# Stroke

## CLINICAL AND POPULATION SCIENCES

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

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**BACKGROUND AND PURPOSE:** The computed tomography angiography or contrast-enhanced computed tomography based spot sign has been proposed as a biomarker for identifying on-going hematoma expansion in patients with acute intracerebral hemorrhage. We investigated, if spot-sign positive participants benefit more from tranexamic acid versus placebo as compared to spot-sign negative participants.

**METHODS:** TICH-2 trial (Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage) was a randomized, placebo-controlled clinical trial recruiting acutely hospitalized participants with intracerebral hemorrhage within 8 hours after symptom onset. Local investigators randomized participants to 2 grams of intravenous tranexamic acid or matching placebo (1:1). All participants underwent computed tomography scan on admission and on day 2 (24±12 hours) after randomization. In this sub group analysis, we included all participants from the main trial population with imaging allowing adjudication of spot sign status.

**RESULTS:** Of the 2325 TICH-2 participants, 254 (10.9%) had imaging allowing for spot-sign adjudication. Of these participants, 64 (25.2%) were spot-sign positive. Median (interquartile range) time from symptom onset to administration of the intervention was 225.0 (169.0 to 310.0) minutes. The adjusted percent difference in absolute day-2 hematoma volume between participants allocated to tranexamic versus placebo was 3.7% (95% CI, −12.8% to 23.4%) for spot-sign positive and 1.7% (95% CI, −8.4% to 12.8%) for spot-sign negative participants ($P_{heterogenity}$=0.85). No difference was observed in significant hematoma progression (dichotomous composite outcome) between participants allocated to tranexamic versus placebo among spot-sign positive (odds ratio, 0.85 [95% CI, 0.29 to 2.46]) and negative (odds ratio, 0.77 [95% CI, 0.41 to 1.45]) participants ($P_{heterogenity}$=0.88).

**CONCLUSIONS:** Data from the TICH-2 trial do not support that admission spot sign status modifies the treatment effect of tranexamic acid versus placebo in patients with acute intracerebral hemorrhage. The results might have been affected by low statistical power as well as treatment delay.

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**Key Words:** angiography ▪ cerebral hemorrhage ▪ computed tomography angiography ▪ hematoma ▪ tranexamic acid

I ntraparenchymal hematoma expansion is widely recognized as a target for therapeutic interventions aiming at improving the outcome in patients with spontaneous intracerebral hemorrhage.[1] Recent studies have indicated that the risk of hematoma expansion is greatest during the first hours after symptom onset and gradually

> ## Nonstandard Abbreviations and Acronyms
>
> **aPD**     adjusted percent difference
> **CT**       computed tomography
> **IMP**     investigational medicinal product
> **OR**       odds ratio
> **TICH-2**  Tranexamic Acid for Hyperacute Primary
>              Intracerebral Haemorrhage

decreases during the first 24 hours.[2,3] Hematoma expansion is known to occur after hospital admission in about 30% of patients with acute intracerebral hemorrhage[2] and has been causally linked to neurological deterioration during admission,[4] early mortality, and poor functional outcome at 90 days.[5]

In the TICH-2 trial (Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage; published in 2018),[6] as well as in previous trials randomizing anticoagulation-naive participants with acute spontaneous intracerebral hemorrhage to hemostatic agents versus placebo,[7,8] it has been shown that while hematoma expansion could be limited to some extent, improvement in day-90 functional outcome has not yet been demonstrated. As previous trials have not been able to demonstrate that administration of hemostatic agents improve functional outcome in a relatively wide selection of participants with intracerebral hemorrhage, selective administration of hemostatic agents to participants at a high risk of hematoma expansion has been suggested.[9] The hypothesis behind this proposal being that only patients with hematoma expansion will benefit from hemostatic agents.

One, repeatedly proposed biomarker for hematoma expansion is the spot sign on computed tomography (CT)-angiography or contrast-enhanced CT. The spot sign is assumed to represent active leakage of contrast-enriched blood into the hematoma[10,11] and has in several independent studies been found to be a powerful predictor of hematoma expansion.[10,12] As spot-sign positive patients are believed to harbor ongoing hematoma expansion, it has been hypothesized that these patients would experience a greater benefit from administration of hemostatic agents compared to spot-sign negative patients. To date, 3 smaller clinical trials have randomized spot-sign positive participants to hemostatic agents versus placebo. Unfortunately, overall neutral results on the prevention of hematoma expansion have been presented.[13,14] In this prespecified TICH-2 subgroup analysis, we aimed to investigate, whether participants with a spot sign on admission scan would experience greater benefit from acute administration of tranexamic acid versus placebo compared to spot-sign negative participants.

