SUPPLEMENTAL MATERIAL

Tranexamic Acid for Prevention of Hematoma Expansion in Intracerebral Hemorrhage Patients With or Without Spot Sign

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Supplemental Tables

Supplementary Table I: Comparison Between the Population Included in This Sub-Group Analysis and the Rest of the TICH-2 Population

	CTA or CECT available (n=254)	Remaining TICH-2 population (n=2071)
Age, years	63.8 (14.0) [20.0-94.0]	69.5 (13.7) [22.0-101.0]
Sex, male	153 (60.2%)	1148 (55.4%)
Ethnic origin		
White	204 (80.3%)	1774 (85.7%)
Other	50 (19.7%)	296 (14.3%)
Onset to CTA or CECT, minutes	123.0 (89.0-190.0) [9.0-415.0]	NA.
Onset to randomization, minutes	206.5 (149.0-282.0) [80.0-477.0]	220.0 (157.0-305.0) [51.0-1246.0]
Onset to IMP administration, minutes	225.0 (169.0-310.0) [82.0-481.0]	245.0 (180.0-334.0) [60.0-1404.0]
≤3 hours	81 (32.0%)	524 (25.6%)
≤4.5 hours	160 (63.2%)	1200 (58.5%)
Antiplatelet therapy on admission	58 (22.8%)	553 (26.7%)
Statin therapy on admission	56 (22.4%)	566 (27.5%)
History of ischemic stroke or TIA	26 (10.4%)	304 (14.8%)
History of ischemic heart disease	21 (8.5%)	181 (8.8%)
History of thromboembolism	3 (1.2%)	31 (1.5%)
Pre-stroke modified Rankin scale	0.0 (0.0-0.0) [0.0-4.0]	0.0 (0.0-1.0) [0.0-4.0]
Admission GCS score	15.0 (13.0-15.0) [6.0-15.0]	15.0 (12.0-15.0) [5.0-15.0]
Admission NIHSS score	12.0 (6.0-19.0) [0.0-30.0]	12.0 (7.0-19.0) [0.0-42.0]
Systolic blood pressure, mmHg	175.9 (29.9) [99.0-255.5]	172.2 (26.8) [98.0-264.5]
Diastolic blood pressure, mmHg	95.9 (18.7) [58.0-156.0]	92.9 (18.0) [35.5-179.0]
Hematoma location		
Supratentorial lobar	74 (29.1%)	664 (32.1%)
Supratentorial deep	155 (61.0%)	1216 (58.7%)
Infratentorial	18 (7.1%)	131 (6.3%)
Combination	7 (2.8%)	60 (2.9%)
Admission intraparenchymal hematoma volume, mL	25.6 (27.1) [0.1-132.8]	23.8 (27.2) [0.0-206.8]
Admission intraventricular hemorrhagic extension	65 (25.6%)	643 (31.5%)
Admission intraventricular hematoma volume, mL*	10.7 (10.8) [0.0-47.1]	10.3 (12.5) [0.0-156.5]
Admission subarachnoid hemorrhagic extension	32 (12.6%)	290 (14.2%)

Data are presented as mean (SD) [range], median (IQR) [range] or no. (%) as appropriate.
*Only participants with intraventricular hemorrhagic extension on admission scan included.
CTA – computed tomography angiography, CECT – contrast-enhanced CT, NA. – not applicable, IMP – investigational medicinal product, GCS – Glasgow Coma Scale, NIHSS – National Institute of Health Stroke Scale, mL – millilitre,

Supplementary Table II: Absolute and Relative Expansion in Hematoma Volumes From Admission to Day-2 – Spot sign on CT-Angiography or Contrast-Enhanced CT

	Spot Sign Positive		Spot Sign Negative	
	Tranexamic acid	**Placebo**	**Tranexamic acid**	**Placebo**
Change in intraparenchymal hematoma volume				
Absolute expansion	5.4 (2.4 to 24.1) mL [27]	5.4 (0.8 to 21.3) mL [30]	0.7 (-0.2 to 4) mL [80]	0.4 (-0.2 to 2.3) mL [78]
Relative expansion	16.2% (9.6% to 68.8%) [27]	30.8% (1% to 57.1%) [30]	11.6% (-2.1% to 29.6%) [80]	7.3% (-3.8% to 26.5%) [78]
Change in combined intraparenchymal and intraventricular hematoma volume				
Absolute expansion	7.9 (3.3 to 31.9) mL [27]	5.9 (0.9 to 21.4) mL [30]	0.8 (-0.1 to 4.4) mL [80]	0.4 (-0.3 to 3.1) mL [78]
Relative expansion	20.5% (11.6% to 64.8%) [27]	28.1% (2.1% to 70.6%) [30]	11.6% (-.8% to 31.8%) [80]	8% (-4.2% to 26.5%) [78]

Data are presented as median (interquartile range) [total no.]. Absolute expansion is calculated by subtracting the admission hematoma volume from the day-2 or clinical scan hematoma volume. Relative expansion is calculated by dividing absolute expansion with admission hematoma volumes. Only participants with an unbiased day-2 or clinical scan are included above.

CT – computed tomography, mL – milliliter.

Supplementary Table III: Secondary safety outcome – spot sign on CT-angiography or contrast-enhanced CT

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Any serious adverse event (at least one reported within 7 days)				0.64
Spot sign positive	18/30 (60.0%)	17/34 (50.0%)	OR 1.28 (0.45 to 3.61)	
Spot sign negative	42/95 (44.2%)	29/95 (30.5%)	OR 1.71 (0.92 to 3.19)	
Any safety events (at least one reported during the first 90 days)				0.59
Spot sign positive	14/30 (46.7%)	13/34 (38.2%)	OR 1.18 (0.41 to 3.39)	
Spot sign negative	23/95 (24.2%)	23/95 (24.2%)	OR 0.83 (0.41 to 1.67)	
Any thromboembolic events (at least one reported during the first 90 days)†				0.60
Spot sign positive	3/30 (10.0%)	3/34 (8.8%)	OR 1.15 (0.21 to 6.17)	
Spot sign negative	4/95 (4.2%)	6/95 (6.3%)	OR 0.65 (0.18 to 2.39)	

Data are presented as no./total no. (%). Treatment effect is presented as odds ratio (95% CI). An odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
No. – number, CI – confidence interval.
† Unadjusted effect estimates presented due to a limited number of events.

