, DAPT may be extended up to 90 days, provided that the potential benefits outweigh the risks following careful clinical evaluation.^{16,17}

1.3.4 The boundaries of short-term dual antiplatelet therapy landmark trials

The inclusion and exclusion criteria across the main randomized controlled trials evaluating DAPT in MIS or TIA, namely CHANCE,³⁹ POINT,⁴⁰ and THALES,⁴³ were notably heterogeneous, reflecting differences in target populations, risk stratification strategies, and trial designs.

In terms of age criteria, CHANCE³⁹ and THALES⁴³ required participants to be ≥ 40 years old, while POINT allowed inclusion from 18 years of age, thereby encompassing a broader and younger population. The NIHSS threshold also varied slightly: both CHANCE³⁹ and POINT⁴⁰

restricted inclusion to patients with NIHSS scores ≤ 3 , while THALES⁴³ allowed inclusion of patients with slightly more severe strokes, with NIHSS scores up to ≤ 5 .

Regarding stroke risk stratification, all trials used the ABCD² score, but with differing cut-offs. CHANCE³⁹ and POINT⁴⁰ included patients with scores ≥ 4 , whereas THALES selected patients with higher baseline risk, requiring an ABCD² score of ≥ 6 or the presence of symptomatic arterial stenosis $\geq 60\%$, thereby focusing on patients with higher recurrence potential.

The time window for DAPT initiation was also variable: ≤ 24 hours in CHANCE³⁹ and THALES,⁴³ and ≤ 12 hours in POINT,⁴⁰ which may have implications for treatment efficacy and feasibility in real-world settings.

Exclusion criteria further underline the heterogeneity across studies. All three trials^{39,40,43} excluded patients with intravenous thrombolysis, endovascular thrombectomy, carotid endarterectomy and history of non-traumatic intracerebral hemorrhage (ICH). CHANCE³⁹ also excluded patients with specific stroke syndromes (e.g., isolated sensory symptoms or isolated visual field deficits), Modified Rankin Scale (mRS) score ≥ 2 , stroke due to procedure-related causes. In contrast, POINT⁴⁰ and THALES⁴³ did not explicitly exclude patients based on stroke symptoms or mRS, possibly allowing for broader inclusion, though their designs did not necessarily focus on post-procedural strokes.

Overall, this heterogeneity in inclusion/exclusion criteria across landmark trials (**Table 1**) reflects differences in clinical priorities, populations studied, and definitions of "high risk," which should be considered when translating trial findings into clinical practice.

Table 1. Main inclusion and exclusion criteria of dual antiplatelet therapy landmark trials.

	CHANCE (2013) ³⁹	POINT (2018) ⁴⁰	THALES (2020) ⁴³
Main inclusion criteria			
<i>Age, years</i>	≥ 40	≥ 18	≥ 40
<i>NIHSS score</i>	≤ 3	≤ 3	≤ 5
<i>ABCD₂ score</i>	≥ 4	≥ 4	≥ 6 or symptomatic arterial stenosis ($\geq 60\%$)
<i>Time to DAPT start</i>	$\leq 24\text{h}$	$\leq 12\text{h}$	$\leq 24\text{h}$
Main exclusion criteria			

<i>Specific stroke symptoms^a</i>	X	-	-
<i>mRS_{≥2}</i>	X	-	-
<i>Intravenous thrombolysis</i>	X	X	X
<i>Endovascular thrombectomy</i>	X	X	X
<i>Carotid endarterectomy</i>	X	X	X
<i>History of non-traumatic ICH</i>	X	X	X
<i>Ischemic event caused by procedure</i>	X	-	-

Abbreviations. DAPT: dual antiplatelet therapy; ICH: intracranial hemorrhage; mRS: modified Rankin scale score; NIHSS: National Institute of Health Stroke Scale score; a: Isolated or pure sensory symptoms, visual changes, or dizziness/vertigo without evidence of acute infarction.

1.4 Dual antiplatelet therapy versus intravenous thrombolysis for patients with acute minor or minor non-disabling ischemic stroke

The role of intravenous thrombolysis in patients with minor or minor non-disabling ischemic stroke has been increasingly questioned in light of recent clinical trials and real-world data. The Potential of rt-PA for Ischemic Strokes with Mild Symptoms (PRISMS) trial, conducted between 2014 and 2017, enrolled 313 patients presenting within 3 hours of symptom onset and a NIHSS score between 0 and 5.⁵¹ Participants were randomized to receive either intravenous alteplase or aspirin 325 mg.⁵¹ The study found no significant difference in functional outcomes at 90 days between the two groups, while symptomatic intracerebral hemorrhage (sICH) occurred more frequently in the alteplase arm, raising safety concerns about thrombolysis in this subgroup.⁵¹

Building on these findings, the Aspirin and Clopidogrel vs. Alteplase in Minor Ischemic Stroke (ARAMIS) trial investigated whether DAPT could offer a safer and equally effective alternative.⁵² In this Chinese multicenter study, 760 patients with NIHSS ≤ 5 and non-disabling symptoms (absence of disabling deficits such as complete hemianopia, severe aphasia, significant motor weakness as defined as ≥ 2 points in NIHSS motor items, or any clinical deficit that, in the judgment of the treating physician, would lead to significant long-term disability without thrombolysis), were randomized to receive either DAPT for 12 days (aspirin plus clopidogrel with a 300 mg loading dose), or intravenous alteplase followed by standard

care.⁵² At 90 days, DAPT was found to be non-inferior to thrombolysis for achieving excellent functional outcomes, suggesting that thrombolysis may not provide additional benefit over antiplatelet therapy in this population.⁵²

Further supporting these findings, a retrospective cohort study conducted across Austrian stroke units evaluated outcomes in acute ischemic stroke patients with NIHSS ≤ 3 , comparing those treated with alteplase versus those receiving DAPT.⁵³ After propensity score matching to adjust for baseline differences, patients treated with alteplase showed higher rates of sICH and early neurological deterioration compared to those managed with DAPT, reinforcing concerns regarding the risk-benefit profile of thrombolysis in minor stroke.⁵³

The recently published Tenecteplase in Stroke Patients With Minor Symptoms and Proven Occlusion (TEMPO-2) randomized trial enrolled 886 patients from 48 hospitals across 10 countries, comparing intravenous tenecteplase (0.25 mg/kg) to standard non-thrombolytic care (early short-term DAPT), with treatment initiated within 12 hours from stroke onset.⁵⁴ The primary outcome, return to baseline function at 90 days, was achieved in 72% of patients in the tenecteplase group versus 75% in the control group, showing no significant benefit of thrombolysis (RR 0.96; 95% CI 0.88–1.04).⁵⁴ Furthermore, tenecteplase was associated with a significantly higher mortality rate (5% vs. 1%; HR 3.8; 95% CI 1.4–10.2) and a numerically greater risk of symptomatic intracranial hemorrhage (2% vs. <1%). The trial was terminated early due to futility, and its findings strongly question the utility and safety of intravenous thrombolysis with tenecteplase in this subset of minor stroke patients.⁵⁴

Collectively, these data suggest that in patients with non-disabling or minor ischemic stroke, DAPT may offer a safer and equally effective alternative to intravenous thrombolysis, particularly in those with low NIHSS scores and absent large vessel occlusion.

1.5 Dual antiplatelet therapy after mild-to-moderate ischemic stroke

Recent data have shown potential benefit from early short-term DAPT also in patients with mild-to-moderate (NIHSS of up to 10) ischemic stroke.⁵⁵ The Aspirin and Ticagrelor vs. Aspirin and Clopidogrel in Moderate Ischemic Stroke (ATAMIS) randomized clinical trial, conducted in China between 2014 and 2023, enrolled 2,915 patients with acute non-cardioembolic ischemic stroke and NIHSS scores between 4 and 10, within 48 hours of symptom onset.⁵⁵ Participants were randomized to receive either aspirin plus clopidogrel (with

a 300 mg loading dose of clopidogrel) or ASA alone for 90 days.⁵⁵ The primary outcome, defined as early neurological deterioration at 7 days, occurred in significantly fewer patients in the DAPT group (4.8% vs. 6.7%; absolute risk reduction -1.9%).⁵⁵ Although there was no statistically significant difference in 90-day excellent functional outcomes (mRS 0–1: 76.9% vs. 74.6%) nor in the rate of 90-day ischemic stroke recurrences (0.7% vs. 0.8%), DAPT was not associated with increased risks of major bleeding or symptomatic intracranial hemorrhage, which remained low in both groups (0.1%).⁵⁵

1.6 Dual antiplatelet therapy in specific etiological subtypes

➤ *Small-artery occlusion*

Patients with stroke related to small-artery occlusion (SAO), also referred to as lacunar subtype, have traditionally been excluded from long-term DAPT with aspirin plus clopidogrel due to a heightened risk of bleeding. This concern was underscored by the SPS3 trial,²⁴ which demonstrated no added benefit from prolonged DAPT and nearly doubled rates of major hemorrhagic events in this population. However, emerging evidence indicates that short-term DAPT may be both safe and effective in selected patients with lacunar stroke.

Although neither the CHANCE³⁹ nor POINT⁴⁰ trials explicitly stratified participants by stroke subtype, both included individuals with minor ischemic stroke (NIHSS score ≤ 3), a group that likely encompassed many with lacunar infarcts. In these trials, the duration of DAPT was limited to 21 days, a strategy that may minimize bleeding complications typically associated with extended therapy.^{39,40} These findings support a more nuanced approach, suggesting that short-term DAPT could be a viable option for patients with SAO-related stroke, particularly if administered early.

Further supporting this approach, a retrospective hospital-based study conducted in Heidelberg between 2010 and 2017 evaluated outcomes in SAO-related stroke patients who experienced early neurological deterioration.⁵⁶ The majority were treated with short-course DAPT (typically for 5 days), and the results suggested improved outcomes compared to standard therapy.⁵⁶ These findings indicate that patients with lacunar stroke, particularly those presenting with mild deficits (NIHSS ≤ 3), should not be categorically excluded from consideration for early DAPT, especially when early deterioration is observed.

➤ *Large-artery-atherosclerosis*

The Initiation of Dual Antiplatelet Therapy in Minor Stroke and Transient Ischemic Attack Patients With Intracranial or Extracranial Artery Stenosis) INSPIRES trial was a large, multicenter, randomized controlled trial conducted in China between 2018 and 2023.⁵⁷ It enrolled 6100 patients who presented within 72 hours of symptom onset with either a minor ischemic stroke (defined as NIHSS ≤ 5) or a high-risk TIA (ABCD² score ≥ 4), all of whom had symptomatic extracranial or intracranial LAA.⁵⁷ Participants were randomly assigned to receive either DAPT with aspirin plus clopidogrel for the initial 21 days followed by clopidogrel monotherapy from day 22 to day 90, or ASA monotherapy for 90 days.⁵⁷ Notably, the trial population had a high burden of atherosclerosis: 82% of participants had $\geq 50\%$ symptomatic arterial stenosis, and the majority (87%) were enrolled in a delayed time window of 24 to 72 hours after symptom onset,⁵⁷ which differs from earlier DAPT trials like CHANCE³⁹ and POINT,⁴⁰ where most patients were treated within 12 to 24 hours. The results demonstrated that DAPT significantly reduced the risk of recurrent stroke at 90 days (7.3% vs. 9.2%).⁵⁷ However, this benefit came at the cost of a significantly higher rate of moderate to severe bleeding (0.9% vs. 0.4%), underscoring the importance of individualized risk-benefit assessment when considering DAPT in this etiological subtype.⁵⁷

1.7 The REAL-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack (READAPT)

The Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack – READAPT - study (NCT05476081) is an observational prospective multicenter real-world investigation coordinated by the University of L'Aquila and supported by the Italian Stroke Association – Associazione Italiana Ictus (ISA-AAII). The study received approval from the Internal Review Board of the University of L'Aquila in February 2021 (code 03/2021) and all patients gave written informed consent for being included in the study. Patients were recruited across 64 Italian Stroke centers from February 1st, 2021, to February 28th, 2023.

The READAPT study enrolled all individuals aged ≥ 18 years, whether hospitalized or not, who suffered from acute non-cardioembolic stroke or TIA and received a brief course (i.e., up to 90 days) of DAPT irrespective of the time elapsed from symptoms onset and from stroke severity. All patients consecutively admitted to hospitals and emergency departments and assessed in open-access outpatient clinics for neurological emergency were recruited for the READAPT

study. The diagnosis of the index stroke or TIA was adjudicated by investigators as per local practice and according to the criteria of the World Health Organization (WHO).⁵⁸ Apart from diagnosis of acute non-cardioembolic stroke or TIA, no other criteria were provided to guide patient enrollment. Patients were considered eligible irrespective of the time elapsed between symptoms onset and DAPT initiation, as well as the specific antiplatelet combination used. Additionally, patients were included regardless of whether a loading DAPT dose (≥ 300 mg for aspirin and clopidogrel, or ≥ 180 mg for ticagrelor) was administered. The exclusion criteria were involvement in interventional randomized controlled trials at the onset of stroke, continuous DAPT for endovascular stenting procedures, and conditions that could potentially impact compliance with the study protocols. Patients were enrolled shortly after the index event and followed up for 90 ± 10 days, with local investigators conducting face-to-face or remote visits at the end of the follow-up period.

A baseline case report form was utilized to gather data on patients' demographics, vascular risk factors, pre-event treatments, NIHSS and ABCD² scores, mRS scores before and after the event, time to initiation of DAPT, treatment regimen, concurrent therapies, neuroimaging findings, and etiology of the index event based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.⁵⁹ Information on acute interventions, such as thrombolysis, thrombectomy, and endarterectomy, was also recorded.

All data were entered into an anonymized electronic database created using Research Electronic Data Capture (REDCap) software, hosted by the University of L'Aquila. Access was provided via a secure link, password, or QR code. Study staff conducted remote monitoring of participating centers, promoted patient enrollment, and distributed regular newsletters to update sites on study progress. Weekly quality checks were performed, and data queries were routinely issued to ensure data accuracy and follow-up completeness. Cases were excluded if any of the following mandatory variables were missing or incorrect: age, NIHSS score, ABCD² score, thrombolysis, thrombectomy, endarterectomy, DAPT loading dose, time to DAPT initiation, mRS score, prior ICH, or procedure-related index event.

Investigators at the coordinating center, the University of L'Aquila, had full access to the dataset and were responsible for ensuring its accuracy and conducting data analyses.

Main centers contributing data to the READAPT study are listed in **Table 2**.



Table 2. Main centers contributing data to the READAPT study.

City	Site
Alessandria	Stroke Unit-Department of Neurology, SS. Biagio e Arrigo
Ancona	Experimental Medicine and clinical Department-Marche Polytechnic University
Ancona	Department of Neurology INRCA
Avezzano	Neurology Unit, S.Filippo and Nicola Hospital
Bari	Department of Neurology and Stroke Unit- "F. Puca" AOU Consorziato Policlinico
Barletta	Department of Neurology and Stroke Unit, "M. R. Dimiccoli" General Hospital, Barletta, ASL BT, Italy
Bologna	IRCCS Istituto delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center-Maggiore Hospital
Bologna	IRCCS Ospedale S.Orsola-Malpighi
Cesena	Department of Neurology and Stroke Unit-Bufalini Hospital
Chieti	Clinics of Neurology, Stroke Unit, ospedale SS Annunziata, Stroke Unit Ospedale SS Annunziata
Città di Castello	Department of Neurology-Città di Castello Hospital
Crema	Department of Cardiocerebrovascular diseases; Neurology-Stroke Unit-ASST Ospedale Maggiore di Crema
Cremona	Department of Neurology-ASST Cremona Hospital
Fermo	Department of Neurology-Fermo Hospital
Florence	Stroke Unit-Careggi University Hospital
Florence	Internal Medicine, San Giovanni di Dio Hospital
Genoa	Neuroscience, IRCCS Ospedale Policlinico San Martino
L'Aquila	Neurology Unit-University of L'Aquila-San Salvatore Hospital
Legnano	Department of Neurology - ASST-Ovest Milanese
Lecce	Department of Neurology-Vito Fazi Hospital
Lucca	Unit of Neurology-San Luca Hospital
Mirano-Venice	Department of Neurology- ULSS 3 Serenissima
Monza	Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori Monza
Naples	Department of Neurology and Stroke Unit, AORN Antonio Cardarelli
Novara	SCDU Neurologia - Stroke Unit, Azienda Ospedaliero-Universitaria "Maggiore
Novi Ligure	Department of Neurology-San Giacomo Hospital
Parma	Department of Medicine and Surgery, University of Parma, Stroke Care Program, Department of Emergency, Parma University Hospital
Pescara	Stroke Unit -"S.Spirito" Hospital
Pistoia	Department of Neurology-San Jacopo Hospital
Ravenna	Department of Neuroscience, Neurology Unit, S.Maria delle Croci Hospital
Reggio Emilia	Department of Neurology, AUSL-IRCCS di Reggio Emilia
Rimini	Neurology Unit, "Infermi" Hospital, AUSL Romagna
Rome	Department of Neurology -San'Andrea Hospital
Rome	Department of Systems Medicine-Tor Vergata University Hospital
Rome	Department of Neurology and Stroke Unit- S. Eugenio Hospital
Rome	Stroke Unit, Azienda Ospedaliera San Camillo,
Rome	Stroke Unit, Emergency Department, Policlinico Umberto I Hospital, Rome, Italy
Rome	Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli
San Benedetto del Tronto	UOC Neurologia, Ospedale "Madonna del Soccorso"
San Giovanni Rotondo	Department of Neurology Casa sollievo della sofferenza
Siena	Urgency and Emergency Department -Azienda Ospedaliera Universitaria Senese
Siracusa	Department of Neurology, Umberto I Hospital,
Verona	Department of Neuroscience-Azienda Ospedaliera Universitaria Intergrata Verona
Vicenza	Department of Neuroscience-San Bortolo Hospital

1.7.1 Divergence between clinical trial evidence and actual practice in the READAPT study

A first analysis of the READAPT study comprehensively evaluated the baseline characteristics of patients included in the study up to July 31, 2022, including 1,070 eligible individuals from 51 centers across the country.⁶⁰ This work focused on characterizing the real-world population receiving DAPT in clinical practice, and on identifying the extent to which they would have

met inclusion criteria or followed treatment procedures adopted in the landmark randomized trials (CHANCE³⁹, POINT⁴⁰, and THALES⁴³) that support current clinical guidelines.

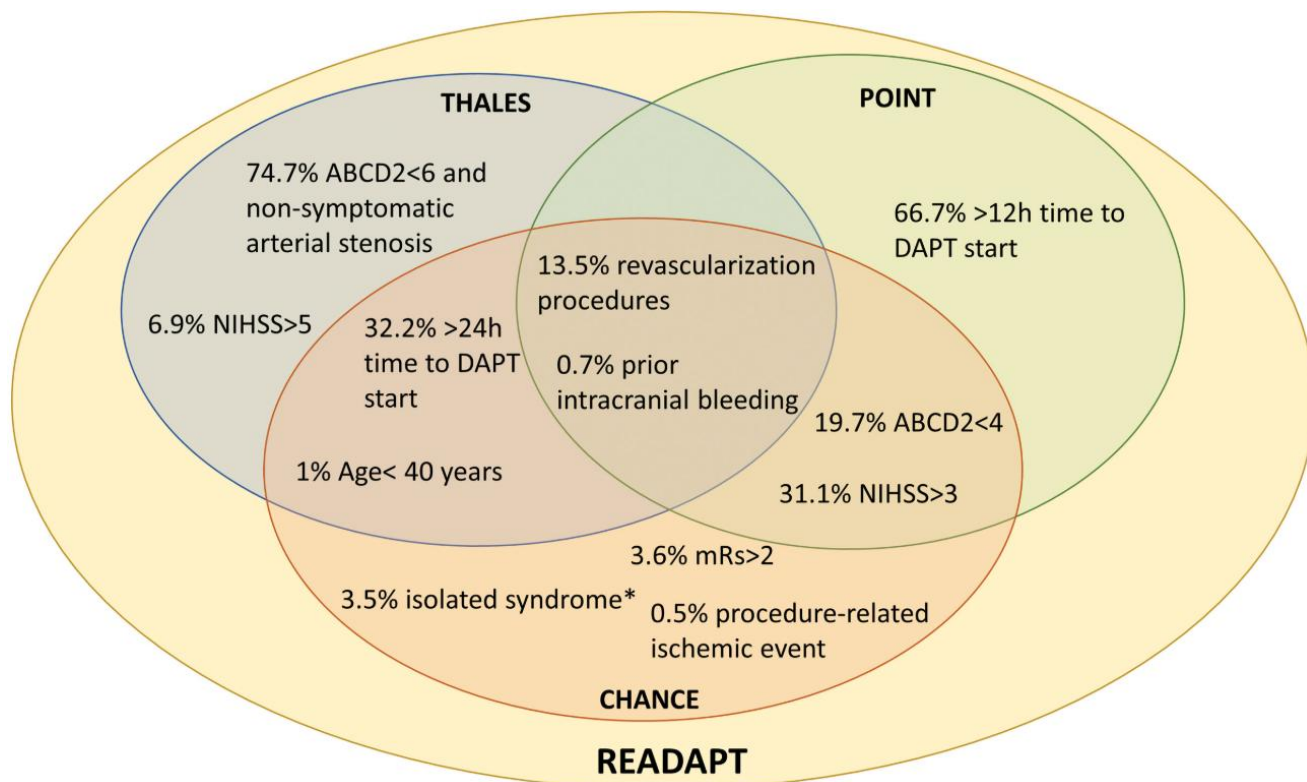
The READAPT cohort diverged substantially from the populations enrolled in randomized clinical trials. Most notably:

- **Demographics and baseline characteristics:** The median age was 72 years (IQR 62–79), higher than that observed in RCTs.^{39,40,43} Approximately 66% of patients were male, and 97.7% were Caucasian — reflecting the demographic profile of the Italian healthcare system. A significant proportion of patients had vascular comorbidities, including hypertension (78%), hypercholesterolemia (57.5%), and diabetes (28.6%).⁶⁰
- *Type and severity of index events:* Of the total cohort, 726 patients (67.9%) had an ischemic stroke and 344 (32.1%) a TIA, with a median NIHSS score of 2. However, 31% of stroke patients had NIHSS >3 (exclusion criterion in CHANCE³⁹ and POINT⁴⁰), and 6.9% had NIHSS >5 (exclusion criterion in THALES⁴³). Among TIA cases, only a minority fulfilled high-risk criteria based on ABCD² score and arterial stenosis.⁶⁰
- *Adherence to trials protocols:* Only 8.6% of patients would have met all inclusion criteria and followed treatment procedures as defined in CHANCE³⁹, POINT⁴⁰, or THALES⁴³; 32.2% started DAPT later than 24 hours after symptom onset, despite trials protocols requiring initiation within 12–24 hours;⁶⁰ 72.5% did not receive an ASA loading dose, and 63.2% did not receive a clopidogrel loading dose, even though these were required in all three trials; 13.5% underwent revascularization procedures, including thrombolysis, thrombectomy, or urgent carotid endarterectomy, all excluded from the trials.⁶⁰
- *Variation by index event and treatment:* Patients with TIA were more likely to receive DAPT within 24 hours and to be given a clopidogrel loading dose compared to those with ischemic stroke.⁶⁰ Conversely, patients treated with thrombolysis were more likely to start DAPT after 24 hours and less likely to receive loading doses.⁶⁰

This first analysis of the READAPT highlighted a profound disconnect between the populations and protocols of RCTs and those seen in real-world clinical practice.⁶⁰ While clinical trials^{39,40,43} provide high-level evidence for the efficacy and safety of DAPT in narrowly selected patients, most patients treated with DAPT in daily practice would not have qualified for trial participation. This underscores the importance of real-world evidence in complementing RCTs and informing clinical decision-making. For instance, while late initiation of DAPT or omission of loading doses might deviate from trial protocols, they reflect physician concerns about

hemorrhagic risk, diagnostic uncertainty, or logistical delays, factors not captured in controlled trial settings.

Figure 2. Graphic representation of the READAPT cohort.



*In circles, there are proportions of READAPT patients who do not match the THALES (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death), POINT (Platelet Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke), and CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) inclusion criteria and procedures. ABCD² indicates age, blood pressure, clinical features, duration of transient ischemic attack, presence of diabetes; DAPT, dual antiplatelet therapy; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and RCT, randomized controlled trial. *Isolated sensory, visual, or dizziness/vertigo syndrome without an ischemic lesion at neuroimaging. (Figure from De Matteis E, et al. Divergence Between Clinical Trial Evidence and Actual Practice in Use of Dual Antiplatelet Therapy After Transient Ischemic Attack and Minor Stroke. *Stroke*. 2023;54(5):1172-1181. doi: 10.1161/STROKEAHA.122.041660).*

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2. Experimental study

Given this background, at the conclusion of the READAPT study, we conducted a series of focused analyses to investigate the effectiveness and safety of DAPT in patient subgroups with transient ischemic attack (TIA) or ischemic stroke who fell outside the inclusion criteria of landmark randomized controlled trials or for whom robust evidence was *lacking*. Specifically, we examined outcomes in patients with (1) mild-to-moderate ischemic stroke (beyond the NIHSS thresholds of CHANCE, POINT and THALES), (2) specific stroke/TIA etiologies including (SAO)-related and LAA-related strokes, (3) those who received intravenous thrombolysis, and (4) patients with relevant comorbidities, including active cancer. These analyses aimed to expand our understanding of DAPT's real-world applicability and risk–benefit profile across a broader and clinically relevant population.

2.1 Patients with mild-to-moderate ischemic stroke

2.1.1 Paper 1: Dual versus single antiplatelet treatment in patients with non-cardioembolic mild-to-moderate ischemic stroke: a real-world propensity matched analysis

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Abstract

Background. Short-term dual antiplatelet therapy (DAPT) has been shown to outperform single antiplatelet therapy (SAPT) in preventing recurrent events after non-cardioembolic minor ischemic stroke or high-risk TIA. Since DAPT is widely used in clinical practice, often beyond the strict eligibility criteria of randomized trials, assessing its benefit–risk profile in a broader patient population is clinically relevant.

Methods. We conducted a post-hoc analysis using prospectively collected data from the READAPT cohort together with three additional prospective stroke registries. The study included patients with mild-to-moderate ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score 0–10) who initiated DAPT or SAPT early after onset. The primary effectiveness endpoint was the recovery of pre-stroke neurological functioning at 90 days, measured using the modified Rankin Scale (mRS). Secondary endpoints included 90-day mRS shift, new ischemic stroke or TIA, vascular and all-cause mortality, and early neurological changes within 24 hours. Safety was assessed through the rate of intracranial hemorrhage within 90 days.

Results. After propensity-score matching, 1,008 patients treated with DAPT were compared with 1,008 patients receiving SAPT. DAPT was associated with a greater probability of achieving the primary 90-day outcome (87.5% vs 84.4%; risk difference 3.1%, 95% CI 0.1%–6.1%, $p=0.047$; risk ratio 1.03, 95% CI 1.01–1.07, $p=0.043$) and with a higher rate of early neurological improvement at 24 hours (25.3% vs 15.4%; risk difference 9.9%, 95% CI 6.4%–13.4%, $p<0.001$; risk ratio 1.65, 95% CI 1.37–1.97, $p<0.001$). No between-group differences emerged for the other predefined outcomes. In subgroup analyses, the advantage of DAPT over SAPT for the primary endpoint was consistent among patients with moderate stroke, those receiving intravenous thrombolysis, and those given an antiplatelet loading dose.

Conclusions. In this large real-world dataset, DAPT appeared both safe and potentially more effective than SAPT, even in patients who would not have qualified for major randomized trials, supporting its use in broader clinical scenarios.

Introduction

Short-term dual antiplatelet therapy (DAPT) represents a key strategy for secondary prevention after non-cardioembolic minor ischemic stroke or high-risk transient ischemic attack (TIA).¹⁻⁴ In everyday clinical practice, however, DAPT is frequently used in scenarios that extend beyond those examined in pivotal randomized trials, including patients with more pronounced neurological deficits, individuals with pre-existing disability, or those treated with acute reperfusion therapies.^{5,6}

More recently, the Antiplatelet Therapy in Acute Mild to Moderate Ischemic Stroke (ATAMIS) randomized trial demonstrated that early treatment with aspirin plus clopidogrel may reduce the risk of early neurological deterioration (END) in patients presenting with a National Institute of Health Stroke Scale (NIHSS) score between 4 and 10.⁷ Despite this finding, ATAMIS did not identify significant differences between DAPT and aspirin alone with respect to 90-day functional outcomes or other efficacy endpoints such as recurrent stroke, other vascular events, or mortality.⁷ It is also noteworthy that the ATAMIS population predominantly consisted of patients with an NIHSS of 4–7 (82.8%, median NIHSS 5 [IQR 4–6]).⁷

By contrast, large DAPT trials have mainly focused on patients with lower baseline NIHSS scores, ranging from 0 to 3 in the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)² and Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)¹ trials, and from 0 to 5 in The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES)³ trial.

Taken together, these observations highlight the limited availability of real-world evidence on the comparative outcomes of DAPT versus single antiplatelet therapy (SAPT) in patients with mild-to-moderate ischemic stroke—data that are essential to understand how these strategies perform outside the controlled environment of randomized trials.

In this study, we therefore aimed to assess clinical outcomes in non-cardioembolic mild-to-moderate ischemic stroke patients treated with early short-term DAPT compared with SAPT in a real-world setting.

Methods

Study design

This work represents a post-hoc analysis of data that were collected prospectively. Specifically, we integrated information from patients included in the multicenter, prospective observational cohort “Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient

Ischemic Attack” (READAPT, NCT05476081) together with data derived from three single-center prospective stroke registries. The READAPT cohort enrolled adults (≥ 18 years) with acute non-cardioembolic ischemic stroke or TIA who received DAPT, recruiting patients across 64 Italian stroke centers between February 1, 2021, and February 28, 2023. The study design and procedures have been previously described in detail.^{5,6}

The three contributing local registries included patients aged ≥ 18 years admitted with acute ischemic stroke to S. Orsola-Malpighi Hospital in Bologna (BO), S. Maria della Misericordia Hospital in Perugia (PG), and Udine University Hospital (UD), with enrollment starting from each registry’s inception (BO 2010, PG 2003, UD 2018).^{8,10}

Across all datasets, demographic characteristics (age and sex), vascular risk factors, clinical information including pre-stroke modified Rankin Scale (mRS) score, stroke severity and presumed etiology, concomitant therapies, and 90-day clinical outcomes were collected prospectively.

Data extraction and study population

From the READAPT cohort and the local stroke registries, we identified patients with mild-to-moderate (NIHSS 0–10) non-cardioembolic ischemic stroke as of June 2024. The inclusion of individuals with a baseline NIHSS of up to 10 allowed us to explore the real-world balance between benefits and risks of DAPT across a broader range of stroke severity, extending beyond the populations studied in previous randomized trials, where DAPT demonstrated superiority over SAPT.^{1,4-7}

To reduce potential selection bias in antiplatelet treatment assignment, data from the local registries were extracted only for patients treated with SAPT and enrolled between January 1, 2018, and December 31, 2020—that is, before the widespread adoption of international guidelines recommending DAPT for all minor strokes and high-risk TIAs.¹¹⁻¹²

Patients were included in the analysis if they met the following criteria:

1. stroke symptoms lasting ≥ 24 hours, or < 24 hours with imaging evidence of recent ischemic lesion(s) on brain NCCT or MRI;
2. initiation of DAPT or SAPT within 24 hours from symptom onset (extended to 48 hours for those undergoing hyperacute therapies);
3. completion of a follow-up evaluation within 80 ± 10 days of the index stroke.

Exclusion criteria comprised urgent carotid endarterectomy or stenting during follow-up, incomplete follow-up data (≥ 1 missing outcome), and early discontinuation of DAPT (< 21 days) or SAPT (before the follow-up visit) because of the need to start anticoagulation. The latter criterion was applied to avoid confounding related to the bleeding risk associated with anticoagulant therapy, which could interfere with the assessment of DAPT and SAPT safety profiles.

Propensity score matching

Propensity scores were calculated basing on a multivariable logistic regression model which included demographics (age and sex), risk factors (arterial hypertension, diabetes, dyslipidemia, current smoking), pre-stroke mRS, stroke severity (NIHSS) and presumed cause, symptoms duration, hyperacute treatment, DAPT/SAPT loading dose. Patients treated with DAPT were matched with those treated with SAPT in a 1:1 ratio and within 0.2 x standard deviation (sd) of the logit of the propensity score by using a greedy nearest neighbor matching without replacement. The overall quality of the matching was evaluated by comparing the standardized difference of means and the ratio of the variances between the propensity scores of treatment groups and by inspecting graphics of propensity scores and covariates balance distributions between the matched samples.

Outcomes

The primary effectiveness outcome was the return to baseline neurological functioning at 90 days, as defined by a mRS score of 0-1 in patients with pre-stroke mRS < 2 or by the 90-day return to the pre-stroke mRS score in those with baseline mRS ≥ 2 . The secondary effectiveness outcomes included the 90-day ordinal shift of mRS, 24-h early neurological improvement (ENI, decrease of 2 or more points in the NIHSS score) or END (increase of 2 or more points in the NIHSS score not due to cerebral hemorrhage), 90-day new stroke/TIA, vascular (death due to stroke, systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death or arrhythmia) and all-cause mortality. The safety outcome was 90-day intracranial hemorrhage as defined by any category of the Heidelberg bleeding classification system.¹³

Statistical analysis

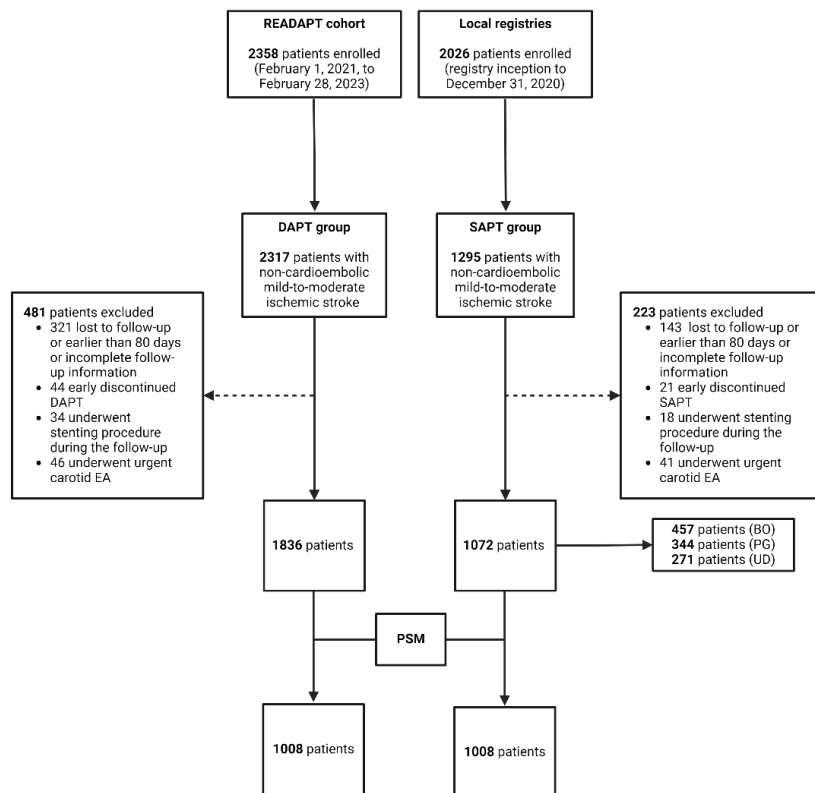
Categorical variables were presented as number and percentage, continuous as mean and standard deviation (sd) or median and interquartile range (IQR) according to distribution. For the primary effectiveness outcome, we calculated the risk difference and ratio of 90-day return to pre-stroke neurological functioning between the DAPT and SAPT groups with the 2-sided 95% confidence intervals (CIs). For the secondary effectiveness outcomes, the 90-day ordinal distribution of mRS

scores was compared using an ordinal generalized linear model and results were presented as odds ratio (OR) with 95% CIs. Risk differences and ratios (95% CIs) between groups were calculated for 24-h ENI or END. The time-to-event 90-day risk of new stroke/TIA, vascular and all-cause death was compared using Cox regression and the corresponding treatment effect was presented as hazard ratio (HR) and 95% CIs. For the safety outcome, we calculated risk difference and ratio with 95% CIs. All outcomes were analyzed separately also in the unmatched cohort. Subgroup analysis of the primary effectiveness outcome was performed calculating risk differences of DAPT versus SAPT in 11 prespecified subgroups (age [<65 or ≥ 65 years], sex [females or males], NIHSS [0-5 or 6-10], presumed stroke cause, pre-stroke mRS [<2 or ≥ 2], symptoms duration [≥ 24 hours or <24 hours], intravenous thrombolysis (IVT), endovascular thrombectomy (EVT), history of diabetes, SAPT/DAPT loading dose [prescription of ≥ 300 mg for aspirin/clopidogrel, ≥ 180 mg for ticagrelor]). Lastly, we conducted a sensitivity analysis within the overall cohort comparing the 90-day risk of new stroke or TIA and the 24-hour incidence of END, between DAPT and SAPT in patients with baseline NIHSS scores 0-3 and 4-10, respectively, to align with the main outcomes and stroke severity of the populations in the POINT³ and ATAMIS⁷ trials. All statistical analyses were performed using R software, version 4.2.0. A 2-sided P value less than 0.05 was considered statistically significant.

Results

A total of 2908 patients with mild-to-moderate non-cardioembolic stroke were included in the analysis, of whom 1836 (63.1%) were treated DAPT and 1072 (36.9%) with SAPT. The number of excluded patients with reasons is reported in the study flow-chart. **Figure 1**

Figure 1. Study flow-chart.



BO: Bologna; DAPT: dual antiplatelet treatment; PG: Perugia; PSM: propensity score matching; SAPT: single antiplatelet treatment; UD: Udine.

No missing data were recorded in the variables used to calculate the propensity scores. We paired 1008 DAPT and 1008 SAPT patients. Patients treated with DAPT mostly received aspirin plus clopidogrel (99.7%) for a median time of 21 days (IQR 21-30). Conversely, patients treated with SAPT were mostly treated with aspirin (71.9%) or clopidogrel (27.1%). Measures of balance diagnosis indicated that the samples were adequately matched, with a standardized difference of the propensity scores between groups of 0.17 (good balance <0.25), ratio of variances of propensity scores 1.10 (good balance from 0.5 to 2).¹⁴ Graphics of propensity scores and covariates balance distributions between the matched samples confirmed a good overall quality of the matching. **Figure 2 and 3**

Figure 2. Mirrored histogram of propensity scores distribution between unmatched and matched samples.

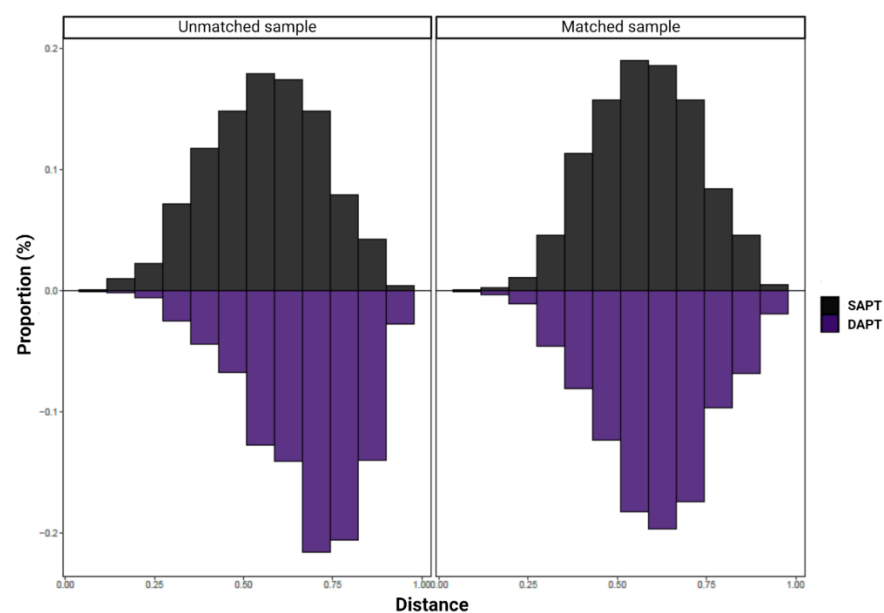
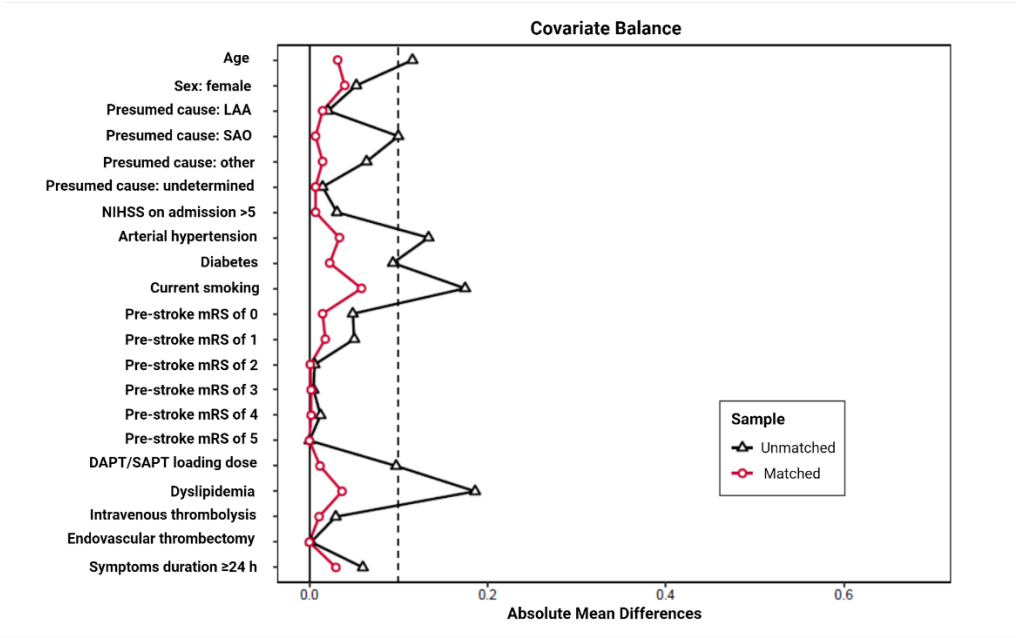


Figure 3. Love plot of covariate balance between the DAPT and SAPT groups before and after propensity score matching.



Abbreviations. DAPT: dual antiplatelet treatment; LAA: large artery atherosclerosis; SAO: small artery occlusion; SAPT: single antiplatelet treatment. Dashed line indicates Absolute Mean Difference cut-off for optimal balance between matched samples.

The comparison of baseline characteristics further supported the good balance of our matched samples with a standardized difference of the propensity scores <0.25 in all variables. **Table 1**

Table 1. Baseline characteristics.