## METHODS

This study is a prespecified subgroup analysis of the TICH-2 trial. Before locking the main TICH-2 trial database, a statistical analysis plan for this subgroup analysis was submitted for publication.[15] The design, statistical analysis, and main results of the TICH-2 trial have previously been published.[6,16–18] In short, the TICH-2 trial was a pragmatic, randomized, parallel, placebo-controlled, phase III clinical trial powered to assess the hypothesis that administration of 2 grams of tranexamic acid versus matching placebo to noncomatose (Glasgow Coma Scale score ≥5) patients with presumed spontaneous intracerebral hemorrhage within 8 hours after symptom onset (or last seen well) would cause a more favorable functional outcome at day 90.

### Participants

The complete list of inclusion and exclusion criteria has previously been published.[18] Informed consent was obtained in accordance with national legislation. After publication of the preplanned primary and secondary analyses, the deidentified individual participant trial data, accompanying meta-data and statistical analytic code can be shared upon reasonable request to the corresponding author and the TICH-2 trial steering committee.

In the present subgroup analysis, we included all participants from the TICH-2 main trial population having either CT-angiography or contrast-enhanced CT performed before administration of the first dose of the investigational medicinal product (IMP). No constraints regarding scanner settings or radiological scanning protocol for the CT-angiography or contrast-enhanced CT were imposed, but the scanning needed to cover the entire hematoma, and the qualifying scan had to be available for central spot sign adjudication. CT-angiography or contrast-enhanced CT not covering the entire hematoma were accepted, if a spot sign fulfilling the definition below was present on the included slides.

After 24 hours (±12 hours), the participant underwent day-2 noncontrast CT and physical examination (National Institutes of Health Stroke Scale and Glasgow Coma Scale). All serious adverse events, as defined by the International Conference on Harmonization Guideline for Good Clinical Practice,[16,18] were reported by local investigators until day seven after randomization. Predefined safety events (death, thromboembolism [arterial and venous], or seizures) were reported until day 90. At day 90, a telephone or postal interview was conducted assessing mortality status, safety outcomes after discharge, and functional outcome (modified Rankin Scale and Barthel Index).

Two central adjudicators (Drs Ovesen and Dineen) independently adjudicated CT-angiograms and contrast-enhanced CTs for presence of a spot sign. Differences were resolved by discussion. The trial database had been unblinded at the time of spot sign adjudication, but the 2 central adjudicators were blinded to treatment allocation of the participants during spot sign adjudication sessions.

On CT-angiography, we defined the spot sign as at least one element with either serpiginous or spot-like appearance, >1.5 mm in diameter (maximal dimension), at least double density (Hounsfield unit) compared to background hematoma, and located within the margin of the parenchymal hematoma without connection to outside vessels.[15,19] On contrast-enhanced

CT (postcontrast sequence), we defined the spot sign as at least one hyperdensity (relative to the hematoma) within the hematoma indicative of contrast extravasation on postcontrast imaging (not present on precontrast CT).[15,20] In addition local investigators were asked to report the presence or absence of the spot sign on the randomization case-record form. The local investigators were not asked to comply with any predefined definition of the spot sign.

Blinded radiological assessment and volume measurements of admission and day-2 CTs have previously been described.[6] In short, the local sites were required to send the conducted radiological examinations to the trial office for blinded radiological adjudication. All hematoma volumes (intraventricular and intraparenchymal) were measured using semi-automated segmentation. The segmentation was performed using the active contour tool in the ITK-SNAP software (version 3.6, www.itksnap.org). One of 3 assessors did manual controlling and editing of the contours to ensure the best fit to the segmented structure.[6] Four noncontrast scans were adjudicated by Dr Ovesen, as they were not adjudicated by central radiological adjudication.

## Outcomes

All participants were included in the primary outcome analysis, provided they had an unbiased day-2 CT performed within 24±12 hours after randomization. A biased CT was defined as a CT obtained after any surgical procedure potentially influencing either the intraparenchymal or intraventricular hematoma volume (radiological signs of surgery on CT). If no unbiased day-2 CT performed within the time-window was available, an unbiased CT obtained after randomization, but before the day-2 time-window (clinical scan), was included if available.

The primary outcome was absolute day-2 intraparenchymal hematoma volume. We also analyzed the primary outcome as the combined day-2 intraparenchymal and intraventricular hematoma volume.