Supplementary Table IV: Secondary functional outcomes - spot sign on CT-angiography or contrast-enhanced CT

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Poor functional outcome at day-90 (dichotomous modified Rankin Scale 4-6)				0.51
Spot sign positive	21/30 (70.0%)	23/34 (67.6%)	OR 0.72 (0.21 to 2.55)	
Spot sign negative	45/95 (47.4%)	37/94 (39.4%)	OR 1.18 (0.60 to 2.32)	
Barthel index on day-90, points†				0.86
Spot sign positive	35.2 (44.6) [28]	45.3 (43.5) [32]	MD -0.1 (-18.4 to 18.2)	
Spot sign negative	59.4 (44.4) [89]	67.9 (42.2) [91]	MD -2.0 (-12.6 to 8.5)	
Mortality during the first 90 days				0.24
Spot sign positive	11/30 (36.7%)	9/34 (26.5%)	HR 1.50 (0.62 to 3.67)	
Spot sign negative	15/95 (15.8%)	15/95 (15.8%)	HR 0.75 (0.36 to 1.55)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as mean difference (95% CI), odds ratio (95% CI) or hazard ratio (95% CI). A mean difference above 0 (Barthel index) and an odds/hazard ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
SD – standard deviation, no. – number, CI – confidence interval.
† Barthel index of -5 imputed if participant died before day 90.

Supplementary Sensitivity Analysis – Spot Sign on CT-Angiography Only

For the purpose of this sensitivity analysis we grouped participants as spot-sign negative or positive based on the results of the obtained CT-angiographies only.

Supplementary Table V: Primary and composite secondary outcome – spot sign on CT-angiography only

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Primary outcome				
Day 2 CT intraparenchymal hematoma volume†				0.78
Spot sign positive	66.3 (45.5) mL [23]	53.5 (39.1) mL [26]	4.0 (-13.8 to 25.6)%	
Spot sign negative	23.2 (26.6) mL [79]	21.7 (26.6) mL [81]	1.0 (-9.1 to 12.1)%	
Day 2 CT intraparenchymal and intraventricular hematoma volume†				0.75
Spot sign positive	78.0 (54.2) mL [23]	58.0 (40.3) mL [26]	4.9 (-13.7 to 27.4)%	
Spot sign negative	25.8 (28.1) mL [79]	23.9 (28.4) mL [81]	1.2 (-9.2 to 12.7)%	
Secondary outcome				
Hematoma progression (composite secondary outcome)				0.74
Spot sign positive	16/25 (64.0%)	19/30 (63.3%)	0.91 (0.29 to 2.86)	
Spot sign negative	29/92 (31.5%)	35/97 (36.1%)	0.73 (0.39 to 1.38)	
Hematoma progression (excluding neurological deterioration and death)‡				0.61
Spot sign positive	15/23 (65.2%)	17/26 (65.4%)	0.96 (0.28 to 3.27)	
Spot sign negative	25/79 (31.6%)	32/81 (39.5%)	0.66 (0.33 to 1.31)	
Individual components of the composite hematoma progression outcome				
Significant intraparenchymal hematoma expansion				0.99
Spot sign positive	11/23 (47.8%)	14/26 (53.8%)	0.76 (0.24 to 2.46)	
Spot sign negative	21/79 (26.6%)	26/81 (32.1%)	0.77 (0.38 to 1.57)	
Significant intraventricular hematoma expansion				0.97
Spot sign positive	9/23 (39.1%)	6/26 (23.1%)	2.16 (0.59 to 7.83)	
Spot sign negative	8/79 (10.1%)	4/81 (4.9%)	2.08 (0.59 to 7.36)	
Delayed intraventricular or subarachnoid hematoma extension				0.31
Spot sign positive	10/22 (45.5%)	4/24 (16.7%)	4.78 (1.12 to 20.31)	
Spot sign negative	11/77 (14.3%)	6/78 (7.7%)	1.89 (0.64 to 5.55)	
Neurological deterioration or death within the first 24 hours				0.57
Spot sign positive	9/25 (36.0%)	7/30 (23.3%)	1.83 (0.54 to 6.17)	
Spot sign negative	16/92 (17.4%)	14/97 (14.4%)	1.20 (0.53 to 2.69)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as percent difference (95% CI) or odds ratio (95% CI). A percent difference below 0 and an odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† In addition to above mentioned covariates treatment effect also adjusted for baseline hematoma volume.
‡ The hematoma progression outcome applied to participants with an unbiased day-2 CT or clinical scan available.
CT – computed tomography, ML – milliliter, SD – standard deviation, no. – number, CI – confidence interval.

Supplementary Table VI: Secondary safety outcome – spot sign on CT-angiography only

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Any serious adverse event (at least one reported within 7 days)				0.59
Spot sign positive	15/25 (60.0%)	15/30 (50.0%)	1.28 (0.42 to 3.89)	
Spot sign negative	42/94 (44.7%)	29/97 (29.9%)	1.82 (0.98 to 3.40)	
Any safety events (at least one reported during the first 90 days)				0.81
Spot sign positive	11/25 (44.0%)	13/30 (43.3%)	0.86 (0.28 to 2.62)	
Spot sign negative	23/94 (24.5%)	21/97 (21.6%)	1.00 (0.50 to 2.03)	
Any thromboembolic events (at least one reported during the first 90 days)†				0.94
Spot sign positive	2/25 (8.0%)	3/30 (10.0%)	0.78 (0.12 to 5.10)	
Spot sign negative	5/94 (5.3%)	6/97 (6.2%)	0.85 (0.25 to 2.89)	

Data are presented as no./total no. (%). Treatment effect is presented as odds ratio (95% CI). An odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† Unadjusted effect estimates presented due to a limited number of events.
No. – number, CI – confidence interval.

Supplementary Table VII: Secondary functional outcomes - spot sign on CT-angiography only

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Poor functional outcome at day-90 (dichotomous modified Rankin Scale 4-6)				0.46
Spot sign positive	17/25 (68.0%)	20/30 (66.7%)	0.63 (0.17 to 2.41)	
Spot sign negative	44/94 (46.8%)	38/96 (39.6%)	1.11 (0.56 to 2.20)	
Barthel index on day-90, points†				0.53
Spot sign positive	38.0 (45.1) [23]	44.6 (44.4) [28]	3.7 (-16.3 to 23.7)	
Spot sign negative	58.8 (44.5) [89]	68.7 (41.2) [93]	-3.6 (-14.2 to 7.0)	
Mortality during the first 90 days‡				0.48
Spot sign positive	9/25 (36.0%)	9/30 (30.0%)	1.33 (0.52 to 3.37)	
Spot sign negative	14/94 (14.9%)	13/97 (13.4%)	0.86 (0.40 to 1.86)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as mean difference (95% CI), odds ratio (95% CI) or hazard ratio (95% CI). A mean difference above 0 (Barthel index) and an odds/hazard ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† Barthel index of -5 imputed if participant died before day 90.
‡ Cox proportional hazard model stratified for NIHSS due to breach of the proportional hazard assumption. Adjusted for age and time from onset to randomization.
SD – standard deviation, no. – number, CI – confidence interval.

