RESEARCH ARTICLE

IV Thrombolysis vs Early Dual Antiplatelet Therapy in Patients With Mild Noncardioembolic Ischemic Stroke

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Abstract

Background Objectives

It is unclear whether IV thrombolysis (IVT) outperforms early dual antiplatelet therapy (DAPT) in the acute setting of mild ischemic stroke. The aim of this study was to compare the early safety and efficacy of IVT with that of DAPT.

Methods

Data of mild noncardioembolic stroke patients with admission NIH Stroke Scale (NIHSS) score ≤3 who received IVT or early DAPT in the period 2018–2021 were extracted from a nationwide, prospective stroke unit registry. Study endpoints included symptomatic intracerebral hemorrhage (sICH), early neurologic deterioration ≥4 NIHSS points (END), and 3-month functional outcome by modified Rankin scale (mRS).

Results

A total of 1,195 mild stroke patients treated with IVT and 2,625 patients treated with DAPT were included. IVT patients were younger (68.1 vs 70.8 years), had less hypertension (72.8% vs 83.5%), diabetes (19% vs 28.8%), and a history of myocardial infarction (7.6% vs 9.2%), and slightly higher admission NIHSS scores (median 2 vs median 1) when compared with DAPT patients. After propensity score matching and multivariable adjustment, IVT was associated with sICH (4 [1.2%] vs 0) and END (adjusted odds ratio [aOR] 2.8, 95% CI 1.1–7.5), and there was no difference in mRS 0–1 at 3 months (aOR 1.3, 95% CI 0.7–2.6).

Discussion

This analysis from a prospective nationwide stroke unit network indicates that IVT is not superior to DAPT in the setting of mild noncardioembolic stroke and may eventually be associated with harm. Further research focusing on acute therapy of mild stroke is highly warranted.

Classification of Evidence

This study provides Class III evidence that IVT is not superior to DAPT in patients with acute mild (NIHSS score ≤3) noncardioembolic stroke. The study lacks the statistical precision to exclude clinically important superiority of either therapy.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Coinvestigators are listed at links.lww.com/WNL/C959.

Glossary

aOR = adjusted odds ratio; **DAPT** = dual antiplatelet therapy; **END** = early ischemic neurologic deterioration; **IPW** = inverse PS weighting; **IVT** = IV thrombolysis; **mRS** = modified Rankin scale; **MT** = mechanical thrombectomy; **NIHSS** = NIH Stroke Scale; **PS** = propensity score; **sICH** = symptomatic intracerebral hemorrhage; **SU** = stroke unit; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Introduction

Up to 50% of stroke patients present with mild neurologic deficits (NIH Stroke Scale [NIHSS] score ≤5) on admission.[1] It is important to underline that strokes with low NIHSS scores are not necessarily nondisabling. Despite, patients with mild stroke symptoms are traditionally excluded from IV thrombolysis (IVT) due to safety concerns potentially outweighing the putative benefits of recanalization therapy. Yet, up to 30% of minor stroke patients may end up with relevant functional deficits.[2-4] Large nonrandomized series suggested a benefit of IVT in mild stroke patients presenting with NIHSS score ≤5.[5,6] The randomized Potential of rtPA for Ischemic Strokes with Mild Symptoms study, however, did not prove functional outcome benefits in IVT-treated patients with NIHSS score ≤5 and nondisabling type of stroke when compared with aspirin therapy.[7] On the contrary, this study suggested harm due to an increased rate of symptomatic intracerebral hemorrhage in the IVT group. Nevertheless, conclusions from this trial should be drawn with caution given its premature termination. In line, a recent observational study suggested possible harm of IVT in the very low NIHSS subgroup (0–1 points) in which the likelihood for nondisabling strokes is high, but not in the NIHSS subgroup with 2–5 points.[8] IVT in stroke with minor and/or nondisabling symptoms remains thus controversial. Another acute therapeutical option in mild stroke patients is the early dual antiplatelet therapy (DAPT). Early DAPT has been shown to prevent further vascular events and suggested to have superior effects on functional outcome after mild stroke when compared with antiplatelet monotherapy.[9-13] In this study, we aimed to analyze the real-world experience with IVT when compared with DAPT in mild noncardioembolic stroke with admission NIHSS score 0–3 in a prospective nationwide cohort. We hypothesize that IVT is not superior to early DAPT in the setting of mild noncardioembolic stroke with admission NIHSS score 0–3.

