Journal of the American Heart Association

ORIGINAL RESEARCH

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

Raffaele Ornello, MD, PhD*; Matteo Foschi, MD*; Federico De Santis, MD; Michele Romoli, MD, PhD; Tiziana Tassinari, MD; Valentina Saia, MD; Silvia Cenciarelli, MD; Chiara Bedetti, MD; Chiara Padiglioni, MD; Bruno Censori, MD; Valentina Puglisi, MD; Luisa Vinciguerra, MD; Maria Guarino, MD; Valentina Barone, MD; Marialuisa Zedde, MD; Ilaria Grisendi, MD; Marina Diomedi, MD; Maria Rosaria Bagnato, MD; Marco Petruzzellis, MD; Domenico Maria Mezzapesa, MD; Pietro Di Viesti, MD; Vincenzo Inchingolo, MD; Manuel Cappellari, MD; Cecilia Zivelonghi, MD; Paolo Candelaresi, MD; Vincenzo Andreone, MD; Giuseppe Rinaldi, MD; Alessandra Bavaro, MD; Anna Cavallini, MD; Stefan Moraru, MD; Pietro Querzani, MD; Valeria Terruso, MD; Marina Mannino, MD; Alessandro Pezzini, MD; Giovanni Frisullo, MD; Francesco Muscia, MD; Maurizio Paciaroni, MD; Maria Giulia Mosconi, MD; Andrea Zini, MD; Ruggiero Leone, MD; Carmela Palmieri, MD; Letizia Maria Cupini, MD; Michela Marcon, MD; Rossana Tassi, MD; Enzo Sanzaro, MD; Cristina Paci, MD; Giovanna Viticchi, MD; Daniele Orsucci, MD; Anne Falcou, MD; Simone Beretta, PhD; Roberto Tarletti, MD; Patrizia Nencini, MD; Eugenia Rota, MD; Federica Nicoletta Sepe, MD; Delfina Ferrandi, MD; Luigi Caputi, MD; Gino Volpi, MD; Salvatore La Spada, MD; Mario Beccia, MD; Claudia Rinaldi, MD; Vincenzo Mastrangelo, MD; Francesco Di Blasio, MD; Paolo Invernizzi, MD; Giuseppe Pelliccioni, MD; Maria Vittoria De Angelis, MD; Laura Bonanni, MD; Giampietro Ruzza, MD; Emanuele Alessandro Caggia, MD; Monia Russo, MD; Agnese Tonon, MD; Maria Cristina Acciarri, MD; Sabrina Anticoli, MD; Cinzia Roberti, MD; Giovanni Manobianca, MD; Gaspare Scaglione, MD; Francesca Pistoia, MD; Alberto Fortini, MD; Antonella De Boni, MD; Alessandra Sanna, MD; Alberto Chiti, MD; Leonardo Barbarini, MD; Marcella Caggiula, MD; Maela Masato, MD; Massimo Del Sette, MD; Francesco Passarelli, MD; Maria Roberta Bongioanni, MD; Danilo Toni, MD, PhD; Stefano Ricci, MD; Eleonora De Matteis, MD; Simona Sacco, MD; on behalf of the READAPT Study Group†

BACKGROUND: The optimal treatment for acute minor ischemic stroke 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 AND RESULTS: This is a prespecified propensity score-matched analysis from a prospective multicentric real-world study (READAPT [Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient

Correspondence to: Simona Sacco, MD, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Via Vetoio, 67100 AQ, Italy. Email: simona.sacco@univaq.it

*R. Ornello and M. Foschi contributed equally and are co–first authors.

†A complete list of the READAPT Study Group members can be found in the Supplemental Material.

This manuscript was sent to Thomas S. Metkus, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036275

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

Ischemic Attack]). We included patients with MIS (National Institutes of Health Stroke Scale score at admission ≤5), without prestroke 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-hour early neurological improvement or deterioration (≥2-point National Institutes of Health Stroke Scale score decrease or increase from the baseline, respectively). From 1373 patients with 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% [95% CI −2.0% to 6.7%]; *P*=0.295; risk ratio, 1.03 [95% CI 0.98–1.08]; *P*=0.312) but more favorable ordinal mRS scores distribution (odds ratio, 0.57 [95% CI 0.41–0.79]; *P*<0.001). Compared with patients treated with DAPT alone, those combining IVT and DAPT had higher 24-hour early neurological improvement (risk difference, 20.9% [95% CI 13.1%–28.6%]; risk ratio, 1.59 [95% CI 1.34–1.89]; both *P*<0.001) and lower 90-day risk of stroke and other vascular events (hazard ratio, 0.27 [95% CI 0.08–0.90]; *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.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05476081.

Key Words: dual antiplatelet treatment ■ functional outcome ■ intravenous thrombolysis ■ ischemic stroke ■ real world ■ safety

RESEARCH PERSPECTIVE

What Is New?