	Unmatched cohort				Matched cohort			
	DAPT (n=1836)	SAPT (n=1072)	Standardize difference	P value	DAPT (n=1008)	SAPT (n=1008)	Standardized difference	P value
Demographics								
Female, n (%)	429 (40.0)	638 (34.7)	0.109	0.005	352 (34.9)	392 (38.9)	0.082	0.071
Age, mean (sd) – years	69.78 (12.04)	68.39 (13.82)	0.108	0.044	69.06 (12.83)	68.68 (13.55)	0.029	0.753
Clinical characteristics								
NIHSS ≤5, n (%)	1725 (94.0)	974 (94.7)	0.117	0.002	930 (92.3)	923 (91.6)	0.025	0.624
NIHSS 6-10, n (%)	111 (6.0)	98 (5.3)			78 (7.7)	85 (8.4)		
mRS score category, n (%)			0.208	<0.001			0.068	0.805
No symptoms (0), n (%)	1447 (83.7)	897 (78.8)			828 (82.1)	843 (83.6)		
Symptoms without any disability (1), n (%)	221 (12.0)	75 (7.0)			93 (9.2)	75 (7.4)		
Symptoms with mild disability (2), n (%)	93 (5.1)	48 (4.5)			48 (4.8)	47 (4.7)		
Symptoms with mild-to-moderate disability (3), n (%)	60 (3.3)	30 (2.8)			27 (2.7)	29 (2.9)		
Symptoms with moderate-to-severe disability (4), n (%)	13 (0.7)	21 (2.0)			11 (1.1)	13 (1.3)		
Symptoms with severe disability (5), n (%)	2 (0.1)	1 (0.1)			1 (0.1)	1 (0.1)		
Symptoms duration <24 h, n (%)	652 (35.5)	445 (41.5)	0.124	0.001	378 (37.5)	408 (40.5)	0.061	0.185
Symptoms duration ≥24 h, n (%)	1184 (64.5)	627 (58.5)			630 (62.5)	600 (59.5)		
Presumed stroke cause, n (%) ^a			0.307	<0.001			0.061	0.594
Undetermined	812 (44.2)	490 (45.7)			462 (45.8)	469 (46.5)		
Small artery occlusion	531 (28.9)	203 (18.9)			209 (20.7)	202 (20.0)		
Large artery atherosclerosis	395 (21.5)	253 (23.6)			256 (25.4)	241 (23.9)		
Other determined cause	98 (5.3)	126 (11.8)			81 (8.0)	96 (9.5)		
Pre-stroke risk factors								
Arterial hypertension, n (%) ^b	1465 (79.8)	712 (66.4)	0.305	<0.001	721 (71.5)	687 (68.2)	0.074	0.109
Dyslipidemia, n (%) ^c	1114 (60.7)	451 (42.1)	0.379	<0.001	479 (47.5)	442 (43.8)	0.074	0.108
Diabetes mellitus, n (%) ^d	501 (27.3)	192 (17.9)	0.226	<0.001	213 (21.1)	190 (18.8)	0.057	0.221
Current smoking, n (%) ^e	780 (42.5)	268 (25.0)	0.376	<0.001	325 (32.2)	268 (26.6)	0.129	0.051
Previous TIA/ischemic stroke, n (%)	348 (19.0)	143 (13.3)	0.153	<0.001	179 (17.8)	143 (14.2)	0.078	0.120
Previous intracerebral hemorrhage, n (%)	14 (0.8)	8 (0.7)	0.002	>0.999	5 (0.5)	8 (0.8)	0.037	0.578
History of myocardial infarction, n (%)	170 (9.3)	43 (4.0)	0.212	<0.001	71 (7.0)	43 (4.3)	0.120	0.090
Hyperacute treatment, n (%)								

Intravenous thrombolysis, n (%)	277 (15.1)	130 (12.1)	0.086	0.030	137 (13.6)	127 (12.5)	0.032	0.508
Endovascular thrombectomy, n (%)	24 (1.3)	12 (1.1)	0.017	>0.999	12 (1.2)	12 (1.2)	<0.001	>0.999
Therapy on admission, n (%)								
Single antiplatelet, n (%)	747 (40.7)	376 (35.1)	0.116	0.003	367 (36.4)	359 (35.6)	0.017	0.715
Antihypertensive drugs, n (%)	1195 (65.1)	613 (57.2)	0.163	<0.001	580 (57.5)	590 (58.5)	0.020	0.685
Lipid-lowering drugs, n (%)	578 (31.5)	286 (26.7)	0.106	0.007	247 (24.5)	276 (27.4)	0.066	0.155
Antidiabetics, n (%)	414 (22.5)	153 (14.3)	0.215	<0.001	174 (17.3)	151 (15.0)	0.062	0.183
DAPT/SAPT characteristics								
Type of DAPT, n (%)								
ASA + clopidogrel	1828 (99.6)				1005 (99.7)			
ASA + ticagrelor	8 (0.4)				3 (0.3)			
Type of SAPT, n (%)								
Aspirin		768 (71.6)				725 (71.9)		
Clopidogrel		292 (27.2)				273 (27.1)		
Ticagrelor		11 (1.0)				10 (1.0)		
Days of DAPT, median (IQR)	21 (2130)				21 (2130)			
Loading dose, n (%)	994 (54.1)	476 (44.4)	0.196	<0.001	478 (47.4)	466 (46.2)	0.024	0.623

DAPT: dual antiplatelet therapy; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SAPT: single antiplatelet therapy; a: According to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system; b: History of blood pressure >140/90 mmHg or current use of antihypertensives; c: 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; d: History of fasting glucose >126 mg/dl or current use of hypoglycemics; e: Consumption of ≥ 1 cigarette/day over the last year.

Primary effectiveness outcome

The percentage of patients returning to pre-stroke neurological functioning at 90-days was 87.5% in the DAPT group and 84.4% in the SAPT group. We found significant risk difference (3.1% [95%CI 0.1%-6.1%]; $p=0.047$) and ratio (1.03 [95%CI 1.01-1.07]; $p=0.043$) between the two groups in the rate of 90-day primary outcome. **Table 2**

Table 2. Study outcomes in the matched cohort.

	DAPT (n=1008)	SAPT (n=1008)	Treatment effect metric	Treatment difference [95%CI]	P value
<i>Primary effectiveness outcome</i>					
90-day return to pre-stroke neurological functioning, n (%)	882 (87.5)	851 (84.4)	Risk difference (%)	3.1 [0.1-6.1]	0.047
			Risk ratio	1.03 [1.01-1.07]	0.043
<i>Secondary effectiveness outcomes</i>					
90-day mRS score distribution					
No symptoms (0), n (%)	527 (52.3)	505 (50.1)			

Symptoms without any disability (1), n (%)	260 (25.8)	254 (25.2)			
Symptoms with mild disability (2), n (%)	120 (11.9)	115 (11.4)			
Symptoms with mild-to-moderate disability (3), n (%)	62 (6.2)	76 (7.5)	Odds ratio	0.90 [0.81-1.01]	0.065
Symptoms with moderate-to-severe disability (4), n (%)	27 (2.7)	43 (4.3)			
Symptoms with severe disability (5), n (%)	3 (0.3)	10 (1.0)			
Death (6), n (%)	9 (0.9)	5 (0.5)			
24-hour early neurological improvement, n (%)	255 (25.3)	155 (15.4)	Risk difference (%)	9.9 [6.4-13.4]	<0.001
			Risk ratio	1.65 [1.37-1.97]	<0.001
24-hour early neurological deterioration, n (%)	14 (1.4)	19 (1.9)	Risk difference (%)	-0.5 [-1.6-0.6]	0.380
			Risk ratio	0.74 [0.37-1.46]	0.381
90-day new ischemic stroke or TIA, n (%)	36 (3.6)	40 (4.0)	Hazard ratio	0.89 [0.57-1.40]	0.630
90-day vascular death, n (%)	2 (0.2)	1 (0.1)	Hazard ratio	1.22 [0.05-5.51]	0.560
90-day all-cause death, n (%)	9 (0.9)	5 (0.5)	Hazard ratio	1.80 [0.60-5.37]	0.282
Safety outcome					
90-day intracranial hemorrhage, n (%)	3 (0.3)	3 (0.3)	Risk difference (%)	0.0 [-0.5-4.8]	>0.999
			Risk ratio	1.0 [0.20-4.94]	>0.999

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; SAPT: single antiplatelet treatment.

Results of primary effectiveness outcome comparison in the unmatched cohort are displayed in **Table 3**. Although the percentage of patients who returned to pre-stroke neurological functioning at 90 days was slightly higher in patients treated with DAPT (87.2%) versus SAPT (84.6%), statistical significance was not reached in the unmatched cohort (risk difference 2.6% [-0.1%-5.2%];p=0.050; risk ratio 1.03 [0.99-1.06];p=0.055). **Table 3**

Table 3. Study outcomes in the unmatched cohort.

	DAPT (n=1836)	SAPT (n=1072)	Treatment effect metric	Treatment difference [95%CI]	P value
Primary effectiveness outcome					
90-day return to pre-stroke neurological functioning, n (%)	1601(87.2)	907 (84.6)	Risk difference (%)	2.6 [-0.1-5.2]	0.050
			Risk ratio	1.03 [0.99-1.06]	0.055
Secondary effectiveness outcomes					
90-day mRS score distribution					
No symptoms (0), n (%)	892 (48.6)	539 (50.3)			
Symptoms without any disability (1), n (%)	510 (27.8)	269 (25.1)			
Symptoms with mild disability (2), n (%)	232 (12.6)	118 (11.0)			

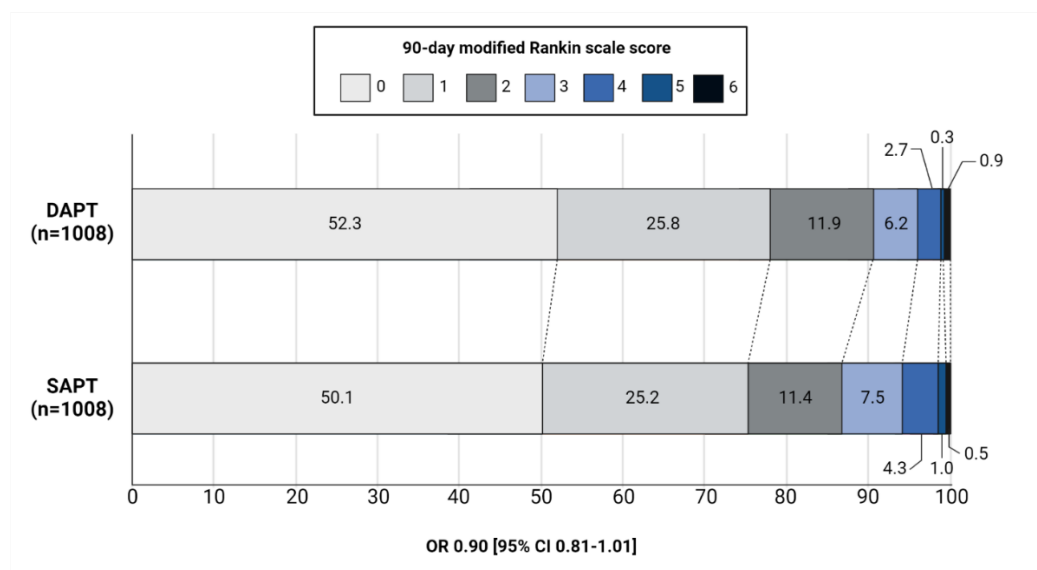
Symptoms with mild-to-moderate disability (3), n (%)	132 (7.2)	77 (7.2)			
Symptoms with moderate-to-severe disability (4), n (%)	46 (2.5)	52 (4.9)	Odds ratio	0.96 [0.87-1.05]	0.329
Symptoms with severe disability (5), n (%)	8 (0.4)	10 (0.9)			
Death (6), n (%)	16 (0.9)	7 (0.7)			
24-hour early neurological improvement, n (%)	401 (21.8)	268 (25.0)	Risk difference (%)	-3.2 [-6.4-0.1]	0.054
			Risk ratio	0.87 [0.76-1.00]	0.051
24-hour early neurological deterioration, n (%)	34 (1.9)	19 (1.8)	Risk difference (%)	0.1 [-0.9-1.1]	0.877
			Risk ratio	1.04 [0.60-1.82]	0.877
90-day new ischemic stroke or TIA, n (%)	64 (3.5)	52 (4.9)	Hazard ratio	0.78 [0.57-1.12]	0.234
90-day vascular death, n (%)	3 (0.2)	2 (0.2)	Hazard ratio	0.87 [0.14-5.24]	0.884
90-day all-cause death, n (%)	8 (0.4)	7 (0.7)	Hazard ratio	0.67 [0.24-1.84]	0.434
Safety outcome					
90-day intracranial hemorrhage, n (%)	3 (0.2)	4 (0.4)	Risk difference (%)	-0.2 [-0.1-0.2]	0.315
			Risk ratio	0.44 [0.10-1.95]	0.266

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; SAPT: single antiplatelet treatment.

Secondary effectiveness outcomes

Compared to SAPT patients, those treated with DAPT showed a higher frequency of 24-h ENI (risk difference: 9.9% [95%CI 6.4%-13.4%]; $p < 0.001$; risk ratio: 1.65, [95%CI 1.37-1.97]; $p < 0.001$). We found a similar risk of 90-day new stroke/TIA between groups, as well as of 90-day vascular and all-cause mortality. There were no significant differences in the 24-h risk of END. Although a slightly higher proportion of patients treated with DAPT (78.1%) showed 90-day excellent functional outcome (mRS 0-1) compared to SAPT (75.3%), we found no significant differences in the 90-day mRS shift (OR 0.90 [95%CI 0.81-1.01]; $p = 0.065$) **Table 2, Figure 4**. Comparison of secondary outcomes in the unmatched cohort showed no significant results. **Table 3**

Figure 4. Ordinal distribution of 90-day mRS scores in matched patients treated with DAPT versus SAPT.



Abbreviations. CI: confidence interval; DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; SAPT: single antiplatelet treatment; OR: odds ratio.

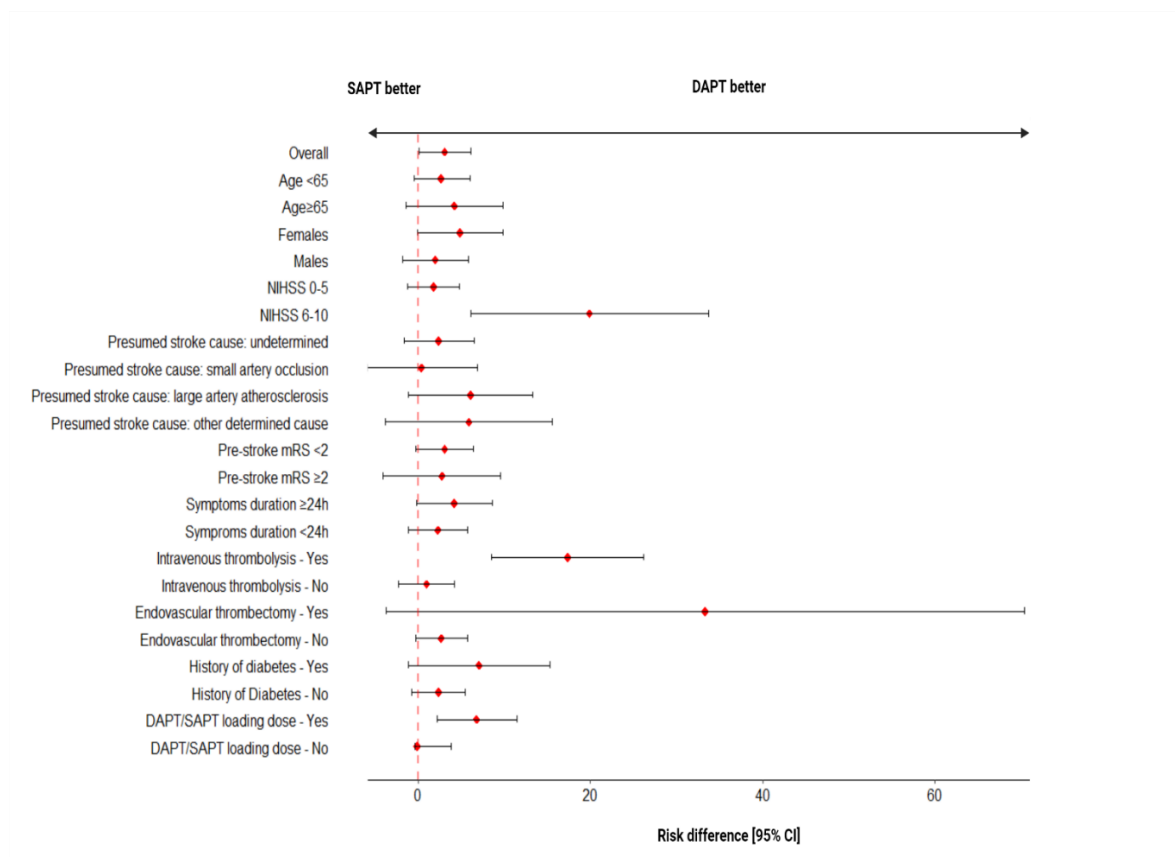
Safety outcome

The 90-day risk of intracranial hemorrhage was very low and did not differ between DAPT and SAPT (both 0.3%; risk difference 0% [95%CI -0.5%-4.8%], risk ratio 1.0 [0.20-4.94]; $p>0.999$). **Table 2** We found no significant difference also in the unmatched cohort. **Table 3**

Subgroup analysis

Results of subgroup analysis are presented in **Figure 5** and **Table 4**. We found a higher frequency of 90-day primary effectiveness outcome in patients with NIHSS 6-10 treated with DAPT versus SAPT (risk difference 19.9% [95%CI 6.1%-33.7%]; $p=0.004$), as well as in those who received IVT (risk difference 17.4% [95%CI 8.5%-26.2%]; $p<0.001$) or antiplatelet loading dose (risk difference 6.8% [95%CI 2.2%-11.1%]; $p=0.005$). There was not significant risk difference in the 90-day rate of primary effectiveness outcome across other prespecified subgroups.

Figure 5. Risk differences in primary effectiveness outcome by prespecified subgroups.



Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SAPT: single antiplatelet treatment. Red dots indicate risk difference, black bars indicate 95% confidence interval (CI).

Table 4. Primary effectiveness outcome by prespecified subgroups in the matched cohort.

	No. of patients	No. of patients with primary outcome/total No. (%)			
		DAPT	SAPT	Risk difference (%) [95 % CI]	P value
Overall	2016	882/1008 (87.5)	851/1008 (84.4)	3.1 [0.1-6.1]	0.047
Age, years					
<65	1222	552/600 (92.0)	555/622 (89.2)	2.7 [-0.5-6.0]	0.096
≥65	794	330/408 (80.9)	296/386 (76.7)	4.2 [-1.4-9.9]	0.148
Sex					
Females	744	311/352 (88.4)	327/392 (83.4)	4.9 [-0.1-9.9]	0.052
Males	1272	571/656 (87.0)	524/616 (85.1)	2.0 [-1.8-5.8]	0.309
NIHSS on admission					
0-5	1853	822/930 (88.4)	799/923 (86.6)	1.8 [-1.2-4.8]	0.236
6-10	163	60/78 (76.9)	52/85 (61.2)	19.9 [6.1-33.7]	0.004

Presumed stroke cause					
Undetermined	931	416/462 (90.0)	411/469 (87.6)	2.4 [-1.6-6.5]	0.243
Small artery occlusion	411	183/209 (87.6)	176/202 (87.1)	0.4 [-5.9-6.9]	0.896
Large artery atherosclerosis	497	209/256 (81.6)	182/241 (75.5)	6.1 [-1.1-13.3]	0.096
Other determined cause	177	74/81 (91.4)	82/96 (85.4)	5.9 [-3.8-15.6]	0.236
Pre-stroke mRS					
<2	1671	721/828 (87.1)	708/843 (84.0)	3.1 [-0.3-6.4]	0.072
≥2	345	161/180 (89.4)	143/165 (86.7)	2.8 [-4.1-9.6]	0.427
Symptoms duration, h					
≥24	1230	524/630 (83.2)	474/600 (79.0)	4.2 [-0.2-8.6]	0.061
<24	786	358/378 (94.7)	377/408 (92.4)	2.3 [-1.1-5.7]	0.186
Intravenous thrombolysis					
Yes	263	126/137 (92.0)	94/126 (74.6)	17.4 [8.5-26.2]	<0.001
No	1753	756/871 (86.8)	757/882 (85.8)	1.0 [-2.3-4.2]	0.555
Endovascular thrombectomy					
Yes	24	9/12 (75.0)	5/12 (42.0)	33.3 [-3.7-70.4]	0.079
No	1992	873/996 (87.7)	846/996 (85.2)	2.7 [-0.3-5.7]	0.078
History of diabetes					
Yes	403	172/213 (80.8)	140/190 (73.7)	7.1 [-1.1-15.3]	0.091
No	1613	710/795 (89.3)	711/818 (86.9)	2.4 [-0.7-5.5]	0.138
DAPT/SAPT loading dose					
Yes	944	414/478 (86.6)	372/466 (79.8)	6.8 [2.2-11.5]	0.005
No	1072	468/530 (88.3)	479/542 (88.4)	-0.1 [-0.4-3.8]	0.970

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SAPT: single antiplatelet treatment.

Sensitivity analysis

Sensitivity analysis within the overall cohort showed that the 90-day risk of new stroke and TIA was significantly lower in patients with baseline NIHSS 0-3 treated with DAPT versus SAPT (2.7% versus 5.8%, HR 0.46 [95%CI 0.30-0.71]; $p<0.001$). We found a lower rate of 24-h END in patients with baseline NIHSS 4-10 treated with DAPT than SAPT (3.3% versus 5.5%, risk difference -2.1 [-5.4%-1.3%], risk ratio 0.62 [0.30-1.30]), although statistical significance was not reached ($p=0.201$). **Table 5**

Table 5. Sensitivity analysis: 90-day risk of new stroke/TIA in patients with baseline NIHSS 0-3 and 24-h early neurological deterioration (END) in patients with baseline NIHSS 4-10.

NIHSS 0-3					
	DAPT (n=1441)	SAPT (n=817)	Treatment effect metric	Treatment difference [95% CI]	P value
90-day new ischemic stroke or TIA, n (%)	39 (2.7)	47 (5.8)	Hazard ratio	0.46 [0.30-0.71]	<0.001
NIHSS 4-10					
	DAPT (n=395)	SAPT (n=255)	Treatment effect metric	Treatment difference [95% CI]	P value
24-hour early neurological deterioration, n (%)	13 (3.3)	14 (5.5)	Risk difference (%)	-2.1 [-5.4-1.3]	0.220
			Risk ratio	0.62 [0.30-1.30]	0.201

Abbreviations. DAPT: dual antiplatelet treatment; SAPT: single antiplatelet treatment.

Discussion

In this real-world cohort of patients with non-cardioembolic mild-to-moderate ischemic stroke, early short-term DAPT was associated with a higher probability of regaining pre-stroke functional status at 90 days compared with SAPT. These findings expand on the evidence from pivotal trials, which demonstrated the superiority of DAPT over aspirin alone for reducing 90-day stroke recurrence in patients with minor stroke (NIHSS upper limit 3–5) or high-risk TIA,¹⁻⁴ by showing potential benefits on a broader functional endpoint and in a less selected population.

The ATAMIS trial reported a reduction in 7-day END with DAPT versus SAPT in patients with baseline NIHSS 4–10,⁷ although no significant differences emerged in 90-day functional outcomes or other major efficacy endpoints.⁷ In our dataset, 24-hour END rates were similarly low in both treatment groups (1.4% vs 1.9%), whereas DAPT was associated with a higher frequency of 24-hour ENI (25.3% vs 15.4%). This early clinical improvement may reflect the more rapid and comprehensive inhibition of platelet activation achieved with combined antiplatelet therapy compared with monotherapy, potentially limiting clot propagation during the hyperacute phase of ischemic stroke.¹⁵

However, given the observational design of our study, the primary effectiveness outcome may have been influenced by unmeasured factors such as stroke symptom profile, management of comorbidities, adherence to therapy, and early rehabilitation. Thus, the results should be interpreted with caution and do not allow firm conclusions regarding a causal effect of DAPT on functional recovery.

Unlike the landmark randomized trials,¹⁻⁴ our study did not identify significant differences between DAPT and SAPT in the 90-day risk of new stroke/TIA or mortality. This may be partly explained by the relatively low number of secondary outcome events, the inclusion of patients with heterogeneous clinical

characteristics (e.g., pre-stroke disability, use of hyperacute treatments), and differences in DAPT regimens such as loading dose exposure and treatment duration. Importantly, in a sensitivity analysis restricted to patients with NIHSS 0–3—mirroring the POINT3 trial population—DAPT was associated with a lower risk of 90-day stroke/TIA. Consistent with ATAMIS⁷ and other recent observational studies,^{16,17} intracranial hemorrhage rates were very low (0.3% in both groups), reinforcing the safety and feasibility of short-term DAPT even in patients with moderate stroke severity.

We also observed that the advantage of DAPT for the primary outcome was more pronounced among patients with moderate baseline deficits (NIHSS 6–10), those treated with IVT, and individuals who received an antiplatelet loading dose. ATAMIS reported a similar trend for reduction in END at 7 days in patients with NIHSS 4–10.⁷ In our analysis, a sensitivity assessment in patients with NIHSS 4–10 also suggested potential benefit of DAPT on early neurological deterioration, although results did not reach statistical significance, likely due to differing END definitions (24 hours vs 7 days) and the predominance of mild strokes in our sample (91.1%). As such, subgroup findings should be interpreted cautiously and validated in larger datasets.

For patients treated with IVT, the observed greater probability of returning to pre-stroke functional status when receiving alteplase plus DAPT may indicate complementary effects: alteplase rapidly counteracts clot propagation, while early DAPT may reduce the likelihood of further platelet-driven thrombus growth. This observation aligns with a subgroup analysis from the READAPT study showing improved 90-day mRS distribution in patients treated with IVT plus DAPT, without excess major bleeding.¹⁸ The enhanced primary outcome rates seen in patients who received a loading dose further highlight the relevance of prompt and adequate platelet inhibition—an aspect often underutilized in routine practice.⁵

The main strength of the study lies in the use of rigorous propensity score matching to reduce confounding when comparing outcomes across treatment groups. Nevertheless, residual confounding cannot be excluded, particularly given the observational nature of both the READAPT cohort and local registries. For instance, patient ethnicity was not systematically collected and could not be included in the matching process. The follow-up period was limited to 90 days, corresponding to customary DAPT duration, but longer-term differences between DAPT and SAPT cannot be ruled out. Moreover, despite restricting the SAPT cohort to a time window prior to guideline implementation (January 1, 2018 – December 31, 2020),^{11,12} some patients may still have been preferentially assigned to SAPT or DAPT based on clinical judgment.

Another limitation is the absence of detailed neuroimaging data. Although all patients underwent NCCT/MRI at admission, we did not capture specific imaging findings or vascular imaging results; thus,

stroke diagnosis and presumed etiology relied on local investigators. Additionally, although follow-up was conducted in person or by telephone to ensure documentation of clinically relevant events, mild or transient recurrences may have been missed, contributing to potential underestimation of outcome events. Patients who discontinued DAPT (n=44) or SAPT (n=21) early due to the need for anticoagulation were censored and excluded from outcome assessment, preventing evaluation of the impact of transitioning from antiplatelets to anticoagulation. Finally, because local registries were initiated before the COVID-19 pandemic, we cannot exclude the potential negative impact of pandemic-related care disruptions (delays in reperfusion therapies, reduced access to rehabilitation, suboptimal management of chronic conditions) on 90-day outcomes. Nevertheless, patients enrolled in 2020 accounted for only 4.4% of the original SAPT cohort.

In conclusion, our findings support that DAPT is both safe and potentially more effective than SAPT in patients with non-cardioembolic mild-to-moderate ischemic stroke. Beyond reducing early recurrences,^{1–4} DAPT may also contribute to neurological improvement and enhanced functional recovery. Benefits were also observed in patients with moderate stroke severity and in those treated with IVT, suggesting that the advantages of DAPT may extend to populations who fall outside the strict criteria of major randomized clinical trials.

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2.1.2 Paper 2: Investigating sex differences in outcomes after dual antiplatelet therapy for patients with non-cardioembolic mild-to-moderate ischemic stroke or high-risk TIA: a propensity-matched analysis from the READAPT study cohort.

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Abstract

Background. Sex-related factors may influence clinical outcomes in patients receiving dual antiplatelet therapy (DAPT) after ischemic stroke. In this analysis, we explored whether women and men treated with DAPT differ in their short-term outcomes within a real-world cohort of patients with non-cardioembolic mild-to-moderate ischemic stroke or high-risk transient ischemic attack (TIA).

Methods. We conducted a propensity score-matched analysis using data from the prospective multicenter READAPT cohort, including patients with non-cardioembolic mild-to-moderate stroke (National Institutes of Health Stroke Scale [NIHSS] 0–10) or high-risk TIA (ABCD2 ≥ 4) who received DAPT within 48 hours of symptom onset. The primary effectiveness endpoint was the 90-day incidence of new ischemic stroke or other vascular events. Secondary endpoints included the 90-day modified Rankin Scale (mRS) score ordinal shift, vascular and all-cause mortality, and 24-hour early neurological improvement or deterioration. Safety outcomes were the 90-day risk of moderate-to-severe or any bleeding events, symptomatic intracranial hemorrhage (sICH), and 24-hour hemorrhagic transformation. Sex differences were assessed using Cox regression, generalized ordinal logistic models, and calculations of risk differences and ratios.

Results. Among 2278 patients in the READAPT cohort, 1643 individuals with mild-to-moderate stroke or high-risk TIA treated with DAPT were eligible for analysis (mean age 69.8 ± 12.0 years; 34.3% female). Propensity score matching yielded 531 women and 531 men with comparable baseline characteristics. Women had a significantly lower 90-day risk of new ischemic stroke or other vascular events than men (HR 0.53, 95% CI 0.28–0.99; $p=0.039$). No significant sex differences were detected for secondary effectiveness outcomes. Safety events were rare in both groups, with no differences between women and men (moderate-to-severe bleeding: 0.4% vs 0.8%, $p=0.413$; sICH: 0.2% vs 0.4%, $p=0.563$). Subgroup analyses suggested a lower 90-day risk of recurrent ischemic events among women who were younger than 50 years, had baseline NIHSS 0–5, pre-stroke mRS < 2 , a large-artery atherosclerosis etiology, or no diabetes.

Conclusions. In this real-world cohort, women with non-cardioembolic mild-to-moderate stroke or high-risk TIA treated with DAPT appeared to have a lower short-term risk of recurrent ischemic events than men. Additional investigations are warranted to clarify the biological, clinical, or treatment-related factors underpinning these potential sex-specific differences.

Introduction

Dual antiplatelet therapy (DAPT), most commonly consisting of aspirin combined with a P2Y₁₂ inhibitor such as clopidogrel, is a key strategy for secondary prevention in patients who have experienced a minor ischemic stroke or a high-risk transient ischemic attack (TIA).^{1–3} Although the overall benefit of DAPT in reducing early recurrent ischemic events is well established, recent evidence suggests that treatment effects and safety profiles may vary by sex.^{4–6} Increasing attention has been paid to sex-related differences in cardiovascular outcomes, which appear to involve variations in pharmacokinetic and pharmacodynamic responses and in the distribution of relevant comorbidities—factors that could influence response to antiplatelet therapy in men and women.^{6–8} Moreover, growing data indicate that platelet reactivity under antiplatelet treatment may differ between sexes, with potential implications for both efficacy and safety and important consequences for clinical decision-making.^{9,10}

Randomized trials consistently demonstrated that DAPT is superior to single antiplatelet therapy (SAPT) in preventing short-term recurrent vascular events in both sexes.^{1–3} Subgroup analyses from the CHANCE¹ and ATAMIS¹¹ trials did not show meaningful sex-related differences in the comparative efficacy of DAPT versus SAPT. In contrast, a secondary analysis of the POINT trial suggested a non-significant trend toward a lower risk of recurrent stroke among women under 60, compared with men (HR 0.66; 95% CI 0.42–1.05).¹² Importantly, women were underrepresented in these pivotal trials, typically accounting for 33.8% to 44.9% of enrolled patients.^{1–3} As a result, uncertainties remain regarding whether men and women derive similar benefits from—or face similar risks with—DAPT.

Furthermore, DAPT is frequently used in clinical scenarios that extend beyond the populations enrolled in landmark trials, including patients with more severe neurological deficits, higher pre-stroke disability, or those treated with acute reperfusion therapies.^{13–15} These broader clinical contexts reinforce the need for real-world studies capable of capturing sex-specific differences across a more heterogeneous and representative patient population.

In this study, we sought to evaluate whether short-term outcomes following DAPT differ between women and men within a real-world cohort of patients with non-cardioembolic mild-to-moderate ischemic stroke or high-risk TIA.

Methods

Data availability statement

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

READAPT study

The Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack – READAPT - study (NCT05476081) is an observational prospective multicenter real-world investigation coordinated by the University of L'Aquila and supported by the Italian Stroke Association – Associazione Italiana Ictus (ISA-AAII). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹⁶

The READAPT study enrolled all individuals aged ≥ 18 years, whether hospitalized or not, who suffered from acute non-cardioembolic stroke or TIA and received a brief course (i.e., up to 90 days) of DAPT irrespective of the time elapsed from symptoms onset and of stroke severity. Patients were recruited across 64 Italian Stroke centers from February 1st, 2021 to February 28th, 2023. All patients consecutively admitted to hospitals and emergency departments and assessed in open-access outpatient clinics for neurological emergency were recruited for the READAPT study. To maximize the inclusion of consecutive patients treated with DAPT, we provided local investigators with detailed guidelines and issued regular reminders. The diagnosis of the index stroke was adjudicated by investigators as per local practice and according to the criteria of the World Health Organization (WHO). Apart from diagnosis of acute non-cardioembolic stroke or high-risk ($ABCD_2 \geq 4$) TIA, no other criteria were provided to guide patient enrollment. Patients were considered eligible irrespective of the time elapsed between symptoms onset and DAPT initiation, as well as the specific antiplatelet combination used. Additionally, patients were included regardless of whether a loading DAPT dose (≥ 300 mg for aspirin and clopidogrel, or ≥ 180 mg for ticagrelor) was administered. The exclusion criteria were involvement in interventional randomized controlled trials at the onset of stroke, continuous DAPT for endovascular stenting procedures, and conditions that could potentially impact compliance with the study protocols. Patients were enrolled shortly after the index event and followed up for 90 ± 10 days, with local investigators conducting face-to-face or remote visits at the end of the follow-up period. READAPT study procedures and adopted definitions have been detailed in prior publications^{13–15}.

Study analysis

This is a post-hoc exploratory analysis of the READAPT study including patients with mild-to-moderate ischemic stroke (NIHSS score on admission of 0 to 10) or high-risk TIA (symptoms duration < 24 hours

and ABCD₂ score ≥ 4), regardless of the evidence of acute ischemic lesion(s) at neuroimaging (brain non-contrast computed tomography [NCCT] or magnetic resonance imaging [MRI]) who initiated DAPT within 48 hours of symptoms onset. For this analysis, we selected an upper NIHSS cutoff of 10 to include patients with moderate stroke (NIHSS 5 to 10), as recent evidence suggests the benefit of DAPT may extend to this subgroup¹⁵. Conversely, we excluded patients who underwent urgent carotid endarterectomy, or stenting procedures during the follow-up period. Additionally, we also excluded patients who were lost to follow-up or with last available follow-up earlier than 80 days after the index event, as well as those who early discontinued DAPT because of the diagnosis of a condition requiring anticoagulation. This latter exclusion was based on concerns about the potential confounding effect of anticoagulation-related bleeding risks on the safety assessment of DAPT.

Propensity score matching

We calculated propensity scores for each patient using a multivariable logistic regression model that included prespecified variables potentially acting as confounders when comparing sex subgroups: demographics (age, ethnicity), risk factors (arterial hypertension, diabetes, dyslipidemia, smoking status), pre-stroke functional status (mRS), stroke severity (NIHSS score on admission), symptoms duration (<24 hours or ≥ 24 hours), presumed stroke cause, acute stroke treatment (intravenous thrombolysis, endovascular thrombectomy), and DAPT characteristics (loading dose, days of DAPT duration). Female patients treated with DAPT were matched with male patients in a 1:1 ratio, within 0.1 standard deviations of the logit of the propensity score, using greedy nearest neighbor matching. The quality of the matching was assessed by comparing the standardized difference of means and the ratio of variances between the propensity scores of treatment groups, as well as by inspecting graphical distributions of propensity scores and covariates balance in the matched cohort.

Outcomes

The primary effectiveness outcome was the 90-day risk of ischemic stroke or other vascular events (i.e., transient ischemic attack, myocardial infarction, death due to vascular causes). The secondary effectiveness outcomes were the 90-day shift in patient mRS scores between women and men, 24-h early neurological improvement and deterioration (≥ 2 points decrease or increase in the NIHSS score from baseline, respectively), 90-day vascular death (defined as death due to stroke, systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death or arrhythmia) and 90-day all-cause mortality. The safety outcomes were 90-day moderate-to-severe bleeding events, any bleeding events, 90-day symptomatic intracranial hemorrhage (sICH) and 24-h hemorrhagic transformation. The severity of bleeding events was assessed according to the Global Utilization of

Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery (GUSTO) trial definitions¹⁷. sICH was defined as any intracranial hemorrhage with worsening of 4 or more points on the NIHSS score¹⁸. All outcomes were compared between unmatched and propensity score-matched groups (women versus men). The occurrence of all outcomes was adjudicated by local investigators through the electronic follow-up case-report form.

Statistical analysis

Categorical variables were reported as number and percentage, continuous variables as mean and SD or median and interquartile range (IQR), according to their distribution. For the primary effectiveness outcomes, the time-to-event 90-day risk of ischemic stroke and other vascular events was compared using Cox regression and the corresponding treatment effect was presented as hazard ratio (HR) and 95% confidence intervals (CIs). Kaplan-Meier hazard functions were used to compare the overall risk of ischemic stroke and other vascular events between sex groups and log-rank test was used to test differences. Competing risk analysis was carried out to estimate the cumulative incidence of new ischemic stroke and vascular events at 90 days, with death as a competing event that prevents occurrence of primary effectiveness outcome. Gray's test was used to assess equality of cumulative incidence functions for primary effectiveness outcome and all-cause death across sexes. For the secondary effectiveness outcomes, the 90-day shift of mRS scores was compared using an ordinal generalized linear model (GLM) and results were presented as Odds ratio (OR) with 95% CIs. Furthermore, we calculated risk differences and risk ratios (95% CIs) between groups for the rate of 24-h neurological improvement and 24-h neurological deterioration, while Cox regression analysis was used to compare the risk of 90-day vascular death and all-cause mortality. For all the safety outcomes, we also calculated risk differences and risk ratios with 95% CIs between the sex groups. All outcomes analyses were performed also in the unmatched cohort. Subgroup analysis of the primary effectiveness outcome in the matched cohorts was performed by calculating risk differences between sexes in 10 prespecified subgroups (age [<50 years or ≥ 50 years], NIHSS score on admission [0 to 5 or 6 to 10], presumed stroke cause, pre-stroke mRS [<2 or ≥ 2], symptoms duration [≥ 24 hours or <24 hours], intravenous thrombolysis, endovascular thrombectomy, history of diabetes). Lastly, we used a GLM model with sex, subgroup variable, and their interaction term as independent variables to assess the homogeneity in the effect of sex by each subgroup variable. The p value was presented for the interaction term. All statistical analyses were performed using R software, version 4.2. Statistical significance was set at a p value <0.05 .

Ethics statement

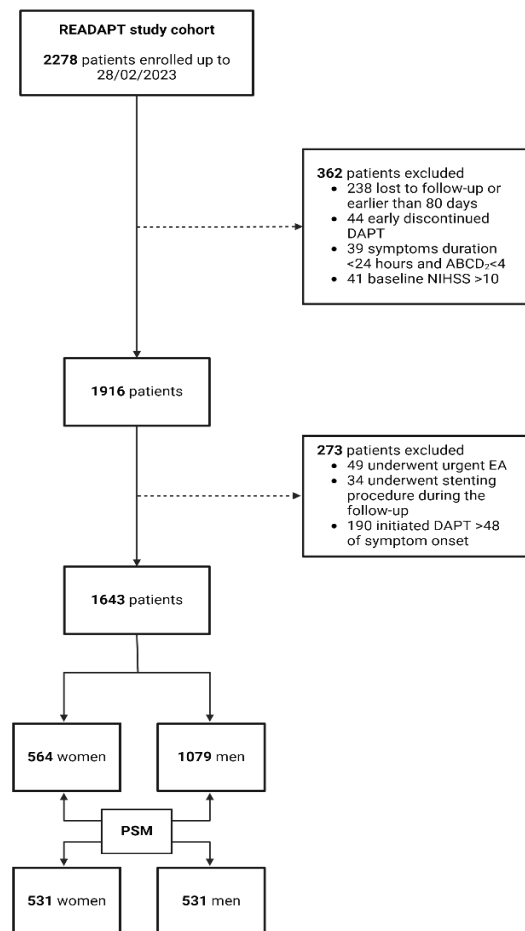
The READAPT study received approval from the Internal Review Board of the University of L'Aquila in February 2021 (code 03/2021). All patients were required to provide written informed consent in accordance with the Declaration of Helsinki.

Results

From 2278 patients in the READAPT study cohort, a total of 1643 patients (mean age 69.8 ± 12.0 years; 68.0% mild-to-moderate strokes and 32.0% high-risk TIAs) were included in the analysis, of whom 564 (34.3%) were women. The number of excluded patients with reasons is reported in the study flow-chart.

Figure 1 The proportion of patients lost to follow-up was comparable between women and men (11.4% and 9.8%, respectively; $p=0.198$).

Figure 1. Study flow-chart.



Abbreviations. DAPT: dual antiplatelet treatment; EA: endarterectomy; PSM: propensity-score matching.

Within the unmatched cohort, women were significantly older than men at the time of the index stroke (median age 74 years [IQR 64-81] versus 71 years [IQR 61-78]; $p<0.001$). The distribution of risk factors was similar between sex groups, except for a lower frequency of current cigarette smoking among women (27.1% versus 50.8%; $p<0.001$). **Table 1**

Table 1. Baseline characteristics.