Methods

Study Design and Population

The Austrian Stroke Unit Registry is a prospective database collecting data of all patients with stroke treated in 1 of 38 Austrian stroke units (SUs). Founded in 2002 and administrated by the Federal Ministry of Health, the registry includes anonymized patient's data including epidemiologic, demographic, clinical, therapeutical, and outcome variables using a web-based interface. Data collection, clinical ratings, and data entry are performed at the respective SU on admission and discharge using standardized definitions of variables and scores. Stroke severity on admission and at 24 hours is assessed using the NIHSS score.[14] Stroke etiology is classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[15] Functional assessment is performed at SU discharge and 3 months poststroke using the modified Rankin scale (mRS). If an in-person visit at 3 months is not possible, a telephone interview can be used instead. Classification of strokes, clinical ratings, and outcome assessment are mandated to be performed by a certified neurologist. More details on the Austrian Stroke Unit Registry, the definition of variables, and ratings have been previously described.[16]

Standard Protocol Approvals, Registrations, and Patient Consents

The Austrian Stroke Unit Registry is part of a governmental quality assessment program for nationwide stroke care and is financed by the Federal Ministry of Health. All data are anonymized and centrally administered by a third party, the Gesundheit Oesterreich GmbH—the national research and planning institute for health care, a competence and funding center of health promotion. As a part of a quality assessment program, no informed consent for data collection is required by the Austrian legislation. All scientific analyses included in this study were approved and supervised by a national academic review board.[17]

Data and Endpoint Definitions

Data of patients with confirmed ischemic stroke, older than 18 years, with admission NIHSS score 0–3 and coded as noncardioembolic by the TOAST criteria were extracted from the Austrian Stroke Unit Registry. The cutoff NIHSS score 0–3 has been chosen in line with randomized controlled trials introducing the use of DAPT in the acute phase of mild stroke.[9,13] Patients coded as "transient ischemic attack" or "stroke mimics," those with previous or newly diagnosed atrial fibrillation, with previous DAPT or DAPT after IVT, and those undergoing mechanical thrombectomy (MT) were excluded. The following variables entered the analysis: age, sex, IVT, DAPT, NIHSS score at admission and discharge, mRS—prestroke and at 3 months, hypertension, diabetes, hypercholesterolemia, smoking, previous stroke, coronary heart disease, etiology according to TOAST criteria, and symptomatic intracranial hemorrhage according to the European Cooperative Acute Stroke Study 3 criteria (symptomatic intracerebral hemorrhage [sICH]).[18] For the purposes of this study, patients were grouped according to IVT or DAPT treatment. The decision whether to use IVT or DAPT was based on the treating physician's discretion. DAPT comprised aspirin and clopidogrel initiated within the first 24 hours after onset using a loading dose of 300 mg of aspirin and 300–600 mg of clopidogrel, followed by 100 mg of aspirin and

75 mg of clopidogrel from the second day until 3 weeks, according to local guidelines.[19] Safety endpoints included sICH and early neurologic deterioration (END) defined as clinical deterioration by equal to or more than 4 NIHSS points in the first 24–48 hours after admission. Efficacy endpoints were defined as achieving mRS 0–1 point at SU discharge and at 3 months.