Supplementary Sensitivity Analysis – Spot Sign as Adjudicated by the Local Investigators

For the purpose of this sensitivity analysis we grouped participants as spot-sign negative or positive based on the adjudication of the local investigators during the randomization process.

Supplementary Table VIII: Primary and composite secondary outcome - spot sign adjudicated by the local investigators

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Primary outcome				
Day 2 CT intraparenchymal hematoma volume†				0.69
Spot sign positive	65.1 (45.2) mL [18]	50.1 (47.1) mL [21]	-3.1 (-21.7 to 19.8)%	
Spot sign negative	26.3 (28.7) mL [75]	25.1 (28.3) mL [70]	1.7 (-8.9 to 13.5)%	
Day 2 CT intraparenchymal and intraventricular hematoma volume†				0.65
Spot sign positive	76.6 (56.0) mL [18]	56.4 (48.2) mL [21]	-2.7 (-21.4 to 20.4)%	
Spot sign negative	28.8 (31.3) mL [75]	26.7 (29.9) mL [70]	2.9 (-7.8 to 14.9)%	
Hematoma progression (composite secondary outcome)				0.86
Spot sign positive	13/21 (61.9%)	15/26 (57.7%)	0.92 (0.26 to 3.23)	
Spot sign negative	30/85 (35.3%)	28/82 (34.1%)	1.04 (0.53 to 2.03)	
Hematoma progression (excluding neurological deterioration and death)‡				0.66
Spot sign positive	11//18 (61.1%)	14/21 (66.7%)	0.68 (0.17 to 2.75)	
Spot sign negative	27/75 (36.0%)	26/70 (37.1%)	0.97 (0.48 to 1.97)	
Individual components of the composite hematoma progression outcome				
Significant intraparenchymal hematoma expansion				0.42
Spot sign positive	8/18 (44.4%)	12/21 (57.1%)	0.55 (0.15 to 2.11)	
Spot sign negative	21/75 (28.0%)	20/70 (28.6%)	1.04 (0.49 to 2.21)	
Significant intraventricular hematoma expansion				0.98
Spot sign positive	6/18 (33.3%)	3/21 (14.3%)	2.56 (0.49 to 13.29)	
Spot sign negative	10/75 (13.3%)	4/70 (5.7%)	2.62 (0.75 to 9.20)	
Delayed intraventricular or subarachnoid hematoma extension				0.66
Spot sign positive	5/17 (29.4%)	3/20 (15.0%)	1.92 (0.34 to 10.67)	
Spot sign negative	16/74 (21.6%)	6/68 (8.8%)	2.99 (1.05 to 8.52)	
Neurological deterioration or death within the first 24 hours				0.64
Spot sign positive	9/21 (42.9%)	5/26 (19.2%)	2.53 (0.62 to 10.28)	
Spot sign negative	14/85 (16.5%)	9/82 (11.0%)	1.68 (0.65 to 4.34)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as percent difference (95% CI) or odds ratio (95% CI). A percent difference below 0 and an odds ratio below 1.00 favor tranexamic acid.

*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).

† In addition to above mentioned covariates treatment effect also adjusted for baseline hematoma volume.

‡ The hematoma progression outcome applied to participants with an unbiased day-2 CT or clinical scan available.

CT – computed tomography, ML – milliliter, SD – standard deviation, no. – number, CI – confidence interval.

Supplementary Table IX: Secondary safety outcome - spot sign adjudicated by the local investigators

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Any serious adverse event (at least one reported within 7 days)				0.99
Spot sign positive	14/21 (66.7%)	12/26 (46.2%)	1.94 (0.55 to 6.89)	
Spot sign negative	37/86 (43.0%)	23/82 (28.0%)	1.96 (0.99 to 3.89)	
Any safety events (at least one reported during the first 90 days)				0.92
Spot sign positive	11/21 (52.4%)	11/26 (42.3%)	1.08 (0.31 to 3.82)	
Spot sign negative	22/86 (25.6%)	17/82 (20.7%)	1.17 (0.54 to 2.51)	
Any thromboembolic events (at least one reported during the first 90 days)†				0.06
Spot sign positive	4/21 (19.0%)	1/26 (3.8%)	5.88 (0.60 to 57.30)	
Spot sign negative	3/86 (3.5%)	6/82 (7.3%)	0.46 (0.11 to 1.89)	

Data are presented as no./total no. (%). Treatment effect is presented as odds ratio (95% CI). An odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† Unadjusted effect estimates presented due to a limited number of events.
No. – number, CI – confidence interval.

Supplementary Table X: Secondary functional outcomes - spot sign adjudicated by the local investigators

Variable	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Poor functional outcome at day-90 (dichotomous modified Rankin Scale 4-6)				0.69
Spot sign positive	14/21 (66.7%)	15/26 (57.7%)	0.85 (0.19 to 3.82)	
Spot sign negative	40/86 (46.5%)	33/82 (40.2%)	1.20 (0.58 to 2.49)	
Barthel index on day-90†				0.91
Spot sign positive	34.5 (47.0) [20]	51.5 (47.2) [24]	-3.3 (-23.7 to 17.1)	
Spot sign negative	61.6 (43.9) [80]	68.5 (40.9) [79]	-1.9 (-12.6 to 8.8)	
Mortality during the first 90 days				0.49
Spot sign positive	8/21 (38.1%)	7/26 (26.9%)	1.64 (0.58 to 4.59)	
Spot sign negative	15/86 (17.4%)	11/82 (13.4%)	1.04 (0.47 to 2.27)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as mean difference (95% CI), odds ratio (95% CI) or hazard ratio (95% CI). A mean difference above 0 (Barthel index) and an odds/hazard ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† Barthel index of -5 imputed if participant died before day 90.
SD – standard deviation, no. – number, CI – confidence interval.

Supplementary Sensitivity Analysis – Generalized Estimating Equations

For the purpose of this sensitivity analysis, we used generalized estimating equation to account for clustering within levels of the stratification variable – i.e. country. For all analysis, we use an exchangeable correlation structure. Identify (continuous) or logit (dichotomous) link function is chosen as appropriate. For this sensitivity analysis, we used the same spot sign definition as in the main set of analyses.