	Unmatched cohort				Matched cohort			
	Women (n=564)	Men (n=1079)	Standardized difference*	P value	Women (n=531)	Men (n=531)	Standardized difference*	P value
Demographics								
Age, mean $\pm$ sd	71.7 $\pm$ 12.1	68.9 $\pm$ 11.8	0.239	<0.001	71.1 $\pm$ 12.0	70.2 $\pm$ 11.4	0.070	0.121
Ethnicity, n (%)			0.072	0.092			0.030	0.951
Non-Hispanic White	555 (98.4)	1052 (97.5)			523 (98.5)	525 (98.9)		
Hispanic White	1 (0.2)	7 (0.6)			1 (0.2)	1 (0.2)		
Black	3 (0.5)	16 (1.5)			3 (0.5)	2 (0.4)		
Other	5 (0.9)	4 (0.4)			4 (0.8)	3 (0.5)		
Clinical characteristics								
NIHSS $\leq$ 5 on admission, n (%)	521 (92.4)	1002 (92.9)	0.018	0.794	488 (91.9)	492 (92.7)	0.028	0.730
NIHSS 6-10 on admission, n (%)	43 (7.6)	77 (7.1)			43 (8.1)	39 (7.3)		
ABCD ₂ , median (IQR)**	4 (4-5)	4 (4-5)	0.065	0.489	4 (4-5)	4 (4-5)	0.026	0.785
mRS score category, n (%)			0.192	<0.001			0.001	0.966
No symptoms (score of 0), n (%)	409 (72.5)	875 (81.2)			408 (76.8)	408 (76.8)		
Symptoms without any disability (score of 1), n (%)	75 (13.3)	123 (11.4)			72 (13.6)	72 (13.6)		
Symptoms with mild disability (score of 2), n (%)	40 (7.1)	54 (5.0)			35 (6.6)	33 (6.2)		
Symptoms with mild-to-moderate disability (score of 3), n (%)	35 (6.2)	18 (1.7)			13 (2.4)	16 (3.0)		
Symptoms with moderate-to-severe disability (score of 4), n (%)	3 (0.5)	9 (0.8)			3 (0.6)	2 (0.4)		
Symptoms with severe disability (score of 5), n (%)	2 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)		
Symptoms duration <24 h, n (%)	195 (34.6)	331 (30.7)	0.082	0.121	182 (34.3)	191 (36.0)	0.036	0.607
Symptoms duration $\geq$ 24 h, n (%)	369 (65.4)	748 (69.3)			349 (65.7)	340 (64.0)		
Presumed stroke cause, n (%) ^a			0.110	0.172			0.030	0.764
Undetermined	267 (47.3)	463 (39.9)			248 (46.7)	239 (45.0)		
Small artery occlusion	163 (28.9)	318 (29.5)			155 (29.2)	149 (28.1)		
Large artery atherosclerosis	102 (18.1)	241 (22.3)			98 (47.6)	108 (20.3)		
Other determined cause	32 (5.7)	57 (5.3)			30 (5.7)	35 (6.6)		
Pre-stroke risk factors								
Arterial hypertension, n (%) ^b	464 (82.2)	856 (79.3)	0.077	0.175	433 (81.5)	426 (80.2)	0.029	0.640
Dyslipidemia, n (%) ^c	362 (64.2)	673 (62.4)	0.038	0.504	340 (64.0)	341 (64.2)	0.001	>0.999
Diabetes mellitus, n (%) ^d	139 (24.7)	295 (27.3)	0.063	0.264	134 (25.2)	127 (23.9)	0.031	0.669
Current smoking, n (%) ^e	153 (27.1)	548 (50.8)	0.532	<0.001	153 (28.8)	159 (29.9)	0.025	0.736

Previous TIA/ischemic stroke, n (%)	104 (18.4)	209 (19.4)	0.054	0.621	92 (17.3)	104 (19.6)	0.065	0.569
Previous intracerebral hemorrhage, n (%)	6 (1.1)	8 (0.7)	0.034	0.695	4 (0.2)	2 (0.4)	0.050	0.682
Hyperacute treatment, n (%)								
Intravenous thrombolysis, n (%)	106 (18.8)	188 (17.4)	0.013	0.535	102 (19.2)	104 (19.6)	0.001	0.938
Endovascular thrombectomy, n (%)	11 (2.0)	17 (1.6)	0.004	0.721	10 (1.9)	10 (1.9)	0.001	>0.999
Therapy on admission, n (%)								
Single antiplatelet treatment, n (%)								
Aspirin	200 (35.5)	376 (34.9)	0.013	0.847	184 (34.7)	194 (36.5)	0.039	0.564
Clopidogrel	37 (6.6)	71 (6.6)	0.001	>0.999	32 (6.0)	37 (7.0)	0.038	0.619
Ticagrelor	1 (0.2)	1 (0.1)	0.023	>0.999	1 (0.2)	1 (0.2)	0.001	>0.999
Antihypertensive drugs, n (%)	385 (68.3)	698 (64.7)	0.076	0.163	357 (67.2)	348 (65.5)	0.036	0.603
Lipid-lowering drugs, n (%)	199 (35.3)	330 (30.6)	0.100	0.060	179 (33.7)	172 (32.4)	0.028	0.696
Antidiabetics, n (%)	118 (20.9)	248 (23.0)	0.050	0.373	113 (21.3)	116 (21.8)	0.014	0.881
DAPT characteristics								
Type of DAPT, n (%)			0.080	0.191			0.133	0.123
Aspirin + clopidogrel	559 (99.1)	1076 (99.7)			527 (99.3)	531 (100.0)		
Aspirin + ticagrelor	5 (0.9)	3 (0.3)			4 (0.7)	0 (0.0)		
Days of DAPT, median (IQR)	21 (21-30)	21 (21-30)	<0.001	0.154	21 (21-30)	21 (21-30)	0.086	0.530
Loading dose, n (%)	290 (51.4)	610 (56.5)	0.102	0.054	278 (52.4)	286 (53.4)	0.030	0.667
Therapy on discharge								
Antihypertensive drugs, n (%)	491 (87.1)	918 (85.1)	0.057	0.310	460 (86.6)	459 (86.4)	0.006	>0.999
Lipid-lowering drugs, n (%)	515 (91.3)	981 (90.9)	0.014	0.861	486 (91.5)	494 (93.0)	0.056	0.421
Antidiabetics, n (%)	155 (27.5)	332 (30.8)	0.072	0.184	149 (28.1)	153 (28.8)	0.017	0.838
Type of antiplatelet continued after DAPT, n (%)								
Aspirin	347 (61.5)	668 (61.9)			328 (61.8)	314 (59.1)		
Clopidogrel	204 (36.2)	385 (35.7)			190 (35.8)	203 (38.2)		

*Abbreviations. DAPT: dual antiplatelet therapy; IQR: interquartile range; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; sd: standard deviation. Statistically significant P values (<0.05) are reported in bold. *: A standardized difference (of means) <0.10 indicates that groups are well balanced; **: Only patients with symptoms duration <24 hours; a: Presumed stroke cause was classified according to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system; b: Arterial hypertension was defined as a history of blood pressure >140/90 mmHg or the current use of antihypertensive medications; c: Dyslipidemia was defined as history of total blood cholesterol levels >220 mg/dL and/or total triglycerides levels >130 mg/dL and/or current used lipid-lowering drugs; d: Diabetes mellitus was defined as history of fasting glucose >126 mg/dL or the current use of hypoglycemic medications; e: Current smoking was defined as the consumption of ≥1 cigarette per day over the last year.*

We paired 531 women, and 531 men treated with DAPT. No missing data were recorded in the variables used to calculate the propensity scores, nor in any baseline variables within the unmatched and matched cohorts. Measures of balance diagnosis indicated that the samples were adequately matched, with a standardized difference of the propensity scores means between groups of 0.02 (good balance <0.25)¹⁹, ratio of variances of propensity scores 1.04 (good balance between 0.5-2)¹⁹. Graphics of propensity

scores and covariates balance distributions confirmed a good overall quality of the matching. **Figure 2 and 3**

Figure 2. Mirrored histogram of propensity scores distribution between unmatched and matched cohorts

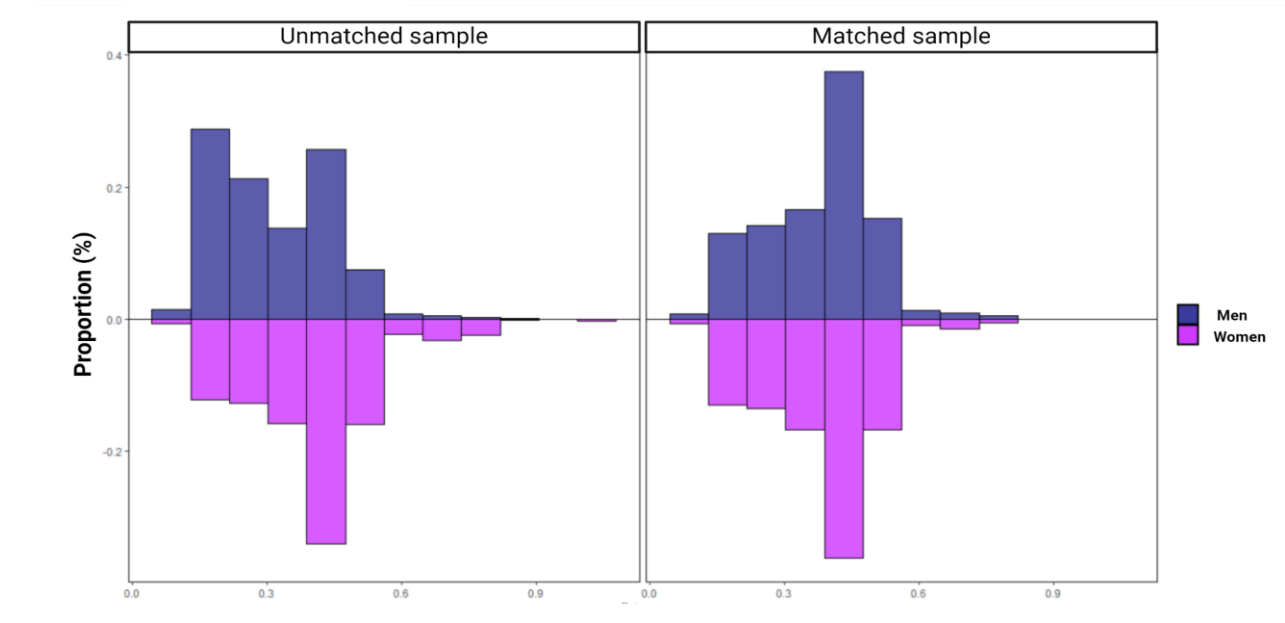
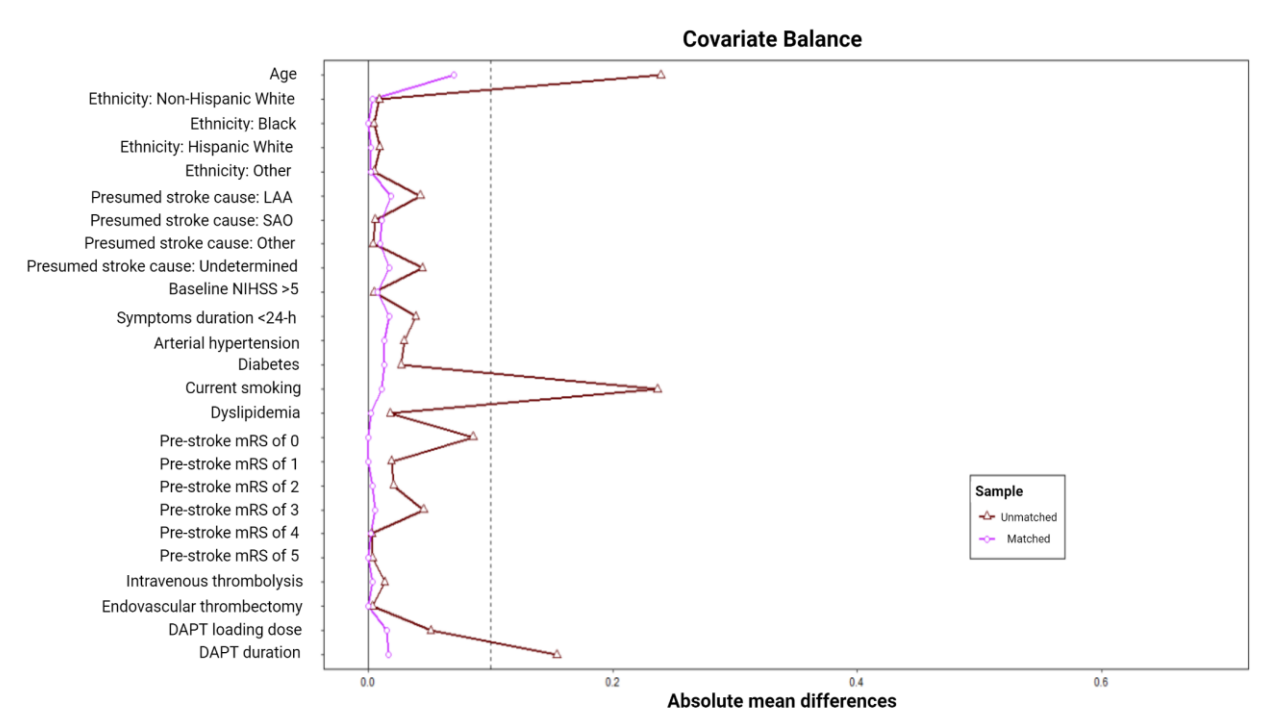


Figure 3. Love plot of covariate balance between women and men before and after propensity score matching



Abbreviations. DAPT: dual antiplatelet treatment; LAA: large artery atherosclerosis; mRS: modified Rankin Scale; NIHSS: National Institute of Stroke Scale; SAO: small artery occlusion.

The comparison of baseline characteristics further supported the good balance of our matched cohort with a standardized difference (SD) of the propensity scores <0.10 in all variables, except for DAPT type (SD=0.133). Nevertheless, aspirin plus clopidogrel was the predominant regimen (>99%) in both sexes. **Table 1**

Primary effectiveness outcome

The rate of 90-day new ischemic stroke or other vascular events was significantly lower in women than in men (HR 0.41 [95% CI 0.19 to 0.86]; p=0.019). **Table 2**

Table 2. Outcomes comparison in the matched cohort.

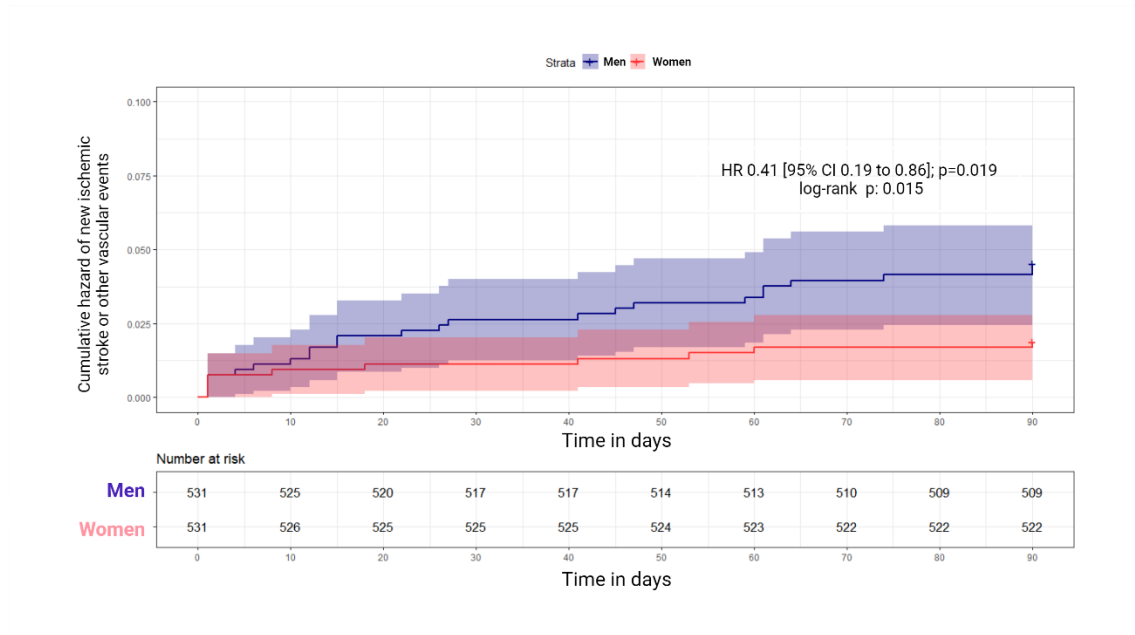
	Women (n=531)	Men (n=531)	Treatment effect metric	Treatment difference [95% CI]	P value
<i>Primary effectiveness outcome</i>					
90-day new ischemic stroke or other vascular events, n (%)	10 (1.8)	24 (4.5)	Hazard ratio	0.41 [0.19 to 0.86]	0.019
<i>Secondary effectiveness outcomes</i>					
90-day mRS score distribution					
No symptoms (score of 0), n (%)	256 (48.2)	260 (49.0)	Odds ratio	0.99 [0.87 to 1.14]	0.915
Symptoms without any disability (score of 1), n (%)	154 (29.0)	152 (28.6)			
Symptoms with mild disability (score of 2), n (%)	68 (12.8)	66 (12.4)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	40 (7.5)	34 (6.4)			
Symptoms with moderate-to-severe disability (score of 4), n (%)	8 (1.5)	12 (2.3)			
Symptoms with severe disability (score of 5), n (%)	1 (0.2)	1 (0.2)			
Death (score of 6), n (%)	4 (0.8)	6 (1.1)	Risk difference (%)	0.4 [-5.2 to 6.0]	0.895
24-hour early neurological improvement, n (%)	171 (32.2)	169 (31.8)			
			Risk ratio	1.01 [0.85 to 1.21]	
24-hour early neurological deterioration, n (%)	12 (2.3)	8 (1.5)	Risk difference (%)	0.8 [-0.8 to 2.4]	0.367
			Risk ratio	1.5 [0.62 to 3.64]	
90-day vascular death, n (%)	1 (0.2)	1 (0.2)	Hazard ratio	1.00 [0.06 to 15.97]	0.999
90-day all-cause death, n (%)	4 (0.8)	6 (1.1)	Hazard ratio	0.20 [0.02 to 1.71]	0.087
<i>Safety outcomes</i>					
90-day moderate-to-severe bleedings, n (%)	2 (0.4)	4 (0.8)	Risk difference (%)	-0.4 [-1.2 to 0.5]	0.413
			Risk ratio	0.50 [0.09 to 2.72]	
90-day any bleedings, n (%)	15 (2.8)	14 (2.6)	Risk difference (%)	0.2 [-1.8 to 2.2]	0.851
			Risk ratio	1.07 [0.52 to 2.20]	
90-day symptomatic intracranial hemorrhage, n (%)	1 (0.2)	2 (0.4)	Risk difference (%)	-0.2 [-0.8 to 0.5]	0.563
			Risk ratio	0.50 [0.05 to 5.50]	
24-h hemorrhagic transformation, n (%)	6 (1.1)	7 (1.3)	Risk difference (%)	-0.2 [-1.5 to 1.1]	0.780

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; Statistically significant *P* values (<0.05) are reported in bold.

Kaplan-Meier hazard functions showed that the overall 90-day risk of ischemic stroke and other vascular events was lower in women compared to men in the matched cohort (log-rank test *p*-value: 0.015).

Figure 4

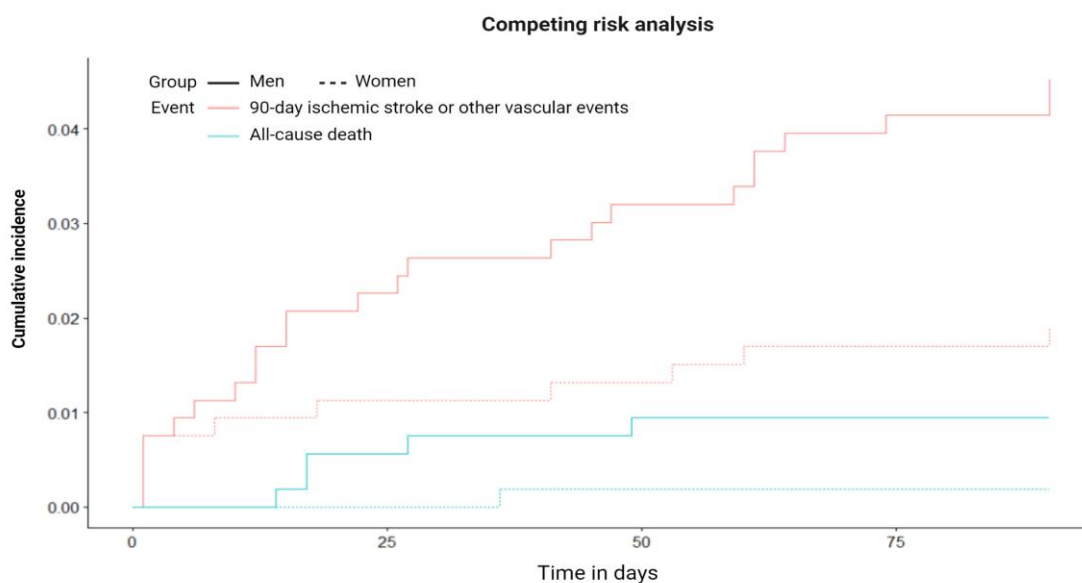
Figure 4. Kaplan Meier hazard function of new ischemic stroke or other vascular events at 90 days.



Abbreviations: CI: confidence intervals; HR: hazard ratio (women versus men). Shaded areas indicate 95% confidence intervals.

Competing risk analysis confirmed the lower cumulative incidence of recurrent ischemic stroke or other vascular events among women compared to men. **Figure 5**

Figure 5. Cumulative incidence of ischemic stroke and new vascular events at 90 days in competing risk analysis



Gray's test showed that cumulative incidence curves were statistically different for primary effectiveness outcome ($p=0.014$) but not for death ($p=0.101$). Results of the primary effectiveness outcome analysis in the unmatched cohort are shown in **Table 3**

Table 3. Outcomes comparison in the unmatched cohort.

	Women (n=564)	Men (n=1079)	Treatment effect metric	Treatment difference [95% CI]	P value
<i>Primary effectiveness outcome</i>					
90-day new stroke or other vascular events, n (%)	12	43	Hazard ratio	0.53 [0.28 to 0.99]	0.039
<i>Secondary effectiveness outcomes</i>					
90-day mRS score distribution					
No symptoms (score of 0), n (%)	257 (45.6)	544 (50.4)			
Symptoms without any disability (score of 1), n (%)	156 (27.7)	303 (28.1)			
Symptoms with mild disability (score of 2), n (%)	75 (13.3)	138 (12.8)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	53 (9.4)	57 (5.3)	Odds ratio	1.17 [1.04 to 1.32]	0.010
Symptoms with moderate-to-severe disability (score of 4), n (%)	15 (2.7)	24 (2.2)			
Symptoms with severe disability (score of 5), n (%)	3 (0.5)	3 (0.3)			
Death (score of 6), n (%)	5 (0.9)	10 (0.9)			
24-hour early neurological improvement, n (%)	183 (32.4)	317 (29.4)	Risk difference (%)	3.0 [-1.7 to 7.7]	0.211
			Risk ratio	1.10 [0.95 to 1.28]	

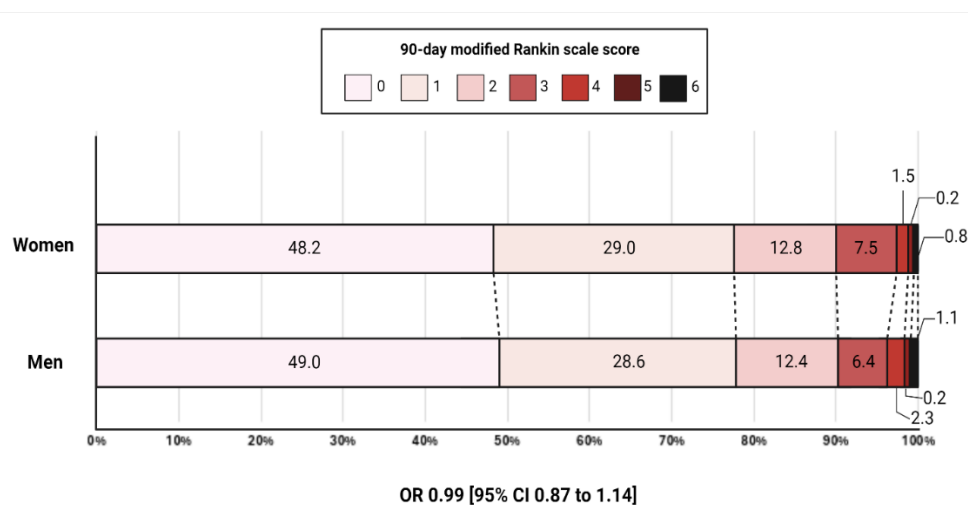
24-hour early neurological deterioration, n (%)	13 (2.3)	27 (2.5)	Risk difference (%)	-0.2 [-1.7 to 1.4]	0.803
			Risk ratio	0.92 [0.48 to 1.77]	
90-day vascular death, n (%)	1 (0.2)	1 (0.1)	Hazard ratio	1.91 [0.11 to 30.6]	0.650
90-day all-cause death, n (%)	5 (0.9)	10 (0.9)	Hazard ratio	0.32 [0.04 to 2.64]	0.229
Safety outcomes					
90-day moderate-to-severe bleedings, n (%)	3 (0.5)	10 (0.9)	Risk difference (%)	-0.4 [-1.2 to 0.4]	0.351
			Risk ratio	0.57 [0.16 to 2.08]	
90-day any bleedings, n (%)	16 (2.8)	35 (3.2)	Risk difference (%)	-0.4 [-0.2 to 1.3]	0.645
			Risk ratio	0.87 [0.49 to 1.57]	
90-day symptomatic intracranial hemorrhage, n (%)	1 (0.2)	3 (0.3)	Risk difference (%)	-0.1 [-0.6 to 0.4]	0.673
			Risk ratio	0.64 [0.07 to 6.11]	
24-h hemorrhagic transformation, n (%)	8 (1.4)	12 (1.1)	Risk difference (%)	1.28 [0.52 to 3.10]	0.591
			Risk ratio	0.3 [-0.8 to 1.5]	

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; Statistically significant P values (<0.05) are reported in bold.

Secondary effectiveness outcomes

The 90-day ordinal mRS distribution was similar between sexes (OR 0.99 [95% CI 0.87 to 1.14]; $p=0.913$). **Figure 6** Moreover, women and men showed similar rates of 24-h early neurological improvement or deterioration. The 90-day risk of vascular and all-cause mortality rates were very low and did not differ between women and men. **Table 2** Secondary effectiveness outcomes in the unmatched cohort are compared in **Table 3**

Figure 3. 90-day ordinal mRS distribution.



Abbreviations. CI: confidence interval; mRS: modified Rankin Scale score; OR: odds ratio (women versus men).

Safety outcomes

For the safety outcomes, we found a low rate of 90-day moderate-to-severe bleeding and any bleeding events in both women and men (0.4% versus 0.8% and 2.8% versus 2.6%, respectively). Hemorrhagic transformation at 24 hours occurred in 6 women (1.1%) and 7 men (1.3%). Symptomatic intracranial hemorrhage was extremely rare in both sex groups (0.2% of women versus 0.4% of men in the matched sample). There were no significant differences in the risk of any safety event between women and men both in unmatched and matched cohorts. **Table 2 and 3**

Subgroup analysis for the primary effectiveness outcome

Results of subgroup analysis for the primary effectiveness outcome in the matched cohort are presented in **Table 4** and **Figure 5**. Compared to men, we found a significantly lower frequency of 90-day new ischemic stroke or other vascular events in women aged <50 years (risk difference -21.8% [95% CI -40.2% to -3.5%]; p=0.019), those with baseline NIHSS of 0 to 5 (risk difference -2.6% [95% CI -4.9% to -0.4%]; p=0.019), large artery atherosclerosis etiology (risk difference -6.4% [95% CI -11.7% to -1.1%]; p=0.018), pre-stroke mRS <2 (risk difference -2.7% [95% CI -5.0% to -0.4%]; p=0.021), and no history of diabetes (risk difference -2.9% [95% CI -5.3% to -0.6%]; p=0.014). There was not significant risk difference between women and men across other subgroups. We found no heterogeneity when testing the interaction between sex and each subgroup variable. **Table 4**

Table 4. Primary effectiveness outcome by prespecified subgroups.

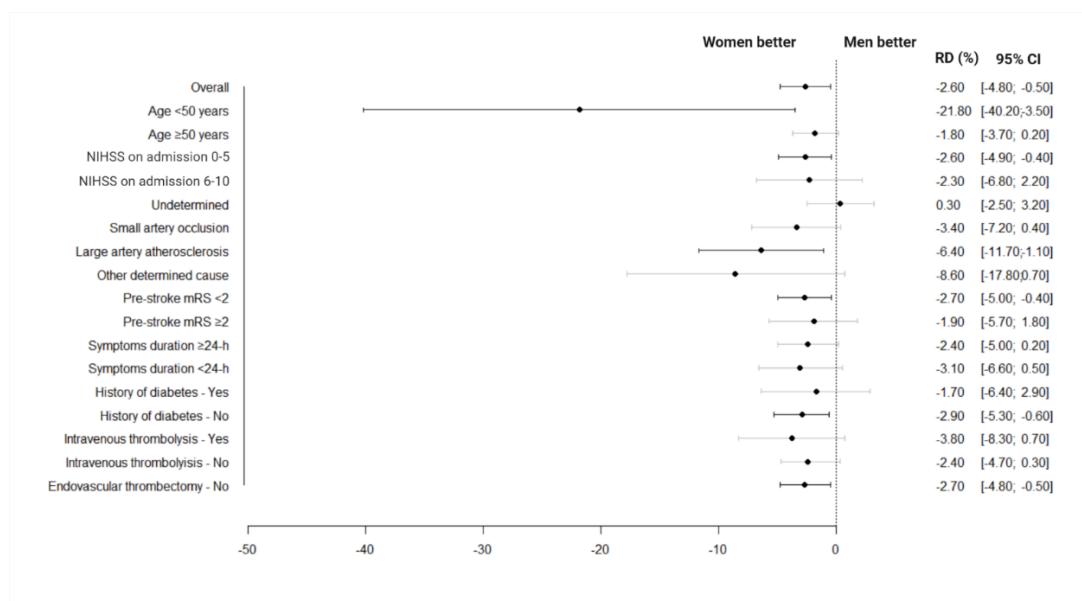
	No. of patients	No. of patients with primary effectiveness outcome/total No. (%)						
		Women	Men	Risk difference (%)	P value risk difference	Risk ratio	P value risk ratio	P value interaction
				[95 % CI]		[95 % CI]		
Overall	1062	10/531 (1.9)	24/531 (4.5)	-2.6 [-4.8 to -0.5]	0.014	0.42 [0.20 to 0.86]	0.015	
Age, years								
<50	56	1/32 (3.1)	6/24 (25.0)	-21.8 [-40.2 to -3.5]	0.019	0.12 [0.02 to 0.97]	0.015	0.121
≥50	1006	9/499 (1.8)	18/507 (3.6)	-1.8 [-3.7 to 0.2]	0.085	0.51 [0.23 to 1.12]	0.087	
NIHSS score on admission								
0-5	980	10/492 (2.0)	23/488 (4.7)	-2.6 [-4.9 to -0.4]	0.019	0.02 [0.21 to 0.90]	0.020	0.423
6-10	82	0/39 (0.0)	1/43 (2.3)	-2.3 [-6.8 to 2.2]	0.312	-	0.341	
Presumed stroke cause								
Undetermined	487	7/248 (2.8)	6/239 (2.5)	0.3 [-2.5 to 3.2]	0.831	1.12 [0.38 to 3.30]	0.831	
Small artery occlusion	304	2/155 (1.3)	7/149 (4.7)	-3.4 [-7.2 to 0.4]	0.082	0.28 [0.06 to 1.30]	0.080	0.074
Large artery atherosclerosis	206	1/98 (1.0)	8/108 (7.4)	-6.4 [-11.7 to -1.1]	0.018	0.14 [0.02 to 0.99]	0.025	
Other determined	65	0/30 (0.0)	3/35 (8.6)	-8.6 [-17.8 to 0.7]	0.071	-	0.103	

cause

Pre-stroke mRS								
<2	960	10/480 (2.1)	23/480 (4.8)	-2.7 [-5.0 to -0.4]	0.021	0.43 [0.21 to 1.03]	0.021	0.403
≥2	102	0/51 (0.0)	1/51 (2.0)	-1.9 [-5.7 to 1.8]	0.313	-	0.317	
Symptoms duration, h								
≥24	689	7/349 (2.0)	15/340 (4.4)	-2.4 [-5.0 to 0.2]	0.073	0.45 [0.19 to 1.10]	0.072	0.925
<24	373	3/182 (1.6)	9/191 (4.7)	-3.1 [-6.6 to 0.5]	0.088	0.34 [0.10 to 1.27]	0.094	
History of diabetes								
Yes	261	4/134 (3.0)	6/127 (4.7)	-1.7 [-6.4 to 2.9]	0.466	0.63 [0.18 to 2.19]	0.465	0.291
No	801	6/397 (1.5)	18/404 (4.5)	-2.9 [-5.3 to -0.6]	0.014	0.34 [0.14 to 0.85]	0.015	
Intravenous thrombolysis								
Yes	206	1/102 (1.0)	5/104 (4.8)	-3.8 [-8.3 to 0.7]	0.098	0.20 [0.02 to 1.71]	0.103	0.557
No	856	9/429 (2.1)	19/427 (4.5)	-2.4 [-4.7 to 0.3]	0.051	0.47 [0.22 to 1.03]	0.053	
Endovascular thrombectomy								
Yes	20	0/10 (0.0)	0/10 (0.0)	-	-	-	-	>0.999
No	1042	10/521 (1.9)	24/521 (4.6)	-2.7 [-4.8 to -0.5]	0.014	0.42 [0.20 to 0.86]	0.015	
DAPT loading dose								
Yes	564	4/278 (1.4)	12/286 (4.2)	-2.8 [-5.5 to -0.1]	0.047	0.34 [0.11 to 1.05]	0.049	0.533
No	498	6/253 (2.4)	12/245 (4.9)	-2.5 [-5.8 to 0.8]	0.132	0.48 [0.18 to 1.27]	0.131	

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; Statistically significant P values (<0.05) are reported in bold.

Figure 5. Forest plot of women versus men risk differences of the primary effectiveness outcome by prespecified subgroups.



Abbreviations. CI: confidence interval; DAPT: dual antiplatelet treatment; mRS: modified Rankin scale score; NIHSS: National Institute of Health Stroke Scale score; RD: risk difference.

Discussion

Our exploratory analysis of the prospective multicenter READAPT study offers new insights into potential sex-related differences in short-term outcomes among patients with mild-to-moderate ischemic stroke or high-risk TIA treated with DAPT in routine clinical practice. In this real-world cohort, women appeared to have a lower 90-day risk of new ischemic stroke or other vascular events compared with men.

Prior studies have yielded conflicting results on the relationship between sex and stroke recurrence.^{1–3,19–21} For instance, an analysis from the Swedish Stroke Register¹⁹ reported a higher recurrence risk in men even after adjusting for major demographic variables, although the proportion of patients receiving DAPT by sex was not specified. Conversely, randomized trials have generally not shown sex playing a major role in determining the effectiveness of DAPT versus SAPT, as illustrated by subgroup analyses of the CHANCE¹ and ATAMIS¹¹ trials. Notably, our cohort was largely composed of non-Hispanic White participants, whereas landmark trials enrolled more ethnically diverse populations.^{1–3} These differences in ethnic composition, baseline vascular risk, and possible variation in treatment responsiveness may limit direct comparison of our findings with previous randomized evidence.

Regarding functional outcomes, no sex differences were observed in the 90-day mRS distribution once baseline characteristics were balanced. Findings from population-based cohorts (e.g., the Framingham Study) have shown that women tend to exhibit greater post-stroke disability; however, after accounting for age and stroke subtype, these differences appear driven primarily by older age at stroke onset rather than by sex-specific biological factors.^{21,22} In our study, early neurological deterioration at 24 hours did not differ between sexes, aligning with observations from the ATAMIS trial subgroup analysis.¹¹ The frequency of early deterioration in women (2.3%) was lower than that reported in ATAMIS (5.3%), likely reflecting differences in the time window used to define deterioration (24 hours versus 7 days). We also did not detect sex differences in vascular or all-cause mortality at 90 days.

Bleeding events within 90 days were infrequent overall and did not differ between women and men, consistent with the excellent safety profile of short-term DAPT reported in earlier trials.^{1,2} This suggests that both sexes tolerate early DAPT similarly in the context of mild-to-moderate ischemic stroke or high-risk TIA.

Subgroup analyses revealed that the apparent benefit of DAPT among women was more pronounced in specific clinical contexts. Women aged <50 years had fewer recurrent vascular events than their male counterparts, whereas no difference emerged in older patients. This finding mirrors trends previously

reported in a secondary analysis of the POINT trial,¹² and may reflect the combination of higher prevalence and greater severity of conventional vascular risk factors in younger men,^{23,24} lifestyle influences (e.g., smoking frequency, lower engagement in preventive care),^{6,25} and age-related differences in residual platelet reactivity.²⁶ Hormonal factors may also contribute, as pre-menopausal women may retain some cardiovascular protection not present in younger men.²⁷

Women also showed lower recurrence rates when presenting with mild stroke severity (NIHSS 0–5), low pre-stroke disability (mRS <2), large-artery atherosclerotic etiology, and no diabetes. These findings may relate to interactions among baseline stroke severity, comorbidities, functional reserve, and adherence to therapy.^{23–25} In landmark DAPT trials, patients typically had lower stroke severity and minimal pre-stroke disability,^{1–3} potentially explaining why women in these lower-risk subgroups derived disproportionate benefit. We observed no sex differences in recurrence among patients with moderate stroke severity (NIHSS 6–10). Given the small number of moderate strokes in our study (7.8%) and the very low event rate (only one recurrence), larger studies are needed to clarify whether sex influences DAPT effectiveness among patients in this category. Regarding stroke etiology, women with large-artery atherosclerosis may have a lower intrinsic recurrence risk linked to sex-associated differences in plaque morphology—such as smaller, more fibrotic plaques with fewer vulnerability features.²⁸ Moreover, women may have higher levels of systemic and vascular inflammation in atherosclerosis.^{29,30} Since DAPT targets pathways central to both platelet aggregation and inflammation,¹⁰ this therapy might confer greater relative benefit in women with this stroke subtype. Finally, diabetes is known to affect stroke risk differently by sex,^{25,31} with stronger associations in women. The absence of diabetes in women may therefore contribute to the observed lower recurrence risk. These subgroup findings must nonetheless be interpreted with caution. Although we observed risk differences across several subgroups, formal interaction testing did not show significant heterogeneity between sex and subgroup variables, likely due to the low number of recurrent events. Residual confounding cannot be excluded.

Strengths and Limitations

A major strength of this study is the rigorous effort to ensure data accuracy and completeness, supported by regular quality checks of the READAPT electronic database. Nevertheless, several limitations must be acknowledged. First, despite propensity score matching, unmeasured confounding may remain—particularly because only patients treated with DAPT were included, making sex-related differences in treatment selection difficult to evaluate. With men representing more than two-thirds of the overall cohort and a substantial proportion of patients treated outside the strict criteria of landmark DAPT

trials,^{1–3} it is possible that women were preferentially selected for DAPT based on more conservative criteria, effectively resulting in a lower-risk subgroup. Propensity matching cannot fully account for such sex-related selection biases. Second, given that over 90% of both women and men had mild deficits, our statistical power to detect sex differences within moderate stroke subgroups was limited. In addition, analyses were exploratory and not based on pre-specified power calculations. Third, although all patients underwent brain NCCT or MRI at admission, detailed neuroimaging and vascular imaging data were unavailable, meaning stroke subtype adjudication relied on local investigators. Fourth, we were unable to assess antiplatelet pharmacodynamics or adherence, including drug levels, timing of onset of action, or pre-stroke antiplatelet activity. Fifth, patients who discontinued DAPT early because of anticoagulation needs were excluded; their outcomes were not captured at 90 days, limiting assessment of the effect of switching from DAPT to anticoagulation. Finally, the cohort was heavily skewed toward non-Hispanic White patients, limiting external generalizability. Moreover, the number of patients declining participation was not recorded, preventing evaluation of potential participation bias.

In summary, this real-world analysis provides new information on potential sex-based differences in short-term outcomes among patients with non-cardioembolic mild-to-moderate ischemic stroke or high-risk TIA treated with DAPT. Women appeared to experience fewer recurrent ischemic or vascular events at 90 days compared with men, with the difference particularly evident in younger women, those with mild deficits, preserved pre-stroke function, and without diabetes. Safety outcomes were excellent for both sexes, with very low bleeding rates. These exploratory findings underscore the need for further research to clarify the biological, clinical, and treatment-related mechanisms underlying sex differences in response to DAPT.

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2.1.3 Paper 3: Real-world outcomes following dual antiplatelet therapy in mild-to-moderate ischemic stroke with anterior versus posterior circulation infarct: a READAPT study propensity matched analysis

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Abstract

Background. Dual antiplatelet therapy (DAPT) is a cornerstone of secondary prevention in patients with minor ischemic stroke or high-risk TIA. The effectiveness and safety of DAPT may differ between patients with posterior (PCI) and anterior circulation infarct (ACI).

Objectives. We aimed to compare short-term outcomes following DAPT between mild-to-moderate stroke patients with PCI versus ACI.

Design. Propensity-matched analysis from a prospective real-world multicentric cohort study (READAPT).

Methods. We included patients with non-cardioembolic mild-to-moderate stroke (National Institute of Health Stroke Scale [NIHSS] of 0 to 10) who initiated DAPT within 48 hours of symptom onset. Patients were categorized into ACI or PCI based on the infarct(s) location on brain neuroimaging. The primary effectiveness outcome was the 90-day risk of ischemic stroke or other vascular events. The secondary effectiveness outcomes were the 90-day modified Rankin Scale (mRS) score distribution, 24-h early neurological improvement or deterioration and all-cause mortality. The safety outcomes included the 90-day risk of any bleedings and 24-h hemorrhagic transformation.

Results. We matched 281 PCI patients with 651 ACI patients. The 90-day risk of ischemic stroke or other vascular events was low and similar between PCI and ACI groups (3.1% versus 2.9%, respectively; HR 0.98, [95% CI 0.45 to 2.14]; $p=0.845$). Patients with PCI had worse 90-day mRS ordinal distribution compared to those with ACI (OR 1.18 [95% CI 1.01 to 1.39]; $p=0.046$). There were no differences in other secondary outcomes. Safety outcomes had low incidence and did not differ between groups (any bleedings: 3.2% versus 2.6%; 24-h hemorrhagic transformation: 1.8% versus 1.2%). We found no differences in the risk of ischemic stroke or other vascular events between patients with PCI and ACI across subgroups defined by sex, age, presumed stroke etiology, stroke severity, pre-stroke mRS, hypertension, diabetes, acute reperfusion therapies, DAPT loading dose, or presence of symptomatic intracranial stenosis.

Conclusion. Our findings suggest that effectiveness and safety outcomes after DAPT in patients with mild-to-moderate non-cardioembolic ischemic stroke are consistent regardless of infarct location in the anterior or posterior circulation territory. However, patients with PCI may experience worse short-term functional outcome.

Introduction

While most ischemic strokes occur in the anterior circulation, approximately 20% involve the posterior circulation, resulting from reduced blood flow to the brainstem, cerebellum, thalamus, and parieto-occipital lobes.¹ These two subtypes exhibit some differences in risk factors, etiology, prognosis, and therapeutic approaches.^{2,3} Anterior circulation infarctions (ACI) are more commonly associated with embolism,⁴ whereas posterior circulation infarctions (PCI) are more frequently lacunar.⁵ Diagnostically, PCI pose greater challenges due to their non-specific symptoms, which can lead to delayed recognition and treatment.⁶ Moreover, they are associated with a higher risk of stroke recurrences and early neurological deterioration,⁷ particularly in cases of large artery stenosis,⁸ and often result in worse functional outcomes compared to ACI.^{9,10}

Current international guidelines recommend early short-term dual antiplatelet therapy (DAPT) for all patients with minor ischemic stroke or high-risk transient ischemic attack (TIA).^{11,12} Although pivotal DAPT trials¹³⁻¹⁵ included patients regardless of the site of the acute infarct, they did not specifically analyze outcomes based on anterior or posterior circulation involvement. More recently, a secondary analysis from the Ticagrelor or Clopidogrel With Aspirin in High-Risk Patients With Acute Nondisabling Cerebrovascular Events 2 (CHANCE-2) trial found similar 90-day stroke recurrence rates between PCI and ACI patients with minor stroke or TIA who were treated with aspirin plus clopidogrel or ticagrelor.¹⁶ Additionally, a post hoc analysis of the Antiplatelet Therapy in Acute Mild to Moderate Ischemic Stroke (ATAMIS) trial revealed that, compared to mild-to-moderate stroke patients (baseline National Institute of Health Stroke Scale [NIHSS] of 0 to 10) with PCI, those with anterior circulation stroke experienced greater reduction in early neurological deficit with DAPT than with aspirin alone.¹⁷ In the real-world settings, the use of DAPT often extends beyond the indications of pivotal trials, potentially offering benefits to patients with greater stroke severity and those who have undergone acute reperfusion therapies.¹⁸⁻²⁰ Therefore, it is important to clarify whether outcomes following DAPT differ across diverse clinical scenarios and specific patient populations, such as those with PCI.

This study aimed to explore differences in short-term outcomes following DAPT in patients with non-cardioembolic mild-to-moderate ischemic stroke, comparing those with PCI versus ACI.

