SUPPLEMENTAL METHODS

Statistical analysis

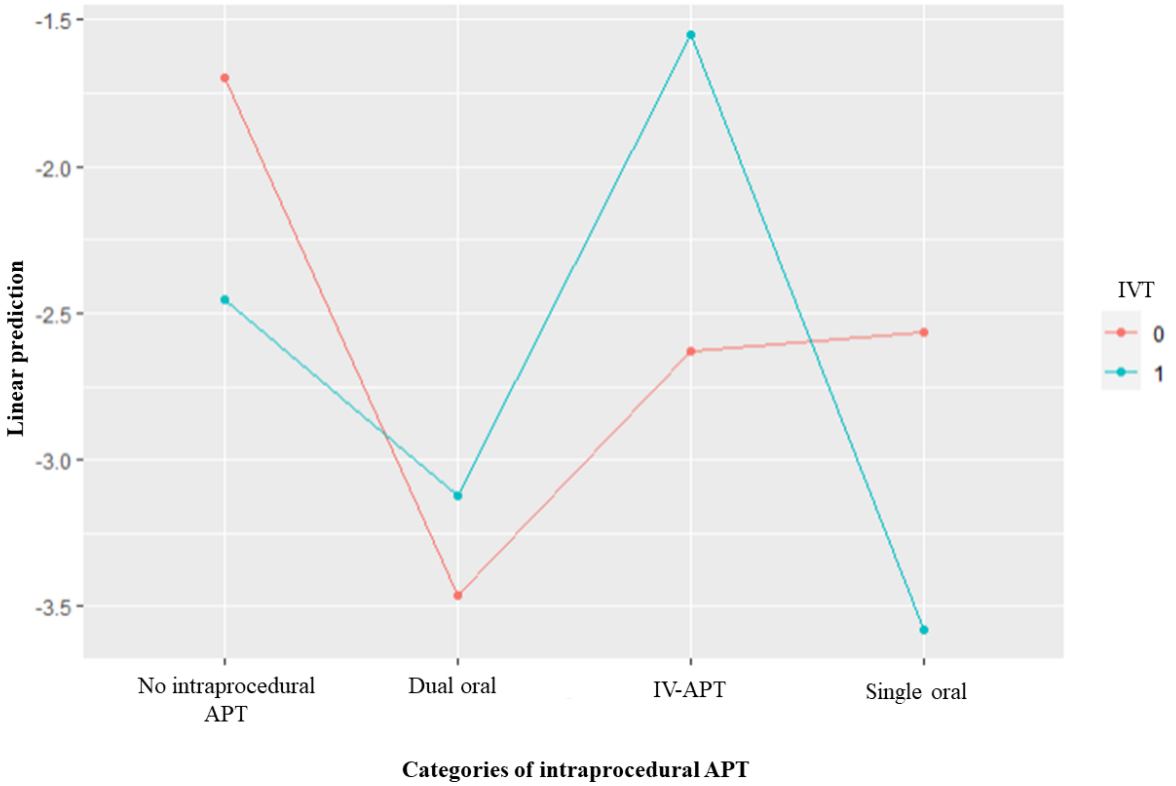
To select regression models, we utilized bidirectional stepwise procedures, and applied the Akaike's information criteria (AIC) and Bayesian information criteria (BIC). AIC was the preferred limiting criteria when the outcome had a significant number of events, and BIC when the number of events was small in at least one of the groups. Then, we selected the model with the smallest AIC or BIC that included important covariates. Subgroup and sensitivity analyses were conducted using 'forced entry' models with the same covariates included in the main analyses.