- It is unclear whether patients with minor ischemic stroke may benefit from combining intravenous thrombolysis and dual antiplatelet treatment without safety concerns.
- This prespecified propensity-matched analysis of the prospective multicentric study READAPT (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack) showed that combined treatment may be associated with more favorable 90-day functional outcome, higher 24-hour early neurological improvement, and lower 90-day risk of recurrent vascular events compared with DAPT alone.

What Question Should Be Addressed Next?

- Given the observational design of our study, our findings must be confirmed by interventional randomized trials; future research should also compare outcomes of minor ischemic stroke patients receiving combined treatment versus intravenous thrombolysis alone.

Nonstandard Abbreviations and Acronyms

ARAMIS	Antiplatelet Versus rtPA for Acute Mild Ischemic Stroke
DAPT	dual antiplatelet treatment
EAST	Early Antiplatelet for Minor Stroke Following Thrombolysis
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery
INSPIRES	Intensive Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis
IVT	intravenous thrombolysis
MIS	minor ischemic stroke
mRS	modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
PRISMS	Potential of rtPA for Ischemic Strokes With Mild Symptoms
READAPT	Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack
TOAST	Trial of ORG 1072 10 172 in Acute Stroke Treatment

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 3 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 studies[3–5]

and a meta-analysis[6] showed a clear benefit, while a randomized clinical trial[7] demonstrated that IVT is not inferior with respect 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 patients with MIS 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 (ie, IVT, endovascular thrombectomy, carotid endarterectomy) were excluded from landmark trials.[11–13]

Recently, some studies compared IVT and DAPT in MIS. The ARAMIS (Antiplatelet Versus rtPA for Acute Mild Ischemic Stroke) 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 patients with MIS.[15] Additionally, the PRISMS (Potential of rtPA for Ischemic Strokes With Mild Symptoms)[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 2 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 with DAPT alone in patients with ischemic stroke.

As short-term DAPT has become the mainstay of early secondary prevention of mild noncardioembolic 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 with those treated with DAPT alone in a real-world population of patients with MIS.

METHODS

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

READAPT Study

The READAPT (Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack; NCT05476081) study 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). It adheres to the Strengthening the Reporting of Observational Studies in Epidemiology 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 1, 2021, to February 28, 2023. The enrollment period was extended to December 31, 2023, for patients treated with acute reperfusion treatments (IVT or endovascular thrombectomy). 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 noncardioembolic 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.[16] Apart from diagnosis of acute minor noncardioembolic 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 software. The READAPT database was hosted at the University of L'Aquila and accessed by investigators through link/password or quick response code. A baseline case report form was implemented to collect patient demographics, vascular risk factors, prestroke treatment, $CHAD_2DS_2$-$VASC_2$, National Institutes of Health Stroke Scale (NIHSS), and $ABCD^2$ scores, pre- and poststroke modified Rankin scale (mRS) score, neuroimaging findings, presumed cause of the index events according to the TOAST (Trial of ORG 1072 10172 in Acute Stroke Treatment) classification, and acute treatment (ie, IVT, endovascular thrombectomy, endarterectomy). 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 Subanalysis

This study subanalysis is aimed to address differences in the 90-day outcome between patients with MIS treated with DAPT alone versus those receiving IVT plus DAPT. Patients were eligible for inclusion in this study subanalysis if they had an 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 prestroke disability (mRS score>2), who underwent endovascular thrombectomy, urgent carotid endarterectomy, or stenting procedures during the follow-up period. Patients with an NIHSS score 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), prestroke functional status (mRS), stroke severity (NIHSS score 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× 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 an 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 (ie, TIA, myocardial infarction, death due to vascular causes), 24-hour early neurological improvement and deterioration (≥2-point decrease or increase in the NIHSS score from baseline, respectively), and 24-hour median change in the NIHSS scores from baseline. The safety outcomes

were 90-day moderate to severe bleeding events, any bleeding events, intracerebral hemorrhage, and 24-hour hemorrhagic transformation. The severity of bleeding events was assessed according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery) 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 according to normal distribution. For the primary outcomes, we calculated the risk difference and risk ratio of 90-day good functional outcome (mRS, 0–2) between the IVT plus DAPT and DAPT-alone groups with 2-sided 95% CIs. The 90-day ordinal distribution of mRS scores was compared using an ordinal generalized linear model and results were presented as odds ratios (ORs) with 95% CIs. For the secondary outcomes, differences, and ratios (95% CIs) between groups were calculated for the risks of 24-hour neurological improvement, 24-hour neurological deterioration, and vascular death. Changes in the 24-hour NIHSS scores from baseline between the IVT plus DAPT and DAPT-alone groups were compared using linear regression, and results were presented as ORs 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 ratios 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 the 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 2 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 (R Foundation for Statistical Computing, Vienna, Austria). 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 in Figure 1. 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 S1 and S2). 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).

