

## ONLINE SUPPLEMENTAL DATA

# **Intra-Arterial Thrombolysis Is Associated With Delayed Reperfusion of Remaining Vessel Occlusions Following Incomplete Thrombectomy**

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## Methods S1 Acquisition of Perfusion Imaging

Pre-interventional and follow-up imaging was performed on either computed tomography (CT; SOMATOM Definition Edge, Siemens, Erlangen, Germany) or magnetic resonance imaging (MRI; 1.5/3T MRI Avanto, Avanto fit, Verio, Aera, Skyra fit and Vida, Siemens, Erlangen, Germany). Perfusion data from CT were postprocessed with syngo.via software (Siemens) and MRI data with Olea Sphere software (Olea Sphere v2.3; Olea Medical). Following perfusion maps were generated: time to maximum (Tmax), time to peak (TTP), relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), mean transit time (MTT) and temporal maximum intensity projection map.

## Methods S2 Inverse Probability of Treatment Weighting Method

Propensity scores present probabilities for every patient to be assigned to the intervention group (i.e. receiving intra-arterial urokinase), conditioned on observed confounders. Patients with similar propensity scores are comparable, meaning that confounding variables are balanced. This helps in estimating the unconfounded effect for the variable of interest (i.e. perfusion imaging outcome: DR and PPD). Effectiveness of propensity score matching and balance between the groups was checked with the measurement of standardized mean differences and empirical cumulative density function statistics. Value of these two measures close to zero indicates good balance.<sup>1,2</sup> IPTW duplicates observations with large weights and creates pseudo-observations where probability of receiving the intervention does not depend on the covariates included in the propensity score estimations. This excludes confounding and enables comparison of weighted averages for the outcome of interest in the population with and without the intervention.<sup>3</sup> IPTW results may be presented as points of average treatment effect, which quantify treatment impact by comparing the outcomes of different treatment values.

Table S1 Intervention and Outcome Characteristics Of Study Population

	<b>Overall</b>	<b>IA Urokinase -</b>	<b>IA Urokinase +</b>	<b>p</b>	<b>Missing (%)</b>
n	459	419	40		
<b>INTERVENTION</b>					
Intravenous Thrombolysis = Yes (%)	182 (39.7)	164 (39.1)	18 (45.0)	0.579	0
Maneuver count (median [IQR])	2 [1, 3]	2 [1, 3]	2 [1, 3]	0.902	
eTICI (%)				<0.001	0
1	3 (0.7)	0 (0.0)	3 (7.5)		
2a	35 (7.6)	26 (6.2)	9 (22.5)		
2b50	76 (16.6)	60 (14.3)	16 (40.0)		
2b67	176 (38.3)	166 (39.6)	10 (25.0)		
2c	169 (36.8)	167 (39.9)	2 (5.0)		
<b>OUTCOME</b>					
Perfusion Imaging Outcome (%)				0.124	0
Delayed Reperfusion	276 (60.1)	257 (61.3)	21 (52.5)		
Persistent Perfusion Deficit	183 (39.9)	162 (38.7)	19 (47.5)		
New infarct on 24-hour follow-up = Yes (%)	243 (53.1)	223 (53.3)	20 (50.0)	0.811	0.2
sICH on 24-hour follow-up = Yes (%)	24 (5.2)	21 (5.0)	3 (7.5)	0.761	0
90-Day mRS score 0-2 (%)	252 (55.1)	226 (54.1)	26 (66.7)	0.179	0.4
90-Day mortality	69 (17.8)	67 (17.8)	2 (6.7)	0.191	11.3

eTICI - extended Thrombolysis in Cerebral Infarction; sICH - symptomatic intracranial hemorrhage; mRS - Modified Rankin scale

Table S2 Multivariable Logistic Regression Analysis of the Unmatched Cohort

Predictor	Delayed reperfusion		
	Adjusted Odds Ratios	95% CI	P-Value
Age	0.99	0.97 – 1.01	0.205
Sex	1.41	0.90 – 2.23	0.138
Atrial fibrillation	1.96	1.15 – 3.39	<b>0.014</b>
Anticoagulants pre-stroke	0.71	0.35 – 1.46	0.344
Antiplatelets pre-stroke	1.07	0.64 – 1.82	0.797
Onset-to-Door time (h)	1.00	0.98 – 1.05	0.803
NIHSS on Admission	0.99	0.97 – 1.02	0.732
Intravenous thrombolysis	0.84	0.52 – 1.37	0.486
Collaterals	1.20	0.95 – 1.52	0.127
eTICI	4.42	3.48 – 5.76	<b>&lt;0.001</b>
Intervention-to-Follow-up time (h)	1.07	1.03 – 1.11	<b>&lt;0.001</b>
IA Urokinase	2.78	1.17 – 6.73	<b>0.022</b>
$\Delta R^2$	0.416		

NIHSS: National Institutes of Health Stroke Scale; eTICI: eTICI: Expanded Thrombolysis in Cerebral Infarction; IA: intra-arterial.