The first secondary outcome included dichotomous hematoma progression defined as a composite of either intraparenchymal hematoma expansion (≥6 mL absolute or 33% relative expansion), delayed intraventricular or subarachnoid extension, or intraventricular hematoma expansion (≥2 mL absolute expansion).[15] All the elements of the dichotomous hematoma progression outcome were evaluated on the day-2 CT with admission CT as reference. Delayed intraventricular or subarachnoid extension were defined as extension not present on admission CT—but supervened on day-2 CT. If no unbiased day-2 CT or clinical scan were available, early neurological deterioration or death occurring between admission and day 2 were regarded as hematoma progression. Neurological deterioration was defined as either a ≥4 points National Institutes of Health Stroke Scale increase, a ≥2 points Glasgow Coma Scale decrease, or a decrease in neurological performance leading to intubation or neurosurgical intervention documented in a serious adverse event report.

Other secondary outcomes included serious adverse events within the first seven days, safety events until day 90, thromboembolic events until day 90, poor functional outcome at day 90 (modified Rankin Scale score, 4–6), Barthel index at day 90, and mortality until day 90.[15]

Due to the heterogeneous methodology concerning CT-angiography and contrast-enhanced CT among the local centers, we conducted the following sensitivity analyses according to the spot-sign status: (1) on CT-angiography only (excluding postcontrast sequences) and (2) as reported by the local investigators.

## Statistical Analysis

The final sample size of this subgroup analysis was determined by enrollment into the TICH-2 trial. We prospectively estimated that if 54 spot-sign positive participants were enrolled in the primary outcome analysis, a mean difference in follow-up hematoma volume between participants allocated to tranexamic acid versus placebo of 10 mL (SD, 17 mL) would yield a power of 84.4%.[15] Interrater reliability was analyzed using Cohen κ. In all outcome analyses, the relative intervention effect (tranexamic acid versus placebo) among spot-sign positive and negative participants respectively was calculated from a regression model containing spot-sign status (yes/no) and trial intervention as main effects in addition to the multiplicative interaction between the 2. The heterogeneity of treatment effect between spot-sign positive and negative participants was judged by the statistical significance of the interaction term. We chose to adjust all outcome analyses for participant age, time from onset to randomization, and National Institutes of Health Stroke Scale, as these are important prognostic factors and are used as minimization factors during the allocation process.[18] The primary outcome analysis was in addition to the previously mentioned covariates also adjusted for admission hematoma volume (admission intraparenchymal hematoma volume for the day-2 intraparenchymal hematoma volume analysis and combined admission intraparenchymal and intraventricular hematoma volume for the day-2 combined intraparenchymal and intraventricular hematoma volume analysis). As preplanned in the statistical analysis plan, we chose to abstain from adjusting for all minimization or stratification factors due to the risk of overfitting.[15] In the published statistical analysis plan, we inadvertently prespecified to adjust for time from onset to treatment, but chose to replace this with time from onset to randomization, as this covariate was used as minimization factor.[15] We repeated all main analyses adjusting for time from onset to treatment, and the results were similar. The primary outcome was analyzed by linear regression, dichotomous secondary outcomes by logistic regression, and time-to-death by Cox proportional hazard model.[15] As the dependent variable in the primary outcome analysis (day-2 hematoma volume) was log-transformed (natural logarithm), parameters in the regression analysis were interpreted as adjusted percent difference (aPD) in geometric means. We tested the model assumptions as specified in the analysis plan (Assumption Check - Main Analysis in the Data Supplement).[15] Due to the tendency for participants in clinical trials to cluster within stratification units (ie, country), we conducted a sensitivity analysis taking clustering within countries into account by use of generalized estimating equations. All analyses were conducted as intention-to-treat analyses. We used a nominal statistical significance level of 5% in all analyses. All statistical analyses were carried out in Stata 15.1 (StataCorp, TX).