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-alone group. The risk difference and risk ratio of having a good functional outcome

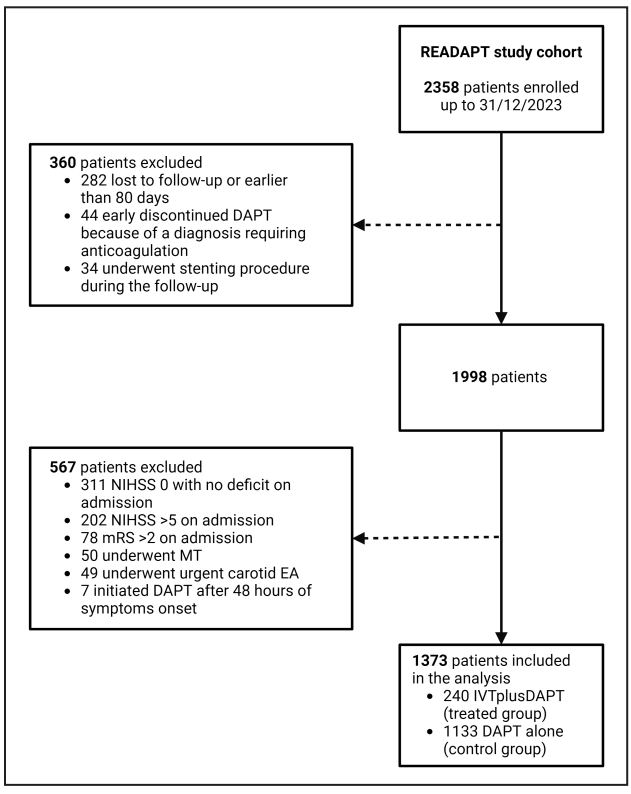

Figure 1. Study flow diagram.
Patients may have ≥1 exclusion criterion. DAPT indicates dual antiplatelet treatment; EA, endarterectomy; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; and READAPT: Real-Life Study on Short-Term Dual Antiplatelet Treatment in Patients With Ischemic Stroke or Transient Ischemic Attack.

were 2.3% (95% CI, –2.0% to 6.7%; *P*=0.295) and 1.03 (95% CI, 0.98–1.08; *P*=0.312; Table 2). We found a significant difference in the 90-day ordinal distribution of mRS scores between patients treated with IVT plus DAPT versus DAPT alone (OR, 0.57 [95% CI, 0.41–0.79]; *P*=0.001) with a higher percentage of patients with an mRS of 0 in those who received the combined treatments (61.3%) versus DAPT alone (46.6%) (Table 2 and Figure 2).

Secondary Outcomes

Compared with patients receiving DAPT alone, those treated with IVT plus DAPT showed a higher frequency of 24-hour early neurological improvement (risk difference, 20.9% [95% CI, 13.1% to 28.6%]; *P*<0.001; risk ratio, 1.59 [95% CI, 1.34–1.89]; *P*<0.001), with a higher 24-hour decrease in the NIHSS scores from baseline (OR, −0.65 [95% CI, −0.89 to −0.41]; *P*<0.001). Conversely, there were no significant differences in the 24-hour 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 (hazard ratio, 0.27 [95% CI, 0.08–0.90]; *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 with 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).

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, 0–2) was similar between the 2 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 after stroke. Of note, no safety concerns emerged from combining IVT and DAPT, as the risk of bleeding events and early (24-hour) hemorrhagic transformation of the ischemic lesion did not differ between groups. On the other hand, the intention to treat patients with MIS 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 with 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 on 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 complementary to randomized controlled trials and can provide effectiveness and safety data in the real-word patient 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 with 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 INSPIRES (Intensive

Table 1. Baseline Characteristics

	Original sample				Matched sample			
	IVTplusDAPT (n=240)	DAPT alone (n=1133)	Standardized differences*	*P* value	IVTplusDAPT (n=235)	DAPT alone (n=427)	Standardized differences*	*P* value
Demographics								
Male sex, n (%)	146 (61.2)	763 (66.4)	0.138	0.063	144 (61.3)	252 (59.0)	0.046	0.628
Age, y, mean (SD)	67.78±12.51	69.45±11.65	0.136	0.057	67.86±12.41	68.68±12.25	0.067	0.354
Race or 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)		
Clinical characteristics								
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)—mm Hg	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)—mm Hg	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 (%)‡			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)		
Prestroke risk factors								
BMI, median (IQR)	26 (23–29)	26 (24–28)	0.042	0.482	26 (23–29)	26 (24–28)	0.061	0.458
CHA_2DS_2-$VASC_2$, 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 (%)§	180 (75.0)	916 (80.9)	0.141	0.049†	178 (75.7)	337 (78.9)	0.076	0.399
Hypercholesterolemia, n (%)‖	143 (59.6)	692 (61.1)	0.030	0.721	141 (60.0)	263 (61.6)	0.033	0.750
Hypertriglyceridemia, n (%)¶	44 (18.3)	242 (21.4)	0.076	0.337	44 (18.7)	98 (23.0)	0.104	0.242
Diabetes, n (%)#	46 (19.2)	311 (27.5)	0.197	0.010†	45 (19.2)	91 (21.3)	0.054	0.577
Current smoking, n (%)**	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