Table S3 Balance of the IPTW-matched Cohort

Variable	Means -Treated	Means - Control	Std. Mean Diff.	Var. Ratio	eCDF Mean
Age	66.9550	69.2138	-0.1632	0.9708	0.0683
Sex (F)	0.3500	0.3150	0.0735	.	0.0350
Sex (M)	0.6500	0.6850	-0.0735	.	0.0350
eTICI	2.9750	3.0134	-0.0384	1.1126	0.0254
Onset-to-Door time (h)	3.1821	3.1834	-0.0005	0.6007	0.0330
Atrial fibrillation (No)	0.7500	0.7514	-0.0032	.	0.0014
Atrial fibrillation (Yes)	0.2500	0.2486	0.0032	.	0.0014
Anticoagulants pre-stroke (No)	0.8250	0.8667	-0.1099	.	0.0417
Anticoagulants pre-stroke (Yes)	0.1750	0.1333	0.1099	.	0.0417
Antiplatelets pre-stroke (No)	0.7500	0.7984	-0.1118	.	0.0484
Antiplatelets pre-stroke (Yes)	0.2500	0.2016	0.1118	.	0.0484
NIHSS on admission	10.9000	10.7108	0.0262	0.7114	0.0400
Intravenous thrombolysis (No)	0.5500	0.6537	-0.2084	.	0.1037
Intravenous thrombolysis (Yes)	0.4500	0.3463	0.2084	.	0.1037
ASITN/SIR collateral score	2.0750	2.0133	0.0673	1.0102	0.0128
Angio-to-Follow-Up time (h)	18.1938	18.3470	-0.0217	1.0907	0.0538

Effectiveness of propensity score matching and balance between the groups was checked with the measurement of standardized mean differences and empirical cumulative density function statistics. Value of these two statistics close to zero indicates good balance. eTICI: eTICI: Expanded Thrombolysis in Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; ASITN/SIR: American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology

Table S4 Differences in Unadjusted Odds Ratios and Point Causal Effects Between Unmatched and Matched Cohort

	Initial unmatched	IPTW fully matched
(Intercept)	0.253***	1.000***
	[0.219, 0.287]	[1.000, 1.000]
IA Urokianse		
Odds Ratios	1.312***	1.625***
95% CI	[1.141, 1.511]	[1.263, 2.091]
Points of Average Treatment Effect	0.272***	0.487***
95% CI	[0.132, 0.413]	[0.236, 0.738]
Num.Obs.	459	459
R2	0.015	0.021
R2 Adj.	0.014	0.019
+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001		

Table S5 Secondary Outcomes In The IPTW Matched Cohort

	New infarct at 24 hours		
Variable	Adjusted Odds Ratios	95% CI	P-Value
IA Urokinase	0.27	0.07 – 0.71	0.04
	mRS score 0-2 at 3 months		
IA Urokinase	1.35	0.43 – 4.13	0.59
	sICH at 24 hours		
IA Urokinase	0.85	0.17 – 3.13	0.82

CI – confidence interval; IA – intra-arterial; mRS – modified Rankin scale; sICH – symptomatic intracranial hemorrhage. All logistic regression analysis were adjusted for following confounders: age, sex, atrial fibrillation, anticoagulants pre-stroke, antiplatelets pre-stroke, Onset-to-Door time (hours), National Institutes of Health Stroke Scale (NIHSS) score on admission, intravenous thrombolysis, collateral score, extended Thrombolysis in Cerebral Infarction (eTICI) score ;Intervention-to-Follow-Up time, perfusion imaging outcome (delayed reperfusion or persistent perfusion deficit) and IA urokinase. All point estimated suggested numerically better outcomes among patients who have received IA urokinase.