## RESULTS

Of the total 2325 participants in the TICH-2 trial population, 254 (10.9%) participants from seven countries had a CT-angiography or a contrast-enhanced CT allowing spot

sign adjudication (Figure I in the Data Supplement). The 254 participants were generally comparable to the rest of the TICH-2 population (Table I in the Data Supplement), but the median (interquartile range) time from onset to IMP administration was shorter among participants with CT-angiography or contrast-enhanced CT compared to the rest of the TICH-2 population (225.0 [169.0 to 310.0] compared to 245.0 [180.0 to 334.0] minutes). We found 64 (25.2%) participants were spot-sign positive. Between the 2 central spot sign adjudicators (Drs Ovesen and Dineen), a good interrater agreement for spot sign on CT-angiography ($\kappa$, 0.82 [95% CI, 0.74 to 0.91]) was observed. The agreement between the 2 central adjudicators and the investigators at the sites was fair ($\kappa$, 0.57 [95% CI, 0.44 to 0.70]). The overall median (interquartile range) delay from symptom onset to CT-angiography or contrast-enhanced CT was 123.0 (89.0 to 190.0) minutes and from CT-angiography or contrast-enhanced CT to IMP administration 76.0 (57.0 to 118.0) minutes. The baseline data were generally well balanced between allocation groups within spot-sign positive and negative participants (Table 1). However, spot-sign positive participants allocated to tranexamic acid had longer median (interquartile range) delay from symptom onset to IMP administration (210.0 [159.0 to 270.0] minutes versus 169.0 [141.0 to 231.0] minutes), and larger mean (SD) admission hematoma volumes (46.0 [31.9] versus 38.4 [27.6] mL) compared to placebo participants.

In total, 215 participants were available for analysis of the primary outcome (Figure 1). Day-2 hematoma volume was comparable between spot-sign positive participants allocated to tranexamic acid versus placebo (aPD, 3.7% [95% CI, −12.8% to 23.4%]). The same was true for spot-sign negative participants (aPD, 1.7% [95% CI, −8.4% to 12.8%]; $P_{heterogeneity}$=0.85). Looking at the combined intraparenchymal and intraventricular hematoma volumes, comparable results were observed with no statistically significant difference among spot-sign positive participants (aPD, 5.0% [95% CI, −12.2% to 25.6%]) or spot-sign negative participants (aPD, 2.1% [95% CI, −8.3% to 13.8%]; $P_{heterogeneity}$=0.80). Absolute and relative expansion in hematoma volumes from admission to day-2 (or clinical scan) are available in Table II in the Data Supplement. The distribution of time from onset to CT-angiography or contrast-enhanced CT against absolute hematoma expansion is presented in Figure II in the Data Supplement. A visual tendency can be observed towards participants experiencing major hematoma expansions also having short time from onset to CT-angiography or contrast-enhanced CT.

We observed no difference in the odds of participants experiencing the composite hematoma progression outcome between allocation groups among spot-sign positive (adjusted odds ratio [OR], 0.85 [95% CI, 0.29 to 2.46]) or spot-sign negative participants (adjusted OR, 0.77 [95% CI, 0.41 to 1.45]; $P_{heterogeneity}$=0.88; Figure 2). When assessing the individual components of the composite outcome, no differences were observed between participants allocated to tranexamic versus placebo within spot-sign positive or negative participants, respectively, with the exception of delayed intraventricular or subarachnoid hemorrhagic extension among spot-sign positive participants (adjusted OR, 5.23 [95% CI, 1.28 to 21.33]; Figure 2).

During the first seven days, 144 serious adverse events occurred in 106 participants, and during the first 90 days, 88 safety events occurred in 73 participants. No statistically significant differences in the odds of serious adverse events, safety outcomes, or thromboembolic events between allocation groups among spot-sign positive or negative participants were observed (Table III in the Data Supplement). At day 90, one participant had been completely lost to follow-up and censored at discharge from hospital. No differences in modified Rankin Scale, Barthel Index, or survival were observed between the allocation groups among spot-sign positive or negative participants (Table IV in the Data Supplement).

The sensitivity analyses of the CT-angiography-based spot sign alone or spot sign status as reported by the local investigators reached comparable results as those presented above (Tables V through X in the Data Supplement). The same was true for the sensitivity analysis taking clustering into account (Tables XI through XIII in the Data Supplement). In a post hoc analysis of the spot signs predictive capability, we affirmed its ability to be an independent predictor of larger day-2 hematoma volume (aPD, 13.8% [95% CI, 1.3% to 27.8%]) as well as hematoma progression (adjusted OR, 2.81 [95% CI, 1.46 to 5.41]; Table XIV in the Data Supplement).

## DISCUSSION

In this prespecified subgroup analysis of the TICH-2 trial, we were not able to demonstrate that the presence of a spot sign modified the treatment effect of tranexamic acid versus placebo. We were also not able to demonstrate that tranexamic acid could reduce the odds of hematoma progression among spot-sign positive or negative participants. These conclusions were robust when considering the CT-angiography-based spot sign alone and when the investigator reported spot sign was used. We further demonstrated that the spot sign can be reliably adjudicated and that the addition of advanced radiological imaging (CT-angiography and contrast-enhanced CT) was not associated with a longer time to IMP compared to the rest of the TICH-2 population.