(*Continued*)

Table 1. Continued

	Original sample				Matched sample			
	IVTplusDAPT (n=240)	DAPT alone (n=1133)	Standardized differences*	*P* value	IVTplusDAPT (n=235)	DAPT alone (n=427)	Standardized differences*	*P* value
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†
<24 h	57 (23.8)	826 (72.9)			56 (23.8)	314 (73.5)		
24–48 h	183 (76.2)	307 (27.1)			179 (76.2)	113 (26.5)		
Type of DAPT, n (%)			0.084	0.723			0.119	0.495
Acetylsalicylic acidplusclopidogrel	240 (100.0)	1129 (99.6)			235 (100.0)	424 (99.3)		
Acetylsalicylic acidplusticagrelor	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
Acetylsalicylic acid	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)		

BMI, indicates body mass index; DAPT, dual antiplatelet therapy; IQR, interquartile range; mRS, modified Rankin Scale; IVT, intravenous thrombolysis; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.

*A standardized difference (of means) <0.250 indicates that groups are well balanced.

†Statistically significant *P* values (<0.05) are reported.

‡Presumed stroke cause was classified according to the TOAST (Trial of ORG 10 172 in the Acute Stroke Treatment) classification system.

§Arterial hypertension was defined as a history.

‖Hypercholesterolemia was defined as history of total blood cholesterol levels >220 mg/dL or currently used lipid-lowering drugs.

¶Hypertriglyceridemia was defined as history of total blood triglycerides levels >150 mg/dL or currently used lipid-lowering drugs.

#Diabetes was defined as history of fasting glucose >126 mg/dL or the current use of hypoglycemic medications.

**Current smoking was defined as the consumption of ≥1 cigarette per day over the past year.

Table 2. Study Outcomes

Outcomes	IVTplusDAPT (n=240)	DAPT alone (n=427)	Treatment effect metric	Treatment difference (95%CI)	*P* value
Primary outcomes					
90-d 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-d mRS score distribution					
No symptoms (score of 0), n (%)	147 (61.3)	199 (46.6)	Odds ratio	0.57 (0.41 to 0.79)	0.001*
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)			
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)			
Secondary outcomes					
24-h 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-h 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-h 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-d stroke or other vascular events, n (%)	3 (1.2)	20 (4.7)	Hazard ratio	0.27 (0.08 to 0.90)	0.034*
90-d 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
Safety outcomes					
90-d 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-d 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-d 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-h 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

DAPT indicates dual antiplatelet treatment; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; and NIHSS, National Institute of Health Stroke Scale.

*Statistically significant *P* values (<0.05) are reported.

Statin and Antiplatelet Therapy for Acute High-Risk Intracranial or Extracranial Atherosclerosis) trial showed that DAPT can be effective even if initiated 72 hours after symptom onset.[20]

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 synergistic 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 2 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 2 treatment approaches, even when considering patients who received DAPT within 24 hours of IVT. All these observations might support