Supplementary Table XI: Primary and composite secondary outcome – generalized estimating equations

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Primary outcome				
Day 2 CT intraparenchymal hematoma volume†				0.83
Spot sign positive	62.6 (43.5) [27] mL	51.7 (38.9) [30] mL	3.9 (-12.4 to 23.3)%	
Spot sign negative	23.6 (26.9) [80] mL	20.5 (25.6) [78] mL	1.7 (-8.2 to 12.7)%	
Day 2 CT intraparenchymal and intraventricular hematoma volume†				0.78
Spot sign positive	73.0 (52.2) [27] mL	56.6 (40.7) [30] mL	5.2 (-11.8 to 25.5)%	
Spot sign negative	26.2 (28.4) [80] mL	22.4 (26.8) [78] mL	2.1 (-8.2 to 13.5)%	
Hematoma progression (composite secondary outcome)				
Spot sign positive	19/30 (63.3%)	22/34 (64.7%)	‡	
Spot sign negative	29/93 (31.2%)	33/95 (34.7%)	‡	
Hematoma progression (excluding neurological deterioration and death)§				
Spot sign positive	17/27 (63.0%)	20/30 (66.7%)	‡	
Spot sign negative	25/80 (21.3%)	29/78 (37.2%)	‡	
Individual components of the composite hematoma progression outcome				
Significant intraparenchymal hematoma expansion				0.64
Spot sign positive	12/27 (44.4%)	17/30 (56.7%)	0.63 (0.21 to 1.89)	
Spot sign negative	21/80 (26.2%)	23/78 (29.5%)	0.86 (0.43 to 1.75)	
Significant intraventricular hematoma expansion				0.79
Spot sign positive	10/27 (37.0%)	6/30 (20.0%)	2.41 (0.69 to 8.46)	
Spot sign negative	8/80 (10.0%)	4/78 (5.1%)	1.91 (0.55 to 6.61)	
Delayed intraventricular or subarachnoid hematoma extension				0.22
Spot sign positive	11/26 (42.3%)	4/28 (14.3%)	4.74 (1.29 to 17.43)	
Spot sign negative	11/78 (14.1%)	6/75 (8.0%)	1.72 (0.65 to 4.56)	
Neurological deterioration or death within the first 24 hours				0.85
Spot sign positive	11/30 (36.7%)	9/34 (26.5%)	1.49 (0.48 to 4.68)	
Spot sign negative	17/93 (18.3%)	13/95 (13.7%)	1.29 (0.52 to 3.21)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as percent difference (95% CI) or odds ratio (95% CI). A percent difference below 0 and an odds ratio below 1.00 favor tranexamic acid.

*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).

† In addition to above mentioned covariates treatment effect also adjusted for baseline hematoma volume.

‡ Analysis failed to achieve convergence.

§ The hematoma progression outcome applied to participants with an unbiased day-2 CT or clinical scan available.

CT – computed tomography, ML – milliliter, SD – standard deviation, no. – number, CI – confidence interval.

Supplementary Table XII: Secondary safety outcome - generalized estimating equations

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Any serious adverse event (at least one reported within 7 days)				
Spot sign positive	18/30 (60.0%)	17/34 (50.0%)	†	
Spot sign negative	42/95 (44.2%)	29/95 (30.5%)	†	
Any safety events (at least one reported during the first 90 days)				0.60
Spot sign positive	14/30 (46.7%)	13/34 (38.2%)	1.19 (0.42 to 3.34)	
Spot sign negative	23/95 (24.2%)	23/95 (24.2%)	0.85 (0.43 to 1.67)	
Any thromboembolic events (at least one reported during the first 90 days)				
Spot sign positive	3/30 (10.0%)	3/34 (8.8%)	†	
Spot sign negative	4/95 (4.2%)	6/95 (6.3%)	†	

Data are presented as no./total no. (%). Treatment effect is presented as odds ratio (95% CI). An odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
No. – number, CI – confidence interval.
† Analysis failed to achieve convergence.
‡ Unadjusted effect estimates presented due to a limited number of events.

Supplementary Table XIII: Secondary functional outcomes - generalized estimating equations

Outcome	Tranexamic acid	Placebo	Treatment effect*	p for heterogeneity
Poor functional outcome at day-90 (dichotomous modified Rankin Scale 4-6)				0.49
Spot sign positive	21/30 (70.0%)	23/34 (67.6%)	0.70 (0.21 to 2.40)	
Spot sign negative	45/95 (47.4%)	37/94 (39.4%)	1.15 (0.58 to 2.30)	
Barthel index on day-90, points†				0.85
Spot sign positive	35.2 (44.6) [28]	45.3 (43.5) [32]	-0.1 (-18.2 to 18.0)	
Spot sign negative	59.4 (44.4) [89]	67.9 (42.2) [91]	-2.1 (-12.6 to 8.3)	

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Treatment effect is presented as mean difference (95% CI) or odds ratio (95% CI). A mean difference above 0 (Barthel index) and an odds ratio below 1.00 favor tranexamic acid.
*Unless otherwise indicated all effect estimates are adjusted for age (< 70 compared to ≥ 70 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points).
† Barthel index of -5 imputed if participant died before day 90.
SD – standard deviation, no. – number, CI – confidence interval.

Post-hoc Analyses – Predictive Capability of the Spot Sign

We investigated, if the spot sign predicted larger hematoma volume on day 2 scan as well as the secondary composite outcome. This analysis was not pre-planned in the statistical analysis plan. For this analysis, we used the same spot sign definition as in the main set of analyses.