The primary limitation of this subgroup analysis is the low degree of statistical power due to the relatively few participants. This makes a firm conclusion of no treatment effect of tranexamic acid among spot-sign positive or negative participants premature.

Another major limitation of this subgroup analysis is the fact that the overall median delay from CT-angiography or contrast-enhanced CT to administration of the
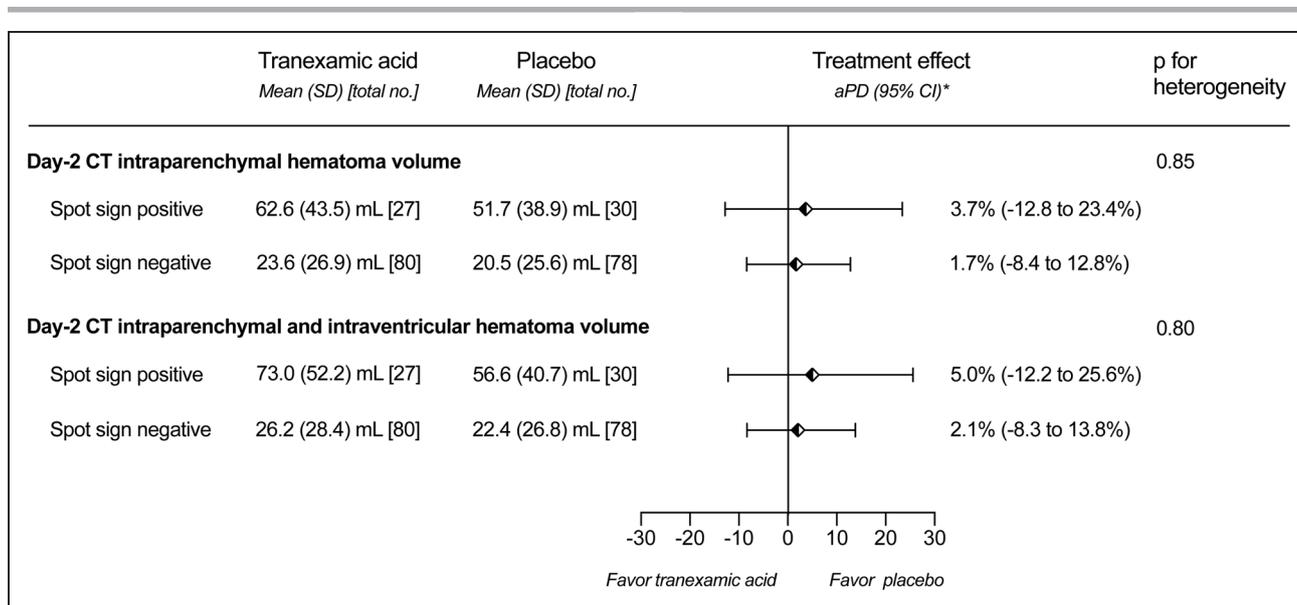
**Table.  Baseline Characteristics**