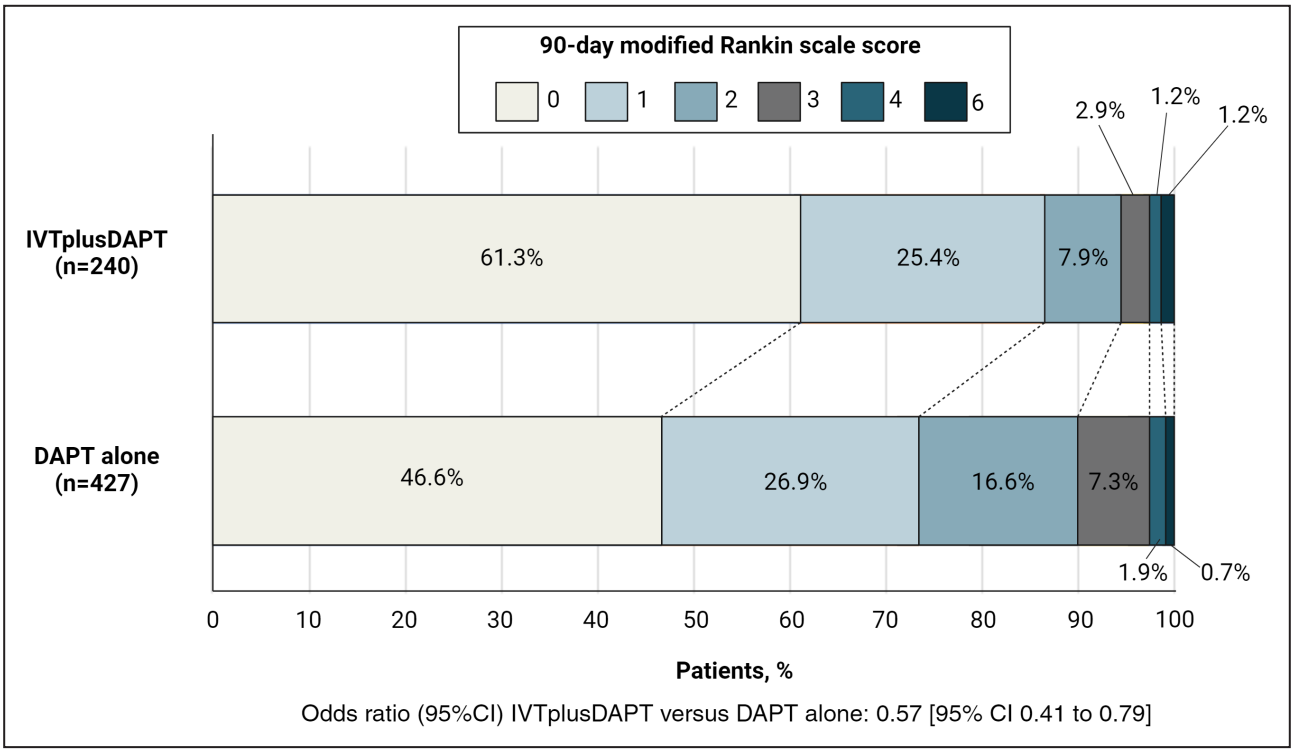

Figure 2. Ordinal distribution of 90-day modified Rankin scale scores.
DAPT indicates dual antiplatelet treatment; and IVT, intravenous thrombolysis.

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 (Figure 1), we cannot disregard the possibility of an increased bleeding risk in patients who transitioned from DAPT to anticoagulation regardless of whether they were treated 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 (ie, TIA/MIS with complete symptom resolution before admission) might have hindered the assessment for eligibility to IVT.[21,22] Hence, the higher prevalence of patients with MIS 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 with 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 PRISMS[7] (57.7% of patients with NIHSS score of 1–2) and ARAMIS[14] (median NIHSS score, 2 [interquartile range 1–3]) trials was lower compared with our cohort (median NIHSS score, 3 [interquartile range 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 with those treated with DAPT only (ie, higher Alberta Stroke Program Early Computed Tomography Score, 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