Statistics

Continuous variables are summarized by their median and interquartile range (calculated by subtracting the 25th percentile [Q1] from the 75th percentile [Q3]), while categorical variables are represented by absolute and relative frequencies. Patients were categorized into groups based on IVT and DAPT administration. The Mann-Whitney *U* test was used to compare the locations of continuous and ordinal variables without a normal distribution. The Pearson χ^2 test and the Fisher exact test were used to compare the frequency and distribution of categorical variables. Multivariable logistic regression models were applied to adjust for covariates including age, sex, prestroke mRS, hypertension, diabetes mellitus, previous stroke, myocardial infarction, stroke etiology (small vessel disease, large vessel disease, other, unknown), stroke localization (anterior vs posterior cerebral circulation), admission NIHSS, and center. Sensitivity analysis included (1) propensity score (PS) matching and (2) inverse PS weighting (IPW), both based on a logistic regression model controlling for the covariates as mentioned earlier, followed by logistic regression and weighted generalized estimation equation models, respectively. Statistical analysis was performed using R statistical software, version 4.0.2, with generalized linear model function from the Modern Applied Statistics with S package and "rpart" function from the "rpart" package and IBM SPSS statistical software, version 27. Due to the exploratory and hypothesis-generating character of the study, the effects of multiple testing have not been adjusted by applying the Bonferroni correction.

Data Availability

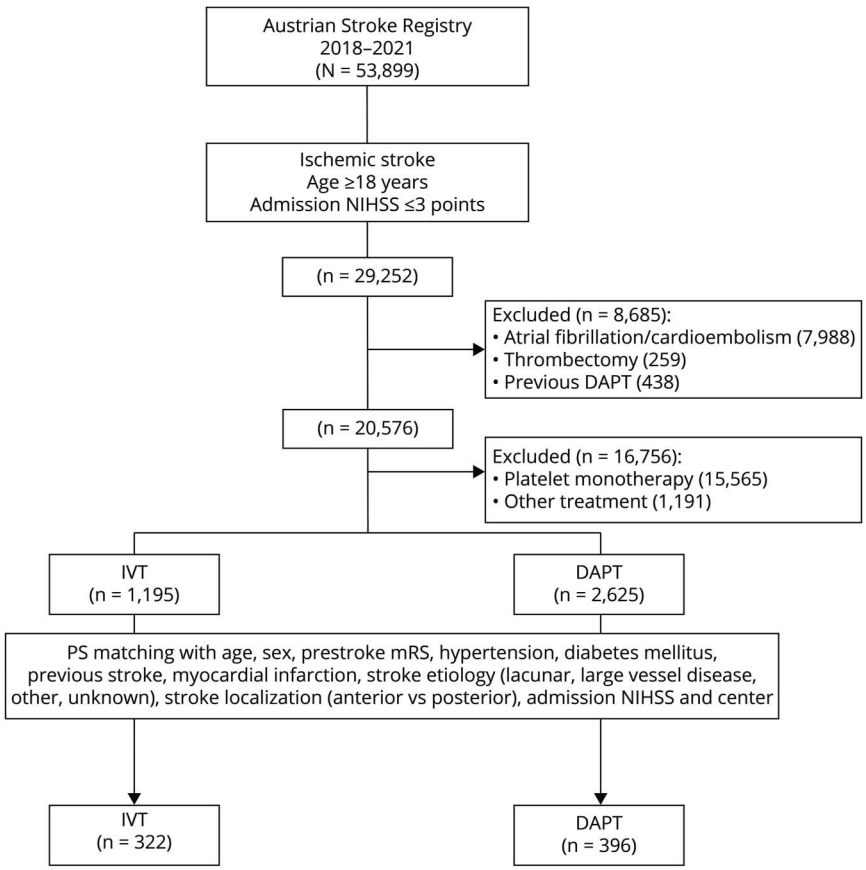
Data that support the findings of this study are available from the corresponding author after academic board review on reasonable request.

Results

Study Population

During the recent download the Austrian Stroke Unit Registry included data of 53,899 ischemic stroke patients admitted to Austrian SUs between 2018 and 2021. We extracted 29,252 (54.3%) individual datasets with confirmed ischemic stroke,

Figure 1 Flowchart of Patient Selection



DAPT = dual antiplatelet therapy; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale.