| | Spot sign positive | | Spot sign negative | |
|---|---|---|---|---|
| | Tranexamic acid (n=30) | Placebo (n=34) | Tranexamic acid (n=95) | Placebo (n=95) |
| Age, y | 66.5 (14.9) | 63.1 (14.4) | 65.8 (14.1) | 61.2 (13.2) |
| Sex, male | 19 (63.3%) | 18 (52.9%) | 56 (58.9%) | 60 (63.2%) |
| Ethnic origin | | | | |
| White | 27 (90.0%) | 27 (79.4%) | 73 (76.8%) | 77 (81.1%) |
| Other | 3 (10.0%) | 7 (20.6%) | 22 (23.2%) | 18 (18.9%) |
| Onset to CTA or CECT, min | 107.0 (88.0–155.0) | 100.0 (68.0–134.0) | 143.0 (99.0–237.0) | 124.0 (92.0–201.0) |
| Onset to randomization, min | 178.0 (136.0–231.0) | 152.0 (122.0–218.0) | 214.0 (156.0–333.0) | 213.0 (157.0–284.0) |
| Onset to IMP administration, min | 210.0 (159.0–270.0) | 169.0 (141.0–231.0) | 231.0 (180.0–366.0) | 240.0 (176.0–309.0) |
| ≤3 h | 12 (41.4%) | 20 (58.8%) | 24 (25.3%) | 25 (26.3%) |
| ≤4.5 h | 22 (75.9%) | 28 (82.4%) | 53 (55.8%) | 57 (60.0%) |
| CTA or CECT to IMP administration, min | 72.0 (44.0–131.0) | 61.0 (42.0–111.0) | 90.0 (57.0–125.0) | 76.0 (63.0–116.0) |
| Antiplatelet therapy on admission | 9 (30.0%) | 8 (23.5%) | 25 (26.3%) | 16 (16.8%) |
| Statin therapy on admission | 4 (13.8%) | 9 (27.3%) | 25 (26.6%) | 18 (19.1%) |
| History of ischemic stroke or TIA | 4 (13.3%) | 4 (12.1%) | 10 (10.6%) | 8 (8.6%) |
| History of ischemic heart disease | 2 (6.9%) | 3 (9.1%) | 10 (10.8%) | 6 (6.5%) |
| History of thromboembolism | 0 (0%) | 0 (0%) | 2 (2.2%) | 1 (1.1%) |
| Prestroke modified Rankin Scale | 0.0 (0.0–1.0) | 0.0 (0.0–0.0) | 0.0 (0.0–1.0) | 0.0 (0.0–0.0) |
| Admission GCS score | 14.0 (10.0–15.0) | 15.0 (11.0–15.0) | 15.0 (13.0–15.0) | 15.0 (13.0–15.0) |
| Admission NIHSS score | 18.0 (14.0–19.0) | 16.5 (11.0–21.0) | 10.0 (6.0–16.0) | 10.0 (5.0–18.0) |
| Systolic blood pressure, mm Hg | 172.8 (30.9) | 178.9 (31.5) | 171.7 (25.6) | 180.0 (32.7) |
| Diastolic blood pressure, mm Hg | 93.4 (17.7) | 97.6 (21.8) | 93.3 (16.6) | 98.7 (19.6) |
| Hematoma location | | | | |
| Supratentorial lobar | 12 (40.0%) | 12 (35.3%) | 30 (31.6%) | 20 (21.1%) |
| Supratentorial deep | 16 (53.3%) | 20 (58.8%) | 55 (57.9%) | 64 (67.4%) |
| Infratentorial | 2 (6.7%) | 1 (2.9%) | 7 (7.4%) | 8 (8.4%) |
| Combination | 0 (0%) | 1 (2.9%) | 3 (3.2%) | 3 (3.2%) |
| Admission intraparenchymal hematoma volume, mL | 46.0 (31.9) | 38.4 (27.6) | 22.5 (25.8) | 17.6 (21.4) |
| Admission intraventricular hemorrhagic extension | 6 (20.0%) | 14 (41.2%) | 23 (24.2%) | 22 (23.2%) |
| Combined admission intraparenchymal and intraventricular hematoma volume, mL | 50.5 (31.5) | 42.9 (29.2) | 24.8 (27.0) | 19.6 (23.1) |
| Admission subarachnoid hemorrhagic extension | 5 (16.7%) | 7 (20.6%) | 14 (14.7%) | 6 (6.3%) |

Data are mean (SD), median (IQR), or number (%). CECT indicates contrast-enhanced CT; CT, computed tomography; CTA, CT-angiography; GCS, Glasgow Coma Scale; IMP, investigational medicinal product; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

IMP was 76 minutes. It is likely that we should perceive the spot sign as a radiological snapshot visualization of an ongoing bleeding episode.[11] Since hematoma expansion is likely to be a multifactorial process driven by factors such as admission hematoma size,[2] blood pressure,[21] and coagulation disturbances,[2] it is difficult to predict how long this ongoing bleeding episode will continue after demonstration of the spot sign. An immediate administration of tranexamic acid, after demonstration of the spot sign, would consequently yield the greatest theoretical benefit. This delay between qualifying imaging and administration of the hemostatic agent was also observed in the SPOTLIGHT and STOP-IT trials, and when contemplating the neutral results of these trials it is important to include the possibility that the relative

extensive treatment delay (≈70 minutes) between baseline CT and IMP administration might have influenced the ability of the IMP to limit hematoma expansion.[13]

In addition to the delay from CT-angiography or contrast-enhanced CT to administration of the IMP, we also observed a relative long overall treatment delay from symptom onset to administration of the IMP. The overall median delay from symptom onset to administration of the IMP was 225 minutes. It is possible that this treatment delay was too extensive as the probability of hematoma expansion has been proposed to decrease rapidly within the first hours after symptom onset.[2] This is supported by a post hoc analysis from the FAST trial (The Factor Seven for Acute Hemorrhagic Stroke) indicating an enhanced treatment benefit, if time to treatment is below 150