Figure S1 Flow Chart

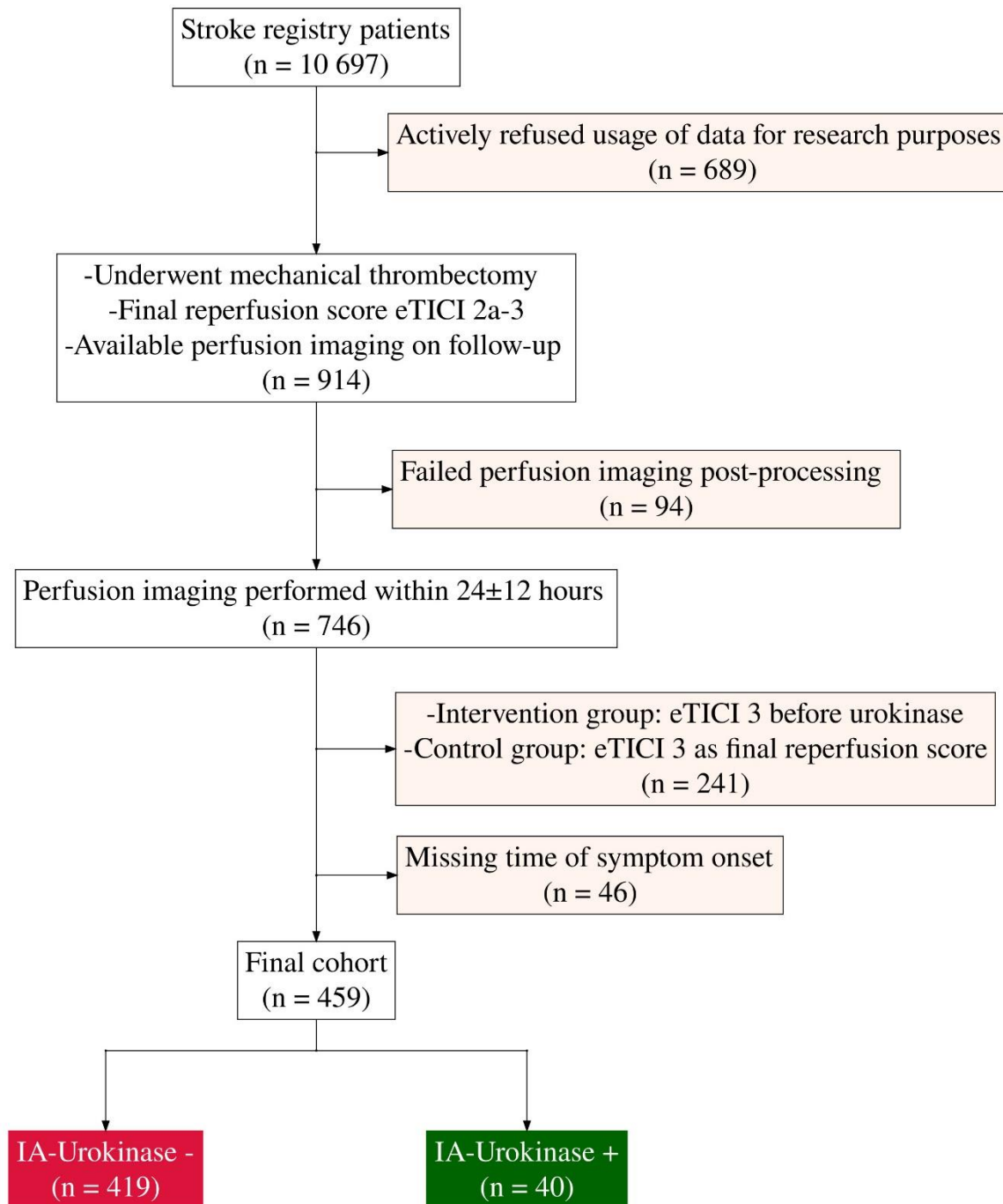