Table 1 Characteristics of the Study Population Categorized by IVT vs DAPT

	IVT (n = 1,195)	DAPT (n = 2,625)	*p* Value
Age, mean (range, SD)	68.1 (21–98, 14)	70.8 (19–99, 12)	<0.001
Sex, female, n (%)	444 (37.2)	1,016 (38.7)	0.4
Admission NIHSS, median (range, IQR)	2 (0–3, 2)	1 (0–3, 2)	<0.001
Prestroke mRS 0–1, n (%)	1,099 (92)	2,351 (89.7)	0.02
Hypertension, n (%)	870 (72.8)	2,193 (83.5)	<0.001
Diabetes mellitus, n (%)	227 (19)	757 (28.8)	<0.001
Previous stroke, n (%)	192 (16.1)	588 (22.4)	<0.001
Myocardial infarction, n (%)	91 (7.6)	242 (9.2)	0.1
Hypercholesterolemia, n (%)	782 (65.4)	1,977 (75.3)	<0.001
Smoking, n (%)	257 (21.5)	709 (27)	<0.001
Etiology, n (%)			<0.001
Small vessel disease	442 (37)	1,091 (41.6)	
Large vessel disease	190 (15.9)	661 (25.2)	
Other	60 (5)	102 (3.9)	
Unknown	388 (32.5)	634 (24.2)	
Missing data	115 (9.6)	137 (5.2)	
Localization			
Anterior vs posterior, n (%)	924 (77.3)	2,102 (80.1)	0.05

Abbreviations: DAPT = dual antiplatelet therapy; IQR = interquartile range; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale.

aged 18 years or older and presenting with mild stroke symptoms with admission NIHSS score 0–3. After excluding those coded as cardioembolic etiology and/or those with known or newly identified atrial fibrillation, 21,264 individuals were left. Further 259 were excluded because of undergoing MT and 438 because of previous DAPT or DAPT after IVT, leaving 20,567. Of those, 15,565 received platelet monotherapy and 1,191 other treatments. Finally, 1,195 patients treated with IVT and 2,625 treated with DAPT entered the analysis (Figure 1). Three-month mRS was available for 465 (38.9%) IVT patients and 1,151 (43.8%) DAPT patients. The baseline characteristics and risk factors did not differ for those with available 3 months mRS and those lost to follow-up (eTable 1, links.lww.com/WNL/C960).

Table 2 Safety and Efficacy Outcomes by IVT and Early DAPT

	IVT (n = 1,195)	DAPT (n = 2,625)	*p* Value
sICH, n (%)	17 (1.4)	3 (0.1)	<0.001
Deterioration NIHSS ≥4 points, n (%)	47 (3.9)	32 (1.2)	<0.001
mRS 0–1 at SU discharge, n (%)	794 (66.4)	1,943 (74)	<0.001
mRS 0–1 at 3 mo, n (%)	345 (74.2) (n = 465)	925 (80.4) (n = 1,151)	0.007

Abbreviations: DAPT = dual antiplatelet therapy; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale; sICH = symptomatic intracranial hemorrhage; SU = stroke unit.

Baseline Characteristics and Risk Factors

Baseline characteristics and risk factors differed significantly between the IVT and DAPT group. Patients treated with IVT when compared with those treated using DAPT were of younger age (68.1 vs 70.8 years, $p < 0.001$), had higher NIHSS scores on admission (median 2 vs median 1, $p < 0.001$), less prestroke disability (prestroke mRS 0–1: 92% vs 89.7%, $p = 0.02$), and less comorbidities (Table 1). The IVT group also had less small vessel disease etiology (37% vs 41.6%), less large vessel disease etiology (15.9% vs 25.2%), and more unknown etiology (32.5% vs 24.2%). Furthermore, patients in the IVT group had marginally less anterior vs posterior circulation stroke syndromes (anterior: 77.3% vs 80.1%, $p = 0.05$) (Table 1). The mean length of SU stay was 2.99 days in the IVT group and 3.03 days in the DAPT group ($p = 0.9$).