After models' selection, we used mixed effects logistic regression for binary outcomes, and mixed effects proportional odds regression for ordinal outcomes, in both cases with center as the random effect. Candidate variables considered to feed the stepwise procedures were selected based in clinical relevance and statistical significance in univariate analyses: age, sex, hypertension, hyperlipidemia, atrial fibrillation, smoking status, previous stroke or transient ischemic attack, prior antiplatelet, initial NIHSS, direct-to-angio strategy (direct delivery of a suspected or confirmed stroke patient to the neuro-angiography suite without admission to the emergency department), mTICI 2b-3, intra-arterial tissue plasminogen activator treatment (locally injection of tissue plasminogen activator during MT), sICH, PH2, heparin, ICA treatment technique (stenting vs non-stenting), cervical revascularization technique in reference to the ICA lesion (anterograde vs retrograde), ethnicity, ICA stenosis/occlusion pre-procedure, etiology of ICA lesion, first pass effect (complete recanalization after one pass of a MT device), post procedure antiplatelets, early window (<6 hours from last known well [LKW]-to-arterial puncture) vs. late window (6-24 hours from LKW-to-arterial puncture), type of anesthesia, and Alberta Stroke Program Early Computed Tomography Score (ASPECTS). The proportional odds models were built to estimate the odds of lower versus higher mRS scores at 90 days, and hemorrhagic transformation of infarction in an ordinal categorization, according to severity (none, petechial [H1, H2], parenchymal hematoma [PH1, PH2]). The ICA treatment technique was forced into the models due to its association with functional outcomes and use of antiplatelet medication, as described in a previous study performed in this registry.[24] Additionally, we explored effect modification by antiplatelet regimen for sICH, PH2, and hemorrhagic transformation. When an interaction was observed, we performed a sensitivity analysis for the subgroups.

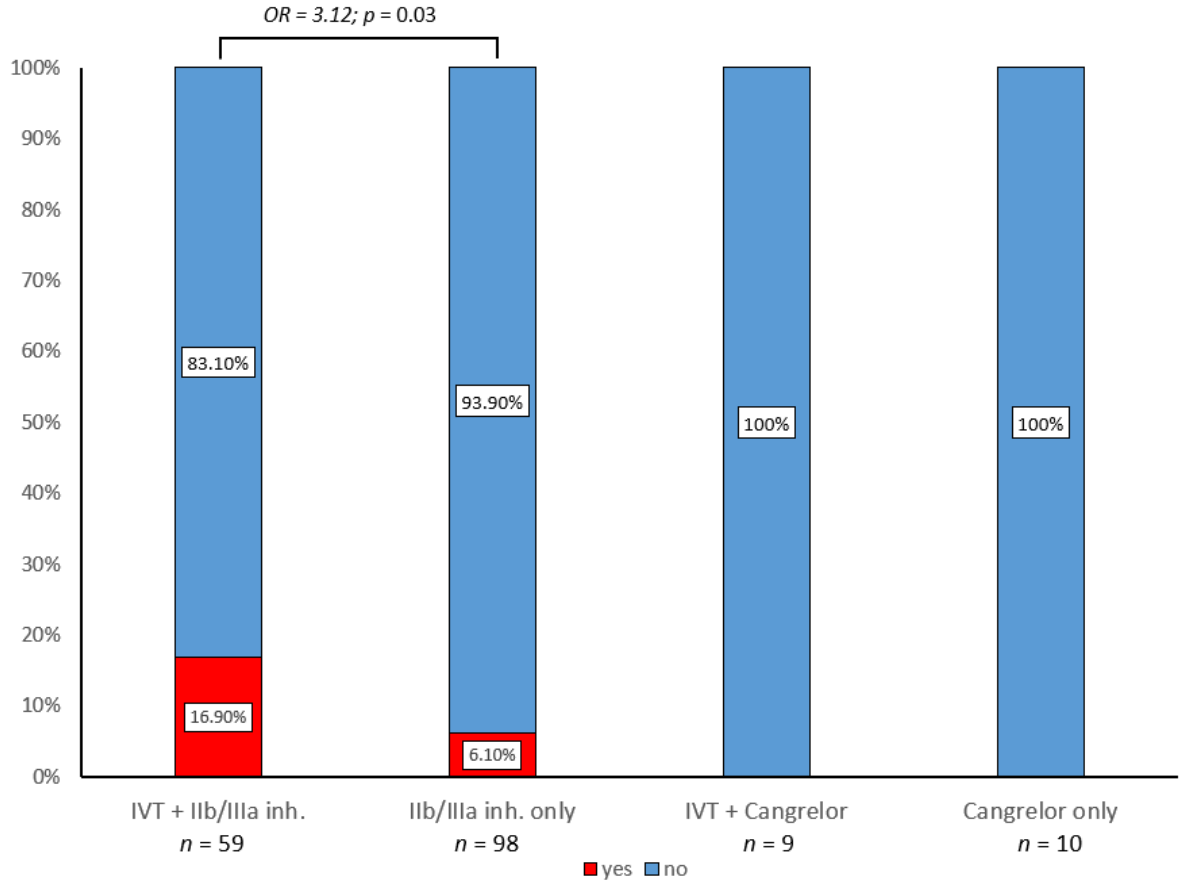
Lastly, we assessed the heterogeneity of the effect of IVT on pre-specified subgroups including procedural heparin, etiology, ASPECTS, intraprocedural antiplatelets, ICA treatment, time window, and ICA occlusion for the safety outcome (rate of sICH). We also looked at the effect of IVT in the subgroups age, ASPECTS, intraprocedural antiplatelets, ICA treatment, time window, and ICA occlusion for the