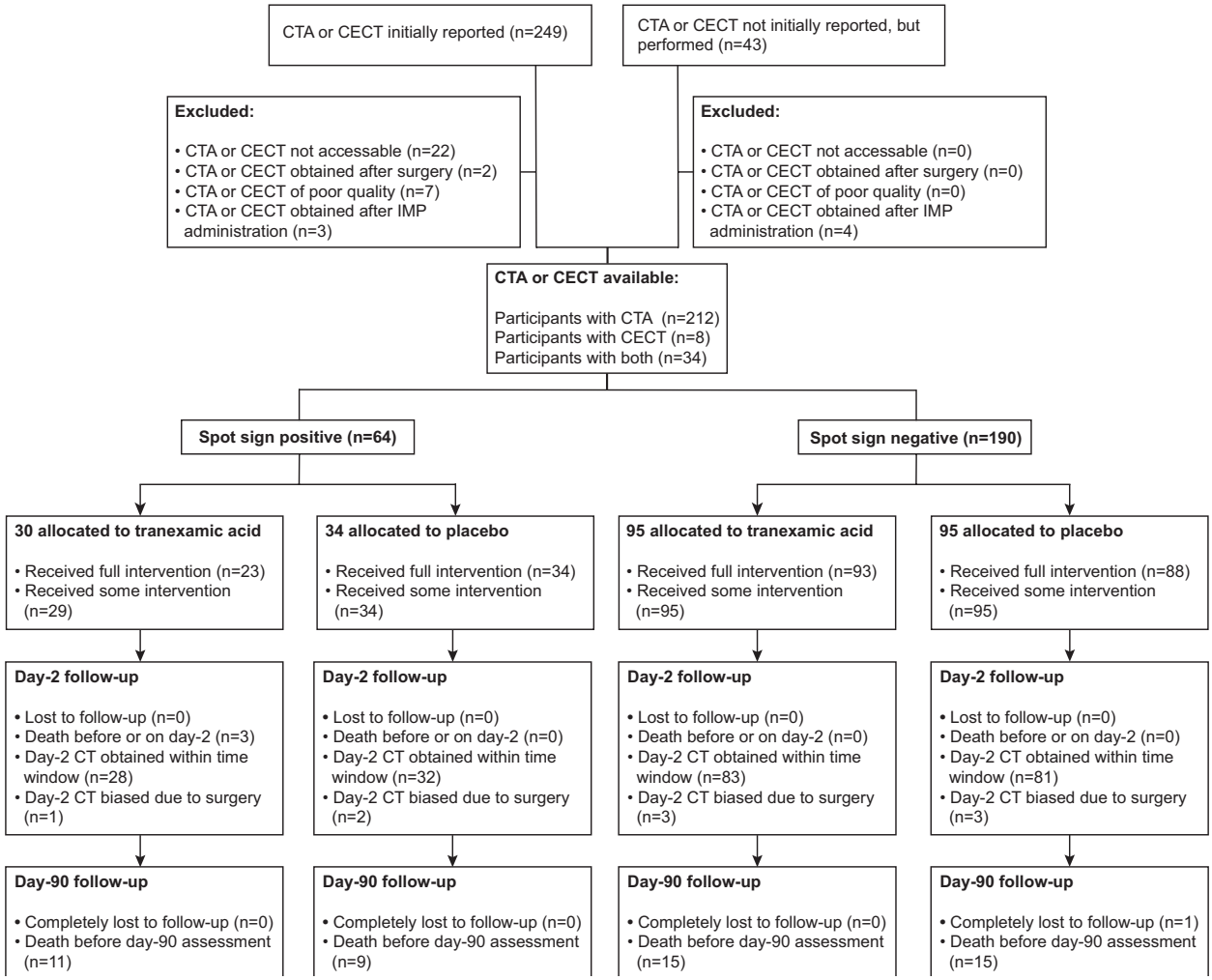
Supplementary Table XIV: Post-hoc analyses - predictive capability of the spot sign

Outcome	Spot sign positive	Spot sign negative	Effect estimate*	p-value
Day 2 CT intraparenchymal hematoma volume†	56.9 (41.2) mL [57]	22.1 (26.3) mL [158]	13.8 (1.3 to 27.8)%	0.03
Day 2 CT intraparenchymal and intraventricular hematoma volume†	64.3 (46.8) mL [57]	24.3 (27.6) mL [158]	14.8 (1.8 to 29.4)%	0.03
Hematoma progression (composite secondary outcome)	41/64 (64.1%)	62/188 (33.0%)	2.81 (1.46 to 5.41)	0.002
Hematoma progression (excluding neurological deterioration and death)‡	37/57 (64.9%)	54/158 (34.2%)	2.58 (1.26 to 5.30)	0.01
Intraparenchymal hematoma expansion	29/57 (50.9%)	44/158 (27.8%)	1.97 (0.98 to 3.96)	0.06
Significant intraventricular hematoma expansion	16/57 (28.1%)	12/158 (7.6%)	3.70 (1.40 to 9.75)	0.01
Delayed intraventricular or subarachnoid hematoma extension	15/54 (27.8%)	17/153 (11.1%)	2.06 (0.82 to 5.13)	0.12
Neurological deterioration within the first 24 hours	20/64 (31.2%)	30/188 (16.0%)	1.76 (0.85 to 3.64)	0.13

Data are presented as mean (SD) [total no.] or no./total no. (%) as appropriate. Effect estimates are presented as percent difference (95% CI) or odds ratio (95% CI).
*Unless otherwise indicated, all effect estimates are adjusted for age (continuous variable), time from onset to CTA or CECT (continuous variable), National Institute of Health Stroke Scale (continuous variable), and treatment allocation.
† In addition to above mentioned covariates; effect estimate also adjusted for baseline hematoma volume.
‡ The hematoma progression outcome applied to participants with an unbiased day-2 CT or clinical scan available.
We did not consider any of the potential interactions between the different covariates in the models plausible from a subject-matter perspective.
CT – computed tomography, ML – milliliter, SD – standard deviation, no. – number, CI – confidence interval, CTA – computed tomography angiography, CECT – contrast enhanced CT.