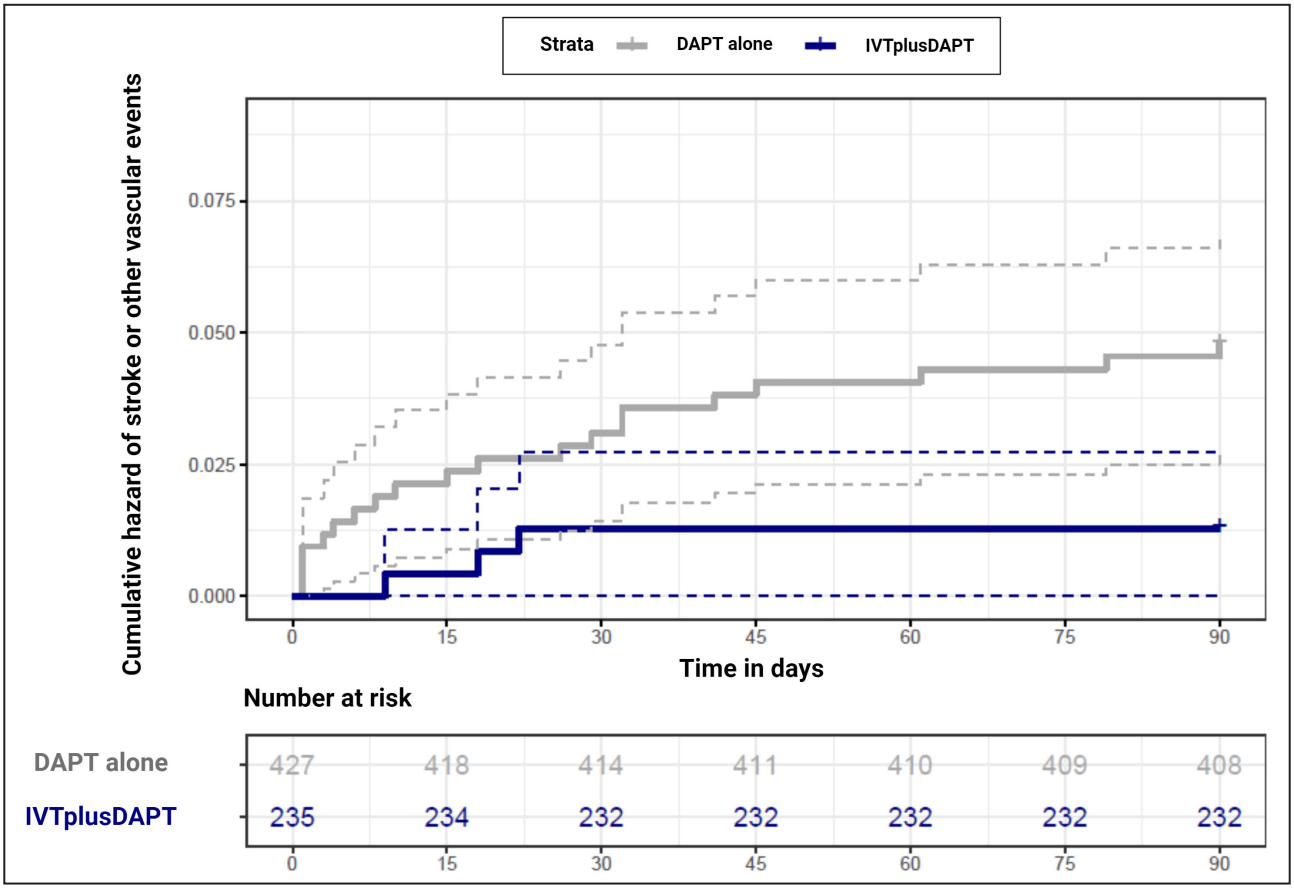

Figure 3. Kaplan–Meier cumulative hazard function of 90-d risk of stroke and other cardiovascular events.
Dashed lines indicate 95% CIs. Log-rank test *P* value=0.020. DAPT indicates dual antiplatelet treatment; and IVT, intravenous thrombolysis.

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 that may negatively impact on the risk of major hemorrhagic events, such as hypertension and diabetes, in the group receiving 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. Finally, the strong imbalance toward the non-Hispanic White population (>90%) may consistently limit the generalizability of our findings outside this specific ethnic group. Fourth, the lack of a prespecified sample size calculation for outcomes might limit the statistical power of our analyses, which were all exploratory.

CONCLUSIONS

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 of better functional outcome and fewer recurrent events at 90 days. Our results hold promise in informing

clinical decision making and indicate that DAPT should not be viewed as a stand-alone 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 patients with minor stroke but also to synergize in preventing new vascular events. Ideally, results from ongoing interventional randomized trials (ie, EAST [Early Antiplatelet for Minor Stroke Following Thrombolysis]; 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.

ARTICLE INFORMATION

Received April 26, 2024; accepted June 18, 2024.