Methods

READAPT study

The READAPT study (NCT05476081) is a prospective, observational, multicenter investigation conducted within real-world clinical settings in Italy. Coordinated by the University of L'Aquila and

supported by the Italian Stroke Association, it adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research.²¹ The study enrolled adults aged 18 and above who had suffered an acute non-cardioembolic ischemic stroke or a transient ischemic attack (TIA) and were prescribed dual antiplatelet therapy (DAPT) for a duration of up to 90 days. The READAPT study was conducted between February 1, 2021, and February 28, 2023, and spanned 64 stroke centers nationwide. Participant recruitment occurred in hospital settings, emergency departments, and open-access neurology clinics. To maximize enrollment, investigators followed structured protocols and issued regular follow-up reminders. Diagnosis of stroke and TIA was established based on standard clinical assessments and the World Health Organization's criteria. All patients initiating DAPT following an acute non-cardioembolic ischemic event were eligible, with no constraints regarding the choice of antiplatelet agents or the timing of DAPT initiation. The decision to prescribe DAPT was left to the discretion of the treating physician, who determined suitability based on individual risk-benefit considerations. Patients were included irrespective of whether they received a loading dose of DAPT (defined as ≥ 300 mg for aspirin and clopidogrel or ≥ 180 mg for ticagrelor). The exclusion criteria were minimal, disqualifying only patients undergoing prolonged DAPT due to stent-related procedures, and those unable to adhere to study requirements. Participants were enrolled shortly after the qualifying ischemic event and monitored over a follow-up period of 90 ± 10 days through in-person or remote assessments. Methodological details and study definitions have been documented in prior publications.^{18,19}

Study analysis

For this secondary analysis, we selected only patients who experienced mild-to-moderate ischemic strokes (defined by a NIHSS score of 0 to 10 on admission) and had ≥ 1 brain infarct detected on admission or follow-up neuroimaging congruous with their stroke symptoms at onset. Selection was limited to those who started DAPT within 48 hours of symptom onset. In contrast, we excluded patients who were prescribed DAPT after carotid endarterectomy or stenting, as well as those who discontinued DAPT prematurely due to the initiation of anticoagulation therapy. These exclusions aimed to reduce potential confounding from procedure-related variables and anticoagulation-associated bleeding risks.

Patients were categorized as having either PCI or ACI based on the acute infarct(s) location. Infarct locations were determined according to the site of hyperintense lesions on the diffusion-weighted imaging (DW) sequences in patients who underwent brain magnetic resonance (MR), or on the site of new hypodense lesion(s) in patients who underwent only brain non-contrast computed tomography (NCCT). Similarly, the number of acute ischemic lesion(s) was assessed using DW sequences on brain MR when available or otherwise using brain NCCT. ACI was defined as the presence of acute infarct(s)

in territories perfused by the anterior cerebral artery, middle cerebral artery, or internal carotid artery, while PCI was defined as lesion(s) occurring in brain regions supplied by the posterior cerebral artery, cerebellar arteries, basilar artery, or vertebral artery. Patients with multiple acute infarcts involving both anterior and posterior circulation territories were categorized as PCI only if they presented exclusively with symptoms attributable to the involvement of posterior circulation territories – namely, isolated hemianopsia, ataxia, vertigo, diplopia, typical brainstem syndromes – otherwise they were categorized as ACI. This symptom-based criterion was adopted to ensure a clinically meaningful classification, in patients where determining the predominant infarct territory based on imaging alone was challenging. Of note, although the presence of lesions in both vascular territories may raise suspicion of a cardioembolic source, we included these patients in the main analysis, as individuals with a confirmed cardioembolic etiology were excluded in accordance with the original READAPT exclusion criteria.^{18,19} Thus, even if some cases may theoretically reflect a cardioembolic mechanism, their inclusion remains consistent with current guideline recommendations for DAPT in patients without confirmed cardioembolism.^{11,12} Conversely, isolated watershed infarcts in territories between the anterior and posterior circulation territories were excluded. The location of the acute infarct(s) was adjudicated by local senior neuroradiologists, who were provided with prespecified criteria. Neuroimaging investigations, including the choice of imaging modality, were conducted at the discretion of the treating physician. However, all patients included in the READAPT study underwent at least two brain imaging: one on admission and another after 24 hours.

Propensity score matching

We calculated propensity scores for each patient using a multivariable logistic regression model that included prespecified variables potentially acting as confounders when comparing PCI and ACI groups: demographics (age, ethnicity), risk factors (arterial hypertension, diabetes, dyslipidemia, smoking status), pre-stroke functional status (mRS), stroke severity (NIHSS score on admission), symptoms duration (<24 hours or $\geq$ 24 hours), presumed stroke cause, acute stroke treatment (intravenous thrombolysis, endovascular thrombectomy), DAPT characteristics (loading dose, days of DAPT duration), type of brain neuroimaging (brain MRI performed or not performed), infarcts in the anterior and posterior circulation territories. PCI and ACI patients were matched in a 1:3 ratio, within 0.1 standard deviations of the logit of the propensity score, using greedy nearest neighbor matching. The quality of the matching was assessed by comparing the standardized difference (SD) of means and the ratio of variances between the propensity scores of treatment groups, alongside inspecting graphical distributions of propensity scores and covariates balance in the matched cohort.

Study outcomes

The primary effectiveness outcome was the risk of new ischemic stroke or other vascular events within 90 days, including TIA, myocardial infarction, or death from vascular causes (stroke, systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmias). Secondary effectiveness outcomes encompassed the 90-day ordinal distribution of the modified Rankin Scale (mRS) scores and all-cause mortality within the same period, 24-h early neurological improvement and deterioration (≥ 2 points decrease or increase in the NIHSS score from baseline, respectively). Safety outcomes included 24-h hemorrhagic transformation, classified according to the Heidelberg bleeding classification system,²² and the 90-day incidence of any bleeding event, categorized based on the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification.²³ Specifically, severe bleeding was defined as fatal hemorrhage, intracranial hemorrhage, or hemorrhage requiring blood or fluid replacement, inotropic support, or surgical intervention. Moderate bleeding referred to events necessitating a transfusion but not posing an immediate life-threatening risk. All other bleeding events were classified as minor.²³

Statistical analysis

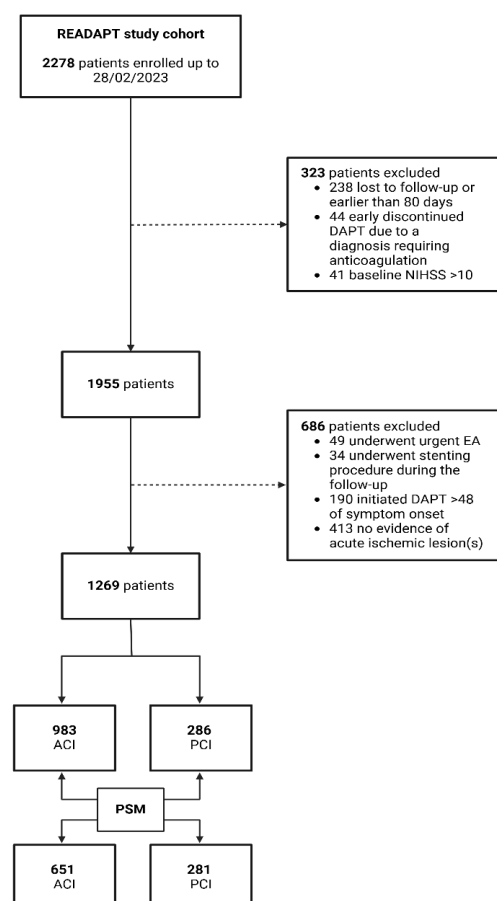
Categorical variables were reported as number and percentage, continuous variables as median and interquartile range (IQR). For the primary effectiveness outcomes, the time-to-event 90-day risk of ischemic stroke and other vascular events was compared using Cox regression and the corresponding treatment effect was presented as hazard ratio (HR) and 95% confidence intervals (CIs). Kaplan-Meier hazard functions were used to compare the overall risk of primary effectiveness outcome between patients with PCI and ACI and log-rank test was used to test differences. Furthermore, we conducted a sensitivity analysis excluding patients with multiple infarcts involving both anterior and posterior circulation territories to ensure the robustness of the primary effectiveness outcome in the matched cohorts. For the secondary effectiveness outcomes, the 90-day shift of mRS scores was compared using an ordinal generalized linear model (GLM) and results were presented as Odds ratio (OR) with 95% CIs. Furthermore, we calculated risk differences (and 95% CIs) between groups for the rate of 24-h neurological improvement and deterioration. Cox regression was used to compare the 90-day risk of all-cause mortality. For the safety outcomes, we calculated risk differences and 95% CIs between patients with PCI and ACI. All outcomes analyses were performed also in the unmatched cohort. Subgroup analysis of the primary effectiveness outcome in the matched cohorts was performed by calculating risk differences between infarct location in 10 prespecified subgroups (sex [males or females], age [<65 years or ≥ 65 years], NIHSS score on admission [0 to 5 or 6 to 10], presumed stroke cause, pre-stroke mRS [<2 or ≥ 2], history of hypertension and diabetes, acute reperfusion therapies, DAPT loading dose,

presence of symptomatic intracranial stenosis). Lastly, we used a GLM model with infarct location (PCI versus ACI), subgroup variable, and their interaction term as independent variables to assess the homogeneity in the effect of infarct location by each subgroup variable. The p value was presented for the interaction term. Since this was an exploratory analysis within an observational real-world study, no predetermined sample size was calculated a priori. All statistical analyses were performed using R software, version 4.2. Statistical significance was set at a p value <0.05.

Results

Overall, the READAPT study cohort included 2278 patients. Our study analysis included 1269 patients (median age 70, IQR 60-77), of whom 65.7% were males. The number of patients excluded with reasons are reported in the study flow-chart.

Figure 1. Study flow-chart.

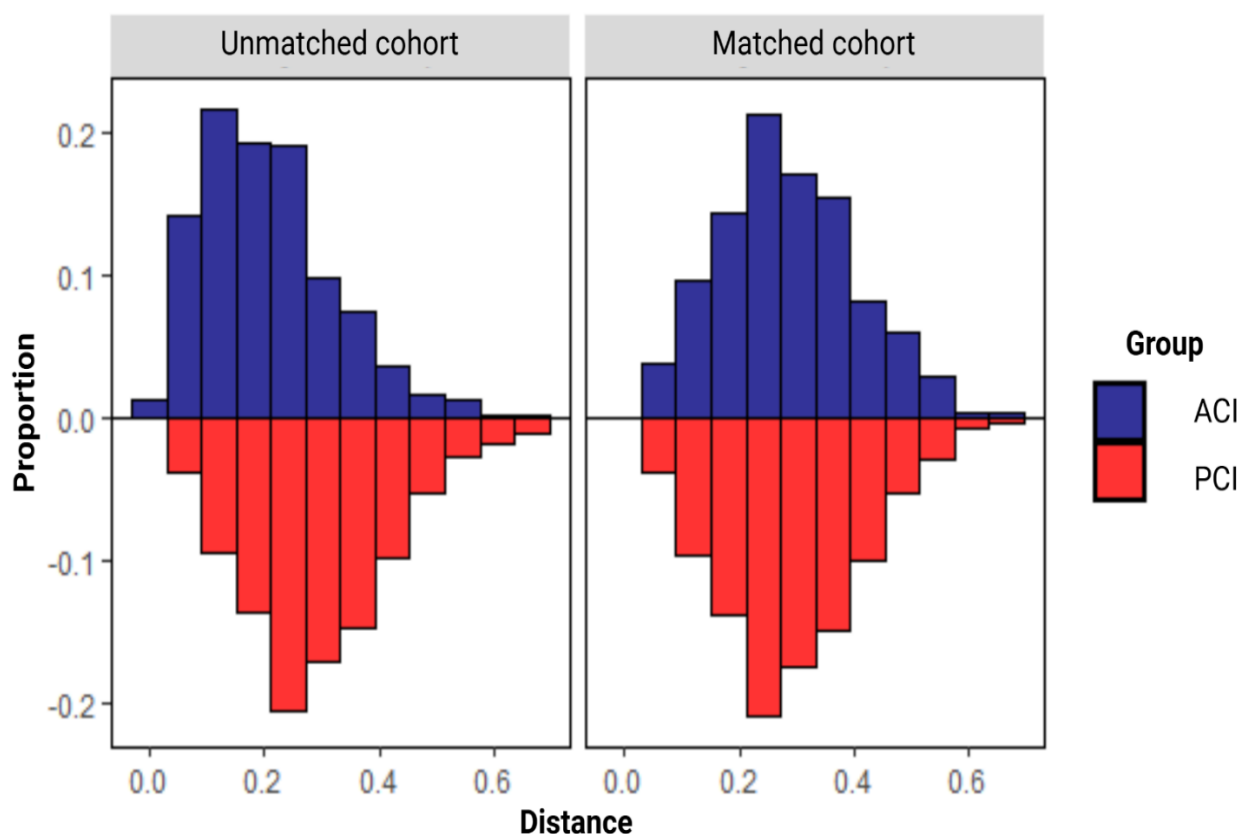


Abbreviations. ACI: anterior circulation infarct; DAPT: dual antiplatelet treatment; EA: endarterectomy; PCI: posterior circulation infarct; PSM: propensity-score matching.

A total of 286 patients (22.5%) were classified as PCI, while the remaining 983 patients (77.5%) were classified as ACI. Considering both admission and 24-h follow-up neuroimaging, brain MR was performed in 1,019 patients (80.3%), while 250 patients (19.7%) underwent only brain non-contrast computed tomography (NCCT). All patients underwent brain vessel imaging, using CT angiography (70.5%), MR angiography (38.8%), Doppler ultrasonography (13.4%) or digital subtraction angiography (4.6%).

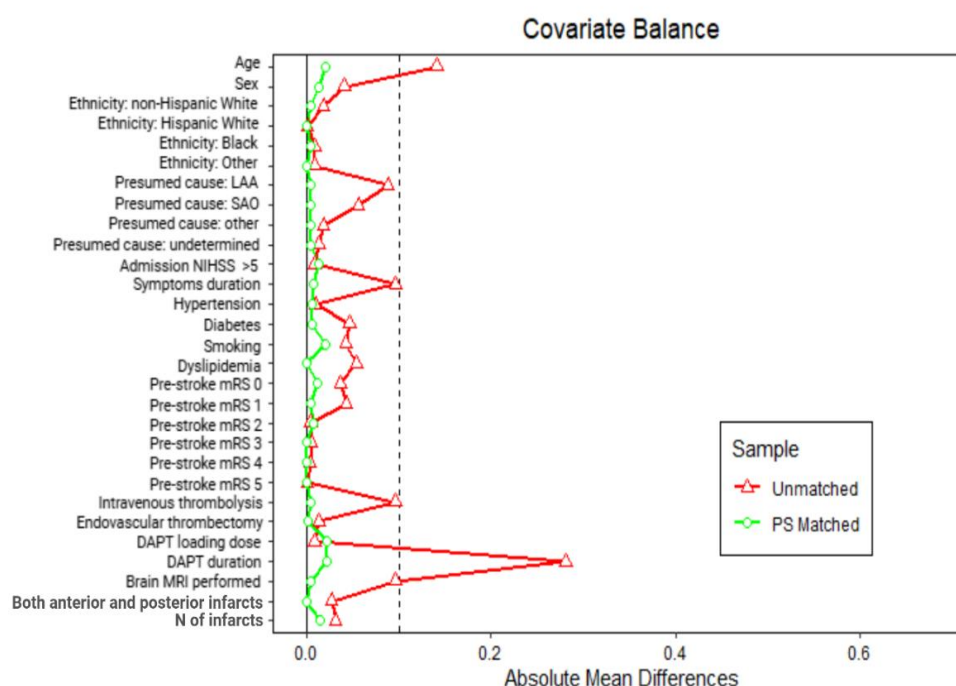
We matched 281 PCI patients with 651 ACI patients. No missing data were present in the variables used for propensity score calculation or in any baseline variable within both the unmatched and matched cohorts. Balance diagnostics confirmed that the samples were well-matched, with a standardized mean difference of propensity scores between groups at 0.02 (good balance <0.25)²⁴ and a propensity score variance ratio of 1.02 (good balance range: 0.5–2).²⁴ Graphical analyses of propensity scores and covariate balance distributions further supported the high quality of the matching. **Figures 2 and 3**

Figure 2. Mirror plot of covariate balance in the unmatched and matched cohorts



Abbreviations. ACI: anterior circulation infarct; PCI: posterior circulation infarct.

Figure 3. Love plot of covariate balance in the unmatched and matched cohorts.



Abbreviations. DAPT: dual antiplatelet treatment; LAA: large artery atherosclerosis; MR: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institute of Stroke Scale; SAO: small artery occlusion.

Furthermore, comparisons of baseline characteristics confirmed the strong balance of the matched cohorts, with SDs of propensity scores remaining below 0.20 for all variables, except for a higher prevalence of vertebrobasilar artery stenosis among patients with PCI (30.6% versus 6.3%; SD = 0.660) and a higher frequency of extracranial internal carotid artery stenosis among patients with ACI (17.7% versus 8.6%; SD = 0.273). **Table 1**

Table 1. Baseline characteristics.

	Unmatched cohorts			Matched cohorts		
	PCI (n=286)	ACI (n=983)	Standardized difference*	PCI (n=281)	ACI (n=651)	Standardized difference*
<i>Demographics</i>						
Sex – males, n (%)	197 (68.9)	597 (64.8)	0.087	194 (69.0)	432 (66.4)	0.057
Age, median (IQR)	68 (59-75)	70 (61-78)	0.140	68 (59-75)	69 (59-77)	0.066
Ethnicity, n (%)			0.116			0.065
Non-Hispanic White	274 (95.8)	960 (97.7)		270 (96.1)	631 (96.9)	
Hispanic White	2 (0.7)	6 (0.6)		2 (0.7)	4 (0.6)	
Black	6 (2.1)	12 (1.2)		5 (1.8)	11 (1.7)	
Other	4 (1.4)	5 (0.5)		4 (1.4)	5 (0.8)	
<i>Clinical characteristics</i>						
NIHSS on admission, median (IQR)	2 (1-4)	3 (2-4)	0.116	2 (1-4)	3 (2-4)	0.107

NIHSS ≤ 5 on admission, n (%)	257 (89.9)	875 (89.0)	0.028	254 (90.4)	581 (89.2)	0.038
NIHSS 6-10 on admission, n (%)	29 (10.1)	108 (11.0)		27 (9.6)	70 (10.8)	
mRS score category, n (%)			0.169			0.062
No symptoms (score of 0), n (%)	226 (79.0)	813 (82.7)		225 (80.1)	526 (80.8)	
Symptoms without any disability (score of 1), n (%)	42 (14.7)	102 (10.4)		38 (13.5)	77 (11.8)	
Symptoms with mild disability (score of 2), n (%)	12 (4.2)	37 (3.8)		12 (4.3)	31 (4.8)	
Symptoms with mild-to-moderate disability (score of 3), n (%)	6 (2.1)	26 (2.6)		6 (2.1)	17 (2.6)	
Symptoms with moderate-to-severe disability (score of 4), n (%)	0 (0.0)	4 (0.4)		0 (0.0)	0 (0.0)	
Symptoms with severe disability (score of 5), n (%)	0 (0.0)	1 (0.1)		0 (0.0)	0 (0.0)	
Symptoms duration <24 h, n (%)	17 (5.9)	153 (15.6)	0.314	17 (6.0)	44 (6.8)	0.029
Symptoms duration ≥ 24 h, n (%)	269 (94.1)	830 (84.4)		264 (94.0)	607 (93.2)	
Presumed stroke cause, n (%) ^a			0.218			0.105
Undetermined	105 (36.7)	374 (38.0)		105 (37.4)	240 (36.9)	
Small artery occlusion	82 (28.7)	337 (34.3)		82 (29.2)	217 (33.3)	
Large artery atherosclerosis	86 (30.1)	209 (21.3)		81 (28.8)	163 (25.0)	
Other determined cause	13 (4.5)	63 (6.4)		13 (4.6)	31 (4.8)	
Pre-stroke risk factors						
Arterial hypertension, n (%) ^b	223 (78.0)	776 (78.9)	0.024	219 (77.9)	509 (78.2)	0.060
Dyslipidemia, n (%) ^c	190 (66.4)	600 (61.0)	0.112	186 (66.2)	414 (63.6)	0.054
Diabetes mellitus, n (%) ^d	84 (29.4)	243 (24.7)	0.105	79 (28.1)	172 (26.4)	0.038
Current smoking, n (%) ^e	146 (51.0)	460 (46.8)	0.085	141 (50.2)	330 (50.7)	0.010
Previous TIA/ischemic stroke, n (%)	48 (16.8)	159 (16.2)	0.016	47 (16.7)	110 (16.9)	0.005
Previous intracerebral hemorrhage, n (%)	1 (0.3)	7 (0.7)	0.050	1 (0.4)	6 (0.9)	0.071
Hyperacute treatment, n (%)						
Intravenous thrombolysis, n (%)	32 (11.2)	205 (20.9)	0.226	32 (11.4)	95 (14.6)	0.095
Endovascular thrombectomy, n (%)	4 (1.4)	27 (2.7)	0.095	4 (1.4)	10 (1.5)	0.009
Therapy on admission, n (%)						
Single antiplatelet treatment, n (%)						
Aspirin	86 (30.1)	306 (31.1)	0.023	85 (30.2)	196 (30.1)	0.003
Clopidogrel	9 (3.1)	58 (5.9)	0.133	9 (3.2)	33 (5.1)	0.094
Ticagrelor	0 (0.0)	2 (0.2)	0.064	0 (0.0)	2 (0.3)	0.079
Antihypertensive drugs, n (%)	174 (60.8)	622 (63.3)	0.050	172 (61.2)	410 (63.0)	0.036
Lipid-lowering drugs, n (%)	80 (28.0)	278 (28.3)	0.007	78 (27.8)	178 (27.3)	0.009
Antidiabetics, n (%)	71 (24.8)	193 (19.6)	0.125	68 (24.2)	136 (20.9)	0.079
DAPT characteristics						
Type of DAPT, n (%)			0.024			0.037
Aspirin + clopidogrel	285 (99.7)	978 (99.5)		280 (99.6)	577 (99.4)	
Aspirin + ticagrelor	1 (0.3)	5 (0.5)		1 (0.4)	4 (0.6)	
Days of DAPT, median (IQR)	30 (21-90)	21 (21-45)	0.299			0.138
Loading dose, n (%)	161 (56.3)	545 (55.4)	0.017	159 (56.6)	380 (58.4)	0.036
Therapy on discharge						
Antihypertensive drugs, n (%)	235 (82.2)	811 (82.5)	0.009	231 (82.2)	536 (82.3)	0.003

Lipid-lowering drugs, n (%)	255 (89.2)	870 (88.5)	0.021	251 (89.3)	578 (88.8)	0.017
Antidiabetics, n (%)	82 (28.7)	260 (26.4)	0.050	77 (27.4)	183 (28.1)	0.016
<i>Type of antiplatelet continued after DAPT</i>			0.087			0.099
Aspirin, n (%)	174 (60.8)	637 (64.9)		170 (60.5)	425 (65.3)	
Clopidogrel, n (%)	104 (36.4)	324 (33.0)		103 (36.7)	210 (32.3)	
<i>Brain neuroimaging (admission and 24-h post-stroke)</i>						
Brain MR performed, n (%)	251 (87.8)	768 (78.1)	0.258	246 (87.5)	553 (84.9)	0.075
N of infarcts at brain imaging – median (IQR)	2 (2-3)	2 (2-3)	0.001			0.007
Infarcts in both anterior and posterior circulation territories, n (%)	10 (3.5)	61 (6.2)	0.126	10 (3.6)	28 (4.3)	0.038
<i>Brain vessel neuroimaging</i>						
Brain vessel CTA performed, n (%)	203 (71.0)	691 (70.3)	0.015	198 (70.5)	453 (69.6)	0.019
Brain vessel MRA performed, n (%)	134 (46.9)	359 (36.5)	0.211	133 (47.3)	261 (40.1)	0.146
Brain vessel Doppler US performed, n (%)	30 (10.5)	140 (14.2)	0.096	30 (10.7)	88 (13.5)	0.081
Brain vessel digital subtraction angiography, n (%)	15 (5.2)	43 (4.4)	0.041	14 (5.0)	24 (3.7)	0.064
Extracranial internal carotid artery stenosis, n (%) ^f	25 (8.7)	152 (15.5)	0.207	24 (8.5)	115 (17.7)	0.273
Vertebrobasilar artery stenosis, n (%) ^g	89 (31.1)	59 (6.0)	0.685	86 (30.6)	41 (6.3)	0.660
Symptomatic intracranial vessel stenosis, n (%) ^h	59 (20.6)	131 (13.3)	0.195	55 (19.6)	99 (15.2)	0.115

*Abbreviations. ACI: anterior circulation infarct; CTA: computed tomography angiography; DAPT: dual antiplatelet therapy; ECST: European Carotid Surgery Trial stenosis; IQR: interquartile range; MRA: magnetic resonance angiography; MR: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; sd: standard deviation; PCA: posterior circulation infarct; US: ultrasonography. Standardized differences >0.20 are reported in bold. *: A standardized difference (of means) <0.20 indicates that groups are well balanced; **: Only patients with symptoms duration <24 hours; a: Presumed stroke cause was classified according to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system; b: Arterial hypertension was defined as a history of blood pressure >140/90 mmHg or the current use of antihypertensive medications; c: Dyslipidemia was defined as history of total blood cholesterol levels >220 mg/dL and/or total triglycerides levels >130 mg/dL and/or current used lipid-lowering drugs; d: Diabetes mellitus was defined as history of fasting glucose >126 mg/dL or the current use of hypoglycemic medications; e: Current smoking was defined as the consumption of ≥1 cigarette per day over the last year; f: Extracranial internal carotid artery stenosis was defined as 50% to 99% stenosis or occlusion of the extracranial internal carotid artery, according to the European Carotid Surgery Trial stenosis (ECST) criteria; g: Vertebrobasilar artery stenosis was defined as 50% to 99% stenosis or occlusion of the vertebral or basilar artery.*

Primary effectiveness outcome

The rate of 90-day new ischemic stroke or other vascular events was low and similar between patients with PCI and ACI (3.1% versus 2.9%, respectively; HR 0.98 [95% CI 0.45 to 2.14]; p=0.845). **Table 2**

Table 2. Outcomes comparison in the matched cohort

	PCI (n=281)	ACI (n=651)	Treatment effect metric (PCI versus ACI)	Treatment difference (95% CI)	P value
<i>Primary effectiveness outcome</i>					
90-day new ischemic stroke or other vascular events, n (%)	8 (2.9)	20 (3.1)	Hazard ratio	0.92 (0.40 to 2.09)	0.845
<i>Secondary effectiveness outcomes</i>					
90-day mRS score distribution					

No symptoms (score of 0), n (%)	112 (39.9)	318 (48.8)			
Symptoms without any disability (score of 1), n (%)	93 (33.1)	180 (27.6)			
Symptoms with mild disability (score of 2), n (%)	42 (15.0)	85 (13.1)	Odds ratio	1.18 (1.01 to 1.39)	0.046
Symptoms with mild-to-moderate disability (score of 3), n (%)	24 (8.5)	49 (7.5)			
Symptoms with moderate-to-severe disability (score of 4), n (%)	5 (1.8)	13 (2.0)			
Symptoms with severe disability (score of 5), n (%)	1 (0.4)	2 (0.3)			
Death (score of 6), n (%)	4 (1.4)	4 (0.6)			
24-hour early neurological improvement, n (%)	52 (18.5)	156 (24.0)	Risk difference (%)	-5.6 (-11.0 to 0.1)	0.055
24-hour early neurological deterioration, n (%)	13 (4.6)	26 (4.0)	Risk difference (%)	0.6 (-2.2 to 3.5)	0.667
90-day all-cause death, n (%)	4 (1.4)	4 (0.6)	Hazard ratio	2.34 (0.58 to 9.33)	0.237

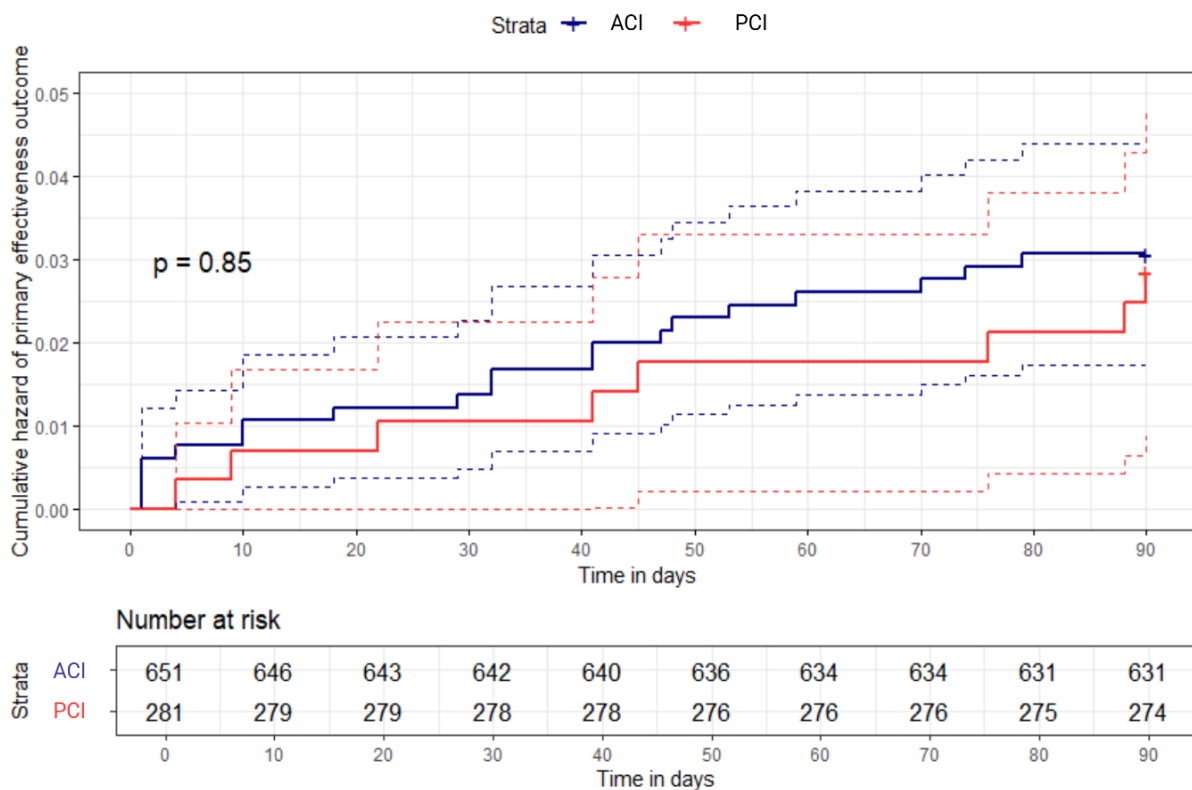
Safety outcomes

90-day any bleedings, n (%)	9 (3.2)	17 (2.6)	Risk difference (%)	0.6 (-1.8 to 3.0)	0.628
24-h hemorrhagic transformation, n (%)	5 (1.8)	8 (1.2)	Risk difference (%)	0.6 (-1.2 to 2.3)	0.540

Abbreviations. ACI: anterior circulation infarct; DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; PCI: posterior circulation infarct. Statistically significant P values (<0.05) are reported in bold.

Kaplan-Meier hazard functions showed no significant differences in the 90-day risk of ischemic stroke or other vascular events (long-rank test p-value: 0.850). **Figure 4**

Figure 4. Kaplan Meier hazard function of 90-day new ischemic stroke or other vascular events.



Abbreviations. ACI: anterior circulation infarct; PCI: posterior circulation infarct. Dashed lines indicate 95% confidence intervals.

Results of the primary effectiveness outcome analysis in the unmatched cohorts are reported in **Table 3**.

Table 3. Outcomes comparison in the unmatched cohort.

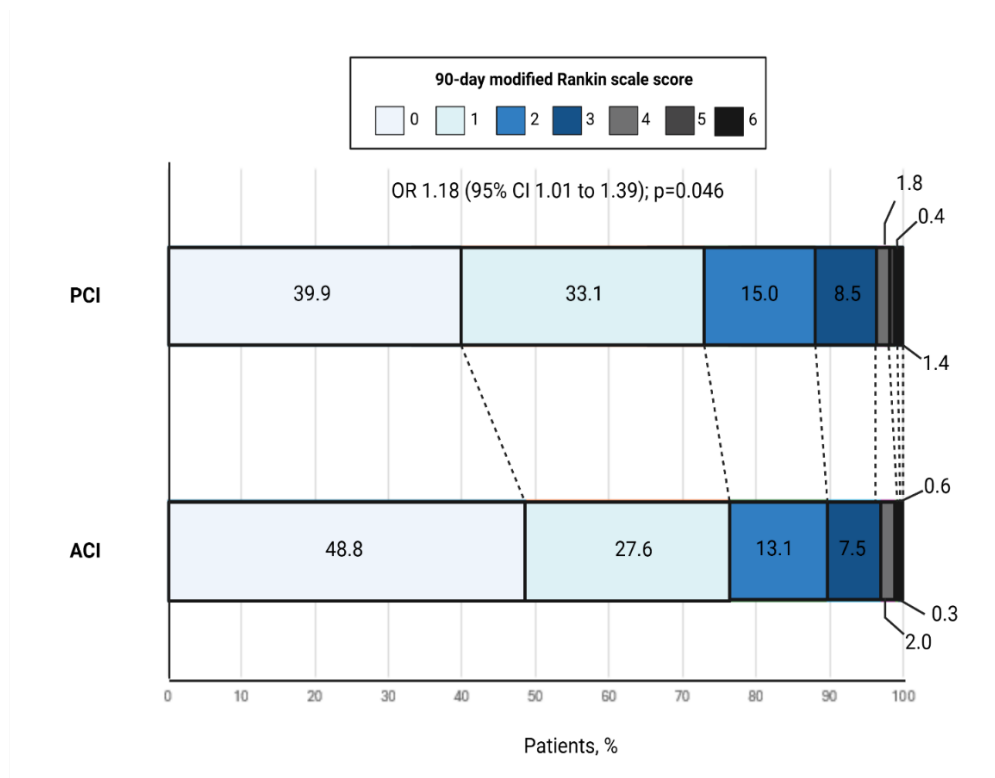
	PCI (n=286)	ACI (n=983)	Treatment effect metric (PCI versus ACI)	Treatment difference (95% CI)	P value
<i>Primary effectiveness outcome</i>					
90-day new ischemic stroke or other vascular events, n (%)	8 (2.8)	28 (2.8)	Hazard ratio	0.98 (0.45 to 2.14)	0.957
<i>Secondary effectiveness outcomes</i>					
90-day mRS score distribution					
No symptoms (score of 0), n (%)	113 (39.5)	497 (51.5)			
Symptoms without any disability (score of 1), n (%)	95 (33.2)	269 (27.4)			
Symptoms with mild disability (score of 2), n (%)	42 (14.6)	116 (11.8)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	24 (8.4)	62 (6.3)			
Symptoms with moderate-to-severe disability (score of 4), n (%)	6 (2.1)	24 (2.4)	Odds ratio	1.22 (1.04 to 1.43)	0.014
Symptoms with severe disability (score of 5), n (%)	1 (0.4)	5 (0.5)			
Death (score of 6), n (%)	5 (1.8)	10 (1.0)			
24-hour early neurological improvement, n (%)	52 (18.2)	283 (28.8)	Risk difference (%)	5.6 (0.4 to 10.8)	0.034
24-hour early neurological deterioration, n (%)	13 (4.5)	34 (3.4)	Risk difference (%)	1.1 (-1.6 to 3.8)	0.425
90-day all-cause death, n (%)	5 (1.7)	10 (1.0)	Hazard ratio	1.73 (0.59 to 5.06)	0.333
<i>Safety outcomes</i>					
90-day any bleedings, n (%)	9 (3.2)	25 (2.5)	Risk difference (%)	0.6 (-1.6 to 2.9)	0.599
24-h hemorrhagic transformation, n (%)	5 (1.7)	14 (1.4)	Risk difference (%)	0.3 (-1.4 to 2.0)	0.707

Abbreviations. ACI: anterior circulation infarct; DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; PCI: posterior circulation infarct. Statistically significant P values (<0.05) are reported in bold.

Secondary effectiveness outcomes

Patients with PCI had worse 90-day ordinal mRS distribution compared to those with ACI (OR 1.18 [95% CI 1.01 to 1.39]; p=0.046). **Table 2, Figure 5** There were no significant differences in other secondary effectiveness outcomes. Secondary effectiveness outcomes in the unmatched cohorts are compared in **Table 3**.

Figure 3. 90-day modified Rankin Scale scores distribution.



Abbreviations. ACI: anterior circulation infarct; CI: confidence interval; mRS: modified Rankin Scale score; PCI: posterior circulation infarct; OR: odds ratio (PCI versus ACI).

Safety outcomes

The 90-day risk of safety outcomes was low in both patients with PCI and ACI, without significant differences. Specifically, bleeding events occurred in 9 patients (3.2%) with PCI and 17 patients (2.6%) with ACI (risk difference 0.6% [95% CI -1.8% to 3.0%]; p=0.628). Bleeding events were predominantly minor in both groups, accounting for 88.8% of total bleedings in patients with PCI and

70.6% in those with PCI. Moderate-to-severe bleedings occurred in only one patient (0.4%) with PCI and 5 patients (0.8%) with ACI. There was no significant difference in bleeding severity between groups (p=0.485). The risk of 24-h hemorrhagic transformation was similarly low in both patients with PCI and ACI (1.8% versus 1.2%, risk difference 0.6% [95% CI -1.2% to 2.3%]; p=0.540). **Table 2** Safety outcomes in the unmatched cohorts are compared in **Table 3**.

Subgroup analysis for the primary effectiveness outcome

Results of subgroup analysis for the primary effectiveness outcome in the matched cohorts are shown in **Table 4**. There was no significant difference in the 90-day risk of new ischemic stroke or other vascular events between patients with PCI and ACI across any prespecified subgroup. Interaction analysis revealed no heterogeneity. **Table 4**

Table 4. Primary effectiveness outcome by prespecified subgroups.

	No. of patients	No. of patients with primary effectiveness outcome/total (%)		Risk difference (%) (95 % CI)	P value risk difference	P value interaction
		PCI	ACI			
<i>Overall</i>	932	8/281 (2.8)	20/651 (3.1)	-0.3 (-2.6 to 2.1)	0.851	-
<i>Sex</i>						0.538
Males	626	7/194 (3.6)	15/432 (2.5)	1.1 (-3.0 to 3.3)	0.924	
Females	306	1/87 (1.1)	5/219 (2.3)	-1.2 (-4.1 to 1.8)	0.457	
<i>Age, years</i>						0.711
<65	389	4/122 (3.3)	8/267 (3.0)	0.3 (-3.4 to 4.0)	0.883	
≥65	543	4/159 (2.5)	12/384 (3.1)	-0.6 (-3.5 to 3.4)	0.989	
<i>NIHSS score on admission</i>						0.986
0-5	835	8/254 (3.1)	19/581 (3.3)	-0.2 (-2.7 to 2.4)	0.928	
6-10	97	0/27 (0.0)	1/70 (1.4)	-1.4 (-4.2 to 1.3)	0.314	
<i>Presumed stroke cause</i>						0.296
Undetermined	345	2/105 (1.9)	9/240 (3.8)	-1.9 (-5.4 to 1.7)	0.309	
Small artery occlusion	299	4/82 (4.9)	4/217 (1.8)	3.1 (-2.0 to 8.0)	0.234	
Large artery atherosclerosis	244	2/81 (2.5)	6/163 (3.7)	-1.2 (-5.7 to 1.2)	0.593	
Other determined cause	44	0/13 (0.0)	1/31 (3.2)	-3.2 (-9.5 to 3.2)	0.309	
<i>Pre-stroke mRS</i>						0.833
<2	866	7/263 (2.7)	17/603 (2.8)	-0.1 (-2.3 to 3.1)	0.783	
≥2	66	1/18 (5.6)	3/48 (6.3)	0.7 (-13.3 to 11.9)	0.914	
<i>History of hypertension</i>						0.854
Yes	728	7/219 (3.2)	17/509 (3.3)	-0.1 (-2.9 to 2.7)	0.920	
No	204	1/62 (1.6)	3/142 (2.1)	-0.5 (-4.4 to 3.4)	0.803	
<i>History of diabetes</i>						0.541
Yes	251	2/79 (2.5)	7/172 (4.1)	-1.5 (-6.1 to 3.0)	0.508	
No	681	6/202 (3.0)	13/479 (2.7)	0.3 (-2.5 to 3.0)	0.855	
<i>Intravenous thrombolysis</i>						0.099
Yes	127	2/32 (6.3)	1/95 (1.1)	5.2 (-3.4 to 13.8)	0.238	

No	805	6/249 (2.4)	19/556 (3.4)	-1.0 (-3.4 to 1.4)	0.417	
<i>Endovascular thrombectomy</i>						
Yes	14	0/4 (0.0)	0/10 (0.0)	-	>0.999	>0.999
No	918	8/277 (2.9)	20/641 (3.1)	-0.2 (-2.6 to 2.2)		
<i>DAPT loading dose</i>						0.605
Yes	539	3/159 (1.9)	10/380 (2.6)	-0.7 (-3.4 to 1.9)	0.583	
No	393	5/122 (4.1)	10/271 (3.7)	0.4 (-3.7 to 4.6)	0.848	
<i>Symptomatic intracranial stenosis</i>						0.744
Yes	154	2/55 (3.6)	3/99 (3.0)	0.6 (-5.4 to 6.6)	0.843	
No	778	6/226 (2.7)	17/552 (3.1)	-0.4 (3.0 to -2.1)	0.743	

Abbreviations. DAPT: dual antiplatelet treatment; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale.

Sensitivity analysis for the primary effectiveness outcome

Our sensitivity analysis of the primary effectiveness outcome, performed after excluding patients with multiple acute lesions involving both the anterior and posterior circulation territories, confirmed that the 90-day risk of new ischemic stroke or other vascular events did not differ between patients with PCI and ACI (3.0% versus 2.9%, respectively; HR 1.02, [95% CI 0.44–2.35]; $p=0.968$). Among patients with multiple infarcts involving both circulation territories, no events were observed in those classified as PCI, while 2 events occurred in those classified as ACI (0% versus 7.1%, respectively), with no statistically significant difference ($p=0.366$).

Discussion

This propensity-matched analysis from the READAPT study demonstrated that patients with non-cardioembolic mild-to-moderate ischemic stroke involving the posterior or anterior circulation territory had a similarly low incidence of new ischemic events at 90 days. Notably, this finding remained consistent across prespecified subgroups supporting its applicability to diverse patient populations, including those with moderate stroke severity and those who underwent acute reperfusion therapies. Additionally, no significant differences were observed in the risk of 24-hour early neurological deterioration. However, patients with PCI experienced worse 90-day functional outcome compared to those with ACI. The 90-day risk of bleeding complications following DAPT was low and did not differ based on the vascular territory affected by the index stroke. Overall, these findings further support DAPT as an effective and safe option for secondary stroke prevention in patients with mild-to-moderate stroke, regardless of stroke location.