efficacy outcome mRS 0-2 at 90 days. To do this assessment we introduced an interaction term in regression models and adjusted for the same covariates utilized in the main analyses. We then conducted likelihood ratio tests (LRT) to evaluate the overall interaction between IVT and intraprocedural antiplatelets comparing the models with and without the interaction term and reported the corresponding p-values (p-het). For sICH we generated interaction plots to further explore and evaluated interactions at each level of the variable “Intraprocedural antiplatelets”. The difference of the effect of IVT was also tested at each level of the interactions and added to forest plots along with LRT p-values.

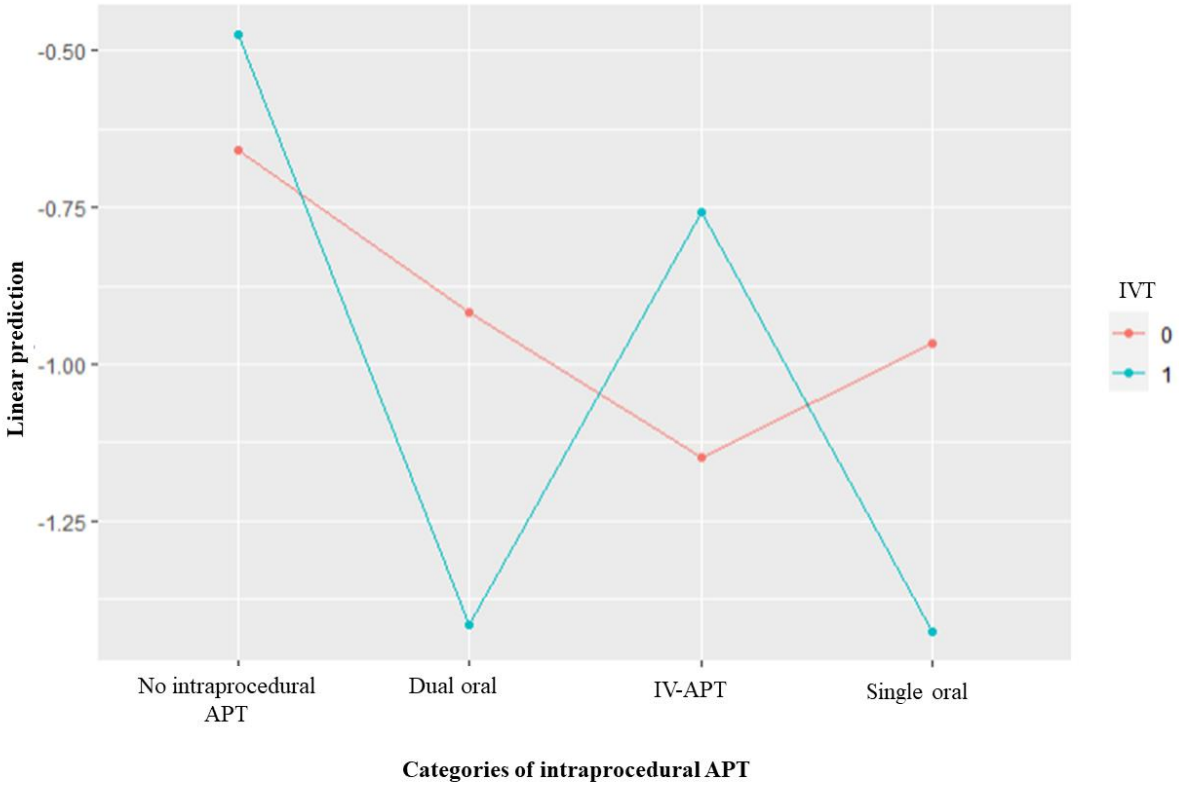
SUPPLEMENTARY FIGURE



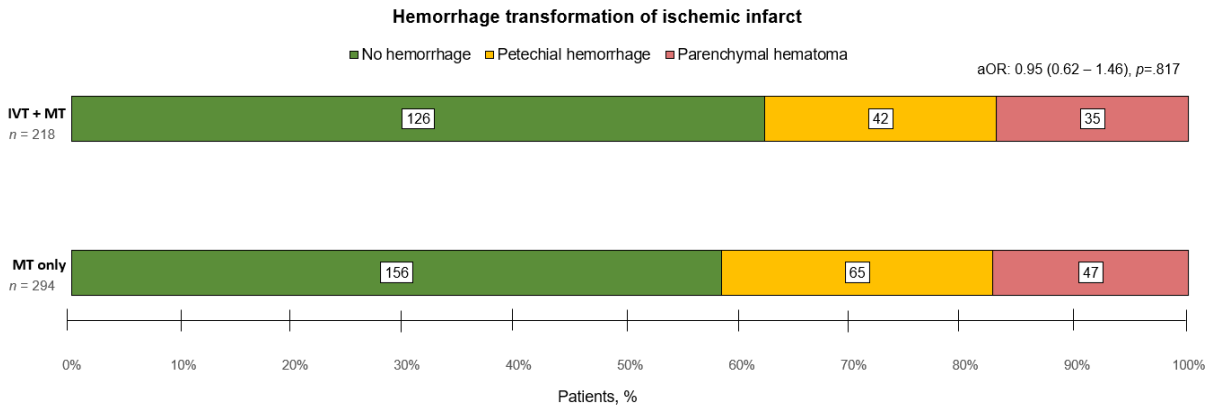
Supplementary Figure 1. Interaction plot for symptomatic intracranial hemorrhage. Intersection between the lines suggests potential interaction effect. APT: Antiplatelet; IV: Intravenous; IVT: Intravenous thrombolysis.



Supplementary Figure 2. Bar chart for symptomatic intracranial hemorrhage in patients showing the effect of the subtype of intravenous antiplatelets with the use of IVT. IVT: Intravenous thrombolysis. sICH: symptomatic intracranial hemorrhage; IIb/IIIa inh.: Glycoprotein IIb/IIIa inhibitor.