Safety Outcomes

sICH occurred in 17 (1.4%) patients in the IVT group when compared with 3 (0.1%) in the DAPT group ($p < 0.001$). END was present in 47 (3.9%) and 32 (1.2%) in IVT-treated and DAPT-treated patients, respectively ($p < 0.001$) (Table 2). After adjustment, IVT was associated with sICH (adjusted odds ratio [aOR] 10.3, 95% CI 2.7–39, $p < 0.001$) and END (aOR 3.7, 95% CI 2.3–6.4, $p < 0.001$) when compared with DAPT (Table 3).

Functional Outcome

mRS at SU discharge was available for all IVT and DAPT patients. In the IVT group, mRS 0–1 at SU discharge was observed in 794 (66.4%) vs 1,943 (74%) in the DAPT group ($p < 0.001$). mRS 0–1 at 3 months was present in 345 (74.2%) of IVT and in 925 (80.4%) of DAPT patients ($p = 0.007$) (Table 2). After adjustment, IVT was not significantly associated with mRS 0–1 at SU discharge (aOR 0.97, 95% CI 0.8–1.2) and with mRS 0–1 at 3 months (aOR 0.83, 95% CI 0.6–1.1) (Table 3).

Sensitivity Analysis Using PS Matching

After PS matching, the cohort consisted of 322 IVT and 396 DAPT patients. There were no significant differences between the groups (eTable 2, links.lww.com/WNL/C960). sICH occurred in 4 (1.2%) patients in the IVT group when compared with 0 (0%) in the DAPT group ($p = 0.04$). END was present in 13 (4%) and 7 (1.8%) in IVT-treated and DAPT-treated patients, respectively ($p = 0.05$) (Table 4). After adjustment, IVT was associated with END (aOR 2.8, 95% CI 1.1–7.5, $p < 0.001$) when compared with DAPT (Table 5). mRS 0–1 at SU

Table 3 Association of IVT/DAPT With Safety and Efficacy Outcomes in the Multivariable Models

IVT vs DAPT	aOR (reference DAPT)	95% CI	*p* Value
sICH	10.3	2.7–39	<0.001
Deterioration NIHSS ≥4	3.7	2.3–6.4	<0.001
mRS 0–1 at SU discharge	0.97	0.8–1.2	0.7
mRS at 3 mo 0–1	0.83	0.6–1.1	0.2

Abbreviations: aOR = adjusted odds ratio; DAPT = dual antiplatelet therapy; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale; sICH = symptomatic intracranial hemorrhage; SU = stroke unit.

discharge was observed in 232 (72.3%) in the IVT group vs 299 (75.7%) in the DAPT group ($p = 0.3$). mRS 0–1 at 3 moths was available for 120 patients in the IVT group and 192 in the DAPT group. mRS 0–1 at 3 moths was present in 102 (85%) and 157 (81.8%) in the IVT and the DAPT group, respectively. After adjustment, there were no significant differences in the functional outcome at SU discharge and at 3 months follow-up between the groups (Table 5).

Sensitivity Analysis Using IPW

Using IPW models, IVT when compared with DAPT was associated with sICH (aOR 10.3, 95% CI 2.2–47.5, $p = 0.003$), END (aOR 2.1, 95% CI 1.2–3.6, $p = 0.01$), mRS 0–1 at SU discharge (aOR 0.9, 95% CI 0.7–1.1, $p = 0.2$), and mRS 0–1 at 3 months (aOR 1.2 95% CI 0.9–1.6, $p = 0.3$) (Table 5).

The Role of Small Vessel Etiology vs Large Vessel Etiology

We explored the effects of small vessel and large vessel etiology for END and functional outcome. In patients with lacunar etiology, END occurred in 93 (1.4%) when compared with 62 (2.7%) patients with large vessel etiology ($p < 0.001$). In those undergoing IVT, END was present in 16 (3.6%) patients with lacunar etiology vs 12 (6.3%) with large vessel etiology ($p = 0.01$). In the DAPT group, END was present in 13 (1.2%) patients with lacunar etiology and in 8 (1.2%) of large vessel stroke patients ($p = 1$) (Figure 2).