Within our cohort, the incidence of new ischemic strokes or other vascular events at 90 days was similarly low in both PCI and ACI patients (2.9% versus 3.1%). This contrasts with a previous study suggesting a higher risk of stroke recurrence in minor stroke or TIA patients with PCI compared to those with ACI.⁸ However, the study included patients with milder symptoms, and not all received DAPT, as it predated its routine use.⁸ Additionally, the time from symptom onset to treatment was not specified, introducing potential inconsistencies.⁸ A recent secondary analysis CHANCE-2 trial found no difference in the risk of 90-day stroke recurrence between PCI and ACI patients with minor stroke or TIA treated with aspirin plus clopidogrel or ticagrelor,¹⁶ aligning with our findings. However, the rate of new ischemic events was consistently higher compared to our population both in patients with PCI (8.3%) and ACI (7.4%).¹⁶ The observed effectiveness of DAPT in reducing the risk of new ischemic stroke in our cohort may appear greater than that reported in the CHANCE-2 trial.¹⁶ This discrepancy could be attributed to differences in baseline risk profiles, such as the predominance of Asian patients (>95% in the CHANCE-2 trial)¹⁶, who are known to have a higher risk of vascular recurrences compared to European patients.²⁵ Additionally, optimal control of comorbidities may have further contributed to the reduced incidence of new vascular events in our population, as more than 80% of patients were discharged on concomitant therapy targeting vascular risk factors. Furthermore, the relatively low prevalence of vertebrobasilar stenosis among PCI patients in our population (30.6%) may have influenced the results, as this condition is known to be associated with a higher risk of recurrent ischemic events.⁸

For the secondary effectiveness outcomes, we observed a worse distribution of 90-day mRS scores among PCI versus ACI patients, consistent with previous studies.^{9,10} Patients with PCI often experience strokes involving critical brainstem structures, the cerebellum, or the thalamus, which can lead to disabling symptoms such as ataxia, dysphagia, dysarthria, or ocular movement abnormalities. These deficits, even in the absence of significant motor impairment, may contribute to a worse functional outcome at 90 days despite similar ischemic event rates.²⁶ Notably, while patients with PCI had significantly worse 90-day mRS scores than those with ACI in the unmatched cohort (**Supplementary Table 1**), this difference was attenuated after matching, remaining marginally significant ($p=0.046$). Thus, we cannot rule out that this residual difference was due to unmeasured confounders. Conversely, the observed rate of early neurological deterioration was similarly low in both patients with PCI and ACI (4.6% versus 4.0%). This finding aligns with prior evidence suggesting that early DAPT may be effective in preventing thrombus propagation in atheromatous branches during the acute phase, even in patients with PCI, which are more prone to early deterioration (reported rates ranging from 10.3% to 28.6%)^{7,27} due to limited collateral circulation, increased susceptibility to branch atheromatous disease, and greater

hemodynamic vulnerability of posterior circulation penetrating arteries in respect to those supplying anterior brain territories. On the other hand, a post hoc analysis of the ATAMIS trial suggested that DAPT may be more effective in reducing the risk of early neurological deterioration in patients with mild-to-moderate posterior circulation stroke compared to those with anterior circulation involvement.¹⁷ However, early neurological deterioration was assessed over a longer time window (up to 7 days), and there were differences in the distribution of stroke causes, including a higher proportion of patients with undetermined etiology (>50%).¹⁷

For the safety outcomes, the overall incidence of 90-day bleeding events and 24-h hemorrhagic transformation was low across our study population, consistent with findings from DAPT landmark trials.¹³⁻¹⁵ Notably, the majority of bleeding events (>70%) were mild in severity in both PCI and ACI patients. This result indicates a consistent and favorable safety profile for DAPT across different infarct locations, with no evidence of varying intracerebral bleeding risk between PCI and ACI patients.

Lastly, we observed no significant differences in the risk of new ischemic events between PCI and ACI patients across subgroups stratified by sex, age, presumed stroke etiology, stroke severity, pre-stroke mRS, hypertension, diabetes, acute reperfusion therapies, DAPT loading dose, or the presence of symptomatic intracranial stenosis. This finding suggests that patients with non-cardioembolic mild-to-moderate stroke may derive similar benefits from early DAPT, regardless of whether the infarct affects brain areas supplied by the anterior or posterior circulation, across key clinical and demographic subgroups. In particular, the absence of a significant risk difference between PCI and ACI patients with mild (NIHSS 0 to 5) or moderate (NIHSS 6 to 10) stroke severity reinforces previous evidence supporting DAPT as an effective treatment option also for moderate stroke patients,^{20,28} which were excluded from pivotal DAPT trials,¹³⁻¹⁵ suggesting that its effectiveness might not be influenced by the affected vascular territory, even in this specific patient population.

Strengths and limitations

The main strengths of this study lie in the adoption of rigorous procedures to ensure data quality, reinforced by regular quality checks of the READAPT electronic database, and the implementation of propensity score matching to control for confounders. However, we cannot rule out residual confounding. Although all patients underwent at least one brain neuroimaging at admission and one after 24 hours, a proportion of patients (19.7%) underwent only brain NCCT. Therefore, we cannot rule out that some brain infarcts, particularly small lesions or those in the posterior circulation, have gone undetected due to the use of NCCT alone, which has lower sensitivity compared to MR. This may have led to patient exclusion, misclassification, or underestimation of the number of acute infarcts.

Specifically, if any lesions were missed, it is possible that some patients actually had multiple infarcts potentially indicative of an underlying cardioembolic source. Nevertheless, brain MR was performed at admission or after 24 hours in most of the patients who were excluded due to negative neuroimaging (84.6%). Also, to account for this potential confounder, we matched patients with PCI and ACI based on the type of brain neuroimaging performed. Similarly, patients with multiple acute infarcts involving both circulations were categorized according to a symptom-based approach. Nonetheless, we cannot completely exclude the possibility that some of these patients had mixed symptomatology that was not fully captured. However, this potential source of misclassification was accounted for in the matching process, and these cases represented only a small proportion (4.8%) of the total study population. Moreover, we performed a sensitivity analysis by excluding these patients, yielding consistent results with the overall study analysis. Another limitation was the use of the NIHSS score, which is known to underestimate the severity of posterior circulation strokes.²⁹ This may have led to an imbalance between groups that was not fully addressed by propensity score matching. Since stroke severity is a strong predictor of long-term functional outcomes,³⁰ any mismatch in actual severity between groups could have influenced the comparison of 90-day mRS scores. However, given that we observed a worse 90-day mRS score distribution in patients with PCI versus ACI, this limitation likely impacted the magnitude of this finding rather than its overall direction. Additionally, outcomes adjudication was performed by local investigators who were not blinded to the infarct location, which may have biased the assessment of some outcomes, such as the 90-day mRS score. Notably, the READAPT study included a short-term follow-up of 90 days, in line with pivotal DAPT trials;¹³⁻¹⁵ however, this follow-up period may have been too short to detect differences in outcomes following DAPT between PCI and ACI patients. Longer-term follow-up studies are needed to confirm whether the absence of a significant difference in the risk of new ischemic stroke and major bleeding events after DAPT persists beyond the 90-day follow-up period. Furthermore, patients who discontinued DAPT early due to the need for anticoagulation were excluded from this analysis. Although this group represented only 1.9% of the initial READAPT population (**Figure 1**), their 90-day outcomes were not recorded, preventing an assessment of the impact of transitioning from DAPT to anticoagulation on outcomes. Lastly, our cohort was predominantly composed of non-Hispanic white patients, which may significantly limit the generalizability of our findings to other ethnic groups.

In conclusion, our findings suggest that effectiveness and safety outcomes following DAPT in patients with mild-to-moderate non-cardioembolic ischemic stroke remain consistent across infarct locations in the posterior or anterior circulation territories. This supports the broad applicability of DAPT as a secondary prevention strategy in both stroke subtypes. However, patients with PCI may experience

worse short-term functional outcomes after DAPT compared to those with ACI, potentially reflecting the inherently poorer functional prognosis associated with this stroke subtype. This underscores the importance of tailored rehabilitation strategies to enhance recovery in PCI patients.

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2.2 Patients with specific stroke/TIA etiologies

2.2.1 Paper 4: 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 $\leq$ 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.

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.

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 guidelines⁹⁻¹² 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 investigatorsto 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.

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.

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 hours 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.

Statistical analysis

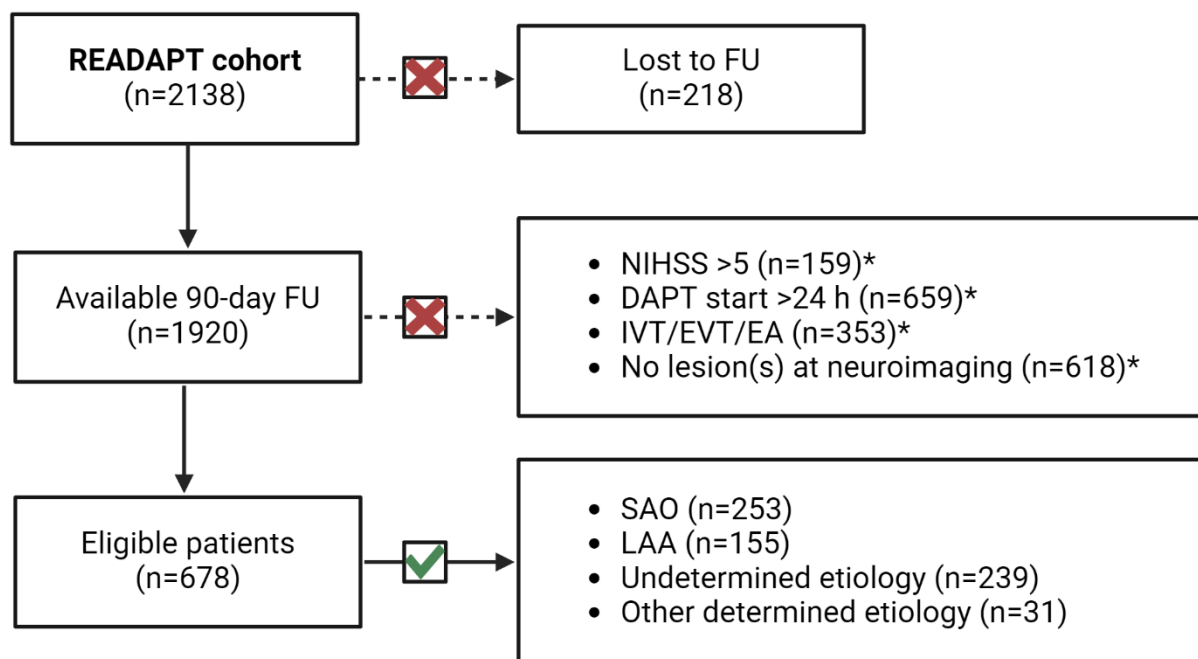
Descriptive statistics were used to report baseline characteristics of SAO-MIS patients. Specifically, categorical variables were reported as absolute numbers with percentages (%), while continuous variables as mean $\pm$ standard deviation (SD), or median and interquartile range (IQR), according to their distribution. The baseline characteristics of SAO-MIS and non-SAO-MIS patients were compared using the Wilcoxon test or the Pearson χ^2 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.

Results

We included 678 patients, of whom 253 (37.3%) had SAO-MIS, while the remaining 425 (62.7%) had other etiologies. **Figure 1**

Figure 1. Study flow-chart.



*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.*

All patients underwent a brain NCCT within 24 hours 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.

Baseline characteristics of SAO-MIS patients

Baseline characteristics of the SAO-MIS population are reported in **Table 1**.

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

	SAO-MIS (n=235)	non-SAO-MIS (n=425)	P value
<i>Demographic characteristics</i>			
Males, n (%)	167 (66.0)	288 (67.8)	0.699
Age – years, mean $\pm$ SD	69 $\pm$ 11	69 $\pm$ 12	0.784
Ethnicity, n (%)			>0.999
Non-Hispanic White	248 (98.0)	417 (98.1)	
Other	5 (2.0)	8 (1.9)	
<i>Clinical characteristics</i>			
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
<i>Cardiovascular risk factors, n (%)</i>			
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
<i>Admission therapy, n (%)</i>			
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
<i>DAPT information</i>			
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)	
<i>Post-discharge therapy, n (%)</i>			
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
<i>Adherence (optimal), n (%)</i>			
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
<i>Reasons for early DAPT discontinuation, n (%)</i>			
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
<i>Neuroimaging findings (brain MRI)</i>			
Number of ischemic lesions, median (IQR)	2 (2-2)	2 (2-4)	<0.001
Leukoaraiosis score, n (%) ^a			0.039
Periventricular (grade)			
0	37/169 (21.9)	81/272 (29.8)	
1	72/169 (42.6)	121/272 (44.5)	
2	38/169 (22.5)	53/272 (19.5)	

3	22/169 (13.0)	17/272 (6.2)	0.018
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

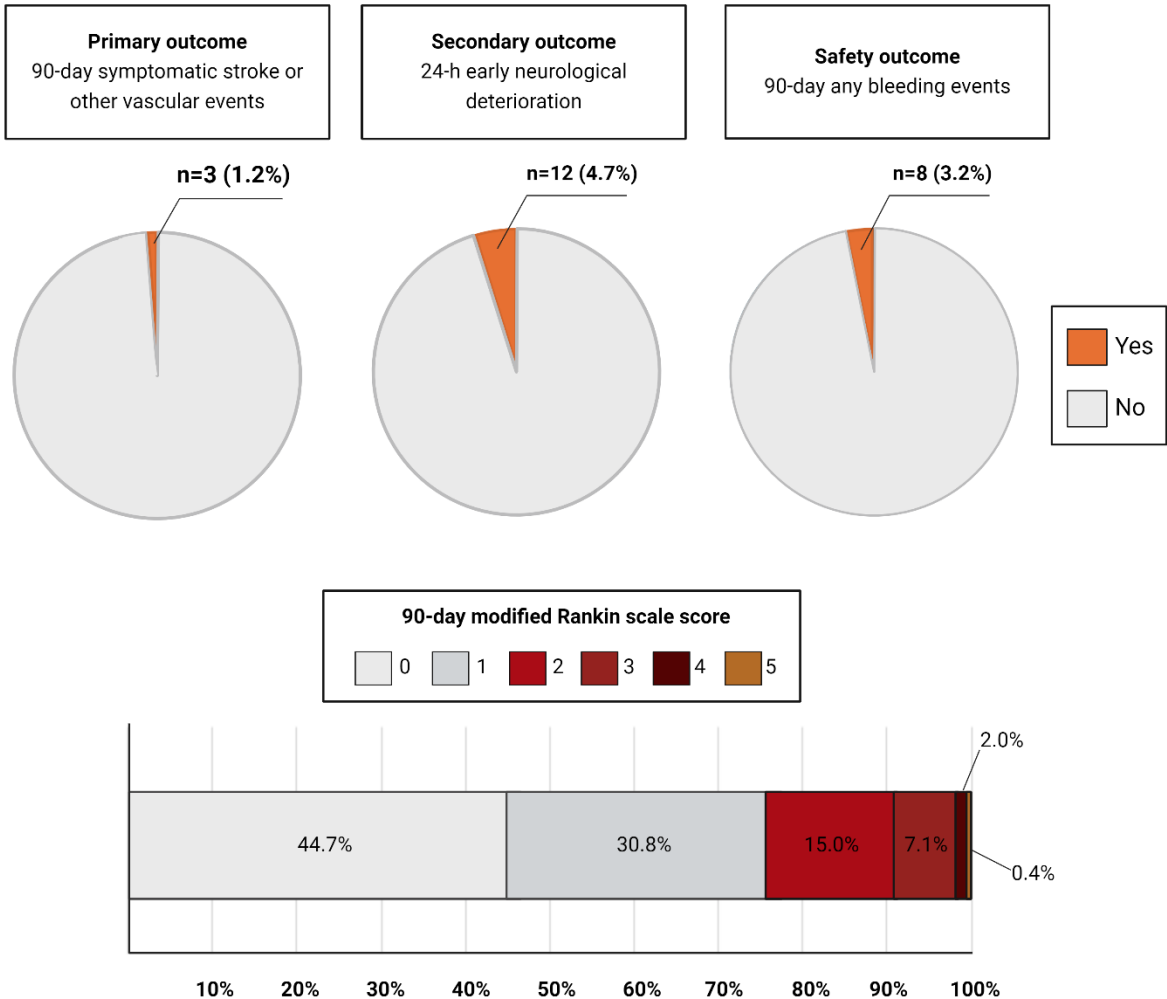
SAO-MIS patients were mostly non-Hispanic white (98.0%) and males (66.0%). The mean age at SAO-MIS onset was 69.37 ± 10.63 years. Most SAO-MIS patients (79.0%) had no symptoms (mRS of 0) prior to the index event (79.5%), while the median NIHSS score at presentation was 2 (IQR 0-3). As regards cardiovascular 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.

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**

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% CI 0.0%-2.2%]). No patient died at 90 days. **Figure 2**

Figure 2. Outcomes of SAO-MIS patients.



MIS: minor ischemic stroke; SAO: small artery occlusion.

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 $\geq 50\%$ extracranial internal carotid artery stenosis, 46 (29.7%) patients had $\geq 50\%$ extracranial vertebral artery stenosis, while symptomatic intracranial arterial stenosis ($\geq 50\%$) 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% 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**

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

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

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. 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-world 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 recurrences 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 regarding 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. 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. Therefore, 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 most 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.

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2.2.2 Paper 5: Real-world dual antiplatelet therapy use exceeds randomized trials boundaries with possible safety Issues in patients with large artery atherosclerosis—Insights from the READAPT study

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ABSTRACT

Background and Aim. According to randomized controlled trials (RCTs), dual antiplatelet therapy (DAPT) is more effective for secondary prevention of ischemic events attributable to large artery atherosclerosis (LAA) than other mechanisms. We investigated whether real-world application may impact DAPT effectiveness and safety in the REAL-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack (READAPT, NCT05476081).

Methods. READAPT was an observational multicenter study including patients with minor ischemic stroke or TIA treated with short-term DAPT. At 90 days, we assessed primary effectiveness (ischemic recurrence, severe bleeding, or vascular death) and safety (severe to moderate bleeding) outcomes. We explored associations between LAA and outcomes using Cox regression. Within patients with and without LAA, outcomes were compared between subgroups based on age, NIHSS score (for ischemic stroke patients), ABCD² score (for TIA patients), presence and number of MRI acute lesions, and DAPT regimen characteristics.

Results. Among 1920 analyzed patients (of 2278 enrolled), 452 had LAA. Unlike RCTs, 21.2% of patients with LAA had NIHSS > 5, and 48.2% received DAPT > 30 days. Patients with LAA had higher bleeding rates (3.5% vs. 2.1%, $p = 0.004$), primarily hemorrhagic infarctions and moderate bleeding, than those without LAA. However, primary effectiveness outcomes were similar (4.9% vs. 3.5%, $p = 0.201$) between the groups. In patients with LAA, prolonged DAPT (> 21 days), multiple MRI lesions, age ≥ 65 , and loading doses increased bleeding risk.

Conclusions. The real-world DAPT use in patients with LAA exceeds RCTs boundaries with possible drawbacks on treatment safety.

Introduction

Large-artery atherosclerosis (LAA), whether extracranial or intracranial, accounts for up to 15% of cerebrovascular ischemic events.^{1,2} Over recent decades, the risk of ischemic recurrences following an LAA-related event has significantly decreased due to advances in secondary prevention strategies.³ However, the short-term risk of ischemic recurrences remains higher after an LAA event than from other causes.³ The 90-day risk is estimated to be around 13% after a minor stroke or high-risk TIA in the presence of $\geq 50\%$ extracranial carotid stenosis⁴ or symptomatic intracranial stenosis.⁵ Randomized controlled trials (RCTs) have demonstrated the superiority of dual antiplatelet therapy (DAPT) compared with single antiplatelet therapy (SAPT) after LAA minor strokes or high-risk TIAs.^{6,7} This benefit is evident even when DAPT is started within 72 h from symptom onset.⁸

Overall, RCTs support the use of DAPT for secondary prevention of LAA cerebrovascular ischemic event,⁶⁻⁹ but they exhibited heterogeneity and some limitations. While DAPT has been associated with a reduced risk of ischemic recurrences compared to SAPT in patients with LAA, subgroup analyses from CHANCE and THALES failed to demonstrate a significant interaction between DAPT and LAA.^{5,7} Additionally, treatment benefits/risks compared with other causes remain unclear. THALES and ATAMIS subgroup analyses suggested greater DAPT benefit in patients with atherosclerotic events.^{6,7} However, in THALES, the definition of ipsilateral atherosclerosis differs from that used in the other RCTs, as do the definitions of minor stroke and high-risk TIA.^{6,7} Lastly, real-world use of DAPT extends beyond RCT settings,¹⁰ with potential benefits observed in patients outside RCT boundaries for treatment regimens and index event characteristics.¹¹

We hypothesized that, in the real world, physicians may prescribe DAPT to patients not strictly meeting RCTs definitions for LAA and non-LAA minor ischemic stroke or high-risk TIA. The characteristics of patients and their index event, as well as deviations from RCTs DAPT regimens, could influence treatment effectiveness and safety. To evaluate these hypotheses, we conducted this subgroup analysis of the REAL-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack (NCT05476081).

Methods

The READAPT methods have been summarized elsewhere.^{10,11} Briefly, this was an observational prospective multicenter real-world study endorsed by the Italian Stroke Association (ISA-AII). The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines¹² and was approved with the number 03/2021 by The Internal review Board of the University of L'Aquila—the coordinating center—in February 2021. We included

patients treated with DAPT at one of the 64 participating Italian centers between February 2021 and February 2023. Patients were included shortly after the index event (i.e., baseline) and had a 90-day follow-up, which concluded with a face-to-face or remotely end of study visit.

Study Inclusion and Exclusion Criteria

We included inpatients or outpatients with non-cardioembolic minor ischemic stroke or high-risk TIA according to the World Health Organization (WHO) time-based definition, older than 18 years, and receiving short-term DAPT. All patients or their proxies had to sign an informed consent to join the study. We excluded patients treated with DAPT because of endovascular stenting procedures and those who were already enrolled in interventional RCTs on stroke prevention. As elsewhere mentioned,^{10,11} no NIHSS and ABCD² threshold were established but we encouraged physicians to adhere to national and international guidelines.¹³⁻¹⁶

For this analysis, we divided the cohort into patients with LAA and those without (non-LAA). The cause of the index event was adjudicated by local physicians and centrally reviewed. We recommend physicians to strictly adhere to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) definition of LAA events—either significant (> 50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis.¹⁷ However, due to the observational design of the study, few events were classified as LAA when the ipsilateral atherosclerotic plaque caused less than 50% stenosis but was unstable, and no other plausible causes were identified. Intracranial CT or MR angiography (CTA or MRA) was mandatory for the diagnosis of intracranial atherosclerosis, whereas various examination methods, including ultrasound, CTA, or MRA, were permitted for assessing extracranial stenosis.

Study Procedures and Data Collection

Similarly to minor ischemic stroke and high-risk TIA definitions, we did not provide physicians strict DAPT regimen indications. Indeed, they chose DAPT dosage, duration, and the type of antiplatelet prescribed at the end of the DAPT period case by case according to the best clinical practice and guidelines.¹³⁻¹⁶

Anonymized data were collected on an electronic database—created with Research Electronic Data Capture (REDCap) software^{18,19}—that was hosted at University of L'Aquila. The study staff regularly checked the integrity of data collection and completeness of follow-up as previously reported.^{10,11}

Outcomes

The primary effectiveness outcome was a composite of new stroke events (ischemic or hemorrhagic) or death due to vascular causes at 90 days. The primary safety outcome was a moderate-to-severe bleeding at 90 days. Secondary outcomes were ischemic stroke (i.e., ischemic stroke or TIA), intracerebral hemorrhage (ICH), subarachnoid hemorrhage, other intracranial hemorrhage (i.e., subdural hematoma, epidural hematoma, or other), symptomatic and asymptomatic hemorrhagic infarction defined according to the Heidelberg Bleeding Classification,²⁰ myocardial infarction, vascular death, non-vascular death, any hospitalization, disability measured by the modified Rankin Scale (mRS), cause of DAPT discontinuation (i.e., adverse events, lack of compliance, other), severe bleeding, moderate bleeding, and mild bleeding—defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial.²¹ Secondary composite outcomes were any bleeding (i.e., any of severe, moderate, or mild bleeding) and any death (i.e., any of death due to vascular or non-vascular causes).

We reported the outcomes in patients with LAA and with non-LAA. Within these two main groups, we reported the rates of primary effectiveness outcome and any bleeding in pre-specified subgroups based on demographics and disease characteristics that could potentially impact treatment effectiveness and safety. These subgroups included age $\geq$ or $<$ 65 years, body mass index (BMI) $<$ or $\geq$ 30, ischemic strokes with NIHSS score $\leq$ 3 or $>$ 3, $<$ or $\geq$ 2 MRI acute lesions when an MRI scan was performed, TIA with ABCD² score $\leq$ or $>$ 4, prior antiplatelet therapy, revascularization procedure, DAPT loading dose, time to DAPT start $\leq$ or $>$ 24 h, DAPT duration $\leq$ or $>$ 21 days, early DAPT discontinuation. Lastly, within patients with LAA, we reported the outcomes in those with ipsilateral extracranial carotid stenosis $<$ 50% and $\geq$ 70%.

Statistical Analysis

We performed intention-to-treat analyses in patients who completed the follow-up or had an outcome event within 90 days. We excluded patients who had a follow-up visit prior to 80 days, and those who underwent stenting procedures or switched to anticoagulation therapy during the follow-up. If multiple outcome events occurred, only the first was retained.

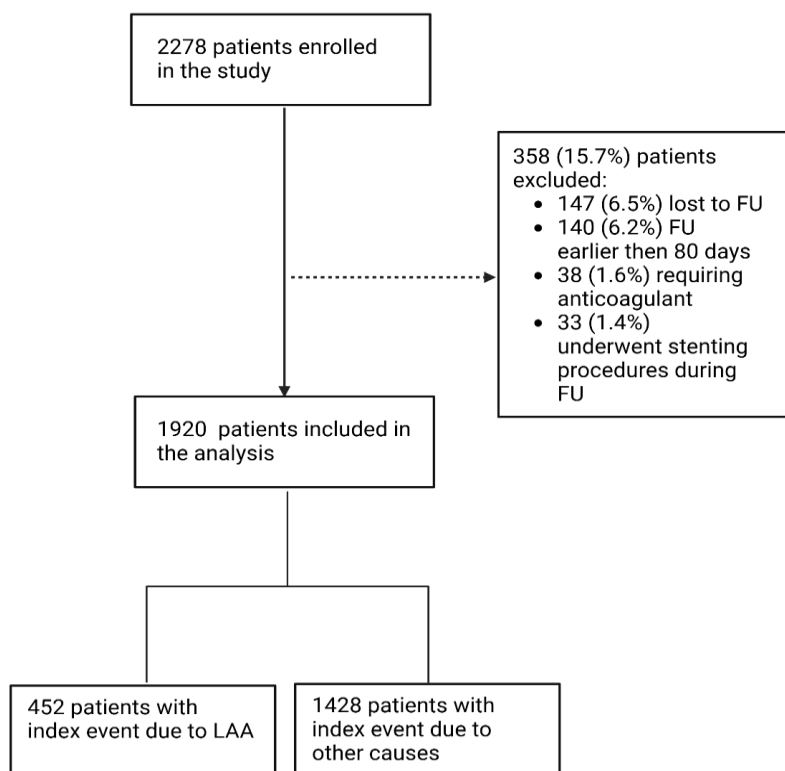
We reported descriptive statistics about demographics, characteristics of the index event, and outcome events. Categorical data were reported as number and percentage. Continuous data had non-normal distribution at the Kolmogorov–Smirnov test and were reported as median and interquartile range (IQR). Categorical and continuous data were compared across patients' groups through the chi-squared and Mann–Whitney *U* tests, respectively. Kaplan–Meier curves and log-rank test were used to represent and compare the cumulative risk of primary effectiveness and any bleeding in patients with LAA and non-

LAA. Univariate and multivariate Cox regressions were used to identify factors associated with the primary effectiveness and any bleeding in the entire study cohort. Only covariates with $p < 0.1$ were included in the multivariate model. Statistics and graphs were performed through R version 4.4.2. and GraphPad version 10.

Results

Of the 2278 patients originally enrolled between February 2021 and February 2023, 1920 (84.3%) had follow-up data and were included in this subgroup analysis. **Figure 1** According to the cause of the index event, 452 (23.5%) patients had an event attributable to LAA.

Figure 1: Study flow-chart.



Abbreviations. LAA: large-artery atherothrombosis.

Baseline Characteristics

Demographics and Comorbidities

Compared with patients receiving DAPT after a non-LAA index event, patients with LAA were older (median age 73, IQR 65–79 vs. 72, IQR 61–79 $p = 0.011$) and more frequently male (318, 70.2% vs. 917, 63.8%, $p = 0.011$). Patients with LAA also had more frequent vascular comorbidities such as hypertension (375, 83.0% vs. 1152, 78.5%, $p = 0.039$), diabetes mellitus (140, 31.0% vs. 381 26.0%, $p = 0.036$), dyslipidemia (292, 64.6% vs. 868 59.1%, $p = 0.037$), hypertriglyceridemia (114, 25.2% vs. 284 19.3%, $p = 0.007$), and peripheral chronic obliterative arteriopathy (39, 8.6% vs. 71, 4.8%, $p = 0.002$) compared with those with non-LAA. Treatment with antiplatelet agents before the index event was similar between the groups (187, 41.4% vs. 596, 40.6%, $p = 0.770$; **Table 1**).

Table 1: Demographics and characteristics of the index event among patients with large-artery atherosclerosis and those with non-large-artery atherosclerosis.

Characteristics	LAA (N=452)	Non-LAA (N=1468)	P value
Age, years, median (IQR)	73 (65-79)	72 (61-79)	0.011
Female gender, N (%)	134 (29.6)	551 (36.2)	0.011
Caucasian, N (%)	444 (98.2)	1433 (97.6)	0.619
BMI, median (IQR)	26 (24-28)	26 (23-28)	0.066
Current smoker, N (%)	131 (29.0)	361 (24.6)	0.837
Hypertension, N (%)	375 (83.0)	1152 (78.5)	0.039
Diabetes mellitus, N (%)	140 (31.0)	381 (26.0)	0.036
Dyslipidaemia, N (%)	292 (64.6)	868 (59.1)	0.037
Hypertriglyceridemia	114 (25.2)	284 (19.3)	0.007
Previous ischemic event (TIA or ischemic stroke), N (%)	103 (22.8)	263 (17.9)	0.508
Previous intracerebral hemorrhage, N (%)	3 (0.6)	12 (0.8)	0.745
Myocardial infarction, N (%)	51 (11.5)	131 (8.9)	0.102
Angina, N (%)	20 (4.4)	42 (2.9)	0.100
Congestive heart failure, N (%)	16 (3.5)	42 (2.9)	0.461
Peripheral Chronic Obliterative Arteriopathy, N (%)	39 (8.6)	71 (4.8)	0.002
Use of antiplatelet prior to the index event, N (%)	187 (41.4)	596 (40.6)	0.770
Symptom duration, N (%)			0.125
>24 h	329 (72.8)	1013 (69.0)	
<24 h	123 (27.2)	455 (31.0)	
Lesions at neuroimaging, N (%)			0.002
Yes	334 (73.9)	968 (65.9)	
No	118 (26.1)	500 (34.1)	
ABCD ² score in patients with qualifying TIA, median (IQR)	5 (4-6)	4 (4-5)	0.179
ABCD ² <4, N (%)	26 (21.1)	124 (22.7)	0.908
ABCD ² <6 and no LAA, N (%)	102 (82.9)	371 (68.0)	0.133
NIHSS score in patients with qualifying ischemic stroke, median (IQR) and [range]	3 (2-5)	3 (2-4)	0.001
NIHSS >3, N (%)	150 (45.6)	325 (32.0)	0.019
NIHSS >5, N (%)	70 (21.2)	89 (8.7)	0.001
mRS baseline, median (IQR)	0 (0-0)	0 (0-0)	0.111
Time to DAPT start, N (%)			0.096
<12 h	146 (32.3)	496 (33.8)	
12-24 h	135 (29.9)	484 (33.0)	
25-48 h	92 (20.4)	298 (20.3)	
>48 h	79 (17.5)	190 (12.9)	
Type of DAPT, N (%)			0.199
Aspirin/Clopidogrel	372 (99.2)	1540 (99.8)	

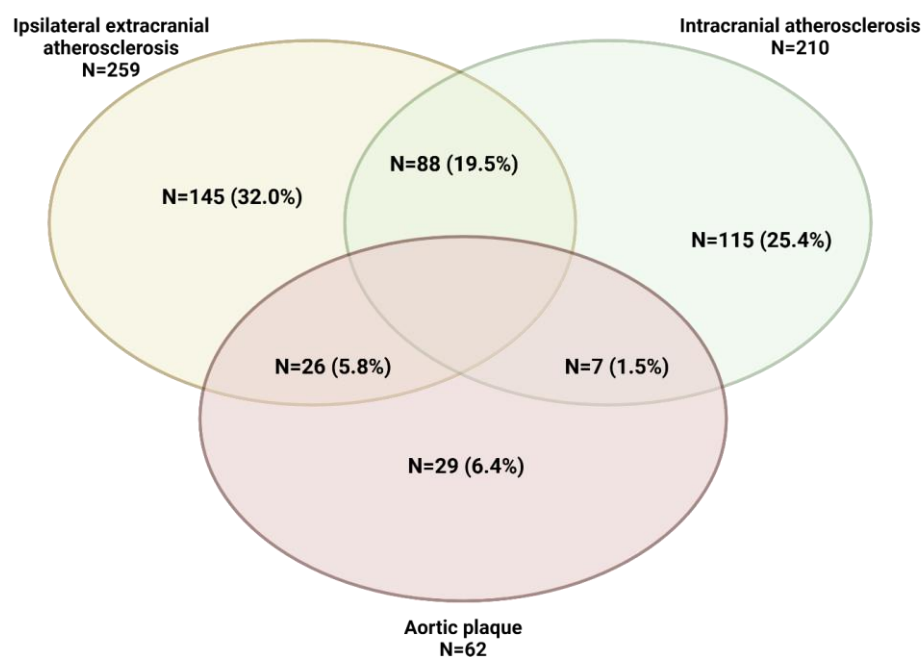
Aspirin/Ticagrelor	3 (0.8)	5 (0.2)	
Loading dose, N (%)	244 (54.0)	677 (46.1)	0.970
Aspirin	152 (33.6)	400 (27.2)	0.009
Clopidogrel	150 (33.2)	553 (37.7)	0.084
Ticagrelor	3 (0.7)	2 (0.1)	0.465
Revascularization procedures, N (%)	98 (19.7)	238 (16.2)	0.085
DAPT duration, median (IQR)	30 (21-90)	21 (21-30)	0.001
DAPT duration <21 days, N (%)	37 (8.2)	87 (5.9)	0.001
DAPT duration 21-30 days, N (%)	197 (43.6)	1059 (72.4)	
DAPT duration 30-90 days, N (%)	218 (48.2)	322 (21.9)	
DAPT discontinuation before expected completion, N (%)			0.178
Adverse events	11 (2.4)	11 (0.7)	
Lack of compliance	3 (0.6)	12 (0.8)	
Other	21 (4.6)	30 (2.0)	

Abbreviations: Body mass index (BMI); Dual Antiplatelet Therapy (DAPT); Hours (h); Interquartile range (IQR); Loading dose (LD); large-artery atherosclerosis (LAA); modified Rankin scale (mRS); Number (N), National Institutes of Health Stroke Scale (NIHSS); transient ischemic attack (TIA). *all patients were evaluable for the analysis.

Vascular Characteristics and Incidence of Carotid Stenosis in Patients With LAA

Among patients with LAA, 259 (57.3%) had ipsilateral extracranial atherosclerosis, which in 183 (70.6%) of the cases affected the carotid district; 210 (46.4%) patients had intracranial stenosis, and 62 (13.7%) had an aortic plaque. **Figure 2** Notably, 88 (19.5%) patients had both extra- and intracranial carotid stenosis ipsilateral to symptom location. Additionally, 36 (23.2%) underwent urgent carotid endarterectomy after the index event.

Figure 2. Presence of ipsilateral extracranial stenosis, symptomatic intracranial stenosis, and/or aortic plaque in patients with an index event attributable to large-artery atherosclerosis.

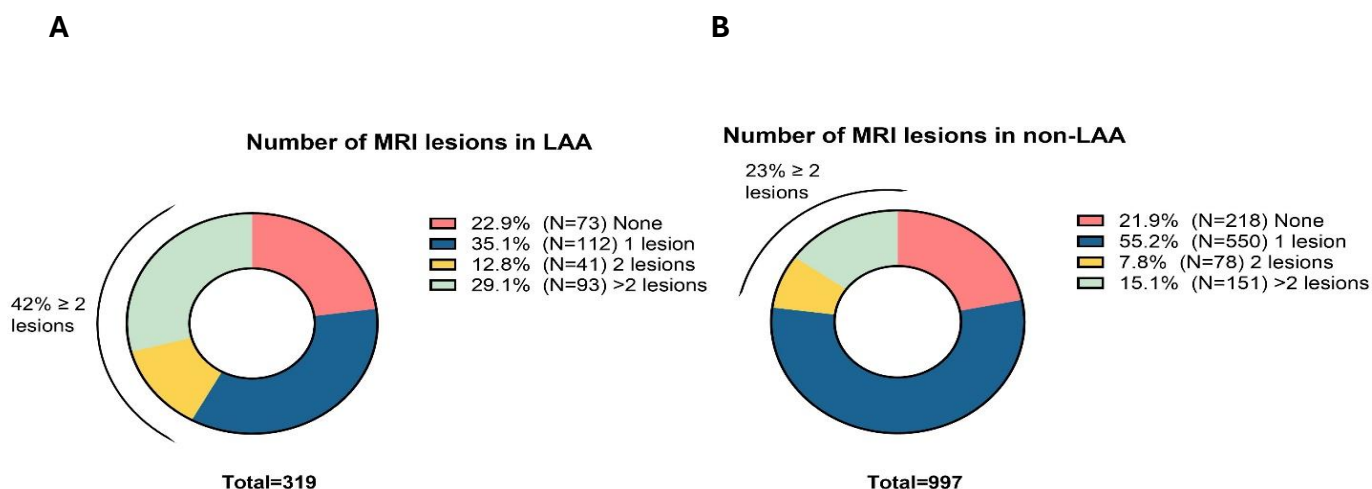


Characteristics of the index event and DAPT regimen.

Similarly to non-LAA counterpart, most patients with LAA received DAPT after an ischemic stroke (329, 72.8% vs. 1013, 69%, $p = 0.125$). In patients with LAA, the severity of the ischemic stroke was significantly higher: 150 (45.6%) patients with LAA presented with an NIHSS > 3 and 118 (26.1%) with an NIHSS > 5 compared with 325 (32.0%, $p = 0.019$) and 89 (8.7%, $p = 0.001$) patients with non-LAA events, respectively. Additionally, median DAPT duration was significantly longer in patients with LAA (30 days, IQR 21–90) than in those with non-LAA (21 days, IQR 21–30, $p \leq 0.001$) with 48.2% patients continuing the therapy after 30 days.

Considering neuroimaging characteristics, patients with LAA more frequently had an acute lesion (334, 73.9% vs. 968, 65.9% $p = 0.002$) at either CT or MRI scan performed in the first days after the index event. Among the 1316 patients who underwent an MRI scan (319 LAA and 997 non-LAA), significantly more patients with LAA had ≥ 2 acute MRI lesions compared with patients with non-LAA (134, 42.0% vs. 193, 23.0%; $p < 0.001$). **Figure 3**

Figure 3: Number of MRI lesions in patients with large-artery atherosclerosis (A) and with non-large-artery atherosclerosis (B).



Abbreviations: LAA: large-artery atherosclerosis.

In patients with LAA, multiple lesions were present in 128 (95.5%) of cases in the same vascular territory. Conversely, patients with and without LAA had similar rates of neuroimaging findings suggestive of cerebral small vessel disease (cSVD). **Table 2** Specifically, the rates of cortical superficial siderosis were comparable between the groups (5 patients, 1.1%, with LAA and 12, 1.2%, with non-LAA, $p = 0.616$), as were the rates of microbleeds (12 patients, 2.7%, with LAA and 58, 5.8%, with non-LAA, $p = 0.154$). The two groups also exhibited similar Fazekas scores for deep white matter (median

of 2, IQR 1–3, for both groups, $p = 0.822$) and periventricular white matter (median of 2, IQR: 1–2 for both groups, $p = 0.501$).

Table 2. Baseline MRI features of cerebral small vessel disease between patients with and without large-artery atherosclerosis.

Covariates	Patients with LAA (N=319)	Non-LAA (N=997)	P value
White matter hyperintensities, N of patients (%)	210 (65.8)	637 (63.9)	0.529
Prior lacunar infarcts, N of patients (%)	151 (47.3)	520 (52.2)	0.134
Perivascular space, N of patients (%)	48 (15.0)	182 (18.3)	0.189
Cortical superficial siderosis, N of patients (%)	5 (1.1)	12 (1.2)	0.616
Microbleeds, N of patients (%)	12 (2.7)	58 (5.8)	0.154
Atrophy, N of patients (%)	56 (17.6)	190 (12.9)	0.549

Abbreviations. LAA: large-artery atherosclerosis.

Outcomes

▪ DAPT Effectiveness and Safety in Patients With LAA and Non-LAA

DAPT effectiveness was similar between patients with and without LAA. Out of the 74 primary effectiveness outcomes, 22 (4.9%) occurred in patients with LAA and 52 (3.5%) in those with non-LAA ($p = 0.201$). **Table 3** Accordingly, the survival analyses showed a similar cumulative risk of primary effectiveness outcome over the 90-day follow-up ($p = 0.200$) between the two groups. **Figure 4** Ischemic recurrences accounted for most of the primary effectiveness outcomes in both groups (19, 4.2% in LAA vs. 45, 3.1% in non-LAA, $p = 0.239$); one vascular death (0.2%) occurred in patients with LAA and 2 (0.1%) in those with non-LAA ($p = 0.351$). **Table 3**

Table 3. Outcomes in the two subgroups: patients with large-artery atherosclerosis and those with non- large-artery atherosclerosis.

Outcome	LAA (N=452)	Non-LAA (N=1428)	P value
Primary effectiveness outcome	22 (4.9)	52 (3.5)	0.201
Primary safety outcome	6 (1.3)	6 (0.4)	0.030
Ischemic event	19 (4.2)	45 (3.1)	0.239
TIA	13 (2.9)	25 (1.7)	
Ischemic stroke	6 (1.3)	20 (1.4)	
Early neurological deterioration	15 (4.6)	36 (3.5)	0.407
Hemorrhagic transformation	9 (1.9)	10 (0.7)	0.007
Asymptomatic	7 (1.5)	10 (0.7)	
Symptomatic	2 (0.4)	0 (0)	
Intracranial hemorrhage	0 (0.0)	3 (0.2)	0.336
Subarachnoid hemorrhage	1 (0.2)	1 (0.1)	0.378
Other intracranial hemorrhage	1 (0.2)	1 (0.1)	0.378
Myocardial infarction	1 (0.2)	2 (0.1)	0.689
Death	3 (0.6)	5 (0.3)	0.351
Vascular	1 (0.2)	2 (0.1)	
Non-Vascular	2 (0.4)	3 (0.2)	
Severe bleeding	3 (0.7)	6 (0.4)	0.488
Moderate bleeding	3 (0.7)	0 (0.0)	0.002
Mild bleeding	15 (3.3)	25 (1.7)	0.035
Any bleeding	13 (3.5)	31 (2.1)	0.004

New hospitalization	21 (4.6)	41 (2.8)	0.030
mRS	1 (0-2)	0 (0-1)	0.001

Abbreviations. LAA: large-artery atherosclerosis; mRS: modified Rankin scale; TIA: transient ischemic attack.

The sole factor associated with a lower risk of primary effectiveness outcome was the female gender (HR 0.56, 95% CI 0.32–0.96, $p = 0.03$). **Table 4**

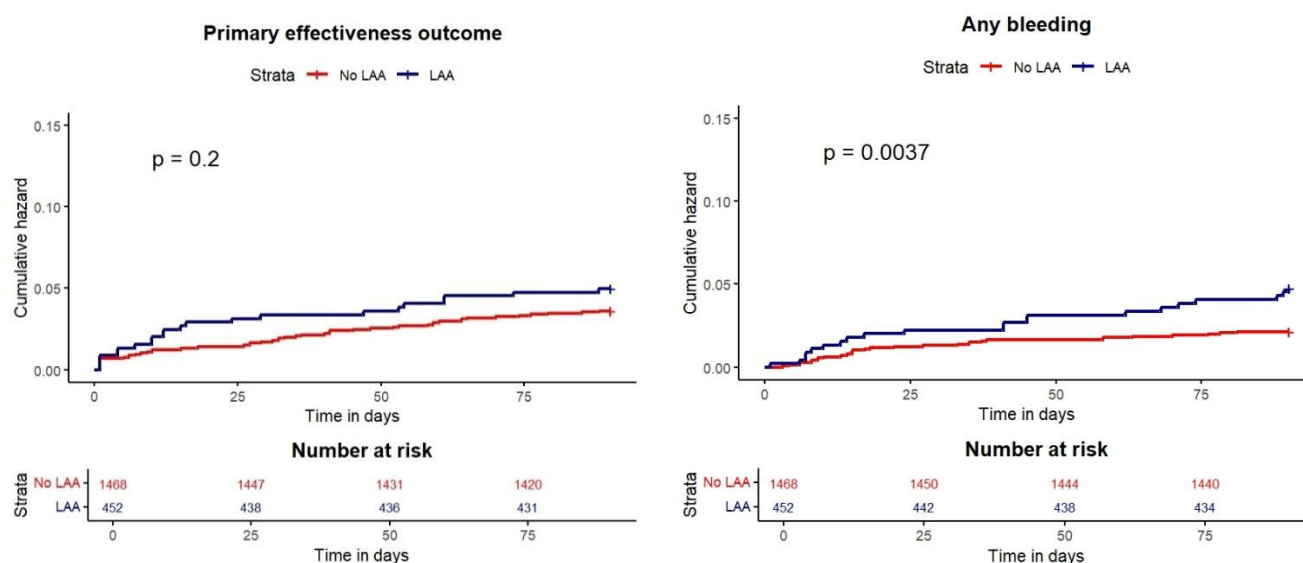
Table 4. Univariate Cox regression to identify factors associated with primary effectiveness outcome

Covariates	HR (95% CI)	P value
LAA	1.39 (0.84-2.28)	0.2
Age	1.00 (0.98-0.1.02)	0.9
Female gender	0.56 (0.32-0.96)	0.03
Diabetes	1.21 (0.73-2.00)	0.4
Hypercholesterolemia	0.72 (0.46-1.15)	0.2
Hypertriglyceridemia	1.14 (0.67-1.97)	0.6
Prior treatment with ASA	1.13 (0.70-1.82)	0.6
Symptom duration	1.26 (0.78-2.03)	0.3
Time to DAPT start >24h	0.70 (0.42-1.17)	0.2
Early DAPT discontinuation	1.53 (0.61-3.80)	0.4
DAPT duration >21 days	1.29 (0.82-2.04)	0.3
IVT	0.53 (0.25-1.17)	0.09

Abbreviations: ASA: aspirin; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IVT: intravenous thrombolysis; LAA: large-artery atherosclerosis.