Supplementary Figure 3. Interaction plot for parenchymal hematoma type 2. Intersection between the lines suggests potential interaction effect. APT: Antiplatelet; IV: Intravenous; IVT: Intravenous thrombolysis.



Supplementary Figure 4. Shift analysis of hemorrhagic transformation according to severity. aOR: Adjusted odds ratio; sICH: symptomatic intracranial hemorrhage. IVT: Intravenous thrombolysis; MT: Mechanical thrombectomy.

Adjusted for: ICA stenting, number of passes, mTICI 2b-3.

SUPPLEMENTARY TABLES

Supplementary Table 1. Interaction model of intravenous thrombolysis with intraprocedural antiplatelets for symptomatic intracranial hemorrhage.

	OR (95% CI)	**p-value**
Intercept	0.14 (0.03 – 0.57)	**0.006**
No IVT	Ref	Ref
IVT	0.41 (0.09 – 1.91)	0.256
No Antiplatelets	Ref	Ref
Single Oral	0.37 (0.09 – 1.53)	0.170
Dual Oral	0.15 (0.03 – 0.87)	**0.034**
IV antiplatelets	0.39 (0.10 – 1.46)	0.163
IVT*No Antiplatelets	Ref	Ref
IVT*Single Oral	0.85 (0.06 – 12.90)	0.905
IVT*Dual Oral	3.01 (0.24 – 37.84)	0.393
IVT*IV antiplatelets	7.02 (1.07 – 46.09)	**0.042**
Number of passes	1.19 (0.97 – 1.47)	0.092
mTICI 0-2a	Ref	Ref
mTICI 2b-3	0.65 (0.24 – 1.71)	0.380

OR: Odds ratio; CI: Confidence interval; IVT: Intravenous thrombolysis; mTICI: modified Thrombolysis in Cerebral Infarction

Supplementary Table 2. Interaction model of intravenous thrombolysis with intraprocedural antiplatelets for parenchymal hematoma type 2.