Table 4 Safety and Efficacy Outcomes by IVT and Early DAPT After PS Matching

IVT vs DAPT, PS matched	IVT (n = 322)	DAPT (n = 396)	*p* Value
sICH, n (%)	4 (1.2)	0 (0)	0.04
Deterioration NIHSS ≥4, n (%)	13 (4)	7 (1.8)	0.05
mRS 0–1 at SU discharge, n (%)	232 (72.0)	299 (75.5)	0.3
mRS 0–1 at 3 mo, n (%)	102 (85.0) (n = 120)	157 (81.8) (n = 192)	0.5

Abbreviations: DAPT = dual antiplatelet therapy; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale; PS = propensity score; sICH = symptomatic intracranial hemorrhage; SU = stroke unit.

Table 5 Association of IVT/DAPT With Safety and Efficacy Outcomes in the Multivariable Models After PS Matching or IPW

	aOR (reference DAPT)	95% CI	*p* Value
IVT vs DAPT, PS matched			
sICH	—	—	—
Deterioration NIHSS ≥4	2.8	1.1–7.5	<0.001
mRS 0–1 at SU discharge	0.9	0.7–1.4	0.8
mRS 0–1 at 3 mo	1.3	0.7–2.6	0.3
IVT vs DAPT, IPW			
sICH	10.3	2.2–47.5	0.003
Deterioration NIHSS ≥4	2.1	1.2–3.6	0.01
mRS 0–1 at SU discharge	0.9	0.7–1.1	0.2
mRS 0–1 at 3 mo	1.2	0.9–1.6	0.3

Abbreviations: aOR = adjusted odds ratio; DAPT = dual antiplatelet therapy; IPW = inverse propensity score weighting; IVT = IV thrombolysis; mRS = modified Rankin Score; NIHSS = NIH Stroke Scale; PS = propensity score; sICH = symptomatic intracranial hemorrhage; SU = stroke unit.

In the multivariable models, etiology (lacunar or large vessel disease) showed no significant effects on the mRS 0–1 at 3 months endpoint (lacunar: aOR 1.31, 95% CI 0.95–1.79; large vessel disease: aOR 0.97, 95% CI 0.68–1.39). However, when entering lacunar or large vessel etiology into the models as interaction with IVT/DAPT, the effects became statistically significant (lacunar × IVT: aOR 1.59, 95% CI 1.01–2.5 and large vessel etiology × IVT: aOR 0.42, 95% CI 0.24–0.74).

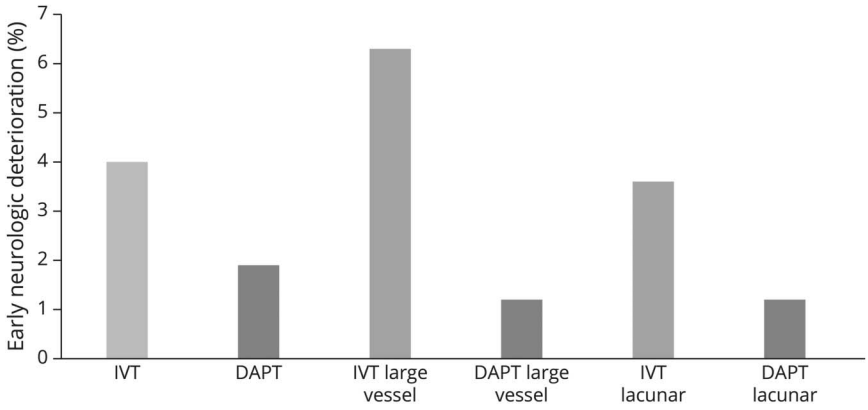
Classification of Evidence

This study provides Class III evidence that IVT is not superior to DAPT in patients with acute mild (NIHSS score ≤3) noncardioembolic stroke. The study lacks the statistical precision to exclude clinically important superiority of either therapy.