In terms of DAPT safety, patients with LAA had a significantly higher rate of primary safety outcome (6, 1.3%) compared with non-LAA patients (6, 0.4%, $p = 0.030$). **Table 3** This result was mainly driven by the significantly higher rates of patients with LAA presenting hemorrhagic transformation (9, 1.9%), although mainly asymptomatic (7, 1.5%), and moderate bleeding (3, 0.7%) compared with non-LAA (10, 0.7% hemorrhagic transformations, $p = 0.007$; 0, moderate bleeding, $p = 0.002$). **Table 3** Also, the rate of any bleeding and its cumulative risk over the follow-up were significantly higher in patients with LAA than in those with non-LAA. **Figure 4**

Figure 4: Primary effectiveness outcome and any bleeding in patients with large-artery atherosclerosis and with non-large-artery atherosclerosis.



Abbreviations. LAA: large-artery atherosclerosis.

The multivariate analyses confirmed LAA as a factor associated with the risk of any bleeding (HR 2.21 95% CI 1.27–3.86, $p = 0.005$) along with older age (HR 1.03, 95% CI 1.00–1.06, $p = 0.018$). **Table 5** Conversely, DAPT start after 24 h from the index event was associated with a reduced occurrence of any bleeding (HR 0.39, 95% CI 0.19–0.81, $p = 0.012$). **Table 5**

Table 5. Univariate and Multivariate Cox regression to identify factors associated with any bleeding.

Covariates	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
LAA	2.28 (1.28-3.87)	0.006	2.21 (1.27-3.86)	0.005
Age	1.03 (1.00-1.06)	0.006	1.03 (1.00-1.06)	0.018
Female gender	0.83 (0.46-1.50)	0.5	-	-
Diabetes	1.09 (0.59-1.98)	0.8	-	-
Hypercholesterolemia	1.04 (0.59-1.82)	0.9	-	-
Hypertriglyceridemia	1.28 (0.68-2.39)	0.5	-	-
Prior treatment with ASA	1.04 (0.59-1.84)	0.9	-	-
Symptom duration	1.13 (0.63-2.01)	0.7	-	-
Time to DAPT start >24h	0.39 (0.19-0.81)	0.006	0.39 (0.19-0.81)	0.012
DAPT duration >21 days	0.84 (0.48-1.47)	0.5	-	-
Loading dose	0.73 (0.42-1.26)	0.3	-	-
IVT	0.67 (0.28-1.56)	0.3	-	-

Abbreviations: ASA: aspirin; CI: confidence interval; DAPT: dual antiplatelet therapy; HR: hazard ratio; IVT: intravenous thrombolysis; LAA: large-artery atherosclerosis.

Among patients with LAA, those with ipsilateral carotid extracranial stenosis $<50\%$ and $\geq 70\%$ exhibited comparable outcomes in terms of DAPT effectiveness, safety, as well as similar index event features. **Tables 6 and 7**

Table 6. Demographics and characteristics of the index event among patients with large-artery atherosclerosis index event and ipsilateral extracranial carotid stenosis 50-70% and $>70\%$

Characteristics	Patients with LAA and $<50\%$ ipsilateral extracranial stenosis (N=55)	Patients with LAA and $>70\%$ ipsilateral extracranial stenosis (N=76)	P value
Age, years, median (IQR)	74 (69-81)	72 (63-81)	0.506
Female gender, N (%)	18 (32.7)	22 (28.9)	0.643
Caucasian, N (%)	55 (100)	76 (100)	-
BMI, median (IQR)	26 (24-28)	25 (24-28)	0.577
Current smoker, N (%)	12 (21.8)	35 (46.1)	0.098
Hypertension, N (%)	50 (90.9)	66 (86.8)	0.471
Diabetes mellitus, N (%)	25 (45.5)	18 (23.7)	0.009
Dyslipidemia, N (%)	37 (67.3)	51 (67.1)	0.984
Hypertriglyceridemia	10 (18.2)	21 (27.6)	0.209
Previous ischemic event (TIA or ischemic stroke), N (%)	13 (23.6)	15 (19.7)	0.591
Previous intracerebral hemorrhage, N (%)	0 (0.0)	0 (0.0)	-
Myocardial infarction, N (%)	4 (7.3)	11 (14.8)	0.201
Angina, N (%)	1 (1.8)	3 (3.9)	0.485
Congestive heart failure, N (%)	2 (3.6)	2 (2.6)	0.741
Peripheral Chronic Obliterative Arteriopathy, N (%)	2 (3.6)	11 (14.5)	0.041
Use of antiplatelet prior to the index event, N (%)	25 (45.5)	29 (38.2)	0.402
Symptom duration, N (%)			0.877
>24 h	51 (92.7)	71 (93.4)	
<24 h	4 (7.3)	5 (6.6)	
Lesions at neuroimaging, N (%)			0.302
Yes	52 (94.5)	68 (89.5)	
No	3 (5.5)	8 (10.5)	
ABCD ² score in patients with qualifying TIA, median (IQR)	4 (3-6)	5 (4-6)	0.556
ABCD ² <4 , N (%)	1 (25.0)	0 (0.0)	0.236
NIHSS score in patients with qualifying ischemic stroke, median (IQR) and [range]	3 (2-5)	3 (2-6)	0.263
NIHSS >3 , N (%)	21 (41.2)	35 (49.3)	0.375
NIHSS >5 , N (%)	9 (17.6)	24 (33.8)	0.048
mRS baseline, median (IQR)	0 (0-1)	0 (0-1)	0.969
Time to DAPT start, N (%)			0.473
<12 h	12 (21.8)	26 (34.2)	
12-24 h	15 (27.3)	19 (25.0)	
25-48 h	12 (21.8)	14 (18.4)	
>48 h	16 (29.1)	17 (22.4)	
Type of DAPT, N (%)			0.094
Aspirin/Clopidogrel	53 (96.4)	76 (100)	
Aspirin/Ticagrelor	2 (3.6)	0 (0.0)	
Loading dose, N (%)			0.373
Aspirin	17 (30.9)	28 (36.8)	0.480
Clopidogrel	21 (38.2)	29 (38.2)	0.998
Ticagrelor	1 (1.8)	0 (0.0)	-
Revascularization procedures, N (%)	11 (20.0)	20 (26.3)	0.401
DAPT duration, median (IQR)	30 (21-90)	30 (21-90)	0.010
DAPT duration <21 days, N (%)	1 (1.8)	11 (14.5)	
DAPT duration 21-30 days, N (%)	32 (58.2)	28 (36.8)	
DAPT duration 30-90 days, N (%)	22 (40.0)	37 (48.7)	
DAPT discontinuation before expected completion, N (%)			0.488
Adverse events	0 (0.0)	2 (2.6)	
Lack of compliance	0 (0.0)	0 (0.0)	
Other	2 (3.6)	8 (10.5)	

Abbreviations. BMI: Body mass index; DAPT: Dual Antiplatelet Therapy; IQR: Interquartile range; LD: Loading dose; LAA: large-artery atherosclerosis; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; TIA: transient ischemic attack. *:all patients were evaluable for the analysis

Table 7. Outcomes among patients with large-artery atherosclerosis index event ipsilateral extracranial carotid stenosis <50% and >70%.

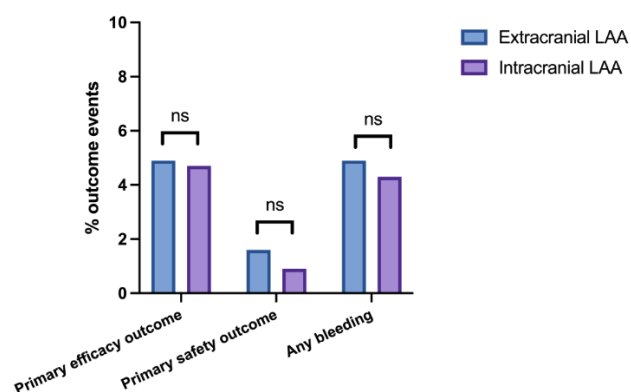
Outcome	LAA patients with <50% ipsilateral extracranial stenosis (N=55)	LAA patients with >70% ipsilateral extracranial stenosis (N=76)	P value
Primary effectiveness outcome	2 (3.6)	1 (1.3)	0.393
Primary safety outcome	0 (0.0)	1 (1.3)	0.381
Ischemic event	2 (3.6)	1 (1.3)	0.381
Ischemic stroke	1 (1.8)	0 (0.0)	0.386
TIA	1 (1.8)	1 (1.3)	
Early neurological deterioration	3 (5.9)	3 (3.9)	0.676
Hemorrhagic transformation	0 (0.0)	3 (3.9)	0.520
Symptomatic	0 (0.0)	2 (2.6)	
Asymptomatic	0 (0.0)	1 (1.3)	
Intracranial hemorrhage	0 (0.0)	0 (0.0)	-
Subarachnoid hemorrhage	0 (0.0)	0 (0.0)	-
Other intracranial hemorrhage	0 (0.0)	0 (0.0)	-
Myocardial infarction	0 (0.0)	0 (0.0)	-
Death	1 (1.8)	0 (0.0)	0.238
Vascular	0 (0.0)	0 (0.0)	-
Non-Vascular	1 (1.8)	0 (0.0)	0.238
Severe bleeding	0 (0.0)	0 (0.0)	-
Moderate bleeding	0 (0.0)	1 (1.3)	0.393
Mild bleeding	2 (3.6)	3 (3.9)	0.927
Any bleeding	2 (3.6)	4 (5.3)	0.660
New hospitalization	3 (5.5)	8 (10.5)	0.302
mRS	1 (0-2)	1 (0-2)	0.450

Abbreviations. LAA: large-artery atherosclerosis; mRS: modified Rankin scale; TIA: transient ischemic attack.

Likewise, patients with intracranial stenosis and those with extracranial stenosis had similar outcomes.

Figure 6

Figure 6. Comparison of the outcome events between patients with intracranial and extracranial carotid large-artery atherosclerosis.



Abbreviations. LAA: large-artery atherosclerosis.

DAPT Effectiveness and Safety in LAA and Non-LAA According to Pre-Specified Subgroups

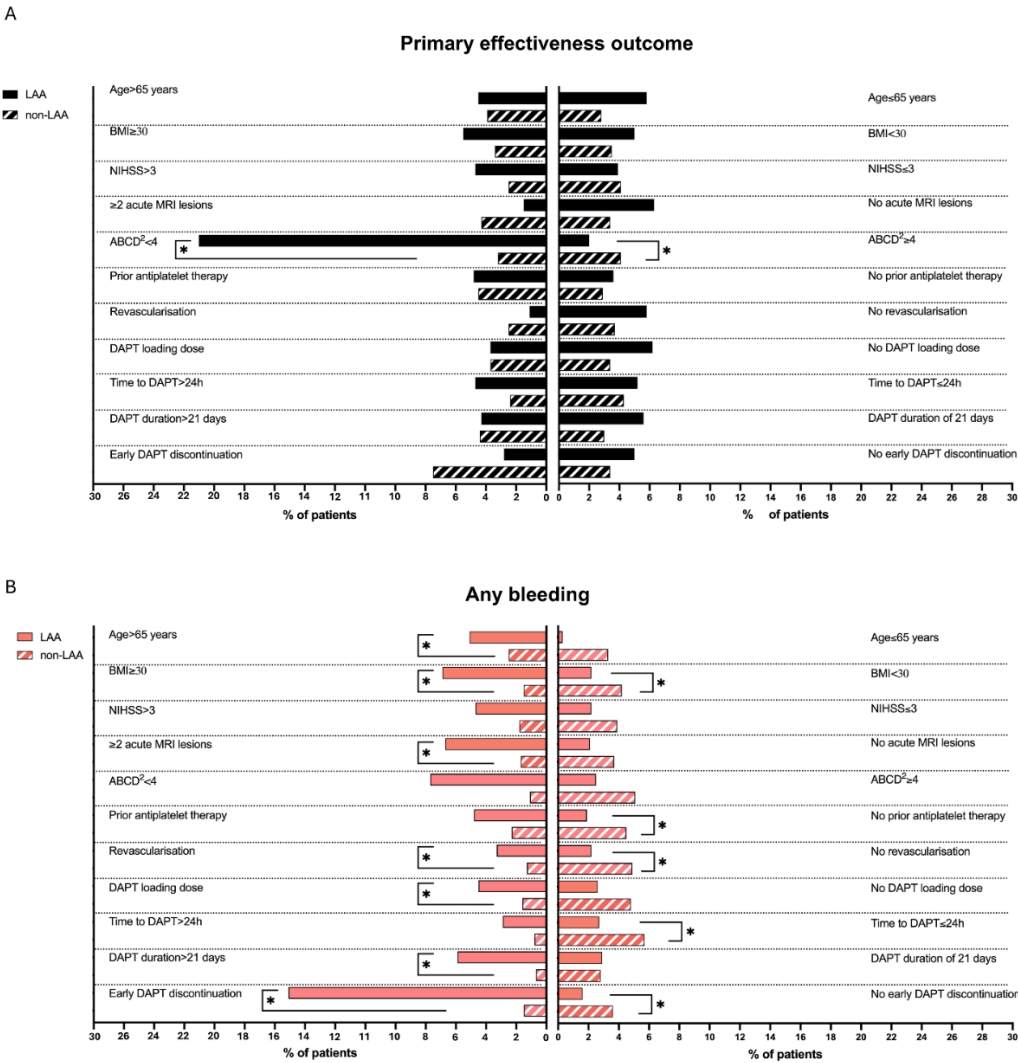
The subgroup analysis on the primary effectiveness outcomes showed a doubled rate of events in patients with LAA and a single MRI acute lesion compared with their counterparts (20, 6.3% vs. 42, 3.4%, respectively, $p=0.018$). Similarly, the primary effectiveness outcome was significantly higher in patients with LAA and TIA reporting an ABCD² score < 4 compared with those with non-LAA (6, 23% vs. 3, 3.2%, respectively, $p<0.001$). When considering the rate of any bleeding, patients with LAA had increased rates of events compared with those with non-LAA. This increase was significantly different in those > 65 years (17, 5.1% vs. 24, 2.5%, $p=0.022$), with ≥ 2 MRI acute lesions (9, 6.7% vs. 4, 1.7%; $p=0.014$), those without prior antiplatelet treatment (12, 4.5% vs. 9, 2.5%; $p=0.020$), and in those who did not undergo a revascularization procedure (18, 4.9% vs. 28, 2.2%, $p=0.007$). Regarding the DAPT regimen, any bleeding was more frequent in patients with LAA who received a loading dose (11, 4.5% vs. 13, 1.6%, $p=0.009$), those who received DAPT for more than 21 days (16, 5.9% vs. 4, 0.8%, $p=0.001$), and those who did not discontinue the therapy early (15, 3.6% vs. 23, 1.6%, $p=0.013$). Notably, the frequency of this outcome event was significantly higher in patients with LAA compared with those with non-LAA independently from the BMI and time to DAPT start. **Table 8 and Figure 7**

Table 8. Comparison of primary effectiveness outcome and any bleeding between patients with large-artery atherosclerosis and non- large-artery atherosclerosis across pre-specified subgroups of interests.

Subgroups	Primary effectiveness outcome (N=74)			Any bleeding (N=52)		
	LAA N (%)	Non-LAA N (%)	P value	LAA N (%)	Non-LAA N (%)	P value
Age						
Age >65 years	15/332 (4.5)	37/944 (3.9)	0.635	17/332 (5.1)	24/944 (2.5)	0.022
Age ≤65 years	7/120 (5.8)	15/524 (2.8)	0.106	4/120 (3.3)	7/524 (1.3)	0.128
BMI						
BMI ≥30	4/72 (5.5)	7/204 (3.4)	0.428	5/72 (6.9)	3/204 (1.5)	0.017
BMI <30	18/362 (5.0)	45/1264 (3.5)	0.295	16/380 (4.2)	28/1264 (2.2)	0.035
NIHSS						
NIHSS >3	7/150 (4.7)	8/325 (2.5)	0.201	7/150 (4.7)	6/325 (1.8)	0.080
NIHSS ≤3	7/179 (3.9)	26/688 (4.1)	0.935	7/179 (3.9)	15/688 (2.2)	0.190
≥2 acute MRI lesions						
Yes	2/134 (1.5)	10/229 (4.3)	0.139	9/134 (6.7)	4/229 (1.7)	0.014
No	20/318 (6.3)	42/1239 (3.4)	0.018	12/318 (3.7)	27/1239 (2.1)	0.105
ABCD²						
ABCD ² <4	6/26 (23.0)	3/94 (3.2)	0.001	2/26 (7.7)	1/94 (1.0)	0.055
ABCD ² ≥4	2/97 (2.0)	15/361 (4.1)	0.333	5/97 (5.1)	9/361 (2.5)	0.176
Prior antiplatelet therapy						
Yes	9/187 (4.8)	27/596 (4.5)	0.872	9/187 (4.8)	14/596 (2.3)	0.080
No	13/265 (3.6)	25/872 (2.9)	0.106	12/265 (4.5)	17/872 (1.9)	0.020
Revascularization procedure						
Yes	1/89 (1.1)	6/238 (2.5)	0.437	3/89 (3.3)	3/238 (1.3)	0.206
No	21/363 (5.8)	46/1230 (3.7)	0.088	18/363 (4.9)	28/1230 (2.2)	0.007
DAPT loading dose						
Yes	9/244 (3.7)	29/791 (3.7)	0.987	11/244 (4.5)	13/791 (1.6)	0.009
No	13/208 (6.2)	23/677 (3.4)	0.069	10/208 (4.8)	18/677 (2.6)	0.121
Time to DAPT >24 h						
Yes	8/171 (4.7)	12/488 (2.4)	0.145	5/171 (2.9)	4/488 (0.8)	0.041
No	14/267 (5.2)	40/980 (4.3)	0.511	16/281 (5.7)	27/980 (2.7)	0.017
DAPT duration >21 days						
Yes	12/273 (4.3)	24/541 (4.4)	0.979	16/273 (5.9)	4/541 (0.7)	0.001
No	10/179 (5.6)	28/927 (3.0)	0.084	5/179 (2.8)	27/927 (2.9)	0.931
Early DAPT discontinuation						
Yes	1/35 (2.8)	4/53 (7.5)	0.352	6/35 (17.1)	8/53 (1.5)	0.797
No	21/417 (5.0)	48/1415 (3.4)	0.121	15/417 (3.6)	23/1415 (1.6)	0.013

Abbreviations. BMI: body mass index (BMI); DAPT: dual antiplatelet therapy; LAA: large-artery atherosclerosis; NIHSS: National Institutes of Health Stroke Scale.

Figure 7. Comparison of primary effectiveness outcome (A) and any bleeding (B) between patients with large-artery atherosclerosis and non- large-artery atherosclerosis across pre-specified subgroups of interests.



Abbreviations. BMI: body mass index (BMI); DAPT: dual antiplatelet therapy; LAA: large-artery atherosclerosis; NIHSS: National Institutes of Health Stroke Scale.

Discussion

The actual benefits and risks of DAPT in patients with LAA have not yet been fully established. The CLAIR and CARESS studies were the first to demonstrate the superiority of DAPT over SAPT in patients with LAA.^{22,23} However, these studies did not specifically include patients with minor ischemic stroke or high-risk TIA, and their primary outcome was microembolism.^{22,23} RCTs involving patients with minor ischemic stroke and high-risk TIA have shown heterogeneity in LAA definition and results.⁵⁻⁹ This subgroup analysis of the READAPT study confirmed that the real-world use of short-term DAPT in patients with LAA differs from RCTs because of increased severity of the index event, delayed time to DAPT start, and prolonged treatment duration. In this study, we also observed that the vascular risk profile of patients with LAA was worse than the profile of those with non-LAA. Rates of bleeding events were higher compared with RCTs,⁶⁻⁹ despite similar or even lower rates of ischemic recurrences. At variance with RCTs, which excluded patients undergoing revascularization procedures and with moderate ischemic strokes,⁶⁻⁹ we did not find a significantly increased risk of ischemic recurrences or a greater DAPT benefit in patients with LAA compared with those without. However, patients with LAA were exposed to a significantly higher bleeding risk.

We observed a 90-day rate of ischemic recurrences in patients with LAA—4.2%—aligned with a wider population-based study.³ Ischemic recurrences were also within the range observed in RCTs—1.8%–10.6%—despite heterogeneity in definitions of LAA, minor stroke, and high-risk TIA⁶⁻⁹. Similarly to most RCTs,^{6,8,9} we applied the TOAST classification for index event etiology.¹⁷ However, still 30% of patients with ipsilateral extracranial carotid stenosis < 50% were classified as LAA by local investigators based on the characteristics of the atherothrombotic plaque and neuroimaging findings. Therefore, our cohort closely resembled that of the THALES trial, which included among the atherothrombotic events those occurring due to symptomatic 30%–50% extracranial carotid stenosis or ≥ 4 mm aortic plaque.⁷ The lower rate of ischemic recurrences observed in READAPT compared with THALES subgroup analysis (7.2%)⁷ requires cautious interpretation due to our study's observational design, which might have led to the underestimation of some outcomes events.

Although the characteristics of the index event and DAPT regimen did not appear to influence ischemic recurrence risk, these factors, along with demographics, might partially explain the higher rate of bleeding events—3.2%—compared with RCTs⁶⁻⁹. Our cohort included older patients and higher rates of males than RCTs¹⁰—both factors were associated with an increased risk of any bleeding, as previously shown.²⁴ In our cohort, LAA was associated with an increased number of any bleedings, mainly driven by moderate bleedings and hemorrhagic transformations, while the rates of ICH and other intracerebral bleedings were null or similar to RCTs.⁶⁻⁹ The increased rate of moderate bleeding might be affected by

prolonged DAPT duration, with around half of patients with LAA receiving DAPT for 30–90 days. Prolonged DAPT duration was a known risk factor for bleeding events²⁵ but still a treatment option in patients perceived at high risk for ischemic recurrences.¹³ The high rate of hemorrhagic transformations can be, partly, attributed to the severity of the ischemic stroke—around 20% of patients had an NIHSS score > 5—possibly suggesting larger ischemic lesions, especially in those with anterior circulation and left hemisphere involvement.²⁶ An increased risk of cerebral amyloid angiopathy in patients with LAA is unlikely, as MRI signs of cSVD were similar to those observed in non-LAA patients.

Similarly, when comparing patients with and without LAA, we observed higher rates of bleeding events and, specifically, hemorrhagic transformations in those with LAA compared with their counterparts. Additionally, patients with LAA had significantly longer DAPT duration, higher baseline NIHSS scores, and more frequently multiple acute lesions at MRI baseline scans compared with those with non-LAA. Similar to subgroup analyses of the ATAMIS⁶, THALES⁷, and CHANCE-2⁹ trials, we observed slightly higher rates of ischemic recurrences in patients with LAA compared to those with non-LAA.

To identify patients most likely to benefit from DAPT, we compared primary effectiveness and any bleeding outcomes across subgroups of patients with LAA and those with non-LAA. DAPT was less effective in reducing ischemic recurrences in patients with LAA and an ABCD² score < 4 or in those with none or a single MRI acute lesion. However, patients with ≥ 2 MRI acute lesions had an increased risk of bleeding events, along with those aged ≥ 65 years. Among DAPT regimen characteristics, DAPT duration > 21 days was associated with higher rates of bleeding only in patients with LAA. Patients with LAA naïve to prior antiplatelet therapies and those receiving a loading dose had significantly higher bleeding events than their counterparts. Conversely, patients with LAA treated with revascularization procedures experienced similar bleeding events compared to those who did not, possibly because they did not receive a DAPT loading dose as previously discussed.^{10,27} The increased rate of bleeding in patients with LAA was independent from the time to DAPT start, despite a delayed time to DAPT start being safer in the entire study cohort and still beneficial as per RCTs data.^{8,28} Similarly, hemorrhagic risk in patients with LAA was independent from BMI cutoffs, suggesting no significant interaction between LAA and body weight. This supports previous findings that did not show an increased hemorrhagic risk related to BMI.²⁹ Overall, these findings underscore a hemorrhagic risk in patients with LAA likely tied to their overall vascular comorbidities.

Although READAPT had a large sample size, its open-label observational design and limited ethnic diversity constrain the generalizability of our findings. We performed only exploratory analyses due to the low number of outcome events, possibly due to their underreporting.¹¹ Index event characteristics and outcome adjudication relied on local investigators, as we lacked direct access to patient records and

neuroimaging, including scan timing. Without MRI scans, we could not consistently measure lesion volume or assess location and distribution. Moreover, some patients with non-LAA might have had a significant atherosclerosis, though insufficient to classify as the cause of ischemic stroke or TIA according to the TOAST classification. Conversely, some patients with ipsilateral atherosclerosis may have been categorized as LAA without certainty of the causal role of atherosclerosis or of the absence of alternative causes. Variability in carotid stenosis assessments (e.g., epiaortic Doppler ultrasonography, CT angiography, or angiography) further limits our findings. Lastly, the single-arm design of the study did not allow us to determine whether short-term DAPT was superior to SAPT in patients with LAA.

In conclusion, this subgroup analysis of the READAPT study indicated a broader use of DAPT in LAA patients in the real world compared with RCTs settings. While patients with LAA face similar ischemic recurrence risks as non-LAA patients in real-world settings, they endure significantly higher bleeding risks. Therefore, short-term DAPT should be carefully considered in LAA patients, particularly in older patients or those with more severe ischemic stroke (i.e., NIHSS > 3) and multiple acute lesions, as they may be at increased risk of intracranial bleeding. Our findings emphasize the need to tailor DAPT therapy according to the individual bleeding risk of LAA patients and the persistence of a knowledge gap from randomized studies in subgroups of patients at highest risk.

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2.3 Patients treated with intravenous thrombolysis

2.3.1 Paper 6: Combining Intravenous Thrombolysis and Dual Antiplatelet Treatment in Patients With Minor Ischemic Stroke: A Propensity Matched Analysis of the READAPT Study Cohort

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Abstract

Background. The optimal treatment for acute minor ischemic stroke (MIS) is still undefined and options include dual antiplatelet treatment (DAPT), intravenous thrombolysis (IVT), or their combination. We aimed to investigate benefits and risks of combining IVT and DAPT versus DAPT alone in patients with MIS.

Methods. This is a prespecified propensity score-matched analysis from a prospective multicentric real-world study (READAPT). We included patients with minor (National Institute of Health Stroke Scale score [NIHSS] at admission ≤ 5) ischemic stroke, without pre-stroke disability (modified Rankin scale [mRS] score ≤ 2). The primary outcomes were 90-day mRS score of 0 to 2 and ordinal mRS distribution. The secondary outcomes included 90-day risk of stroke and other vascular events and 24-h early neurological improvement or deterioration (≥ 2 points NIHSS score decrease or increase from the baseline, respectively).

Results. From 1373 MIS, 240 patients treated with IVT plus DAPT were matched with 427 patients treated with DAPT alone. At 90 days, IVT plus DAPT versus DAPT alone showed similar frequency of mRS 0 to 2 (risk difference: 2.3% [-2.0% to 6.7%]; $p=0.295$; risk ratio: 1.03 [0.98 to 1.08]; $p=0.312$) but more favorable ordinal mRS scores distribution (OR 0.57 [0.41 to 0.79; $p<0.001$]). Compared to patients treated with DAPT alone, those combining IVT and DAPT had higher 24-h early neurological improvement (risk difference: 20.9% [13.1% to 28.6%]; risk ratio: 1.59 [1.34 to 1.89]; both $p<0.001$) and lower 90-day risk of stroke and other vascular events (HR 0.27 [0.08 to 0.90]; $p=0.034$). There were no differences in safety outcomes.

Conclusions. According to findings from this observational study, patients with MIS may benefit in terms of better functional outcome and lower risk of recurrent events from combining IVT and DAPT versus DAPT alone without safety concerns.

Introduction

Up to one half of patients with ischemic stroke in the general population present with mild deficits.¹ The functional outcome of minor ischemic stroke (MIS) is mostly good; however, up to one third of patients with MIS can have functional disability three months after the event.² Intravenous thrombolysis (IVT) can improve neurological outcome in those patients; however, it is also associated with an increased risk of bleeding events, which can overcome the potential benefits of the treatment. The role of IVT in patients with acute MIS is still controversial; some observational studies³⁻⁵ and a meta-analysis⁶ showed a clear benefit, while a randomized clinical trial⁷ demonstrated that IVT is not inferior respective to dual antiplatelet treatment (DAPT) in influencing the 90-day functional outcome. Similarly, a large cohort study did not identify an effect of IVT in all patients with mild stroke symptoms, but noted a suggestion of efficacy in those with higher clinical severity at the presentation.⁸ According to current guidelines, IVT is recommended in MIS patients who meet all the other eligibility criteria for the treatment^{9,10} provided that the neurological deficits caused by the stroke are still measurable at the time of observation^{9,10} and potentially disabling.⁹

Short-term DAPT has emerged as an important secondary prevention strategy for MIS and high-risk transient ischemic attack (TIA). Several randomized controlled trials have demonstrated the superiority of DAPT in preventing early recurrence of ischemic events.¹¹⁻¹³ However, patients who received urgent revascularization (i.e., IVT, endovascular thrombectomy [EVT], carotid endarterectomy) were excluded from landmark trials.¹¹⁻¹³

Recently, some studies compared IVT and DAPT in MIS. The Antiplatelet vs RtPA for Acute Mild Ischemic Stroke (ARAMIS) randomized controlled trial compared IVT with short-term DAPT in patients with mild nondisabling ischemic stroke. The study demonstrated the noninferiority of short-term DAPT over IVT followed by single antiplatelet treatment for several outcomes and mostly for 90-day functional disability in those patients (noninferiority margin of -4.5%).¹⁴ A more recent propensity matched analysis of the Austrian Stroke Registry corroborated findings from the ARAMIS trial by pointing out equivalent efficacy and safety between short-term DAPT and IVT in a large cohort of MIS patients.¹⁵ Additionally, the Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS)⁷ randomized trial found no significant difference in terms of 90-day favorable functional outcome between patients with acute minor nondisabling ischemic stroke treated with IVT or aspirin (81.2% versus 78.2%, respectively).

Despite IVT standing as an acute treatment for MIS and DAPT as a secondary prevention strategy, their combination has not been sufficiently explored. In fact, IVT and short-term DAPT are not mutually exclusive and can be potentially combined to optimize the outcome of patients with MIS.

On the other hand, combining the two approaches might raise concerns for a higher risk of bleeding events, especially intracerebral hemorrhage, or hemorrhagic transformation of the ischemic lesion. Randomized controlled trials of short-term DAPT did not include patients treated with IVT.¹¹⁻¹³ Additionally, as of now, there has been no randomized trial conducted to assess the outcomes of combining IVT with DAPT compared to DAPT alone in patients with ischemic stroke.

As short-term DAPT has become the mainstay of early secondary prevention of mild non-cardioembolic ischemic stroke, it is clinically relevant to assess whether IVT combined with DAPT may confer further benefit over DAPT alone on the short-term outcomes of patients with MIS.

The present study aimed to investigate the difference in short-term outcomes between patients combining IVT and DAPT compared to those treated with DAPT alone in a real-world population of patients with MIS.

Methods

READAPT study

The Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack – READAPT - study (NCT05476081), is an observational prospective multicenter real-world investigation led by the University of L'Aquila and supported by the Italian Stroke Association – Associazione Italiana Ictus (ISA-AAII). It adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and received approval from the Internal Review Board of the University of L'Aquila in February 2021 (code 03/2021), with all enrolled patients providing informed consent. Patient recruitment occurred across 64 Italian Stroke centers from February 1st, 2021 to February 28th, 2023. The enrollment period was extended to December 31st, 2023 for patients treated with acute reperfusion treatments (IVT and/or EVT). The decision to treat patients with IVT was upon local investigators who were recommended to adhere to current international guidelines for IVT treatment in acute ischemic stroke.^{9,10} Furthermore, investigators were not provided with specific recommendations regarding the initiation of DAPT after IVT. Therefore, the decision was made on an individual basis, taking into account potential contraindications and relying on individual clinical judgment.

The READAPT trial enrolled all individuals aged ≥ 18 years, whether hospitalized or not, who suffered from acute minor/moderate non-cardioembolic stroke or TIA and received a brief course of DAPT irrespective of the time elapsed from symptom onset. The diagnosis of the index stroke was adjudicated by investigators as per local practice and following the criteria of the World Health Organization (WHO).¹⁶ Apart from diagnosis of acute minor non-cardioembolic stroke or high-risk

TIA and use of DAPT, no other criteria were adopted to include patients. Patients were considered eligible irrespective of the time elapsed between the event onset and DAPT initiation, as well as the specific antiplatelet combination used. Time to DAPT start was determined as the interval between the index event and the administration of the initial antiplatelet agent of DAPT, regardless of whether a loading dose was prescribed. Additionally, patients were included regardless of whether a loading DAPT dose was administered. This was defined as a prescription of ≥ 300 mg for aspirin and clopidogrel, or ≥ 180 mg for ticagrelor. The exclusion criteria were involvement in interventional randomized controlled trials at the onset of stroke, continuous DAPT for endovascular stenting procedures, and conditions that could potentially impact compliance with the study protocols.

Patients were enrolled shortly after the index event and followed up for 90 ± 10 days, with local investigators conducting face-to-face or remote visits at the end of the follow-up period. 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, vascular risk factors, pre-stroke treatment, CHAD2DS2-VASC2, NIHSS and ABCD2 scores, pre- and post-stroke modified Rankin scale (mRS) score, neuroimaging findings, presumed cause of the index events according to the Trial of ORG 1072 10172 in Acute Stroke Treatment (TOAST) classification, and acute treatment (i.e., IVT, EVT, EA). The follow-up case report form collected data on performed investigations, compliance to treatments, adverse events, mRS, effectiveness and safety events. 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. Detailed procedures and data collection methods of the READAPT study are available elsewhere.¹⁷

Study sub-analysis

This study sub-analysis aims to address differences in the 90-day outcome between patients with MIS treated with DAPT alone versus those receiving IVT+DAPT. Patients were eligible for the inclusion in this study sub-analysis if they had a MIS, as defined by a NIHSS score at admission ≤ 5 , and were treated with DAPT within 48 hours of symptom onset. We excluded patients who had pre-stroke disability (modified Rankin scale - mRS score > 2), who underwent EVT, urgent carotid endarterectomy, or stenting procedures during the follow-up period. Patients with NIHSS of 0 at admission and without any deficit at the time of clinical observation were not considered in the

analysis to prevent cases where complete symptom resolution might have interfered with the assessment for IVT eligibility. Additionally, we also excluded patients who were lost to follow-up or with last available follow-up earlier than 80 days after the index event, as well as those who early discontinued DAPT because of the diagnosis of a condition requiring anticoagulation. The implementation of this latter exclusion criterion was motivated by concerns regarding the potential confounding effect of bleeding risks associated with anticoagulants on the assessment of the safety profiles of DAPT and IVT.

Propensity score matching

We calculated propensity scores for each patient basing on a multivariable logistic regression model which included demographics (age, sex, ethnicity), risk factors (arterial hypertension, diabetes), pre-stroke functional status (mRS), stroke severity (NIHSS at admission) and presumed cause, DAPT characteristics (loading dose, days of DAPT duration). Patients treated with IVT plus DAPT were matched with patients treated with DAPT alone in a 1:2 ratio and within 0.2 x standard deviation (sd) of the logit of the propensity score by using a greedy nearest neighbor matching. The time elapsed between the index event and DAPT start was not considered in the propensity score matching, as current guidelines recommend initiating antiplatelet treatment after at least 24 hours in patients who receive IVT and within 12 hours in those who are not treated.¹⁰ The overall quality of the matching was evaluated by comparing the standardized difference of means and the ratio of the variances between the propensity scores of treatment groups and by inspecting graphics of propensity scores and covariates balance distributions between the matched samples.

Outcomes

All outcomes were compared between propensity score-matched groups (IVT plus DAPT versus DAPT alone). Primary outcomes were good functional outcome at 90 days, defined as a mRS score of 0 to 2, and the ordinal distribution of 90-day mRS scores between IVT plus DAPT and DAPT alone patients. The secondary outcomes included the 90-day risk of stroke or other vascular events (i.e., transient ischemic attack, myocardial infarction, death due to vascular causes), 24-h early neurological improvement and deterioration (≥ 2 points decrease or increase in the NIHSS score from baseline, respectively), 24-h median change in the NIHSS scores from baseline. The safety outcomes were 90-day moderate-to-severe bleeding events, any bleeding events, intracerebral hemorrhage, 24-h hemorrhagic transformation. 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 The occurrence of all outcomes was adjudicated by local investigators through the electronic follow-up case-report form.

Statistical analysis

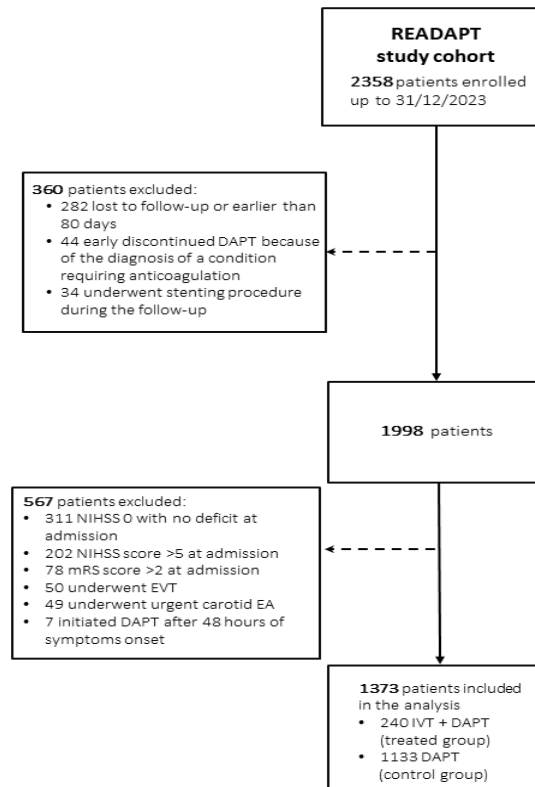
Categorical variables were presented as number and percentage, continuous variables as mean and SD or median and interquartile range (IQR) according to normal distribution. For the primary outcomes, we calculated the risk difference and risk ratio of 90-day good functional outcome (mRS of 0 to 2) between the IVT plus DAPT and DAPT alone groups with the 2-sided 95% confidence intervals (CIs). The 90-day ordinal distribution of mRS scores was compared using an ordinal generalized linear model (GLM) and results were presented as Odds ratio with 95% CIs. For the secondary outcomes, differences, and ratios (95% CIs) between groups were calculated for the risks of 24-h neurological improvement, 24-h neurological deterioration, and vascular death. Changes in the 24-h NIHSS scores from baseline between the IVT plus DAPT and DAPT alone groups were compared using linear regression and results were presented as Odds ratio with 95% CIs. The time-to-event 90-day risk of stroke and other vascular events was compared using Cox regression and the corresponding treatment effect was presented as hazard ratio (HR) and 95% CIs. The proportionality assumption was tested using the Schoenfeld individual test. Kaplan-Meier hazard functions were used to compare the overall risk of stroke and other vascular events between treatment groups and log-rank test was used to test differences. For all the safety outcomes, we also calculated risk differences and risk ratios with 95% CIs between the two treatment groups. As the outcomes of the present study were exploratory and there were no assumptions regarding the propensity score matching, a sample size was not prespecified for this analysis. All statistical analyses were performed using R software, version 4.2. Statistical significance was set at a p value <0.05.

Results

A total of 1373 patients were included in the analysis, of whom 240 (17.5%) were treated with IVT plus DAPT. The number of excluded patients with reasons is reported in the study flow diagram.

Figure 1

Figure 1. Study flow-chart

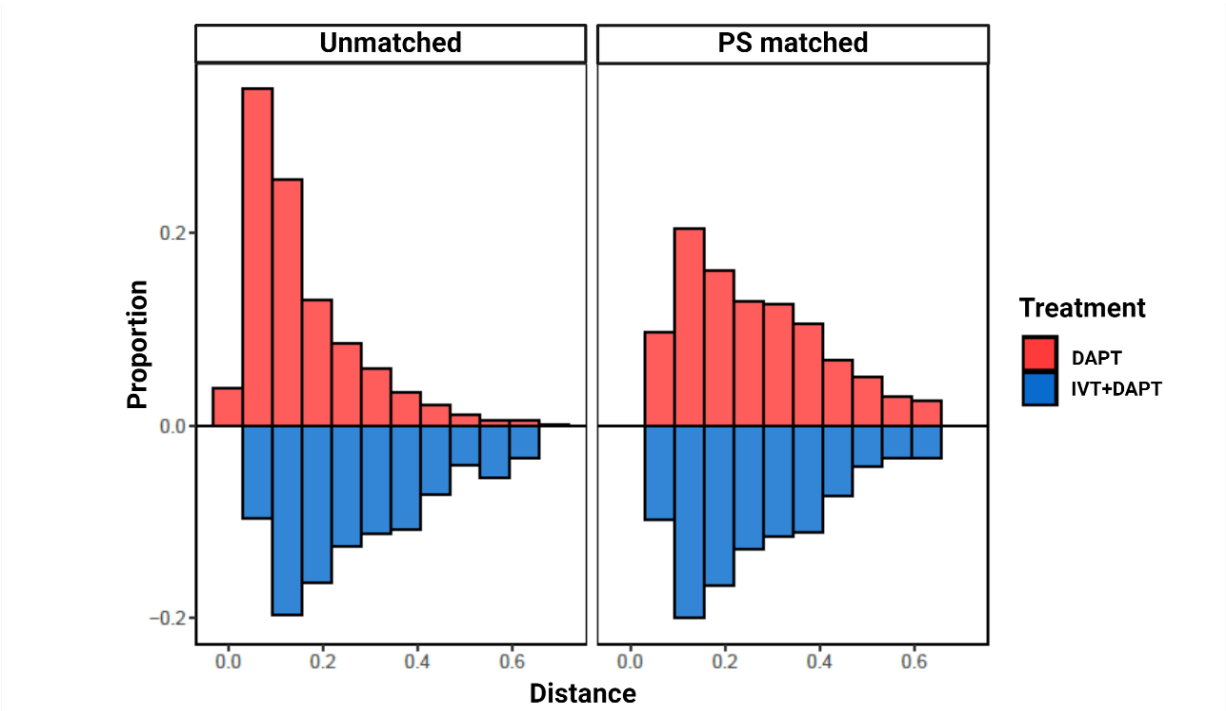


Abbreviations. DAPT: dual antiplatelet treatment; EA: endarterectomy; EVT: endovascular thrombectomy; IVT: intravenous thrombolysis; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke Scale; READAPT: REAL-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack.