Affiliations

Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy (R.O., M.F., F.D.S., F.P., E.D.M., S.S.); Department of Brain Sciences, Imperial College London, London, United Kingdom (E.D.M.); Stroke Unit, Maurizio Bufalini Hospital, Cesena, Italy (M.R.); Department of Neurology, Santa Corona Hospital, Pietra Ligure, Italy (T.T., V.S.); Department of Neurology, Città di Castello Hospital, Città di Castello, Italy (S.C., C.B., C.P., S.R.); Department of Neurology, ASST Cremona Hospital, Cremona, Italy (B.C., V.P., L.V.); IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy (M.G., V.B.); Department of Neurology, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy (M.Z., I.G.); Department of Systems Medicine, Tor Vergata University Hospital, Rome, Italy (M.D., M.R.B.); Stroke Unit, "F. Puca" AOU Consorziale Policlinico, Bari, Italy (M.P., D.M.M.); Department of Neurology, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy (P.D.V., V.I.); Department of Neuroscience, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy (M.C., C.Z.); Stroke Unit, AORN Antonio Cardarelli, Naples, Italy (P.C., V.A.); Department of Neurology, Di Venere Hospital, Bari, Italy (G.R., A.B.); Neurologia d'Urgenza-Stroke Unit, IRCCS Mondino Foundation, Pavia, Italy (A.C., S.M.); Neurology Unit, S.Maria delle Croci Hospital, Ravenna, Italy (P.Q.); Department of Neurology, AOOR Villa Sofia-Cervello, Palermo, Italy (V.T., M.M.); Department of Medicine and Surgery, University of Parma, Italy (A.P.); Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy (G.F.); Department of Neurology, ASST-Ovest Milanese, Legnano, Italy (F.M.); Department of Internal and Cardiovascular Medicine, Santa Maria della Misericordia Hospital, Perugia, Italy (M.P., M.G.M.); IRCCS Istituto delle Scienze Neurologiche di Bologna, Maggiore Hospital, Bologna, Italy (A.Z.); Stroke Unit, "M. R. Dimiccoli" Hospital, Barletta, Italy (R.L.); Medical Department, E. Agnelli Hospital—Local Health Company (ASL) TO3, Pinerolo, Italy (C.P.); Stroke Unit, S. Eugenio Hospital, Rome, Italy (L.M.C.); Department of Neurology, Cazzavillan Hospital, Arzignano, Italy (M.M.); Emergency Department, Azienda Ospedaliera Universitaria Senese, Siena, Italy (R.T.); Department of Neurology, Umberto I Hospital, Siracusa, Italy (E.S.); Neurology Unit, Ospedale "Madonna del Soccorso", San Benedetto del Tronto, Italy (C.P.); Experimental and Clinical Medicine Department, Marche Polytechnic University, Ancona, Italy (G.V.); Neurology Unit, San Luca Hospital, Lucca, Castelnuovo Garfagnana, Italy (D.O.); Stroke Unit, Policlinico Umberto I Hospital, Rome, Italy (A.F.); Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy (S.B.); Stroke Unit, Azienda Ospedaliero-Universitaria "Maggiore della Carità", Novara, Italy (R.T.); Stroke Unit, Careggi University Hospital, Florence, Italy (P.N.); Department of Neurology, San Giacomo Hospital, Novi Ligure, Italy (E.R.); Stroke Unit, SS. Biagio e Arrigo, Alessandria, Italy (F.N.S., D.F.); Department of Cardiocerebrovascular diseases, ASST Ospedale Maggiore di Crema, Crema, Italy (L.C.); Department of Neurology, San Jacopo Hospital, Pistoia, Italy (G.V.); Department of Neurology, Antonio Perrino Hospital, Brindisi, Italy (S.L.S.); Department of Neurology, Sant'Andrea Hospital, Rome, Italy (M.B.); Neurology Unit, "Infermi" Hospital, Rimini, Italy (C.R., V.M.); Stroke Unit, "S.Spirito" Hospital, Pescara, Italy (F.D.B., M.V.D.A.); Department of Neurology, Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy (P.I.); Department of Neurology INRCA, Ancona, Italy (G.P.); Department of Neurology, SS Annunziata Hospital, Chieti, Italy (M.V.D.A.); Dipartimento di Medicina e Scienze dell'Invecchiamento, Università G. d'Annunzio di Chieti-Pescara, Pescara, Italy (L.B.); Department of Neurology, Civil Hospital, Cittadella, Italy (G.R.); Cardio-Neuro-Vascular Department, Neurology Unit, Giovanni Paolo II Hospital, Ragusa, Italy (E.A.C.); Department of Neurology, St Misericordia Hospital, Rovigo, Italy (M.R.); Department of Neurology, Ospedale Civile Ss. Giovanni e Paolo, Venezia, Italy (A.T.); Department of Neurology, A. Murri Fermo Hospital, Fermo, Italy (M.C.A.); Stroke Unit, Azienda Ospedaliera San Camillo, Rome, Italy (S.A.); Department of Neurology, San Filippo Neri Hospital, Rome, Italy (C.R.); Department of Neurology, General Regional Hospital "F. Miulli", Acquaviva delle Fonti, Italy (G.M., G.S.); Internal Medicine, San Giovanni di Dio Hospital, Florence, Italy (A.F.); Department of Neuroscience, San Bortolo Hospital, Vicenza, Italy (A.D.B.); Stroke Unit, AOU Sassari, Sassari, Italy (A.S.); Neurology Unit, Apuane Hospital, Massa, Italy (A.C.); Department of Neurology, Vito Fazi Hospital, Lecce, Italy (L.B., M.C.); Department of Neurology, Mirano Hospital, Mirano, Italy (M.M.); Neuroscience, IRCCS Ospedale Policlinico San Martino, Genoa, Italy (M.D.S.); Department of Neurology, Fatebenefratelli Hospital, Rome, Italy (F.P.); Department of Neurology, SS Annunziata Hospital, Savigliano, Italy (M.R.B.); Department of Human neurosciences, La Sapienza University, Rome, Italy (D.T.); and Coordinatore Comitato Scientifico ISA-AII, Citta' di Castello, Italy (S.R.).

Acknowledgments

Drs Ornello and Foschi drafted the manuscript. Dr Foschhi performed statistical analyses and created tables and figures. Drs Sacco, De Matteis, Russo, and De Santis majorly contributed to data curation. Drs Sacco and Ornello conceived and coordinated the study. Other authors majorly contributed to data acquisition and revised the manuscript for intellectual content.

Sources of Funding

None.