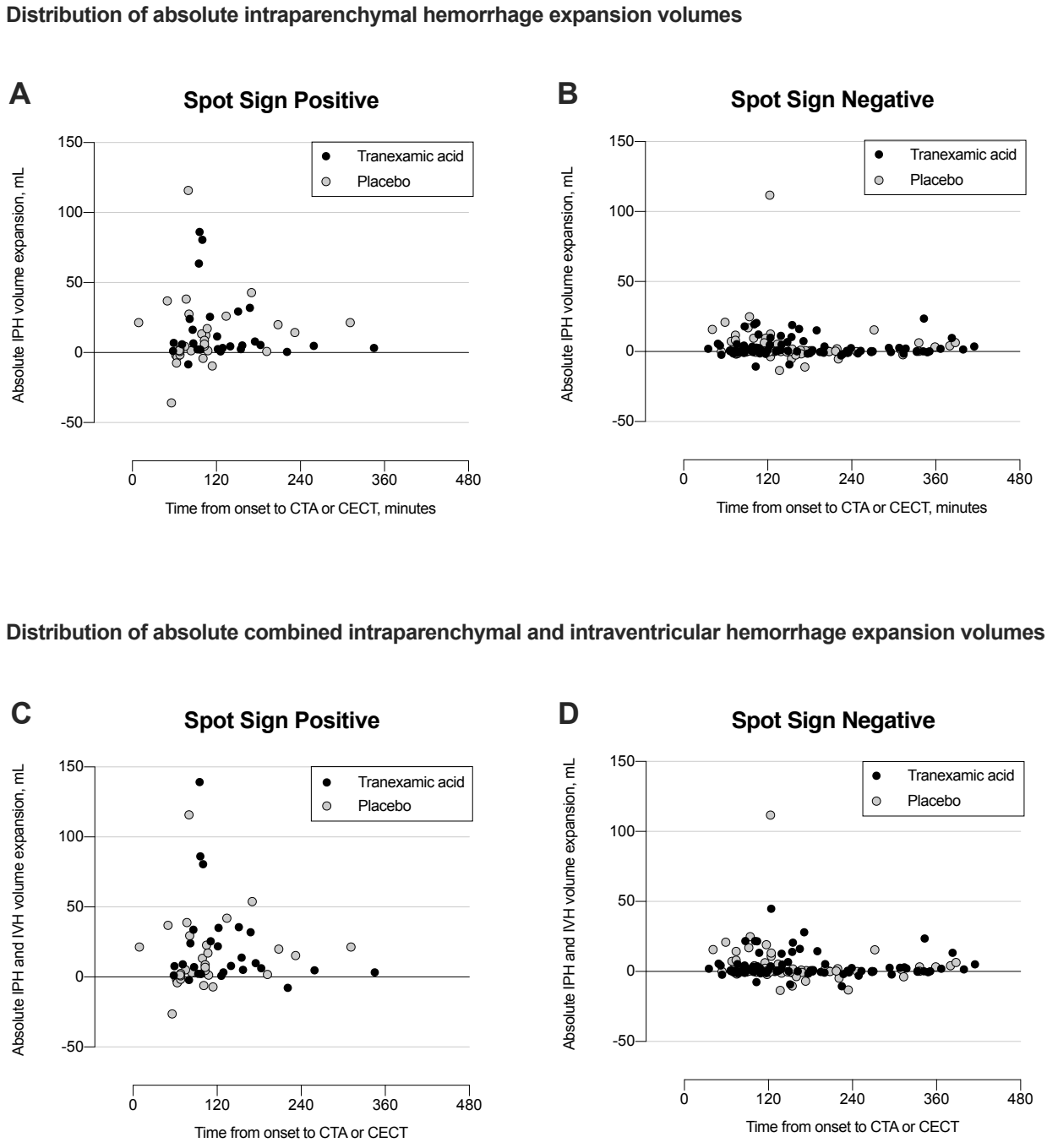
Supplemental Figures

Supplementary Figure I: Flow of Participants in the Study - CONSORT diagram



CONSORT diagram showing participant flow in the study. CT – computed tomography, CTA – CT-angiography, CECT – contrast-enhanced CT.

Supplementary Figure II: Distribution of Absolute Expansion in Hematoma Volumes for Individual Participants by Time From Onset to CT-Angiography or Contrast-Enhanced CT



Absolute change is calculated by subtracting the admission hematoma volume from the day-2 or clinical scan hematoma volume. Only participants with an unbiased day-2 or clinical scan included above. Panel A and B represent the absolute change in intraparenchymal hematoma volume against time from onset to CT-angiography or contrast-enhanced CT. Panel C and D represent the absolute change in combined intraparenchymal and intraventricular hematoma volume against time from onset to CT-angiography or contrast-enhanced CT.
ML – milliliter, IPH – intraparenchymal hematoma, IVH – intraventricular hematoma, CTA – computed tomography angiography, CECT – contrast-enhanced computed tomography.

Assumption Check – Main Analysis

This section presents the assumptions for the regression-analysis used for the main set of analysis presented in this manuscript.

Primary Analysis - Absolute intraparenchymal hematoma volume on day-2 (±12 hours) CT

Assumption 1: Linearity of continuous predictors

Due to the nature of the absolute day-2 intraparenchymal hematoma volume variable, we assume that a log-transformation (natural) might normalize the distribution of the variable. We start by checking the linearity of all the continuous predictors. To do this, we use fractional polynomials.

Supplementary Table XV: Two-dimension fractional polynomial analysis for admission hematoma volume

	Df	Deviance	Dev. dif.	p-value
Omitted	0.000	632.703	509.704	0.000
Linear	1.000	502.138	379.138	0.000
m=1 (Power 0)	2.000	125.818	2.819	0.263
m=2 (Powers 0, 2)	4.000	123.000	0.000	.

Df – degrees of freedom, Dev.dif – deviance difference

Supplementary Table XVI: One-dimension fractional polynomial analysis for admission hematoma volume

	Df	Deviance	Dev. dif.	p-value
Omitted	0.000	632.703	506.885	0.000
Linear	1.000	502.138	376.320	0.000
m=1 (Power 0)	2.000	125.818	0.000	.

Df – degrees of freedom, Dev.dif – deviance difference

As the two-term model is not significantly better than the one-term model, we chose the one-term model (logarithmic transformation)

Assumption 2: Two-way interactions

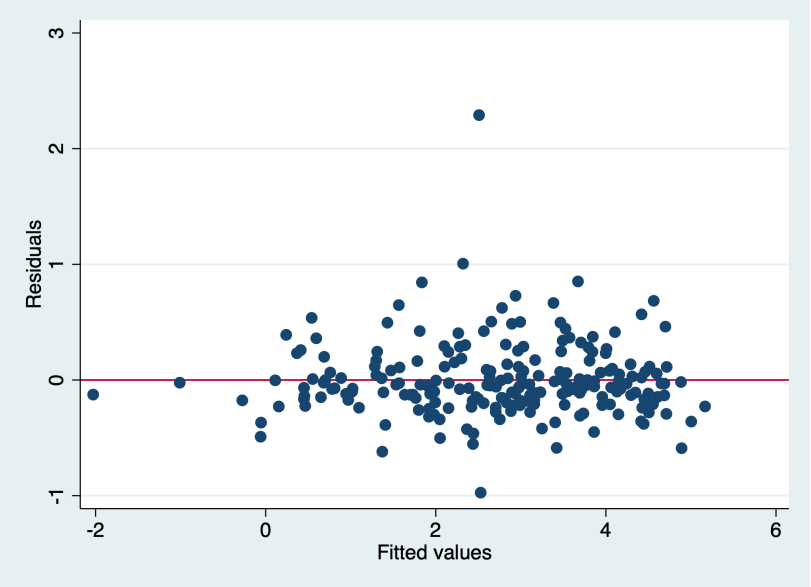
Supplementary Table XVII: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Admission hematoma volume	0.975
Age > 70 years	0.572
Admission NIHSS > 15	0.200
Time to randomization > 3 hours	0.841
Spot sign	0.845

None of the two-way interactions shows statistical significance at a 5% level.

Assumption 3: Homogeneity of variance

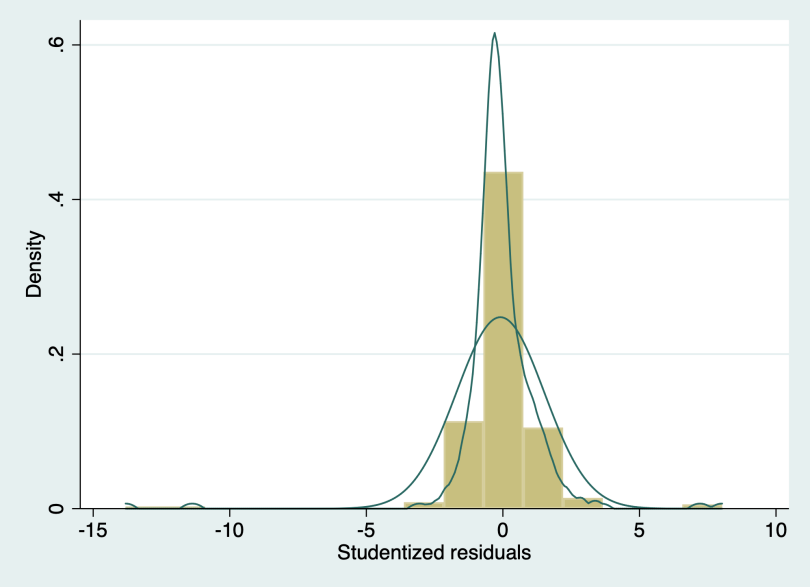
Supplementary Figure III



As the residual plot displays relatively constant shape and the p-value of the Breusch-Pagan / Cook-Weisberg test for heteroskedasticity (p=0.753) is non-significant (at a 5% level), we hold the assumption of constant variance fulfilled.