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| | Tranexamic acid | Placebo | Treatment effect | p for heterogeneity |
|---|---|---|---|---|
| | Mean (SD) [total no.] | Mean (SD) [total no.] | aPD (95% CI)* | |
| **Day-2 CT intraparenchymal hematoma volume** | | | | 0.85 |
| Spot sign positive | 62.6 (43.5) mL [27] | 51.7 (38.9) mL [30] | 3.7% (−12.8 to 23.4%) | |
| Spot sign negative | 23.6 (26.9) mL [80] | 20.5 (25.6) mL [78] | 1.7% (−8.4 to 12.8%) | |
| **Day-2 CT intraparenchymal and intraventricular hematoma volume** | | | | 0.80 |
| Spot sign positive | 73.0 (52.2) mL [27] | 56.6 (40.7) mL [30] | 5.0% (−12.2 to 25.6%) | |
| Spot sign negative | 26.2 (28.4) mL [80] | 22.4 (26.8) mL [78] | 2.1% (−8.3 to 13.8%) | |

-30  -20  -10   0   10   20   30

Favor tranexamic acid        Favor placebo

**Figure 1. Figure is showing the primary outcome analyses expressed as the adjusted percent difference between allocation groups.**
*Treatment effect adjusted for admission hematoma volume, age (<70 compared to ≥70 y), time from onset to randomization (<3 compared to ≥3 h) and National Institutes of Health Stroke Scale (<15 compared to ≥15 points). aPD indicates adjusted percent difference; CT, computed tomography; and no, number of participants.

minutes,[9] as well as data from the STOP-AUST trial (The Spot Sign and Tranexamic Acid On Preventing ICH Growth - Australasia Trial)[14] where administration of tranexamic acid versus placebo to spot-sign positive participants within 3 hours after symptom onset was associated with a nonsignificant trend towards lower odds of hematoma expansion compared to >3 hours. In the STOP-AUST trial, the importance of short duration between symptom onset and administration of the hemostatic agent was further emphasized by a post hoc analysis of participants receiving treatment within 2 hours after symptom onset which demonstrated an impressively small, but nonsignificant, OR towards hematoma expansion.[14] The importance of early treatment is further supported by the data from the CRASH-3 trial (Clinical Randomisation of an Antifibrinolytic in Significant Head Injury) demonstrating efficacy of tranexamic acid among participants with mild to moderate traumatic brain injury when treated within 3 hours.[22]

A further limitation of the present subgroup analysis is the possible heterogeneity of the CT-angiography protocols employed at the different local sites. The CT-angiograms obtained in the TICH-2 centers were predominantly single-pass scans, and no constraints were imposed on the scanning protocol or scanner settings, which might have impacted the detection of the spot sign. Previous studies have indicated that especially the contrast-phase, during which the CT-angiography has been obtained,[23,24] can affect the spot sign prevalence and its predictive capability.

We observed statistically significant higher odds of delayed intraventricular or subarachnoid hemorrhagic extension among spot-sign positive participants allocated to tranexamic acid compared to placebo. This finding is

difficult to explain, and it is likely that this is a chance finding owing to the relatively low numbers of events and inflation of the type 1 error by multiple significance tests.

Our present study has several strengths. First, our methodology was predefined in detail and published before the analysis began.[15] Furthermore, both spot-sign positive and negative participants were treated within the same trial protocol. This allows us to directly compare benefits and risks of tranexamic acid between spot-sign positive and negative participants. Another important strength is that the population undergoing CT-angiography or contrast-enhanced CT did not seem to be vastly different from the rest of the TICH-2 population. The good interrater agreement between the central adjudicators of the spot sign is encouraging, as it demonstrates its reproducible nature. Previous studies have reported heterogeneous interrater agreements varying with study setting and experience of the observers.[12,25,26]

Although our subgroup analysis is limited by low statistical power, the results presented in this article could be used to promote further hypothesis generation. It is our hope that this study can be used in comparisons and meta-analyses with other published trials using spot sign to guide administration of hemostatic therapy.