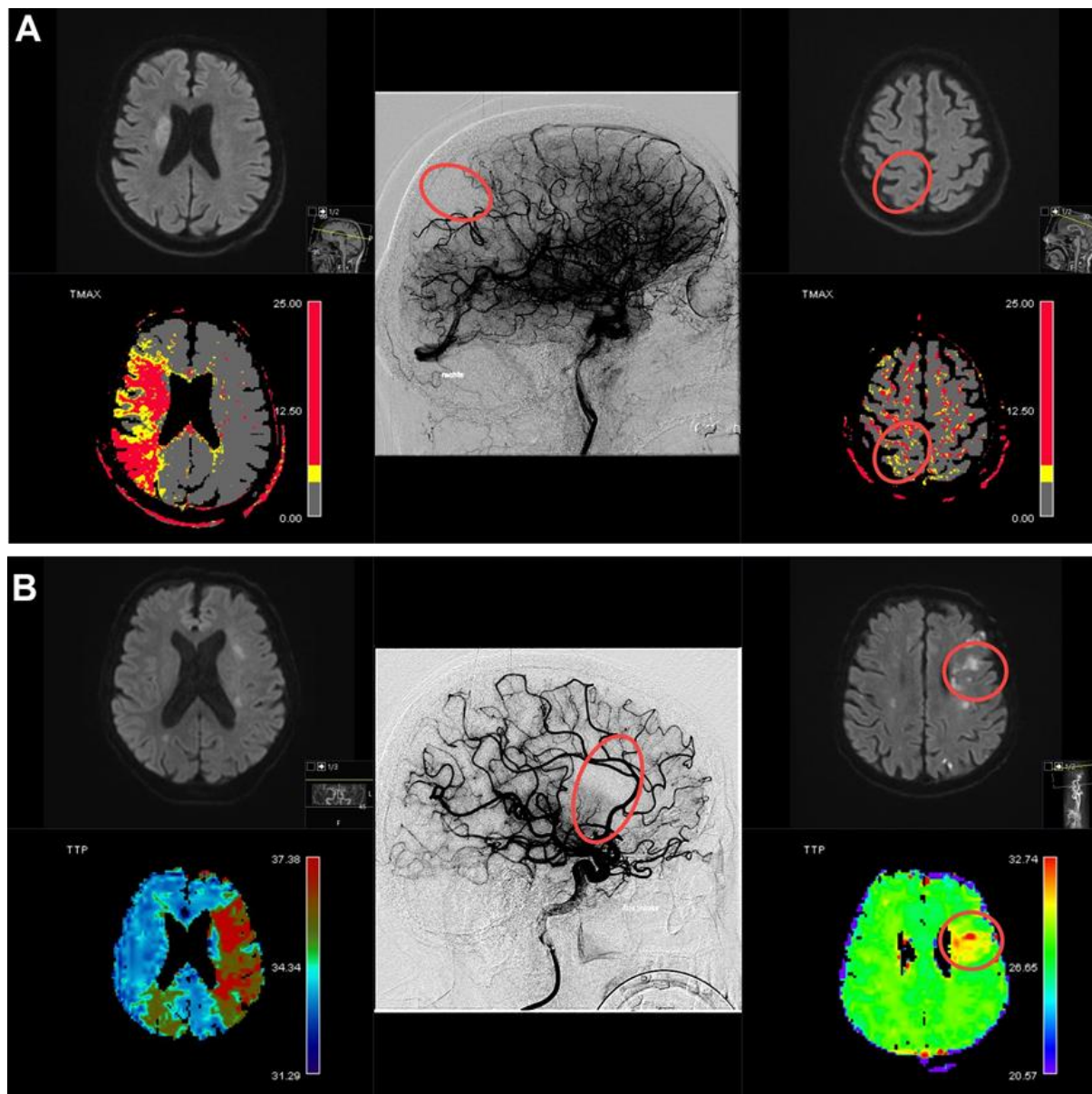