Assumption 4: Distribution of residuals

Supplementary Figure IV



As the residuals seem to follow as near-normal distribution, we hold the assumption fulfilled.

Primary Analysis - Absolute intraparenchymal and intraventricular hematoma volume on day-2 (±12 hours) CT

Assumption 1: Linearity of continuous predictors

Due to the fact that absolute day-2 intraparenchymal hematoma volume required a log-transform, we assume that a log-transform might normalize the distribution of combined intraparenchymal and intraventricular hematoma volume. We start by checking the linearity of all the continuous predictors. To do this, we use fractional polynomials.

Supplementary Table XVIII: Two-dimension fractional polynomial analysis for admission intraparenchymal and intraventricular hematoma volume

	Df	Deviance	Dev. dif.	P-value
Omitted	0.000	642.511	504.939	0.000
Linear	1.000	510.528	372.956	0.000
m=1 (Power 0)	2.000	140.089	2.517	0.303
m=2 (Powers 0, .5)	4.000	137.572	0.000	.

Df – degrees of freedom, Dev.dif – deviance difference

Supplementary Table XIX: One-dimension fractional polynomial analysis for admission intraparenchymal and intraventricular hematoma volume

	Df	Deviance	Dev. dif.	P-value
Omitted	0.000	642.511	502.422	0.000
Linear	1.000	510.528	370.439	0.000
m=1 (Power 0)	2.000	140.089	0.000	.

Df – degrees of freedom, Dev.dif – deviance difference

As the two-term model is not significantly better than the one-term model, we chose the one-term model (logarithmic transformation).

Assumption 2: Two-way interactions

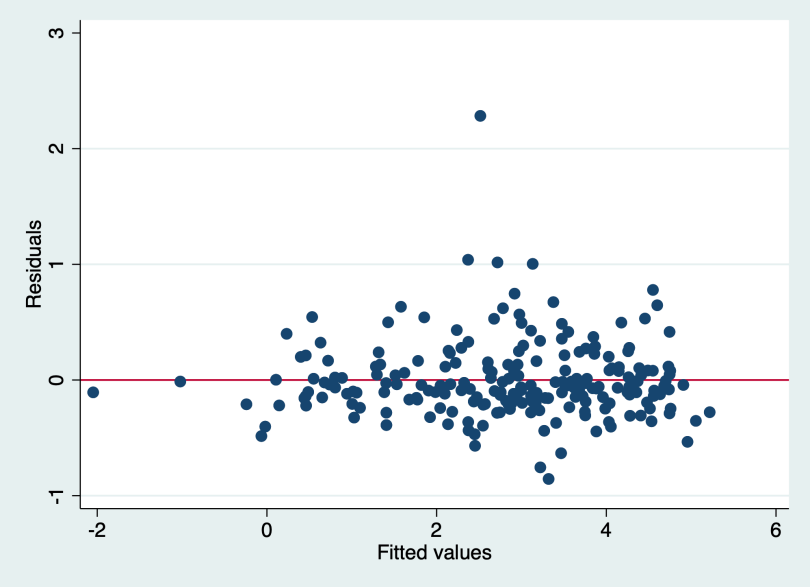
Supplementary Table XX: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Admission hematoma volume	0.764
Age > 70 years	0.442
Admission NIHSS > 15	0.235
Time to randomization > 3 hours	0.903
Spot sign	0.795

None of the two-way interactions shows statistical significance at a 5% level.

Assumption 3: Homogeneity of variance

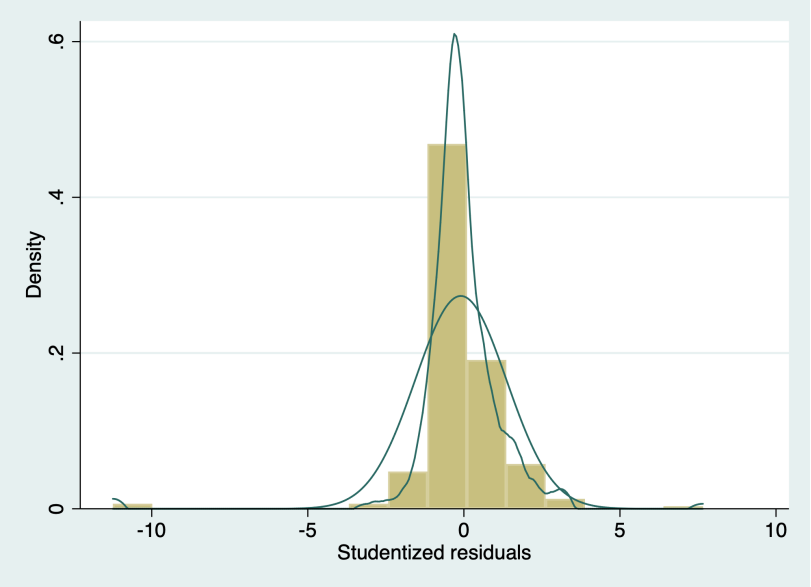
Supplementary Figure V



As the residual plot displays relatively constant shape and the p-value of the Breusch-Pagan / Cook-Weisberg test for heteroskedasticity (p=0.983) is non-significant (at a 5% level), we hold the assumption of constant variance fulfilled.

Assumption 4: Distribution of residuals

Supplementary Figure VI



As the residuals seem to follow as near-normal distribution, we hold the assumption fulfilled.