	OR (95% CI)	**p-value**
Intercept	0.39 (0.02 – 8.34)	0.545
No IVT	Ref	Ref
IVT	4.95 (0.52 – 47.62)	0.166
Age	0.98 (0.95 – 1.01)	0.183
No hypertension	Ref	Ref
Hypertension	2.15 (0.83 – 5.60)	0.117
ASPECTS	0.77 (0.63 – 0.95)	0.013
No Antiplatelets	Ref	Ref
Single Oral	5.40 (0.62 – 46.77)	0.126
Dual Oral	2.83 (0.31 – 25.79)	0.357
IV antiplatelets	3.23 (0.37 – 27.91)	0.287
IVT*No Antiplatelets	Ref	Ref
IVT*Single Oral	0.09 (0.01 – 1.51)	0.094
IVT*Dual Oral	0.19 (0.01 – 2.86)	0.231
IVT*IV antiplatelets	0.18 (0.01 – 2.47)	0.200

OR: Odds ratio; CI: Confidence interval; IVT: Intravenous thrombolysis.

Supplementary Table 3. Secondary outcomes of patients with endovascularly treated tandem occlusion stroke according to the use of intravenous thrombolysis.

	Total	MT alone	IVT + MT	Unadjusted analysis		Adjusted analysis	
				OR (95% CI)	*p* value	OR (95% CI)	*p* value
Primary analysis	**N=512**	**N=294**	**N=218**				
Successful reperfusion[†*], N° (%)	447 (87.3)	253 (86.1)	194 (89)	1.14 (0.62 – 2.14)	0.682	0.95 (0.47–1.93)	0.895
Complete reperfusion[‡**], N° (%)	201 (39.3)	118 (40.1)	83 (38.1)	0.83 (0.54 – 1.26)	0.375	0.72 (0.46–1.12)	0.141
mRS 0-2 at discharge[§], N° (%)	132 (26.2)	73 (25.4)	59 (27.3)	1.33 (0.87 – 2.04)	0.191	1.20 (0.75 – 1.92)	0.436
mRS 0-1 at 90 days[§], N° (%)	88 (19.1)	52 (20.2)	36 (17.6)	1.02 (0.62 – 1.67)	0.943	1.03 (0.61 – 1.75)	0.912
In-hospital mortality[§], N° (%)	50 (9.9)	31 (10.8)	19 (8.8)	0.84 (0.43 – 1.59)	0.594	0.86 (0.44 – 1.70)	0.675
90-day mortality[§], N° (%)	79 (17.1)	50 (19.5)	29 (14.2)	0.77 (0.45 – 1.32)	0.356	0.98 (0.44 – 2.18)	0.956
Early window sensitivity analysis	**N=259**	**N=87**	**N=172**				
Successful reperfusion[†*], N° (%)	227 (87.6)	73 (83.9)	154 (89.5)	1.11 (0.60 – 2.09)	0.736	1.25 (0.47 – 3.35)	0.653
Complete reperfusion[‡**], N° (%)	97 (37.5)	36 (41.4)	61 (35.5)	0.80 (0.52 – 1.22)	0.297	0.73 (0.39 – 1.37)	0.327
mRS 0-2 at discharge[§], N° (%)	70 (27.3)	22 (25.6)	48 (28.2)	1.28 (0.84 – 1.95)	0.256	1.01 (0.52 – 1.97)	0.982
mRS 0-1 at 90 days[§], N° (%)	35 (15)	9 (12.7)	26 (16)	1.04 (0.63 – 1.71)	0.866	1.35 (0.72 – 2.53)	0.345
In-hospital mortality[§], N° (%)	23 (9)	9 (10.5)	14 (8.2)	0.86 (0.44 – 1.63)	0.642	0.85 (0.27 – 2.66)	0.779

IVT: Intravenous thrombolysis; MT: Mechanical thrombectomy; OR: Odds ratio; CI: Confidence interval; IQR: Interquartile range; mRS: modified Rankin scale.

[†]Defined as a mTICI 2b-3. [‡]Defined as a mTICI 3.

*Adjusted for: hypertension, first pass effect, internal carotid artery stenting, and intraprocedural antiplatelet therapy.

**Adjusted for: age, atrial fibrillation, smoking, first pass effect, number of passes, and intraprocedural antiplatelet therapy.

[§]Adjusted for: age, NIHSS, type of anesthesia, successful reperfusion, internal carotid artery stenting, symptomatic intracranial hemorrhage, and postprocedural antiplatelet therapy.