No missing data were recorded in the variables used to calculate the propensity scores. We paired 235 patients who received IVT plus DAPT with 427 patients treated with DAPT alone. Measures of balance diagnosis indicated that the samples were adequately matched, with a standardized difference of the propensity scores means between groups of 0.02 (good balance <0.25), ratio of variances of propensity scores 1.05 (good balance between 0.5-2).¹⁹ Graphics of propensity scores and covariates balance distributions between the matched samples confirmed a good overall quality of the matching.

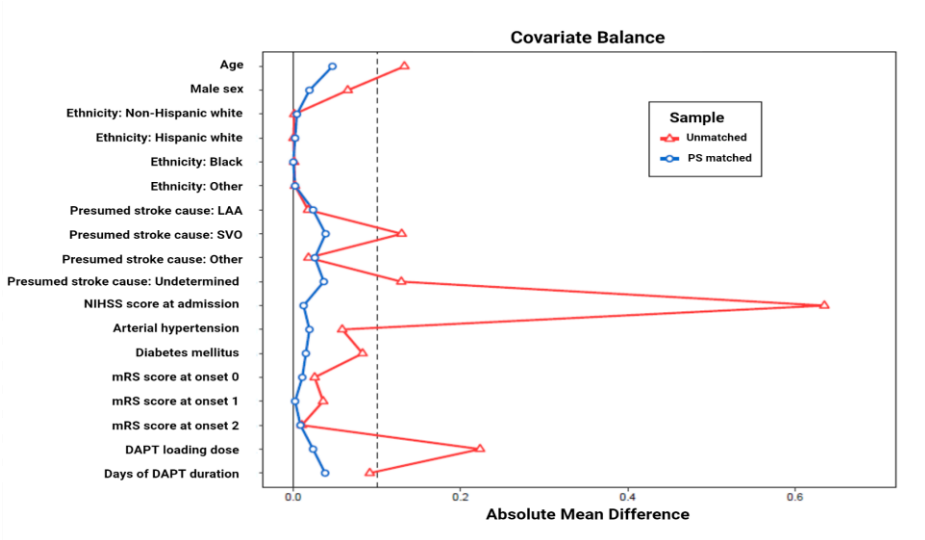
Figures 2 and 3

Figure 2. Mirrored histogram of propensity scores distribution between unmatched and matched samples.



Abbreviations. DAPT: dual antiplatelet treatment; IVT: intravenous thrombolysis; PS: propensity score.

Figure 3. Love plot of covariate balance between the IVT plus DAPT and DAPT alone groups before and after propensity score matching.



Abbreviations. DAPT: dual antiplatelet treatment; IVT: intravenous thrombolysis; LAA: large artery atherosclerosis; PS: propensity score; SVO: small vessel occlusion; Dashed line indicates Absolute Mean Difference cut-off for optimal balance between matched samples.

The comparison of baseline characteristics further supported the good balance of our matched samples with a standardized difference of the propensity scores <0.25 in all variables, except for the time elapsed between the index event and DAPT start. **Table 1**

Table 1. Baseline characteristics.

	Original Sample				Matched Sample			
	IVT + DAPT (n=240)	DAPT alone (n=1133)	Standardized Differences*	P value	IVT + DAPT (n=235)	DAPT alone (n=427)	Standardized Differences*	P value
<i>Demographics</i>								
Male, n (%)	146 (61.2)	763 (66.4)	0.138	0.063	144 (61.3)	252 (59.0)	0.046	0.628
Age, mean (sd) – years	67.78±12.51	69.45±11.65	0.136	0.057	67.86±12.41	68.68±12.25	0.067	0.354
Ethnicity, n (%)			0.030	0.984			0.104	0.543
Non-Hispanic white	235 (97.9)	1108 (97.8)			230 (97.9)	417 (97.7)		
Hispanic White	1 (0.4)	5 (0.4)			1 (0.4)	3 (0.7)		
Black	3 (1.3)	13 (1.2)			3 (1.3)	7 (1.6)		
Other	1 (0.4)	7 (0.7)			1 (0.4)	0 (0.0)		
<i>Clinical characteristics</i>								
NIHSS score at admission, median (IQR)	3 (2-4)	2 (2-3)	0.640	<0.001	3 (2-4)	3 (2-4)	0.101	0.220
Systolic blood pressure at admission, median (IQR) – mmHg	155 (140-175)	153 (140-170)	0.096	0.561	155 (140-175)	155 (140-170)	0.055	0.930
Diastolic blood pressure at admission, median (IQR) – mmHg	85 (79-93)	85 (75-90)	0.064	0.214	85 (79-94)	85 (75-90)	0.103	0.323
mRS score at onset, median (IQR)	0 (0-0)	0 (0-0)	0.028	0.423	1 (1-1)	1 (1-1)	0.102	0.655
mRS score category, n (%)			0.117	0.283			0.038	0.899
Symptoms without any disability (score of 1), n (%)	23 (9.6)	149 (13.2)			22 (9.4)	44 (10.3)		
Symptoms with mild disability (score of 2), n (%)	16 (6.7)	64 (5.7)			16 (6.8)	31 (7.3)		
Presumed stroke cause, n (%) ^a			0.323	<0.001			0.099	0.593
Undetermined	128 (53.3)	458 (40.4)			125 (53.2)	215 (50.4)		
Small artery occlusion	53 (22.1)	397 (35.0)			53 (22.6)	103 (24.1)		
Large artery atherosclerosis	43 (17.9)	223 (19.7)			42 (17.9)	89 (20.8)		
Other determined cause	16 (6.7)	55 (4.9)			15 (6.4)	20 (4.7)		
<i>Pre-stroke risk factors</i>								
BMI, median (IQR)	26 (23-29)	26 (24-28)	0.042	0.482	26 (23-29)	26 (24-28)	0.061	0.458
CHA2DS2-VASC2, median (IQR)	5 (3-6)	5 (4-6)	0.073	0.296	5 (3-6)	5 (3-6)	0.040	0.621
Arterial hypertension, n (%) ^b	180 (75.0)	916 (80.9)	0.141	0.049	178 (75.7)	337 (78.9)	0.076	0.399
Hypercholesterolemia, n (%) ^c	143 (59.6)	692 (61.1)	0.030	0.721	141 (60.0)	263 (61.6)	0.033	0.750
Hypertriglyceridemia, n (%) ^d	44 (18.3)	242 (21.4)	0.076	0.337	44 (18.7)	98 (23.0)	0.104	0.242

Diabetes mellitus, n (%) ^e	46 (19.2)	311 (27.5)	0.197	0.010	45 (19.2)	91 (21.3)	0.054	0.577
Current smoking, n (%) ^f	101 (42.1)	502 (44.3)	0.045	0.576	100 (42.6)	188 (44.0)	0.030	0.776
Previous TIA/ischemic stroke, n (%)	33 (13.8)	208 (18.4)	0.126	0.107	31 (13.2)	80 (18.7)	0.152	0.086
Previous intracerebral hemorrhage, n (%)	1 (0.4)	7 (0.6)	0.028	>0.999	1 (0.4)	2 (0.5)	0.006	>0.999
History of chronic heart failure, n (%)	7 (2.9)	35 (3.1)	0.010	>0.999	7 (3.0)	11 (2.6)	0.024	0.956
History of myocardial infarction, n (%)	32 (13.3)	109 (9.6)	0.117	0.109	32 (13.6)	38 (8.9)	0.149	0.079
Malignancy (prior or active), n (%)	25 (10.4)	140 (12.4)	0.069	0.639	25 (10.6)	47 (11.0)	0.037	0.664
Therapy on admission, n (%)								
Antihypertensives, n (%)	147 (61.3)	746 (65.8)	0.095	0.200	145 (61.7)	264 (61.8)	0.003	>0.999
Lipid-lowering drugs, n (%)	72 (30.0)	350 (30.9)	0.019	0.846	70 (29.8)	129 (30.2)	0.009	0.980
Antidiabetics, n (%)	38 (15.8)	253 (22.3)	0.166	0.032	37 (15.7)	75 (17.6)	0.049	0.625
Antiplatelets, n (%)								
Acetylsalicylic acid	77 (32.1)	396 (35.0)	0.061	0.439	77 (32.8)	134 (31.4)	0.030	0.781
Clopidogrel	14 (5.8)	66 (58.3)	<0.001	>0.999	12 (5.1)	26 (6.1)	0.043	0.730
Ticagrelor	0 (0.0)	1 (0.1)	0.042	>0.999	0 (0.0)	1 (0.2)	0.068	>0.999
DAPT characteristics								
Time to DAPT start, n (%)			0.966	<0.001			1.144	<0.001
<24h	57 (23.8)	826 (72.9)			56 (23.8)	314 (73.5)		
>24h	183 (76.2)	307 (27.1)			179 (76.2)	113 (26.5)		
Type of DAPT, n (%)			0.084	0.723			0.119	0.495
ASA + clopidogrel	240 (100.0)	1129 (99.6)			235 (100.0)	424 (99.3)		
ASA + ticagrelor	0 (0.0)	4 (0.4)			0 (0.0)	3 (0.7)		
Days of DAPT duration, median (IQR)	21 (21-29)	21 (21-28)	0.083	0.542	21 (21-28)	21 (21-28)	0.063	0.688
Loading dose, n (%)	86 (35.8)	659 (58.2)	0.458	<0.001	86 (36.6)	166 (38.9)	0.047	0.621
Type of antiplatelet continued after DAPT, n (%)			0.127	0.105			0.069	0.441
ASA	162 (67.5)	682 (60.2)			160 (68.1)	271 (63.5)		
Clopidogrel	73 (30.4)	425 (37.5)			70 (29.8)	148 (34.7)		
Ticagrelor	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)		

*Abbreviations. BMI: body mass index; DAPT: dual antiplatelet therapy; IQR: interquartile range; mRS: modified Rankin Scale; IVT: intravenous thrombolysis; NIHSS: National Institute of Health Stroke Scale; sd: standard deviation. Statistically significant P values (<0.05) are reported in bold. *: A standardized difference (of means) <0.250 indicates that groups are well balanced. a: Presumed stroke cause was classified according to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system; b: Arterial hypertension was defined as a history; c: Hypercholesterolemia was defined as history of total blood cholesterol levels >220 mg/dl and/or currently used lipid-lowering drugs; d: Hypertriglyceridemia was defined as history of total blood triglycerides levels >150 mg/dL and/or currently used lipid-lowering drugs; e: Diabetes mellitus was defined as history of fasting glucose >126 mg/dl or the current use of hypoglycemic medications; f: Current smoking was defined as the consumption of ≥1 cigarette per day over the last year.*

Primary outcomes

The percentage of patients with 90-day mRS scores of 0 to 2 was 92.5% in the IVT plus DAPT group and 90.2% in the DAPT group. The risk difference and risk ratio of having a good functional outcome were 2.3% (-2.0% to 6.7%; $p=0.295$) and 1.03 (0.98 to 1.08; $p=0.312$). **Table 2**

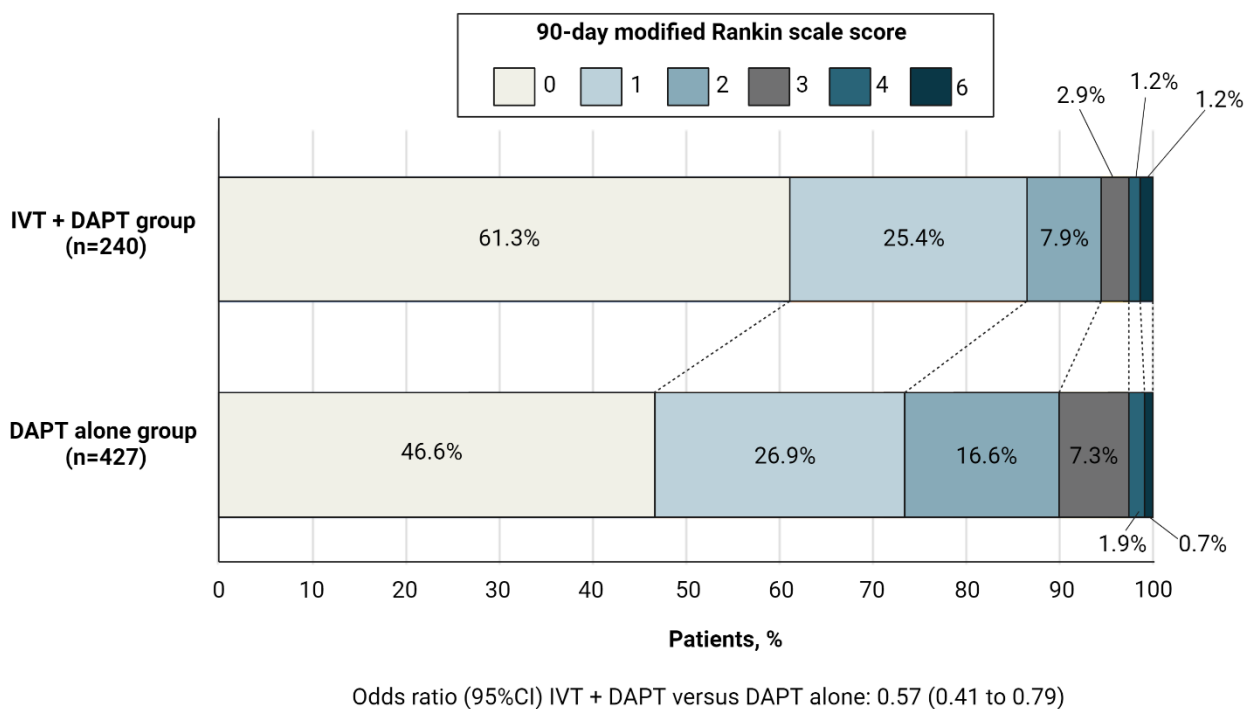
Table 2. Study outcomes

Outcomes	IVT + DAPT (n=240)	DAPT alone (n=427)	Treatment effect metric	Treatment difference (95%CI)	P value
<i>Primary outcomes</i>					
90-day mRS score 0-2, n (%)	222 (92.5)	385 (90.2)	Risk difference (%)	2.3 (-2.0 to 6.7)	0.295
			Risk ratio	1.03 (0.98 to 1.08)	0.312
90-day mRS score distribution					
No symptoms (score of 0), n (%)	147 (61.3)	199 (46.6)			
Symptoms without any disability (score of 1), n (%)	61 (25.4)	115 (26.9)			
Symptoms with mild disability (score of 2), n (%)	19 (7.9)	71 (16.6)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	7 (2.9)	31 (7.3)	Odds ratio	0.57 (0.41 to 0.79)	0.001
Symptoms with moderate-to-severe disability (score of 4), n (%)	3 (1.2)	8 (1.9)			
Symptoms with severe disability (score of 5), n (%)	0 (0.0)	0 (0.0)			
Death (score of 6), n (%)	3 (1.2)	3 (0.7)			
<i>Secondary outcomes</i>					
24-hour early neurological improvement, n (%)	135 (56.3)	151 (35.4)	Risk difference (%)	20.9 (13.1 to 28.6)	<0.001
			Risk ratio	1.59 (1.34 to 1.89)	<0.001
24-hour early neurological deterioration, n (%)	3 (1.2)	5 (1.2)	Risk difference (%)	0.1 (-1.7 to 1.8)	0.929
			Risk ratio	1.07 (0.26 to 4.43)	0.928
24-hour change in NIHSS score from baseline, median (IQR)	-2 (-3 to -1)	-1 (-2 to 0)	Odds ratio	-0.65 (-0.89 to -0.41)	<0.001
90-day stroke or other vascular events, n (%)	3 (1.2)	20 (4.7)	Hazard ratio	0.27 (0.08 to 0.90)	0.034
90-day vascular death, n (%)	2 (0.8)	2 (0.5)	Risk difference (%)	0.4 (-1.0 to 1.7)	0.589
			Risk ratio	1.78 (0.25 to 12.55)	0.558
<i>Safety outcomes</i>					
90-day moderate-to-severe bleeding events, n (%)	2 (0.8)	3 (0.7)	Risk difference (%)	0.1 (-1.3 to 1.5)	0.854
			Risk ratio	1.19 (0.20 to 7.05)	0.851
90-day any bleeding events, n (%)	7 (2.9)	16 (3.8)	Risk difference (%)	-0.8 (-3.6 to 2.0)	0.560
			Risk ratio	0.78 (0.32 to 1.87)	0.573
90-day intracerebral hemorrhage, n (%)	0 (0.0)	2 (0.5)	Risk difference (%)	-0.5 (-1.1 to 0.2)	0.156
			Risk ratio	Not applicable	0.289
24-hour hemorrhagic transformation, n (%)	4 (1.6)	4 (1.0)	Risk difference (%)	0.7 (-1.1 to 2.6)	0.442
			Risk ratio	1.78 (0.45 to 7.05)	0.406

Abbreviations. DAPT: dual antiplatelet treatment; IVT: intravenous thrombolysis; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale. Statistically significant P values (<0.05) are reported in bold.

We found a significant difference in the 90-day ordinal distribution of mRS scores between patients treated with IVT plus DAPT versus DAPT alone (odds ratio 0.57, 0.41 to 0.79; $p=0.001$) with a higher percentage of patients with a mRS of 0 in those who received the combined treatments (61.3%) versus DAPT alone (46.6%). **Table 2. Figure 2.**

Figure 2. Ordinal distribution of 90-day modified Rankin scale scores



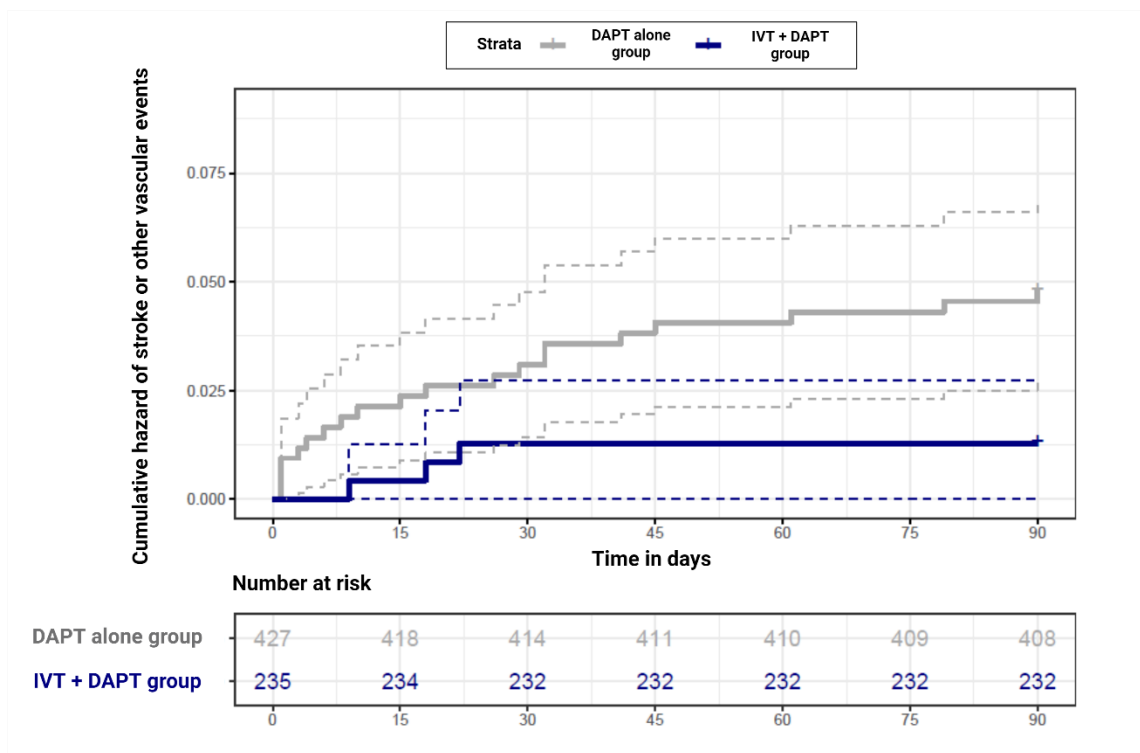
Abbreviations. CI: confidence interval; DAPT: dual antiplatelet treatment; IVT: intravenous thrombolysis.

Secondary outcomes

Compared to DAPT alone patients, those treated with IVT plus DAPT showed a higher frequency of 24-h early neurological improvement (risk difference: 20.9%, 13.1% to 28.6%; $p<0.001$; risk ratio: 1.59, 1.34-1.89; $p<0.001$), with a higher 24-h decrease in the NIHSS scores from baseline (odds ratio -0.65, -0.89 to -0.41; $p<0.001$). Conversely, there were no significant differences in the 24-h risk of early neurological deterioration. **Table 2** We found a significantly lower risk of 90-day stroke and

other vascular events in patients treated with IVT plus DAPT versus those treated with DAPT alone (HR 0.27, 0.08 to 0.90; $p=0.034$). Kaplan-Meier hazard functions confirmed that the overall risk of stroke and other vascular events was lower in those who combined IVT and DAPT compared to those who received DAPT alone (log-rank test p : 0.020). **Figure 3** The 90-day risk of vascular death was similar between groups. **Table 2**

Figure 3. Kaplan-Meier cumulative hazard function of 90-day risk of stroke and other cardiovascular events.



Abbreviations. DAPT: dual antiplatelet treatment; IVT: intravenous thrombolysis. Dashed lines indicate 95% confidence intervals. Log-rank test p -value: 0.020.

Safety outcomes

For safety events, we found a low rate of 90-day moderate-to-severe (0.8% versus 0.7%) and any bleeding (2.0% versus 3.8%) events in both treatment groups. No patients who received IVT had intracerebral hemorrhage, while hemorrhagic transformation occurred in 4 patients both within the IVT plus DAPT and DAPT alone groups (1.6% and 1.0%, respectively). The risk of hemorrhagic transformation was similar between those who started DAPT within 24 hours of the index event both in the IVT plus DAPT and DAPT alone groups ($n=1/56$, 1.8% versus $2/314$, 0.6%; $p=0.941$). We found no differences in the risk of any safety event between treatment groups. **Table 2**

Discussion

This READAPT observational study showed that combining IVT and DAPT conferred some clinical advantages over DAPT alone in patients with MIS. Specifically, we found a more favorable distribution of mRS scores at 90 days after stroke among patients treated with IVT plus DAPT versus DAPT alone, while the proportion of patients with 90-day good functional outcome (mRS of 0 to 2) was similar between the two treatment approaches. Furthermore, the combining approach was associated with a higher rate of early neurological improvement at 24 hours versus DAPT alone and with a lower risk of recurrent stroke and other vascular events at 90 days post-stroke. Of note, no safety concerns emerged from combining IVT and DAPT, as the risk of bleeding events and early (24-h) hemorrhagic transformation of the ischemic lesion did not differ between groups. On the other hand, the intention to treat MIS patients with DAPT should not raise safety concerns for the bleeding risks associated with IVT. Globally, our data indicated that it is reasonable to combine IVT and DAPT in patients with minor disabling ischemic stroke since this combined strategy may offer advantages as compared to DAPT alone.

It is important to note that our data are caught from the real-world setting, where patients were not randomly assigned to treatments and the decision to treat or not to treat patients with IVT was based upon clinical considerations. As shown in **Table 1**, the group of patients treated with IVT plus DAPT presented several differences in baseline characteristics compared with those who received DAPT alone. Propensity score matching was performed in our study to control those differences and mitigate the effect of some known confounders. While randomized controlled trials offer the highest quality of evidence to inform clinical practice, replication of their results in clinical practice is affected by difference in characteristics of patients and in application of trial procedures. Thus, real-world studies are complimentary to randomized controlled trials and can provide effectiveness and safety data in the real-world patients population.

As regards the secondary outcomes, patients combining IVT and DAPT had a higher rate of early neurological improvement at 24 hours, with a higher median decrease in the NIHSS scores from the baseline, compared to patients who received DAPT alone. To correctly interpret these findings, it is important to consider that most of the patients treated with IVT (>75%) started DAPT after at least 24 hours of IVT to minimize the risk of bleeding events related to the procedure, as recommended from current IVT guidelines.¹⁰ Therefore, the higher rate of early neurological improvement observed within the IVT plus DAPT group versus DAPT alone might be mostly related to the effect of IVT, rather than to DAPT itself. It is worth noting that the proportion of patients who were treated with a loading dose of DAPT was low in both groups even after propensity score matching (<40%, **Table**

1). In the real-world setting, DAPT loading dose is often withdrawn, especially in patients who have undergone IVT due to safety concerns.¹⁷ This practice could negatively impact on the short-term risk of new vascular events, even if the Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis (INSPIRES) trial showed that DAPT can be effective even if initiated 72 hours after symptom onset.²²

Of note, we also observed a lower risk of recurrent stroke and other vascular events at 90 days in patients combining IVT and DAPT versus DAPT alone. This observation may suggest a synergic effect of the combined interventions in preventing new vascular events. Indeed, IVT might play a role as a short-lived agent in countering the progression of acute thrombosis, while DAPT might confer longer-lasting protection against recurrent vascular events.¹¹⁻¹³ The potential for a synergistic action of IVT and DAPT in reducing 90-day vascular events is also suggested by our finding of significantly lower rates of recurrences in patients combining IVT plus DAPT versus DAPT alone (1.2% versus 4.7%), which contrasts with the observations of the ARAMIS trial, where no differences were found between patients undergoing IVT or DAPT as exclusive intervention (0.6% versus 0.3%).¹⁴

For the safety outcomes, we found no significant differences between patients combining IVT and DAPT versus those treated with DAPT alone. The rate of moderate-to-severe bleeding events at 90 days was low and similar between the two groups. Furthermore, no patients combining IVT and DAPT had intracerebral hemorrhage during the follow-up period. Notably, the risk of early (24 hours) hemorrhagic transformation did not differ between the two treatment approaches, even when considering patients who received DAPT within 24 hours of IVT. All these observations might support an excellent safety profile for the combined approach in terms of bleeding risks. It should be considered that patients who discontinued DAPT due to a need for anticoagulants were not included in the current analysis, because of the bleeding risk potentially conferred by subsequent anticoagulation, which might have affected the assessment of safety of DAPT and of IVT. Although this subset represented only 1.9% of the initial READAPT sample, we cannot disregard the possibility of an increased bleeding risk in patients who transitioned from DAPT to anticoagulation regardless of whether they were treated or not with IVT.

It is noteworthy to highlight that our analysis also excluded patients with NIHSS of 0 and without neurological deficit upon admission. This criterion was applied to avoid cases where complete symptoms regression at the time of clinical observation (i.e., TIA/MIS with complete symptoms resolution before admission) might have hindered the assessment for eligibility to IVT. Hence, the higher prevalence of MIS patients with more disabling symptoms in our cohort might explain the higher benefits of IVT on the 90-day functional disability observed within our population compared

to prior trials, which randomized patients to IVT versus aspirin or DAPT but showed no significant differences in terms of 90-day favorable functional outcome.^{7,14} Indeed, the median baseline NIHSS of patients who received IVT in the PRISMS⁷ (57.7% of patients with NIHSS of 1 to 2) and ARAMIS¹⁴ (median NIHSS 2 [IQR 1-3]) trials was lower compared to our cohort (median NIHSS 3 [IQR 2-4]).

The main study strength lies in 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. Conversely, our findings should be interpreted in light of some limitations. Due to the observational design of the READAPT study, we cannot exclude residual confounding even if we have implemented a rigorous propensity score matching. In particular, the main limit lies in the likelihood that patients deemed eligible for IVT may possess baseline characteristics associated with more favorable outcomes compared to those treated with DAPT only (i.e., higher Alberta Stroke Program early CT scores [ASPECTS], favorable perfusion mismatch, lower clot dimension and more distal clot location, better collateral circulation, faster hospital admission after the index event). While patients who underwent combined treatment were more likely to experience favorable early evolution compared with those undergoing DAPT alone, those with unfavorable early outcomes after IVT were likely not treated with DAPT leading to their exclusion from the READAPT study. This potential effect could have contributed to a reduction in the risk of early unfavorable outcomes within the combined treatment group, such as early neurological deterioration, as well as of major safety outcomes. Indeed, there was a lower prevalence of factors which may negatively impact on the risk of major hemorrhagic events, such as hypertension and diabetes, in the group combining IVT plus DAPT versus DAPT alone. Similarly, the risk of recurrent stroke or other vascular events may have been reduced by the exclusion from the READAPT study of patients who were not treated with DAPT for new severe vascular events after IVT. Furthermore, to ensure better comparability between groups, we excluded patients without deficits at the time of medical consultation, as they are usually excluded from the IVT decision; however, this exclusion might have hampered the generalizability of our findings to this specific group of patients. Other limitations include the low number of safety outcomes which did not allow us to identify factors associated with an increased risk of bleeding events, nor to assess whether there was an imbalance in their prevalence between investigated cohorts at the baseline. Moreover, the appropriateness of stroke diagnosis, as well as of collected variables and outcome adjudication, was upon local investigators, who received specific training before the READAPT study was initiated. However, the core clinical staff did not have direct access to patient medical records. Also, we were unable to determine the blood levels of antiplatelets, which prevented us from precisely pinpointing the onset of action of DAPT or discerning whether there was ongoing

antiplatelet activity in patients already receiving aspirin or clopidogrel. Lastly, the strong imbalance towards the non-Hispanic white population (>90%) may consistently limit the generalizability of our findings outside this specific ethnic group. Fourth, the lack of a pre-specified sample size calculation for outcomes might limit the statistical power of our analyses, which were all exploratory.

In conclusion, based on our findings, patients with MIS could potentially derive clinical benefits from combining IVT and DAPT over DAPT alone, with no apparent safety issues. The benefits consist in better functional outcome and less recurrent events at 90-day. Our results hold promise in informing clinical decision-making and indicate that DAPT should not be viewed as a standalone alternative, but rather as a complementary therapy alongside IVT. This combined strategy might yield the potential not only to optimize the short-term functional outcome of minor stroke patients, but also to synergize in preventing new vascular events. Hopefully, results from ongoing interventional randomized trials (i.e., Early Antiplatelet for Minor Stroke Following Thrombolysis [EAST] - NCT05193071) will help to clarify outcomes of the combined approach in a controlled study setting. Future trials should also compare outcomes between patients receiving combined treatment versus IVT alone to mitigate selection bias arising from the more favorable characteristics often observed in patients who received DAPT after IVT in real-world settings

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2.4 Patients with relevant comorbidities

2.4.1 Paper 7: Effectiveness and safety of dual antiplatelet therapy in patients with minor ischemic stroke or transient ischemic attack and cancer: A secondary analysis of the READT study

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Abstract

Background and Aims: Patients with ischemic stroke or transient ischemic attack (TIA) and cancer face unique risks of recurrent ischemic events and bleeding. It is unclear whether this increased risk is present even in patients with minor ischemic stroke or transient ischemic attack (TIA) receiving dual antiplatelet therapy (DAPT). This study aimed to evaluate the impact of cancer on the short-term outcomes in patients with non-cardioembolic minor ischemic stroke or high-risk TIA and cancer receiving DAPT.

Methods: This was a secondary analysis of the prospective multicentric READAPT study (NCT05476081), including patients with non-cardioembolic minor ischemic stroke (NIHSS ≤ 5) or high-risk TIA (ABCD2 ≥ 4) who initiated DAPT within 48 hours of symptom onset. The primary effectiveness outcome was the 90-day risk of new ischemic stroke or other vascular events (TIA, myocardial infarction, death due to vascular causes). Secondary outcomes included 90-day mRS score distribution and all-cause mortality. The primary safety outcome was the 90-day risk of any bleeding, with secondary safety outcomes including 24-hour hemorrhagic transformation. We used Inverse Probability Weighting to compare outcomes between patients with and without cancer.

Results: From 2,278 patients in the READAPT study cohort, we included 1,561 patients (mean age 70.3 ± 11.7 years; 65.4% males), of whom 206 (13.2%) had cancer, categorized as either active (27.7%) or non-active (72.3%). After weighting, overall cancer patients had a higher risk of 90-day new ischemic stroke or other vascular events (weighted HR 1.78, 95% CI 1.20-2.63, $p=0.004$) and worse 90-day mRS score distribution (OR 1.24, 95% CI 1.10-1.41, $p<0.001$) compared to patients without cancer. The 90-day risk of bleeding did not differ between cancer and no-cancer groups overall. When analyzing cancer subgroups, patients with active cancer had significantly higher risk of 90-day ischemic stroke or other vascular (weighted HR 2.75, 95% CI 1.70-4.45, $p<0.001$) and any bleeding (weighted HR 2.51, 95% CI 1.27-4.97, $p=0.008$) events compared to no-cancer patients. In contrast, patients with non-active cancer had comparable risks to those without cancer. Furthermore, hematological malignancies were associated with a substantially higher risk of 90-day new ischemic stroke or other vascular events compared to solid tumors (weighted HR 8.15, 95% CI 5.06-13.14, $p<0.001$).

Conclusions: Patients with minor ischemic stroke or high-risk TIA and active cancer have increased risks of ischemic and bleeding events after DAPT. Conversely, patients with non-active cancer have similar outcomes after DAPT compared to those with no cancer.

Introduction

Early short-term dual antiplatelet therapy (DAPT) has become a cornerstone in the secondary prevention of new ischemic events in patients who have experienced non-cardioembolic minor ischemic stroke or high-risk transient ischemic attack (TIA).^{1,2} The combination of aspirin and a P2Y12 inhibitor has been shown to significantly reduce the risk of early vascular recurrences in the general population, particularly within the critical first 21 to 90 days following the index event.³⁻⁵ Real-world data indicate that the risk of outcome events in patients with minor ischemic stroke and high-risk TIA receiving DAPT is low.⁶ To enhance preventive strategies, it is crucial to identify populations with a higher residual risk. In this context, patients with cancer remain an underexplored group.

Cancer has been associated with both risk of ischemic stroke recurrence and bleeding complications.^{7,8} Indeed, cancer-associated hypercoagulability, driven by tumor-mediated prothrombotic factors, systemic inflammation, and endothelial dysfunction, significantly increases the risk of ischemic events. This hypercoagulable state may attenuate the efficacy of antiplatelet therapy, thereby complicating efforts to prevent recurrent stroke in this population.^{7,8} Concurrently, both the presence of cancer and its associated treatments heighten the risk of bleeding,^{7,8} a concern that is further exacerbated by the use of DAPT. Furthermore, the heterogeneous nature of cancer, characterized by variations in tumor type, stage, and treatment regimens, adds significant complexity to the management of DAPT in this patient population. Hematological malignancies, for example, are associated with a substantially higher thrombotic risk compared to solid tumors,⁹ while patients with advanced-stage cancer face a markedly increased risk of bleeding complications.¹⁰

In this study, we aimed to evaluate the impact of cancer on the short-term effectiveness and safety outcomes after DAPT in a real-world cohort of patients with non-cardioembolic minor ischemic stroke or high-risk TIA.

Methods

READAPT Study

The READAPT (NCT05476081) is a prospective, observational, multicenter study carried out in real-world clinical settings across Italy. The study was coordinated by the University of L'Aquila and supported by the Italian Stroke Association. It followed the reporting principles of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research.¹¹ Participants included adults aged 18 and older who experienced an acute non-cardioembolic ischemic stroke or transient ischemic attack (TIA) and were prescribed dual

antiplatelet therapy (DAPT) for up to 90 days. The READAPT study was conducted between February 1, 2021, and February 28, 2023, and spanned 64 stroke centers throughout Italy. Recruitment took place in hospitals, emergency departments, and open-access neurology clinics, aiming for broad representation of the eligible population. Investigators ensured comprehensive inclusion by providing detailed protocols and regular follow-up reminders. Stroke and TIA diagnoses were confirmed according to routine clinical practices and World Health Organization criteria. Eligibility criteria focused solely on patients with acute non-cardioembolic stroke or TIA initiating DAPT, without restrictions regarding the type of antiplatelet agents or the timing of DAPT initiation. The decision to treat the patient with DAPT, and consequently their inclusion in the READAPT study, was made by the treating physician on an individual basis. Physicians were free to make this decision based on their clinical judgment, considering the risk-benefit assessment for each patient. Patients were included whether they received a loading dose of DAPT (≥ 300 mg for aspirin and clopidogrel or ≥ 180 mg for ticagrelor). Exclusion criteria encompassed only patients enrolled in interventional trials at the time of stroke onset, those receiving continuous DAPT for stent-related procedures, and individuals unable to comply with the study protocol. Patients were enrolled soon after the qualifying event and monitored for a follow-up period of 90 ± 10 days through in-person or remote visits. Comprehensive details of the study methodology and definitions used have been published previously.^{12,13}

Study analysis

For the purposes of this exploratory pre-specified analysis, we selected only patients who underwent DAPT according to recommendations from available guidelines.^{1,2} Specifically, we included patients presenting with minor ischemic strokes (defined by a National Institute of Health Stroke Scale [NIHSS] score of 0 to 5 at admission) or high-risk TIAs, characterized by symptom resolution within 24 hours and an ABCD2 score of 4 or higher and no evidence of new ischemic lesion(s) at neuroimaging. Inclusion was limited to those who began dual antiplatelet therapy (DAPT) within 48 hours of symptom onset. Conversely, we excluded patients prescribed DAPT following carotid endarterectomy or stenting, as well as those who discontinued DAPT early due to the initiation of anticoagulation therapy. These exclusions were made to minimize potential confounding from procedure-related factors or anticoagulation-associated bleeding risks, which could impact the safety assessment of DAPT.

Patients with cancer were stratified into 2 groups: those with active cancer and those with non-active cancer. We defined active cancer as (1) a diagnosis of cancer that occurred within 6 months of the index event or during hospitalization, (2) cancer treatment with radiotherapy, chemotherapy or

surgery or a combination of them within 6 months of the index event, (3) a previous history of malignancy and a diagnosis of recurrence or metastasis within 6 months of the index event. Non-active cancer was defined as a previous history of malignancy in the absence of active cancer criteria. The site of cancer (non-active or active) was classified as belonging to one of the following categories: gastrointestinal, lung, genitourinary, breast, hematological, skin, other. Definition of cancer was assessed locally by the treating physician and additional investigations were performed as needed at the physician's discretion. Non-systematic assessment was performed to exclude potential occult malignancies.

Study outcomes

The primary effectiveness outcome was the risk of new ischemic stroke or other vascular events (TIA, myocardial infarction, death due to vascular causes – i.e. death caused by stroke, systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmias) within 90 days. Secondary effectiveness outcomes included the 90-day modified Rankin Scale (mRS) score ordinal distribution and 90-day all-cause mortality. The primary safety outcome was the 90-day risk of any bleeding event, as defined by any category of bleeding severity according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification.¹⁴ Accordingly, we classified bleeding events as severe if they involved fatal hemorrhage, intracranial hemorrhage, or required blood or fluid replacement, inotropic support, or surgical intervention. Moderate bleeding was defined as requiring a transfusion but not posing a life-threatening risk. Bleeding events that did not meet these criteria were classified as mild.¹⁴ The secondary safety outcome was 24-h hemorrhagic transformation, as defined by any category of the Heidelberg bleeding classification system.¹⁵

Statistical analysis

Inverse Probability Weighting

To achieve balanced baseline characteristics between patients with and without cancer, we applied Inverse Probability Weighting to create a pseudo-weighted cohort. Propensity scores were generated using a logistic regression model incorporating pre-defined baseline variables: age, sex, ethnicity, smoking status, arterial hypertension, diabetes, hypercholesterolemia, baseline NIHSS and mRS, presumed stroke/TIA cause, symptoms duration, intravenous thrombolysis, endovascular thrombectomy, DAPT duration and loading dose.

Propensity scores were then used to assign inverse probability weights to each patient. To assess balance between groups, standardized mean differences were calculated for each covariate. We also

checked the overlap of propensity score distributions between groups to ensure sufficient comparability and applied stabilized weights to reduce the impact of extreme values and improve the reliability of the model.

Outcomes analysis in the weighted cohorts

The primary effectiveness outcome was assessed using Cox regression, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported for comparisons between patients with and without cancer. The 90-day shift in the distribution of modified Rankin Scale (mRS) scores was analyzed using an ordinal generalized linear model and presented as odds ratio (OR) with corresponding 95% CIs. Additionally, HRs with 95% CIs were calculated for the 90-day risk of all-cause mortality. The primary safety outcome was similarly evaluated using Cox regression to compare risk between the cancer and no-cancer groups. Risk difference (95% CIs) was calculated for 24-hour hemorrhagic transformation. Weighted Kaplan-Meier cumulative function was used to visualize the overall risk for both primary effectiveness and safety outcomes, with the log-rank test applied to determine the statistical significance of differences between groups. Competing risk analysis was also employed to estimate the 90-day cumulative incidence of primary effectiveness and safety outcomes at 90 days, with death as a competing event which prevents the occurrence of those outcomes. Gray test was used to assess the equality of cumulative incidence functions for primary effectiveness and safety outcomes and all-cause death between the cancer and no-cancer groups. Furthermore, the 90-day risks of primary effectiveness and safety outcomes were compared among patients with active cancer, non-active cancer, and those without cancer using Cox regression models and Kaplan-Meier cumulative hazard curves. To assess the 90-day distribution of mRS scores between patients with active and non-active cancer, we employed an ordinal generalized linear model. Lastly, we compared the 90-day risks of primary effectiveness and safety outcomes between patients with solid (gastrointestinal, genitourinary, breast, skin and other) versus hematological cancers using the same statistical approach. As the outcomes of the present analysis were exploratory and no prior assumptions were made, a sample size was not prespecified.

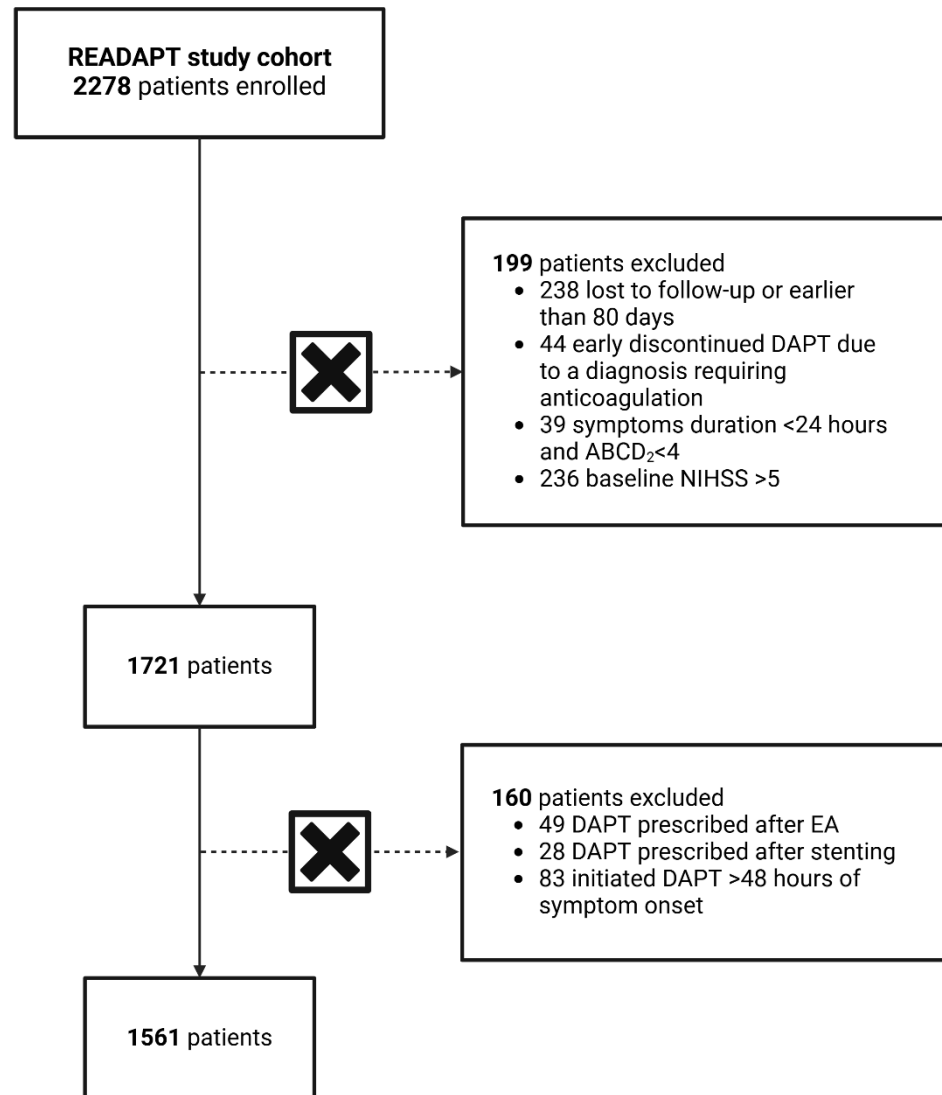
All statistical analyses were conducted using R software (version 4.2.2). Statistical significance was set at a p-value of <0.05.