Discussion

The main findings of this study can be summarized as follows: (1) IVT in minor noncardioembolic stroke patients with admission NIHSS score ≤3 seems not to perform superior compared with early DAPT; (2) IVT was associated with an increased risk of symptomatic intracranial hemorrhage and early neurologic deterioration when compared with early DAPT; (3) interactions between acute therapy and stroke etiology indicated divergent effects on functional outcome: favorable outcome was more frequent after IVT in lacunar stroke patients, whereas it was more frequent after DAPT in patients with large vessel etiology.

Figure 2 Frequencies of Early Neurologic Deterioration by IVT vs DAPT and by Lacunar vs Large Vessel Etiology



DAPT = dual antiplatelet therapy; IVT = IV thrombolysis.

Our observation is in line with previous studies suggesting nonsuperiority and eventual harm in low NIHSS stroke patients undergoing thrombolytic therapy.[7,8] The phenomenon of END seems to be of particular interest in this context. Our rates of END are considerably lower as previously described in unselected (6.7%)[20] stroke patients, those with lacunar stroke (16%) or those with large vessel occlusion receiving thrombolysis (12%).[21,22] This can be explained by the low admission NIHSS, different definitions of END, and different sample sizes. Important predictors of END described in previous studies were large vessel disease, more proximal site of occlusion or thrombus length.[20,22,23] This is in line with our results. Large vessel etiology displayed a 2-fold risk of END when compared with lacunar etiology. Of interest, in our cohort, DAPT seemed to decrease the frequency of END in both etiologies. Observation that DAPT might decrease the frequency of END has been also previously described.[21,24]

Of note, despite having an increased frequency of sICH and END, functional outcome in the IVT group did not differ significantly from the DAPT group. We hypothesize that there are different effects of IVT/DAPT within particular etiologic subgroups of the minor noncardiogenic stroke population, which cumulatively result in the observed outcome neutrality. Indeed, we observed signals of divergent outcome effects resulting from interactions between stroke etiology and IVT/DAPT. In line with our results, a benefit of IVT in lacunar stroke has been also observed in previous studies.[25,26] Likewise, large vessel stroke etiology, which has been shown to be associated with END previously,[20,23] may represent an etiologic subpopulation benefiting more from DAPT.[27] More precise identification of subgroups of mild stroke patients who benefit the most from a particular treatment, or treatment combination (e.g., IVT followed by DAPT), seems to be highly justified.

Several limitations of our study have to be discussed. As with all observational studies, the main limitation is the bias by indication. The indication for IVT or DAPT treatment has been performed individually and may have had included unmeasured factors potentially affecting outcome. All attempts have been made to balance the groups equal and to account for bias using advanced statistical methods. Despite consistent results across all performed analyses, one cannot completely rule out the effects of bias by indication. Further limitation arises from the low data granularity on the exact etiology and/or vessel pathologies, which in turn could not be included in the analysis. This limits more detailed interpretation of the data. There is a significant loss of follow-up data (mRS at 3 months) in the registry, rendering this particular endpoint less statistically robust. However, the subgroups with and without follow-up did not differ significantly; thus, the population may be seen as representative. One might argue that the service levels and settings in which the patients were treated might not be equally balanced between the groups and might have influenced outcome. In Austria, all 38 SUs share by legislation the same level of stroke services, with 12 centers additionally offering MT. However, because patients undergoing MT were excluded and the analyses have been adjusted for center, this source of bias seem to be negligible. Summarized, our results have to be interpreted with caution and regarding the abovementioned limitations. On the contrary, the strength of our study includes a rigorously collected large prospective dataset closely reflecting the real-world settings.

In this analysis, from a prospective nationwide registry, IVT in mild noncardioembolic stroke does not seem to perform superior regarding safety and efficacy when compared with DAPT. Particular subpopulations of mild stroke patients may eventually benefit from different acute therapeutical approaches. Because mild stroke constitutes approximately 50% of all ischemic strokes, further studies are highly warranted.

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Disclosure

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Appendix 1 Authors

Name	Location	Contribution
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Dominika Miksova, PhD	Austrian National Public Health Institute, Vienna, Austria	Study concept or design; analysis or interpretation of data
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C959.

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