## CONCLUSIONS

In this TICH-2 subgroup analysis, we were not able to demonstrate that the presence of a spot sign modified the treatment effect of tranexamic acid versus placebo. The results might, however, have been affected by low statistical power as well as treatment delay. Further
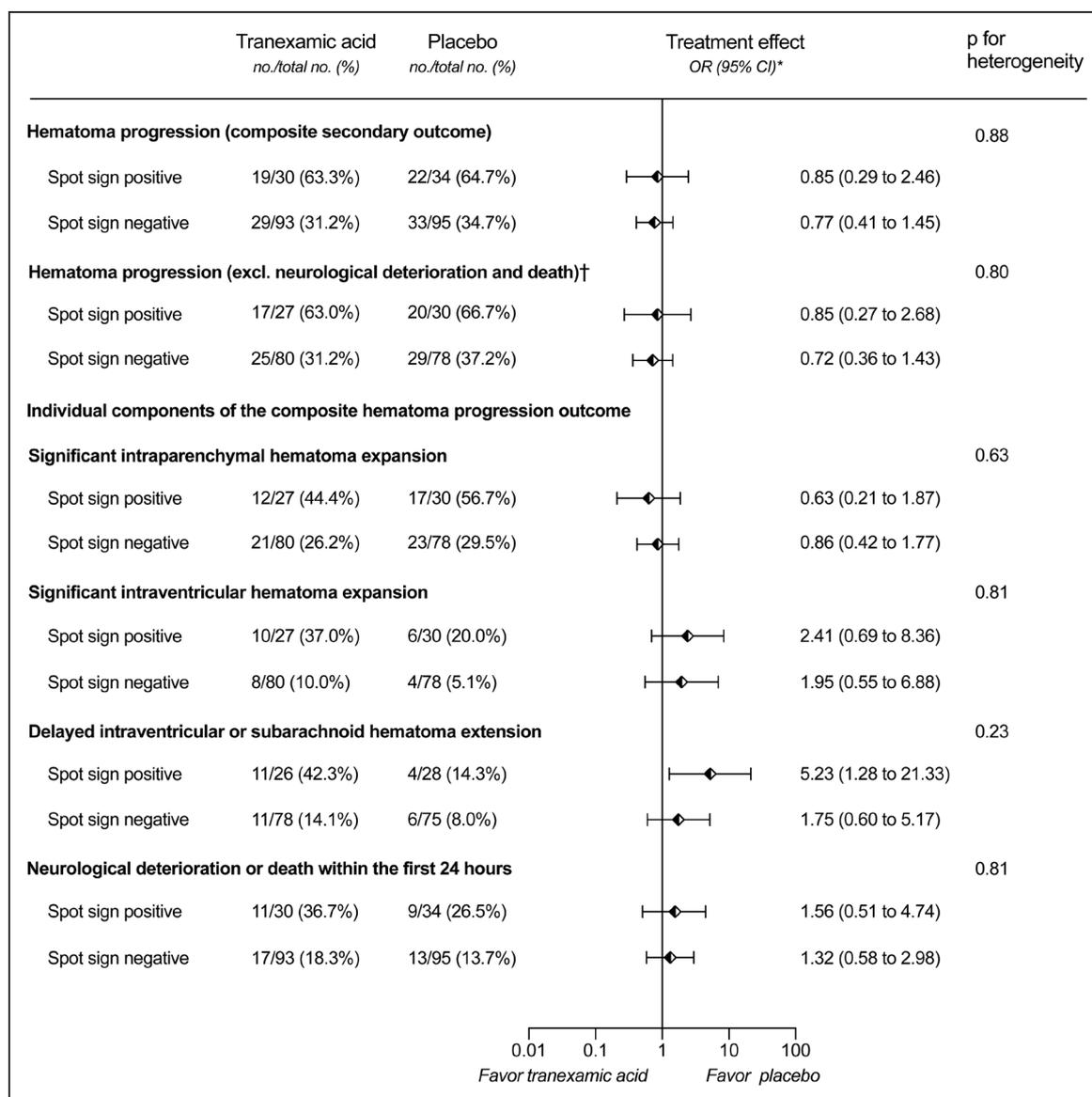
**Figure 2. Figure is showing the secondary hematoma progression outcome measure and its components.**
*Treatment effect adjusted for admission hematoma volume, age (<70 compared to ≥70 y), time from onset to randomization (<3 compared to ≥3 h) and National Institutes of Health Stroke Scale (<15 compared to ≥15 points). †The hematoma progression outcome applied to participants with an unbiased day-2 CT or clinical scan available. CT indicates computed tomography; no, number of participants; and OR, odds ratio,

research is needed to determine the role of the spot sign in guiding early administration of hemostatic agents.

## Affiliations

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### Supplemental Materials

Online Tables I–XIV
Online Figures I and II
Assumption Check–Main Analysis

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