Disclosures

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

Supplemental Material

Data S1
Figures S1–S2

REFERENCES

1. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Long-term functional recovery after first ischemic stroke: the Northern Manhattan Study. *Stroke*. 2009;40:2805–2811. doi: 10.1161/STROKEAHA.109.549576
2. Khatri P, Conaway MR, Johnston KC, Acute stroke accurate prediction study I. Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke*. 2012;43:560–562. doi: 10.1161/STROKEAHA.110.593897
3. Choi JC, Jang MU, Kang K, Park JM, Ko Y, Lee SJ, Cha JK, Kim DH, Park SS, Park TH, et al. Comparative effectiveness of standard care with

IV thrombolysis versus without IV thrombolysis for mild ischemic stroke. *J Am Heart Assoc*. 2015;4:e001306. doi: 10.1161/JAHA.114.000596
4. Greisenegger S, Seyfang L, Kiechl S, Lang W, Ferrari J, Austrian Stroke Unit Registry C. Thrombolysis in patients with mild stroke: results from the Austrian stroke unit registry. *Stroke*. 2014;45:765–769. doi: 10.1161/STROKEAHA.113.003827
5. Tsivgoulis G, Goyal N, Katsanos AH, Malhotra K, Ishfaq MF, Pandhi A, Frohler MT, Spiotta AM, Anadani M, Psychogios M, et al. Intravenous thrombolysis for large vessel or distal occlusions presenting with mild stroke severity. *Eur J Neurol*. 2020;27:1039–1047. doi: 10.1111/ene.14199
6. You S, Saxena A, Wang X, Tan W, Han Q, Cao Y, Liu CF. Efficacy and safety of intravenous recombinant tissue plasminogen activator in mild ischaemic stroke: a meta-analysis. *Stroke Vasc Neurol*. 2018;3:22–27. doi: 10.1136/svn-2017-000106
7. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN Jr, Starr M, Mejilla J, Broderick J, Chatterjee A, Jauch EC, Levine SR, et al. Effect of Alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. *JAMA*. 2018;320:156–166. doi: 10.1001/jama.2018.8496
8. Romano JG, Gardener H, Campo-Bustillo I, Khan Y, Tai S, Riley N, Smith EE, Sacco RL, Khatri P, Alger HM, et al. Predictors of outcomes in patients with mild ischemic stroke symptoms: MaRISS. *Stroke*. 2021;52:1995–2004. doi: 10.1161/STROKEAHA.120.032809
9. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
10. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I–LXII. doi: 10.1177/2396987321989865
11. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
12. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med*. 2020;383:207–217. doi: 10.1056/NEJMoa1916870
13. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY, Clinical research collaboration NETTN, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
14. Chen HS, Cui Y, Zhou ZH, Zhang H, Wang LX, Wang WZ, Shen LY, Guo LY, Wang EQ, Wang RX, et al. Dual antiplatelet therapy vs Alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA*. 2023;329:2135–2144. doi: 10.1001/jama.2023.7827
15. Sykora M, Krebs S, Miksova D, Badic I, Gattringer T, Fandler-Hofler S, Marko M, Greisenegger S, Knoflach M, Lang W, et al. IV thrombolysis vs early dual antiplatelet therapy in patients with mild noncardioembolic ischemic stroke. *Neurology*. 2023;101:e933–e939. doi: 10.1212/WNL.0000000000207538
16. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58:113–130.
17. De Matteis E, De Santis F, Ornello R, Censori B, Puglisi V, Vinciguerra L, Giossi A, Di Viesti P, Inchingolo V, Fratta GM, 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;54:1172–1181. doi: 10.1161/STROKEAHA.122.041660
18. investigators G. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682. doi: 10.1056/NEJM199309023291001
19. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*. 2010;25:1–21. doi: 10.1214/09-STS313
20. Gao Y, Chen W, Pan Y, Jing J, Wang C, Johnston SC, Amarenco P, Bath PM, Jiang L, Yang Y, et al. Dual antiplatelet treatment up to 72 hours after ischemic stroke. *N Engl J Med*. 2023;389:2413–2424. doi: 10.1056/NEJMoa2309137
21. Asdaghi N, Wang K, Ciliberti-Vargas MA, Gutierrez CM, Koch S, Gardener H, Dong C, Rose DZ, Garcia EJ, Burgin WS, et al. Predictors of thrombolysis administration in mild stroke: Florida-Puerto Rico collaboration to reduce stroke disparities. *Stroke*. 2018;49:638–645. doi: 10.1161/STROKEAHA.117.019341
22. Bergh E, Jahr SH, Ronning OM, Askim T, Thommessen B, Kristoffersen ES. Reasons and predictors of non-thrombolysis in patients with acute ischemic stroke admitted within 4.5 h. *Acta Neurol Scand*. 2022;146:61–69. doi: 10.1111/ane.13622