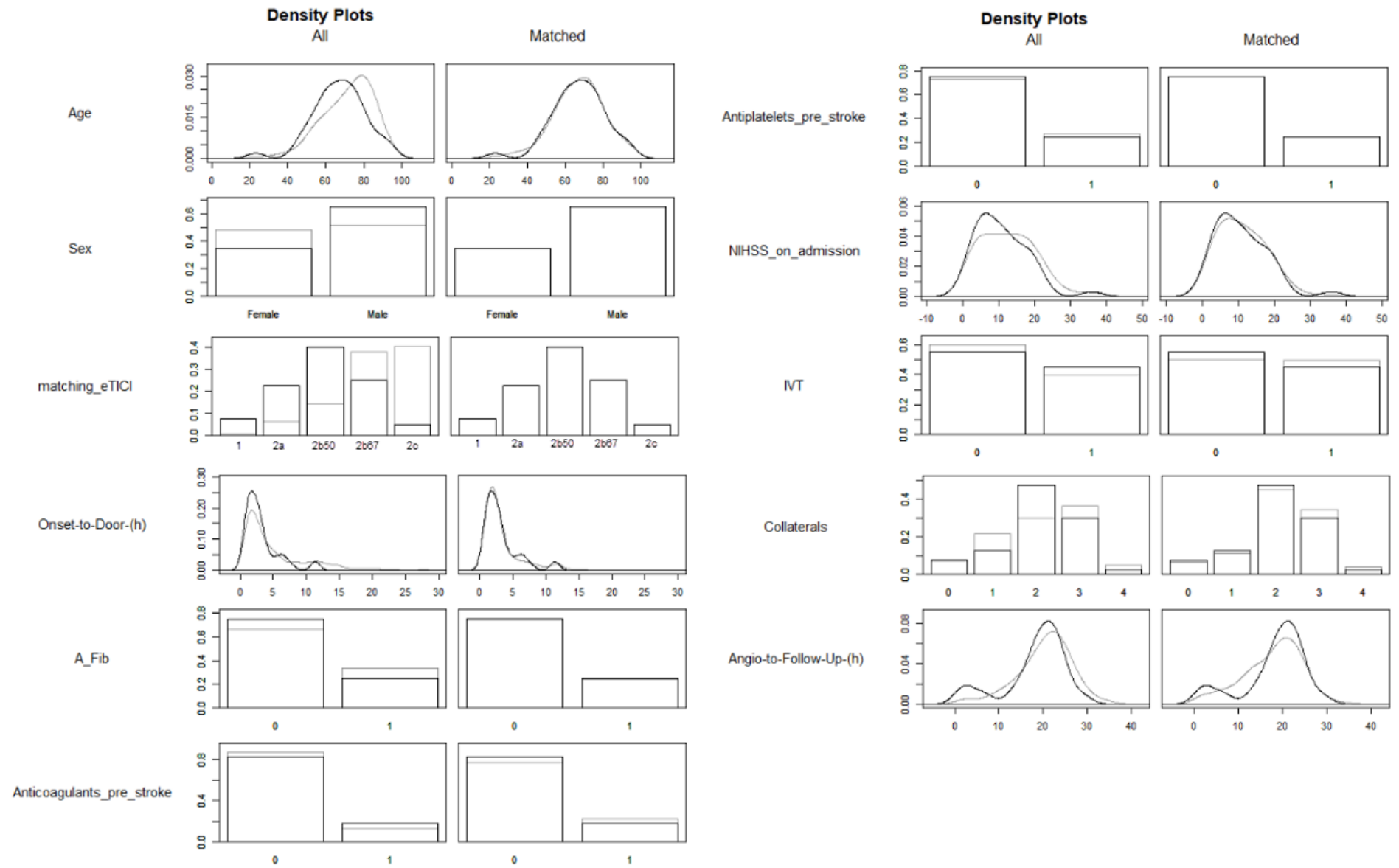


Figure S2 Perfusion Imaging Evaluation



Perfusion maps (Tmax – time-to-maximum and TTP - time-to-peak) and diffusion-weighted imaging (DWI) were evaluated on admission and follow-up examinations. Final angiography runs are displayed with high contrast to emphasize the capillary phase deficits. A) Patient with a right side M1 occlusion with expanded Thrombolysis in Cerebral Infarction (eTICI) 2b67 reperfusion score at the end of the intervention (middle), together with corresponding admission DWI (top-left), admission perfusion imaging (bottom-left) and follow-up DWI (top-right). On the follow-up Tmax perfusion map (bottom-right) there is no wedge-shaped delay suggestive of persisting occlusion which would correspond to the non reperfused area from the final angiography imaging. This was rated as delayed reperfusion. B) Patient with a left side M1 occlusion with expanded Thrombolysis in Cerebral Infarction (eTICI) 2b50 reperfusion score at the end of the intervention (middle), together with corresponding admission DWI (top-left), admission perfusion imaging (bottom-left) and follow-up DWI (top-right). On the follow-up TTP perfusion map (bottom-right) there is a wedge-shaped delay suggestive of persisting occlusion which directly corresponds to the non reperfused area from the final angiography imaging. This was rated as persisting perfusion deficit.<sup>4</sup>

Figure S3 Group Balance Before and After IPTW Matching



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