Secondary Analysis - Hematoma progression (composite secondary outcome)

Assumption 1: Two-way interactions

Supplementary Table XXI: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.839
Admission NIHSS > 15	0.273
Time to randomization > 3 hours	0.218
Spot sign	0.879

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Hematoma progression (excluding neurological deterioration and death)

Assumption 1: Two-way interactions

Supplementary Table XXII: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.512
Admission NIHSS > 15	0.162
Time to randomisation > 3 hours	0.303
Spot sign	0.799

None of the two-way interactions show statistical significance at a 5% level

Secondary Analysis - Intraparenchymal hematoma expansion (12ml or 33%) on day-2 (±12 hours) ct

Assumption 1: Two-way interactions

Supplementary Table XXIII: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.356
Admission NIHSS > 15	0.094
Time to randomization > 3 hours	0.446
Spot sign	0.634

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Intraventricular hematoma expansion (2ml) on day-2 (±12 hours) ct

Assumption 1: Two-way interactions

Supplementary Table XXIV: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.951
Admission NIHSS > 15	0.634
Time to randomization > 3 hours	0.735
Spot sign	0.814

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Delayed intraventricular or subarachnoid hemorrhagic extension on day-2 (±12 hours) ct

Assumption 1: Two-way interactions

Supplementary Table XXV: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.721
Admission NIHSS > 15	0.990
Time to randomization > 3 hours	0.150
Spot sign	0.227

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Neurological deterioration within the first 24 hours

Assumption 1: Two-way interactions

Supplementary Table XXVI: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.620
Admission NIHSS > 15	0.186
Time to randomization > 3 hours	0.639
Spot sign	0.811

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Any serious adverse events within the first 7 days

Assumption 1: Two-way interactions

Supplementary Table XXVII: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.722
Admission NIHSS > 15	0.668
Time to randomization > 3 hours	0.930
Spot sign	0.635

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Safety events during the first 90 days

Assumption 1: Two-way interactions

Supplementary Table XXVIII: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.775
Admission NIHSS > 15	0.102
Time to randomization > 3 hours	0.017
Spot sign	0.586

The time to randomization shows significant interaction with the treatment allocation. We chose to disregard this interaction as it was an isolated finding in this analysis and as it just broke the 5% significance level.

Secondary Analysis - Thromboembolic events within the first 90 days

Due to the scarce number of events, we choose not to adjust the estimates. Consequently, no formal testing of assumptions is necessary.

Secondary Analysis - Day-90 modified Rankin scale

Assumption 1: Two-way interactions

Supplementary Table XXIX: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.574
Admission NIHSS > 15	0.986
Time to randomization > 3 hours	0.799
Spot sign	0.506

None of the two-way interactions shows statistical significance at a 5% level.

Secondary Analysis - Barthel index at day-90

Assumption 1: Two-way interactions

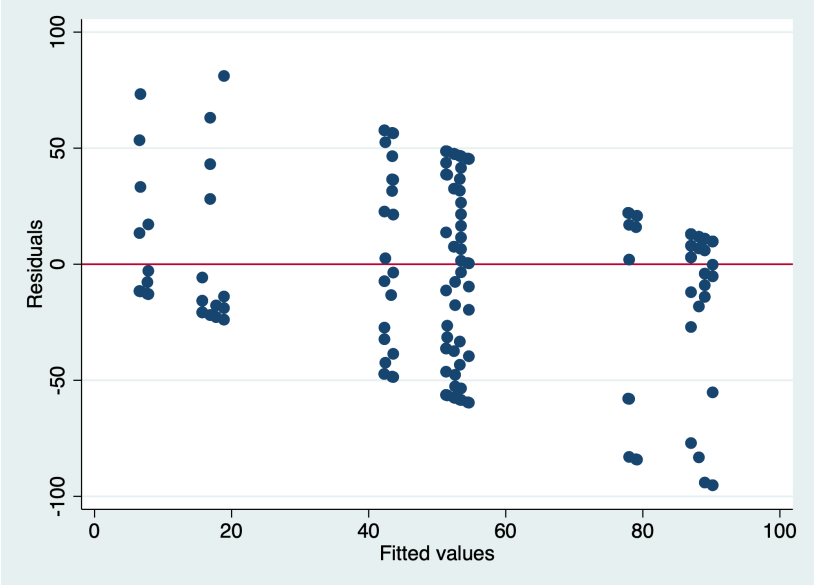
Supplementary Table XXX: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.765
Admission NIHSS > 15	0.508
Time to randomization > 3 hours	0.927
Spot sign	0.862

None of the two-way interactions shows statistical significance at a 5% level.

Assumption 2: Homogeneity of variance

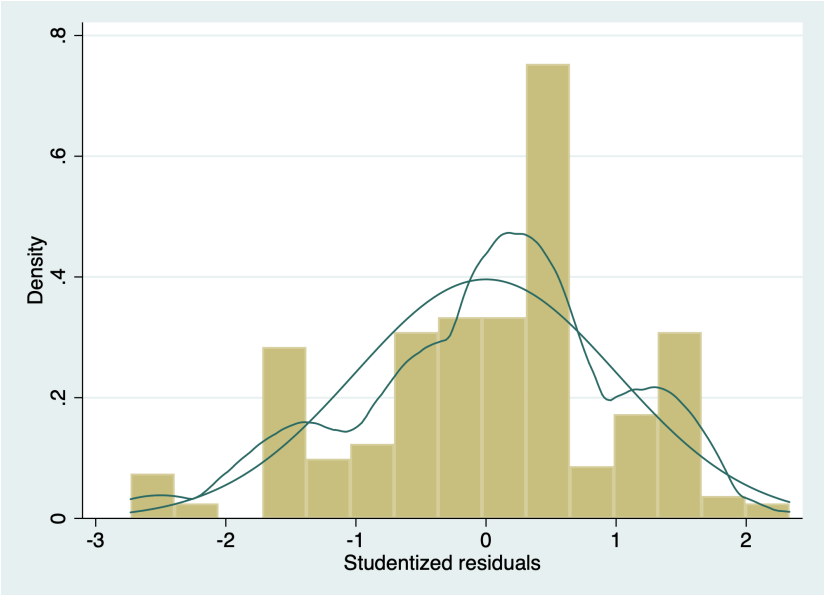
Supplementary Figure VII



As the residual plot displays relatively constant shape and the p-value of the Breusch-Pagan / Cook-Weisberg test for heteroskedasticity (p=0.460) is non-significant, we hold the assumption of constant variance fulfilled.

Assumption 3: Distribution of residuals

Supplementary Figure VIII



As the residuals seem to follow as near-normal distribution we hold the assumption fulfilled.

Secondary Analysis - Mortality within the first 90 days

Assumption 1: Two-way interactions

Supplementary Table XXXI: Significance level of the tested two-way interactions between trial intervention and covariates

	Tranexamic acid or placebo
Age > 70 years	0.773
Admission NIHSS > 15	0.034
Time to randomization > 3 hours	0.296
Spot sign	0.235

The admission NIHSS shows significant interaction with the treatment allocation. We chose to disregard this interaction as it was an isolated finding in this analysis and as it just broke the 5% significance level.

Assumption 2: Proportional hazard assumption

In order to test the proportional hazard assumption, we use a global test based on scaled Schoenfeld residuals. The null hypothesis of the test is that the regression of the scaled Schoenfeld residuals on a function of time displays a zero slope. As the test is non-significant on a 5%-level (p=0.158), we will hold the proportional hazard assumption fulfilled.