Results

Of the 2278 patients in the READAPT study cohort, 1561 were included in the analysis (mean age: 70.3 ± 11.7 years, 65.4% males). Among these, 71.6% had minor ischemic stroke, while 28.4%

experienced high-risk TIA. The number of excluded patients with reasons is reported in the study flow-chart. **Figure 1**

Figure 1. Study flow-chart.



Abbreviations. DAPT: dual antiplatelet therapy; EA: endarterectomy; NIHSS: National Institute of Health Stroke Scale.

Within our sample, 206 patients (13.2%) had cancer. Specifically, 149 patients (72.3%) had non-active cancer while 57 (27.7%) had active cancer. Regarding the cancer site, 26 patients (12.6%) had gastrointestinal cancer, 9 patients (4.4%) had lung cancer, 43 patients (20.9%) had genitourinary cancer, 39 patients (18.9%) had breast cancer, 21 patients (10.2%) had hematological cancer, 13 patients (6.3%) had skin cancer, and 55 patients (26.7%) had cancer at other sites. Among the 57 patients with active cancer, 7 patients (12.3%) had gastrointestinal cancer, 3 patients (5.3%) had lung cancer, 11 patients (19.3%) had genitourinary cancer, 9 patients (15.8%) had breast cancer, 12 patients

(21.1%) had hematological cancer, 4 patients (7.0%) had skin cancer, and 11 patients (19.3%) had cancer at other sites. **Table 1**

Table 1. Baseline characteristics.

	Overall cohort (n=1561)	Cancer (n=206)	No Cancer (n=1355)	SMD unweighted	SMD weighted
Demographics					
Age (years), mean $\pm$ sd	70.3 $\pm$ 11.7	73.8 $\pm$ 9.7	69.8 $\pm$ 11.9	0.365	0.086
Male sex, n (%)	1021 (65.4)	131 (63.6)	890 (65.7)	0.044	0.072
Ethnicity, n (%)				0.164	0.170
Non-Hispanic White	1529 (98.0)	204 (99.0)	1325 (97.8)		
Hispanic White	8 (0.5)	0 (0.0)	8 (0.6)		
Black	14 (0.9)	2 (1.0)	12 (0.9)		
Other	10 (0.6)	0 (0.0)	10 (0.7)		
Clinical characteristics					
NIHSS on admission, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.054	0.011
ABCD ₂ , median (IQR)*	5 (4-6)	5 (4-6)	5 (4-6)	0.040	0.072
mRS score category, n (%)				0.281	0.128
No symptoms (score of 0), n (%)	1225 (78.5)	144 (69.9)	1081 (79.8)		
Symptoms without any disability (score of 1), n (%)	193 (12.4)	34 (16.5)	159 (11.7)		
Symptoms with mild disability (score of 2), n (%)	77 (4.9)	20 (9.7)	57 (4.2)		
Symptoms with mild-to-moderate disability (score of 3), n (%)	52 (3.3)	7 (3.4)	45 (3.3)		
Symptoms with moderate-to-severe disability (score of 4), n (%)	12 (0.8)	1 (0.5)	11 (0.8)		
Symptoms with severe disability (score of 5), n (%)	2 (0.1)	0 (0.0)	2 (0.1)		
Symptoms duration, n (%)				0.092	0.056
≥ 24 h	1118 (71.6)	140 (68.0)	978 (72.2)		
<24 h	443 (28.4)	66 (32.0)	377 (27.8)		
Presumed stroke cause, n (%) ^a				0.056	0.049
Undetermined	312 (20.0)	41 (19.9)	271 (20.0)		
Small artery occlusion	466 (29.9)	62 (30.1)	404 (29.8)		
Large artery atherosclerosis	82 (5.3)	13 (6.3)	69 (5.1)		
Other determined cause	701 (44.9)	90 (43.7)	611 (45.1)		
ESUS, n (%) ^b	229 (14.7)	31 (15.0)	198 (14.6)	0.069	0.020
Cancer history					
Active, n (%)	57 (27.7)	57 (27.7)	-	-	-
mRS score category – active cancer, n (%)					
No symptoms (score of 0), n (%)	42 (73.7)	42 (73.7)	-	-	-
Symptoms without any disability (score of 1), n (%)	3 (5.3)	3 (5.3)	-	-	-
Symptoms with mild disability (score of 2), n (%)	8 (14.0)	8 (14.0)	-	-	-
Symptoms with mild-to-moderate disability (score of 3), n (%)	4 (7.0)	4 (7.0)	-	-	-
Non-active, n (%)	149 (72.3)	149 (72.3)	-	-	-
mRS score category – non-active cancer, n (%)					
No symptoms (score of 0), n (%)	102 (68.5)	102 (68.5)	-	-	-
Symptoms without any disability (score of 1), n (%)	31 (20.8)	31 (20.8)	-	-	-
Symptoms with mild disability (score of 2), n (%)	12 (8.1)	12 (8.1)	-	-	-
Symptoms with mild-to-moderate disability (score of 3), n (%)	3 (2.0)	3 (2.0)	-	-	-

Symptoms with moderate-to-severe disability (score of 4), n (%)	1 (0.7)	1 (0.7)	-	-	-
Cancer site, n (%)					
Gastrointestinal	26 (12.6)	26 (12.6)	-	-	-
Lung	9 (4.4)	9 (4.4)	-	-	-
Genitourinary	43 (20.9)	43 (20.9)	-	-	-
Breast	39 (18.9)	39 (18.9)	-	-	-
Hematological	21 (10.2)	21 (10.2)	-	-	-
Skin	13 (6.3)	13 (6.3)	-	-	-
Other	55 (26.7)	55 (26.7)	-	-	-
Pre-stroke risk factors					
Arterial hypertension, n (%) ^c	1269 (81.3)	169 (82.0)	1100 (81.2)	0.022	0.018
Hypercholesterolemia, n (%) ^d	952 (61.0)	133 (64.6)	819 (60.4)	0.085	0.008
Diabetes mellitus, n (%) ^e	441 (28.3)	53 (25.7)	388 (28.6)	0.065	0.003
Current smoking, n (%) ^f	677 (43.4)	88 (42.7)	589 (43.5)	0.015	0.031
Previous TIA/ischemic stroke, n (%)	294 (18.8)	41 (19.9)	253 (18.7)	0.031	0.085
Previous intracerebral hemorrhage, n (%)	12 (0.8)	1 (0.5)	11 (0.8)	0.041	0.128
Hyperacute treatment, n (%)					
Intravenous thrombolysis, n (%)	245 (15.7)	26 (12.6)	219 (16.2)	0.101	0.012
Endovascular thrombectomy, n (%)	12 (0.8)	2 (1.0)	10 (0.7)	0.025	0.014
Therapy on admission, n (%)					
Single antiplatelet therapy					
Aspirin, n (%)	553 (35.4)	72 (35.0)	481 (35.5)	0.011	0.136
Clopidogrel, n (%)	107 (6.9)	17 (8.3)	90 (6.6)	0.061	0.099
Ticagrelor, n (%)	1 (0.1)	0 (0.0)	1 (0.1)	0.038	0.088
Antihypertensive drugs, n (%)	1044 (66.9)	151 (73.3)	893 (65.9)	0.161	0.086
Lipid-lowering drugs, n (%)	521 (33.4)	79 (38.3)	442 (32.6)	0.120	0.019
Antidiabetics, n (%)	369 (23.6)	41 (19.9)	328 (24.2)	0.104	0.089
DAPT characteristics					
Type of DAPT, n (%)				0.085	0.032
ASA + clopidogrel	1555 (99.6)	204 (99.0)	1351 (99.7)		
ASA + ticagrelor	6 (0.4)	2 (1.0)	4 (0.3)		
DAPT duration ≥21 days, n (%)	1503 (96.3)	200 (97.1)	1303 (96.2)	0.125	0.033
Days of DAPT, median (IQR)	21 (21-30)	21 (21-30)	21 (21-30)	0.159	0.058
Loading dose, n (%)	848 (54.3)	111 (53.9)	737 (54.4)	0.133	0.010
Therapy on discharge					
Antihypertensive drugs, n (%)	1353 (86.7)	185 (89.8)	1168 (86.2)	0.137	0.080
Lipid-lowering drugs, n (%)	1418 (90.8)	192 (93.2)	1226 (90.5)	0.105	0.024
Antidiabetics, n (%)	498 (31.9)	60 (29.1)	438 (33.9)	0.061	0.002
Type of antiplatelet continued after DAPT, n (%)				0.047	0.052
Aspirin	964 (61.8)	123 (59.7)	841 (62.1)		
Clopidogrel	563 (36.1)	78 (37.9)	485 (35.8)		

*Abbreviations. DAPT: dual antiplatelet therapy; ESUS: embolic stroke of unknown source; IQR: interquartile range; mRS: modified Rankin Scale score; NIHSS: National Institute of Health Stroke Scale score; sd: standard deviation; SMD: standardized means difference. SMD <0.20 indicates good balance between groups. *: Only patients with symptoms duration <24 hours; a: Presumed stroke cause was classified according to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification system; b: ESUS was defined as a non-lacunar ischemic stroke in the absence of atherosclerosis causing >50% stenosis in arteries supplying ischemic area, no major risk cardioembolic source, no other specific stroke cause identified; c: Arterial hypertension was defined as a history of blood pressure >140/90 mm Hg or the current use of antihypertensive medications; d: Dyslipidemia was defined as history of total blood cholesterol levels >220 mg/dL and/or total triglycerides levels >130 mg/dL and/or current used lipid-lowering drugs; e: Diabetes mellitus was defined as history of fasting glucose >126 mg/dL or the current use of hypoglycemic medications; f: Current smoking was defined as the consumption of ≥1 cigarette per day over the last year.*

Inverse Probability Weighting

Weighted and unweighted baseline characteristics are summarized in **Table 1**. No missing data were recorded in the variables used to calculate the propensity scores, nor in any baseline variables within the weighted and unweighted cohorts. Overall, a satisfactory balance was achieved for all baseline variables which showed a standardized difference (SD) of propensity scores below 0.20. Balance diagnostics indicated that the samples were well-weighted, with a mean standardized difference in propensity scores between groups of 0.03 (acceptable balance < 0.25) and a variance ratio of propensity scores of 1.15 (acceptable range: 0.5–2).¹⁶ Graphical representations of propensity scores and covariate balance distributions further confirmed the overall quality of the weighting process.

Figure 2 and 3

Figure 2. Propensity score distribution by cancer status in the unweighted and weighted cohorts.

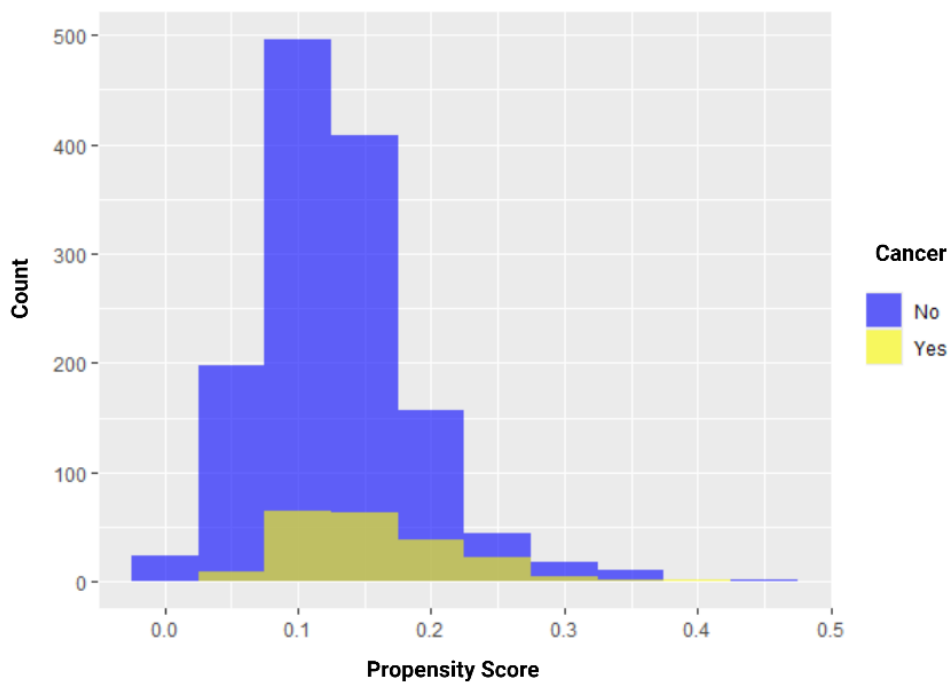
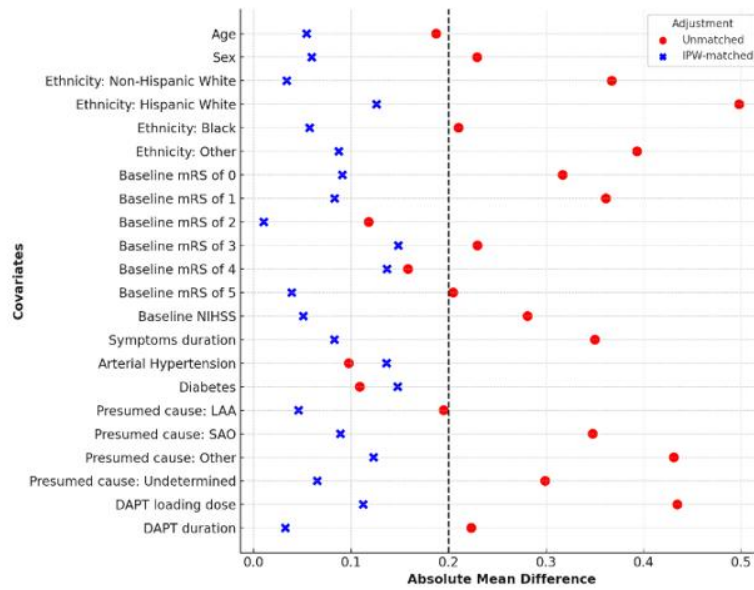


Figure 3. Love plot of covariate balance by cancer status in the unweighted and weighted cohorts.



Abbreviations. *DAPT*: dual antiplatelet therapy; *LAA*: large-artery atherosclerosis; *mRS*: modified Rankin Score; *NIHSS*: National Institute of Health Stroke Scale; *SAO*: small-artery occlusion.

Primary effectiveness outcome

Within the weighted cohorts, patients with concomitant cancer showed a higher risk of 90-day new ischemic stroke or other vascular events compared to those without cancer (5.8% versus 3.0%; weighted HR 1.78 [95% CI 1.20 to 2.63]; $p=0.004$). **Table 2**

Table 2. Outcomes comparison

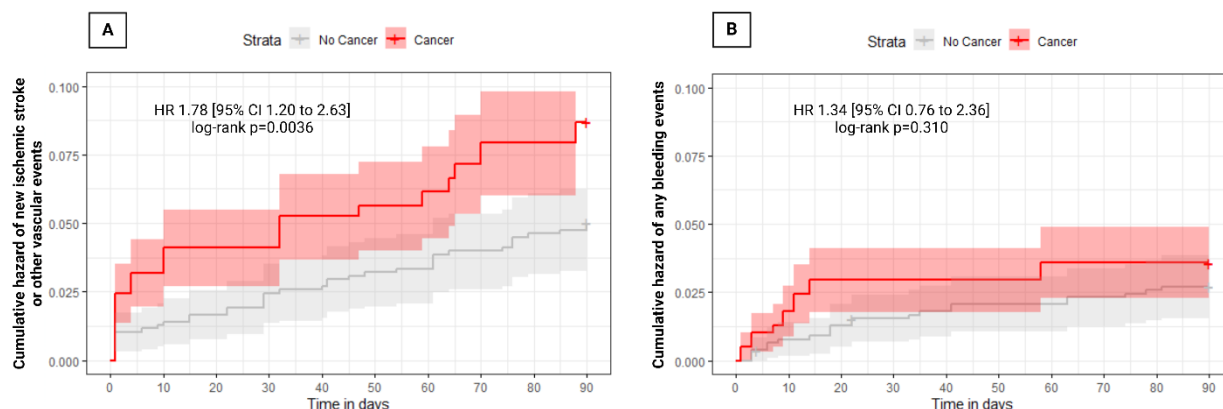
	Cancer (n=206)	No Cancer (n=1355)	Statistical metric	Weighted difference [95% CI]	P value
Primary effectiveness outcome					
90-day new ischemic stroke or other vascular events, n (%)	12 (5.8)	40 (3.0)	Hazard ratio	1.78 [1.20 to 2.63]	0.004
Secondary effectiveness outcomes					
90-day mRS score distribution					
No symptoms (score of 0), n (%)	91 (44.2)	727 (53.7)			
Symptoms without any disability (score of 1), n (%)	60 (29.1)	364 (26.9)			
Symptoms with mild disability (score of 2), n (%)	25 (12.1)	149 (11.0)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	19 (9.2)	76 (5.6)	Odds ratio	1.24 [1.10 to 1.41]	<0.001
Symptoms with moderate-to-severe disability (score of 4), n (%)	5 (2.4)	25 (1.8)			
Symptoms with severe disability (score of 5), n (%)	1 (0.5)	5 (0.4)			

Death (score of 6), n (%)	5 (2.4)	9 (0.7)			
90-day mortality, n (%)	5 (2.4)	9 (0.7)	Hazard ratio	1.74 [0.51 to 5.96]	0.375
Primary safety outcome					
90-day any bleedings, n (%)	7 (3.4)	37 (2.7)	Hazard ratio	1.34 [0.76 to 2.36]	0.310
Secondary safety outcome					
24-h hemorrhagic transformation, n (%)	1 (0.5)	13 (1.0)	Risk difference (%)	-0.5 [-0.2 to 0.4]	0.244

Abbreviations. DAPT: dual antiplatelet therapy; mRS: modified Rankin Scale; Statistically significant P values (<0.05) are reported in bold.

Weighted Kaplan-Meier cumulative function showed that the overall incidence of new ischemic stroke and other vascular events was significantly higher among patients with concomitant cancer versus no cancer (long-rank $p=0.004$). **Figure 4**

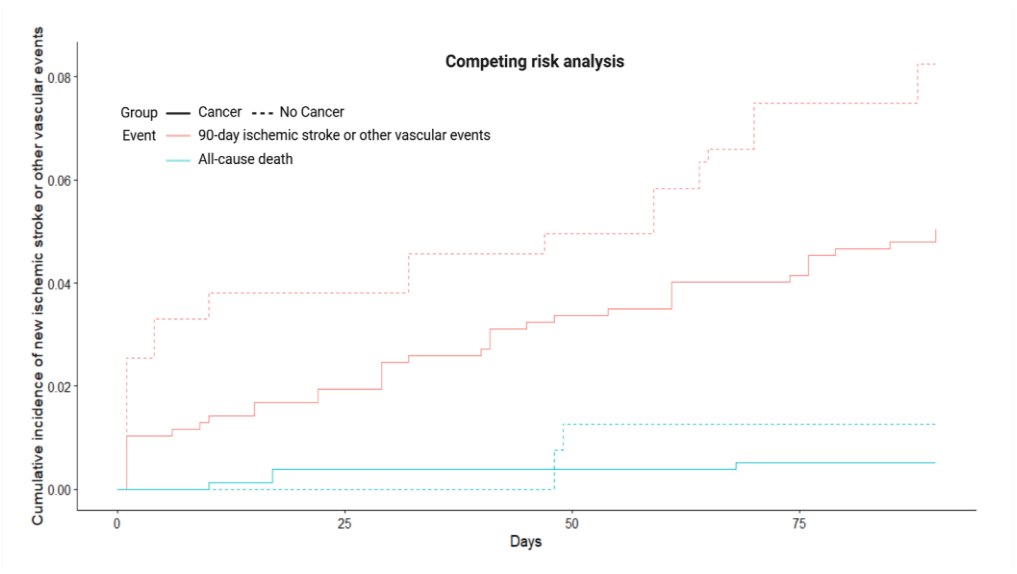
Figure 4. Weighted Kaplan-Meier cumulative function of 90-day A) primary effectiveness and B) safety outcomes by cancer status.



Abbreviations. CI: confidence intervals. HR: hazard ratio. Shaded areas indicate 95% confidence intervals. The estimates and the number at risk shown below the curves reflect the weighted pseudo-population.

Competing risk analysis confirmed the higher 90-day cumulative incidence of primary effectiveness outcome among patients with cancer. **Figure 5** Gray test showed that cumulative incidence curves were statistically different for primary effectiveness outcome ($p=0.011$) but not for all-cause death ($p=0.117$).

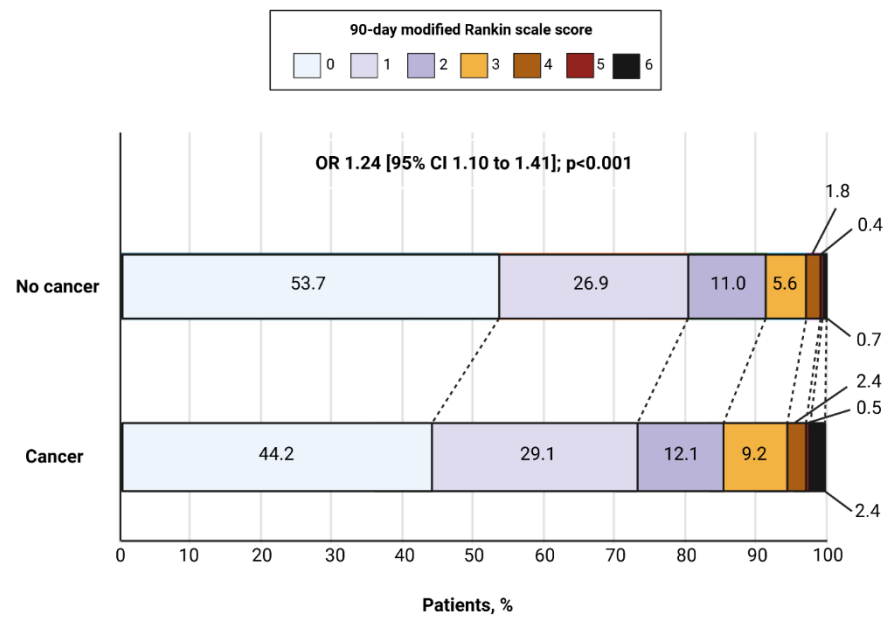
Figure 5. Cumulative incidence of 90-day primary effectiveness outcome in competing risk analysis.



Secondary effectiveness outcomes

Patients with concomitant cancer had less favorable 90-day mRS score distribution compared to those without cancer (weighted OR 1.24 [95% CI 1.10 to 1.41]; $p < 0.001$). **Table 2, Figure 6** Conversely, there was no significant difference between groups in terms of 90-day all-cause mortality (2.4% versus 0.7%; weighted HR 1.74 [95% CI 0.51 to 5.96; $p = 0.375$]). **Table 2**

Figure 6. 90-day modified Rankin Scale (mRS) Score ordinal distribution by cancer status in the weighted cohorts.

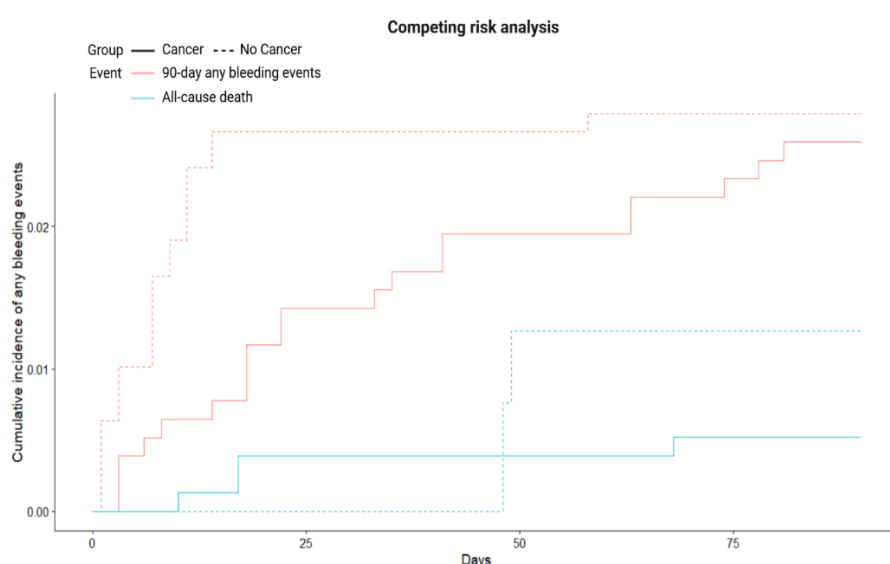


Abbreviations. CI: confidence interval; OR: odds ratio.

Primary safety outcome

The risk of 90-day bleeding events was similar between patients with and without concomitant cancer (3.4% versus 2.7%; weighted HR 1.34 [95% CI 0.76 to 2.36]; $p=0.310$). **Table 2** Weighted Kaplan-Meier cumulative function (long-rank $p=0.300$) and competing risk analysis (Gray test $p=0.787$ for primary safety outcome and $p=0.118$ for all-cause death) confirmed the similar incidence of bleedings. **Figure 4B, Figure 7**

Figure 7. Cumulative incidence of 90-day primary safety outcome in competing risk analysis.



The majority of bleeding events observed in both patients with and without cancer were mild-to-moderate (85.7% versus 83.7%, respectively), while severe bleedings occurred in a single patient with cancer (14.3%) and in 5 patients without cancer (16.3%). There was no significant difference in bleeding severity between groups ($p=0.898$).

Secondary safety outcome

We observed no significant difference in the risk of 24-h hemorrhagic transformation between patients with and without concomitant cancer (0.5% versus 1.0%; weighted risk difference -0.5% [95% CI -0.2% to 0.4%]; $p=0.244$). **Table 2**

Active and non-active cancer versus no cancer

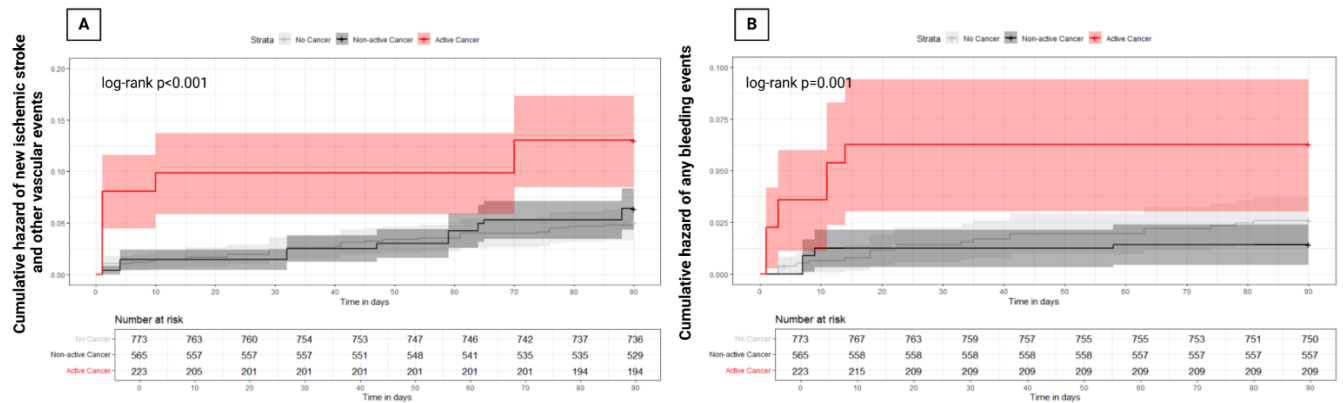
Patients with active cancer showed a significantly higher risk of 90-day ischemic stroke or other vascular events and any bleeding events compared to those without cancer (7.0% versus 2.7%, weighted HR 2.75 [95% CI 1.70 to 4.45]; $p < 0.001$ and 7.0% versus 2.7%, weighted HR 2.51 [95% CI 1.27 to 4.97]; $p = 0.008$, respectively), while those with non-active cancer had similar risks of both outcomes to their counterparts without cancer (5.4% versus 2.7%, weighted HR 1.26 [95% CI 0.80 to 1.99; $p = 0.311$ and 2.0% versus 2.7%, weighted HR 0.55 [95% CI 0.24 to 1.24; $p = 0.184$, respectively). **Table 3, Figure 8** The 90-day mRS score distribution was similar between patients with active and non-active cancer (OR 1.14 [95% CI 0.92 to 1.41; $p = 0.230$).

Table 3. Comparison of 90-day primary effectiveness and safety outcomes between patients with non-active, active and without cancer in the weighted cohorts.

		N/total (%)	Weighted HR	95% CI	P value
90-day new ischemic stroke and other vascular events	No Cancer	40/1355 (2.7)	1	Ref.	-
	Non-active Cancer	8/149 (5.4)	1.26	0.80 to 1.99	0.311
	Active Cancer	4/57 (7.0)	2.75	1.70 to 4.45	<0.001
90-day any bleeding events	No Cancer	37/1355 (2.7)	1	Ref.	-
	Non-active Cancer	3/149 (2.0)	0.55	0.24 to 1.24	0.148
	Active Cancer	4/57 (7.0)	2.51	1.27 to 4.97	0.008

Abbreviations. CI: confidence intervals; HR: hazard ratio. Statistically significant (<0.05) p-values are reported in bold.

Figure 8. Weighted Kaplan-Meier cumulative function of 90-day A) primary effectiveness and B) primary safety outcomes between patients with non-active or active cancer and no cancer.



Shaded areas indicate 95% confidence intervals. The estimates and the number at risk shown below the curves reflect the weighted pseudo-population.

Hematological versus solid cancer

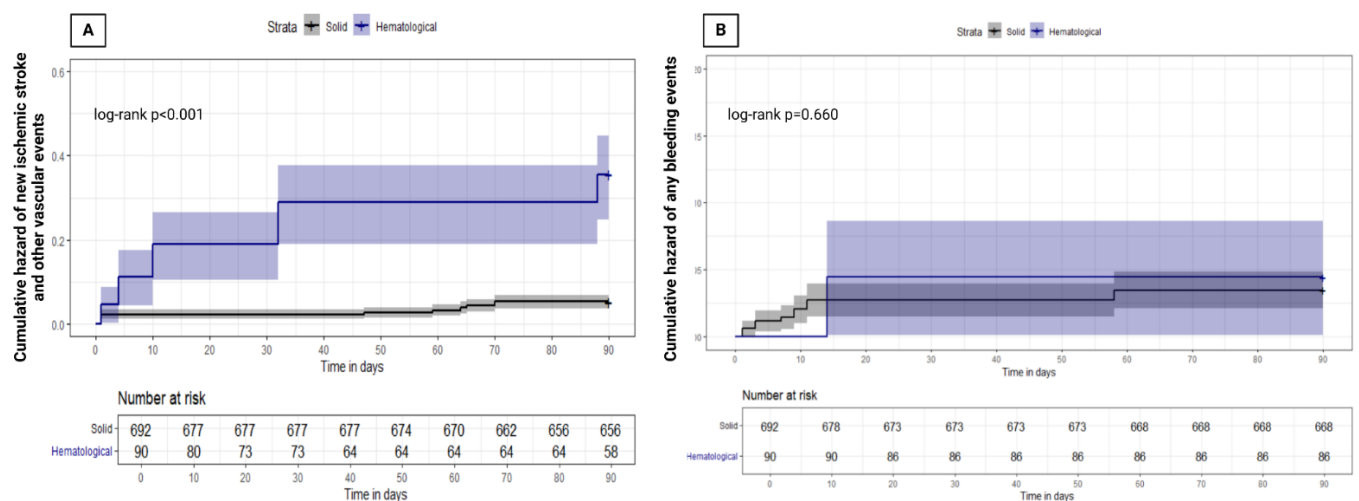
Patients with hematological malignancies had a higher risk of 90-day new ischemic stroke or other vascular events compared to those with solid tumors (23.8% versus 3.8%, weighted HR 8.15 [95% CI 5.06 to 13.14; $p < 0.001$), while the 90-day risk of any bleeding events was similar between the two groups (4.8% versus 3.2%, weighted HR 1.27 [95% CI 0.44 to 3.66]; $p = 0.657$). **Table 4, Figure 9** Of note, the proportion of patients with active cancer was significantly higher in patients with hematological malignancies compared to solid tumors (12/21, 57.1% versus 45/185, 24.3%; $p = 0.029$).

Table 4. Comparison of 90-day primary effectiveness and safety outcomes between patients with solid versus hematological cancer in the weighted cohorts.

		N/total (%)	Weighted HR	95% CI	P value
90-day new ischemic stroke and other vascular events	Solid	7/185 (3.8)	1	Ref.	-
	Hematological	5/21 (23.8)	8.15	5.06 to 13.14	<0.001
90-day any bleeding events	Solid	6/185 (3.2)	1	Ref.	-
	Hematological	1/21 (4.8)	1.27	0.44 to 3.66	0.657

Abbreviations. CI: confidence intervals; HR: hazard ratio. Statistically significant (<0.05) p-values are reported in bold.

Figure 9. Weighted Kaplan-Meier cumulative function of 90-day A) primary effectiveness and B) safety outcomes between patients with solid versus hematological cancer.



Shaded areas indicate 95% confidence intervals. The estimates and the number at risk shown below the curves reflect the weighted pseudo-population.

Discussion

This secondary analysis of the READAPT study evaluated the impact of cancer on the 90-day outcomes in patients with non-cardioembolic minor ischemic stroke or high-risk TIA receiving DAPT. Our findings indicate that patients with cancer have a worse 90-day functional outcome and a significantly higher risk of new ischemic events after DAPT compared to those without cancer.

Notably, patients with active malignancy had not only higher risk of 90-day ischemic stroke or other vascular events but also an increased risk of bleedings. Patients with non-active cancer had similar risks to non-cancer patients. Additionally, hematological malignancies were associated with a higher risk of ischemic stroke recurrence compared to solid tumors. These findings highlight the need to further investigate better secondary prevention strategies in active cancer patients, given their increased risk of both ischemic and hemorrhagic events.

Cancer patients with ischemic stroke or TIA present a clinical challenge due to the heightened risks of both thrombosis and bleeding.^{7,8} Malignancy-driven prothrombotic states, influenced by tumor-related factors and cancer therapies, contribute to ischemic recurrences. Endothelial injury promotes the release of pro-thrombotic mediators, such as von Willebrand factor, enhancing platelet aggregation.¹⁷ Histopathological studies of thrombi in cancer-associated stroke further highlight the role of platelets and thrombin in stroke pathogenesis.^{18,19} Existing research has primarily focused on comparing anticoagulation with antiplatelet therapy for stroke prevention in cancer patients.²⁰⁻²² A retrospective study of 263 stroke patients with active cancer found similar recurrent thromboembolism rates between antiplatelet and anticoagulant therapy.²⁰ Likewise, post-hoc analyses of the Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) and New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. Aspirin to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) showed comparable ischemic stroke recurrence rates between apixaban or rivaroxaban and aspirin in ESUS patients with cancer.^{21,22}

Our findings suggest that the pro-thrombotic state associated with cancer may impair DAPT's effectiveness in preventing recurrent ischemic cerebrovascular events, leading to worse short-term functional outcome. However, our study cannot fully determine whether these recurrences are primarily driven by cancer itself or conventional cardiovascular risk factors. Notably, ESUS prevalence was comparable between cancer and non-cancer patients in our cohort (15.0% vs. 14.6%), suggesting that ischemic risk persists across stroke etiologies.

Regarding bleeding risk, cancer patients face a major bleeding incidence of up to 20% annually, further heightened in those with stroke or brain pathologies.²³ Major bleeding is a key predictor of mortality, particularly in older individuals, those with multiple comorbidities, and patients with gastrointestinal/genitourinary cancers or metastatic disease - common features of cancer-related stroke.²³ In our cohort, active cancer patients had a significantly higher 90-day bleeding risk than non-cancer patients, though most events were mild to moderate. While our analysis does not provide

definitive guidance on optimal antithrombotic strategies, it underscores the importance of individualized bleeding risk assessment to inform safe secondary prevention therapy.

Our findings also highlight the elevated ischemic stroke risk in patients with hematological malignancies compared to solid tumors. While all cancer patients are at an increased thromboembolic risk, this risk is particularly high in hematological malignancies such as multiple myeloma, leukemia, and lymphoma.^{24,25} The mechanisms vary based on comorbidities, cancer type, and treatment. For example, acute promyelocytic leukemia is frequently associated with disseminated intravascular coagulation,²⁶ while therapies like asparaginase, tyrosine kinase inhibitors, and immunomodulatory agents increase thrombotic risk through mechanisms that remain incompletely understood.²⁷⁻²⁹ Although we did not collect detailed data on cancer stage and treatment, the higher prevalence of active cancer among patients with hematological malignancies compared to those with solid tumors within our cohort (57.1% versus 24.3%) may have contributed to their elevated risk of ischemic recurrences, potentially also driven by concurrent exposure to prothrombotic chemotherapies. These patients are also prone to bleeding due to thrombocytopenia.⁹ Interestingly, in our study, the 90-day bleeding risk did not differ between hematological and solid tumor patients treated with DAPT. This may reflect rigorous patient selection and close monitoring, mitigating bleeding risk. However, our study's short follow-up could underestimate cumulative bleeding risk. Additionally, hematological malignancies comprised only 10.2% of our cancer cohort, and we lacked detailed data on thrombocytopenia, limiting subgroup analysis. Therefore, these findings require confirmation in larger prospective cohorts.

Strengths and limitations

The main strength of this study lies in the rigorous procedures implemented to enhance data accuracy and quality, as ensured by regular quality checks of the READAPT electronic database. However, our findings should be interpreted in lights of some relevant limitations. First, despite the use of rigorous inverse probability weighting and adjustment for covariates, residual confounding cannot be fully excluded due to the observational design of the READAPT study. Importantly, we lacked data on cancer stage, laboratory findings, and concurrent treatments, which may have influenced DAPT outcomes. This is particularly relevant for safety assessments, as advanced-stage cancer and chemotherapy might increase the risk of thrombocytopenia and bleeding, especially in patients with active or hematologic malignancies. Furthermore, certain chemotherapeutic agents, particularly those used to treat hematological malignancies, may heighten the risk of ischemic events, as previously discussed. Second, although the vast majority (>95%) of patients in our cohort received DAPT for at least 21 days (**Table 1**), we did not capture the proportion of cancer patients who discontinued the

antiplatelet agent prescribed after DAPT during the follow-up period, either due to anticancer treatment or surgical procedures, which may have impacted on the rate of short-term ischemic recurrences. Similarly, temporary DAPT adjustments due to cytopenia or other cancer treatment-related complications were not accounted for. Third, we were unable to evaluate the impact of frailty or cachexia, both of which may significantly affect clinical outcomes in this high-risk population. Fourth, we cannot rule out the potential presence of occult cancers in the no-cancer group. While this limitation may reduce the strength of the observed associations, it is unlikely to affect their overall direction. Fifth, although all patients underwent brain imaging (non-contrast computed tomography or magnetic resonance imaging) upon admission, we did not collect detailed neuroimaging findings or results from brain vessel examinations. As a result, the stroke diagnosis and presumed cause relied solely on assessments by local investigators. Similarly, the decision to treat patients with DAPT was made by treating physicians on a case-by-case basis, considering the individual risk of bleeding or thromboembolic events. Therefore, we cannot exclude the possibility of selection bias, as some cancer patients at higher risk of bleedings may not have been treated with DAPT and were consequently not included in the READAPT study. Also, investigators were not blinded to cancer status, which may have introduced detection bias, especially for subjective outcomes such as the mRS score. Sixth, patients who discontinued DAPT early due to a need for anticoagulation were excluded from this analysis. Although this subset represented only <2% of the initial READAPT population (**Figure 1**) and no patient with non-active or active cancer transitioned to anticoagulation, we did not record their 90-day outcomes. Lastly, our cohort showed a significant imbalance toward non-Hispanic white participants, which may limit the generalizability of our findings to other ethnic groups.

In conclusion, our results indicate an increased risk of ischemic and bleeding events in patients with minor ischemic stroke or high-risk TIA and active cancer treated with early short-term DAPT, compared to their counterparts without cancer. In contrast, patients with non-active cancer had similar outcomes compared to patients without cancer. The risk of new ischemic stroke and other vascular events is particularly evident in patients with hematological malignancies. Given the high thromboembolic risk, there is the need for further studies to investigate additional strategies. Future research should explore nuanced, cancer-specific strategies for secondary stroke prevention, including optimizing DAPT intensity or duration, evaluating alternative antithrombotic approaches such as anticoagulation, or combining antiplatelet agents with therapies targeting cancer-associated thromboinflammatory pathways. Additionally, integrating baseline coagulation profiles and cancer-specific risk factors—such as tumor type, stage, and treatment status—into stroke prevention protocols may enable more personalized and effective risk reduction strategies.

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Conclusions

The therapeutic boundaries of DAPT in patients with ischemic stroke or TIA have been well defined by landmark RCTs. However, growing real-world evidence and observational data increasingly suggest that the benefits of DAPT may extend safely beyond the populations initially investigated. Our analyses from the READAPT study contribute to this evolving landscape by identifying specific subgroups of patients with acute ischemic stroke or TIA who may derive particular benefit, or face heightened risk, when DAPT is applied in extended or tailored indications.

In patients with moderate ischemic stroke (NIHSS up to 10), DAPT has demonstrated superiority over SAPT in improving functional outcomes at 90 days and in reducing the risk of early neurological deterioration, supporting a broader use of DAPT in this clinical scenario. Moreover, our findings suggest a potential sex-specific benefit: premenopausal women appear to experience a significantly lower risk of early ischemic recurrence, possibly due to hormonal or vascular factors that warrant further investigation.

No significant differences emerged in the effectiveness or safety of DAPT in patients with mild-to-moderate stroke when stratified by infarct location (posterior vs. anterior circulation), although moderate posterior circulation strokes were associated with poorer functional outcomes, overall highlighting the need for more refined prognostic tools in this subgroup.

Regarding specific stroke/TIA etiologies, patients with SAO-related minor strokes appear to benefit more from DAPT in terms of 90-day risk of vascular recurrences and functional recovery compared to other etiologies. Conversely, patients with LAA exhibit similar rates of vascular recurrence but a substantially increased risk of major bleeding when DAPT is used outside the timeframe and populations established by pivotal trials, reinforcing the need for caution and individualized risk assessment.

The combination of DAPT and intravenous thrombolysis appears to be both safe and effective in selected patients, exerting a synergistic effect in reducing early recurrence and improving short-term functional outcomes. This observation supports further exploration of integrated acute and secondary prevention pathways in carefully selected patients treated with intravenous thrombolysis.

Finally, among patients with relevant comorbidities, those with active cancer, particularly hematologic malignancies, are especially vulnerable to both ischemic and bleeding complications during DAPT, exhibiting higher rates of vascular events and major hemorrhages. Conversely, patients with non-active cancer may exhibit similar (low) risk of recurrent ischemic events and bleedings

compared to those without cancer. These findings highlight the need for individualized secondary prevention strategies in oncologic populations, carefully balancing thrombotic and hemorrhagic risks.

Overall, our results advocate for a nuanced, patient-centered approach to DAPT in secondary stroke prevention, moving beyond a rigid application of trial criteria toward a more individualized strategy guided by clinical judgment, biological plausibility, and patient-specific risk-benefit profiles.

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