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

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Abstract

Background and Purpose: The computed tomography (CT) angiography or contrast-enhanced CT 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: Tranexamic Acid for Intracerebral Haemorrhage (TICH-2) trial 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 CT-scan on admission and on day 2 (24 hours ±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 (IQR) 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 (OR 0.85; 95% CI 0.29 to2.46) and negative (OR 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.

Clinical trial registration: Clinical Trial Registration-URL: http://www.controlled-trials.com. Unique identifier: ISRCTN93732214.

Non-standard Abbreviations and Acronyms

CTA – CT-angiography

CECT – contrast-enhanced CT

IMP – Investigational medicinal product (IMP)

APD – adjusted percent difference

AOR – adjusted odds ratio

Introduction

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

In the Tranexamic Acid for Hyperacute Intracerebral Haemorrhage (TICH-2) Trial (published in 2018),[6] as well as in previous trials randomizing anticoagulation-naïve 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 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 on-going 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, three 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 pre-specified 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.

Materials and 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 non-comatose (Glasgow Coma Scale [GCS] ≥ 5) patients with

presumed spontaneous intracerebral hemorrhage within eight 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 pre-planned 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 non-contrast CT and physical examination (NIHSS and GCS). 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 (CO and RD) 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 two 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 and/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 (post-contrast sequence), we defined the spot sign as at least one hyperdensity (relative to the hematoma) within the hematoma indicative of contrast extravasation on post-contrast imaging (not present on pre-contrast 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 carried out using the active contour tool in the ITK-SNAP software (version 3.6, www.itksnap.org). One of three assessors did manual controlling and editing of the contours to ensure the best fit to the segmented structure.[6] Four non-contrast scans were adjudicated by CO, 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 hours ±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 (≥ 6mL 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 NIHSS increase, a ≥ 2 points GCS 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 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 post-contrast 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 (standard deviation [SD] 17 mL) would yield a power of 84.4%.[15] Interrater reliability was analyzed using Cohen's kappa. 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 two. 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 NIHSS, 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 pre-planned 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 in geometric means. We tested the model assumptions as specified in the analysis plan (Supplement F - please see https://www.ahajournals.org/journal/str).[15] Due to the tendency for participants in clinical trials to cluster within stratification units (i.e. 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 utilized a nominal statistical significance level of 5% in all analyses. All statistical analyses were carried out in Stata 15.1 (StataCorp, TX, USA).

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 **(Supplementary Figure I - please see https://www.ahajournals.org/journal/str)**. The 254 participants were generally comparable to the rest of the TICH-2 population **(Supplementary Table I - please see https://www.ahajournals.org/journal/str)**, but the median [interquartile range - IQR] 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). 64 (25.2%) participants were spot-sign positive. Between the two central spot sign adjudicators (CO and RD), a good interrater agreement for spot sign on CT-angiography (κ, 0.82; 95% CI 0.74 to 0.91) was observed. The agreement between the two central adjudicators and the investigators at the sites was fair (κ, 0.57, 95% CI 0.44 to 0.70). The overall median (IQR) 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 [IQR] 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] mL versus 38.4 [27.6] mL) compared with 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 (adjusted percent difference [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 supplementary material **(Supplementary Table II - please see https://www.ahajournals.org/journal/str).** The distribution of time from onset to CT-angiography or contrast-enhanced CT against absolute hematoma expansion is presented in supplementary material **(Supplementary Figure II - please see https://www.ahajournals.org/journal/str).** 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 [aOR], 0.85; 95% CI 0.29 to 2.46) or spot-sign negative participants (aOR, 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 (aOR, 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 **(Supplementary Table III - please see https://www.ahajournals.org/journal/str)**. At day 90, one participant had been completely lost to follow-up and censured 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 **(Supplementary Table IV - please see https://www.ahajournals.org/journal/str).**

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 **(Supplementary Tables V to X - please see https://www.ahajournals.org/journal/str)**. The same was true for the sensitivity analysis taking clustering into account **(Supplementary Tables XI to XIII - please see https://www.ahajournals.org/journal/str)**. 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 (aOR, 2.81; 95% CI 1.46 to 5.41) **(Supplementary Table XIV - please see https://www.ahajournals.org/journal/str)**.

Discussion

In this pre-specified 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 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 indicating an enhanced treatment benefit, if time to treatment is below 150 minutes[9], as well as data from the STOP-AUST trial[14] where administration of tranexamic acid versus placebo to spot-sign positive participants within 3 hours after symptom onset was associated with a non-significant 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 non-significant, odds ratio towards hematoma expansion.[14] The importance of early treatment is further supported by the data from the CRASH-3 trial 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 with 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.

Summary

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

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Supplementary Materials

Supplemental Tables I to XIV

Supplemental Figures I and II

Assumption Check – Main Analysis

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TABLES

Table 1: Baseline characteristics

	Spot sign positive		Spot sign negative	
	Tranexamic acid (n=30)	Placebo (n=34)	Tranexamic acid (n=95)	Placebo (n=95)
Age, years	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, minutes	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, minutes	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, minutes	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 hours	12 (41.4%)	20 (58.8%)	24 (25.3%)	25 (26.3%)
≤ 4.5 hours	22 (75.9%)	28 (82.4%)	53 (55.8%)	57 (60.0%)
CTA or CECT to IMP administration, minutes	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%)
Pre-stroke 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, mmHg	172.8 (30.9)	178.9 (31.5)	171.7 (25.6)	180.0 (32.7)
Diastolic blood pressure, mmHg	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 (%). CTA – CT-angiography, CECT – contrast-enhanced CT, IMP – investigational medicinal product, TIA – transient ischemic attack, GCS – Glasgow Coma Scale, NIHSS – National Institute of Health Stroke Scale

FIGURE LEGENDS

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 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 of participants, aPD – adjusted percent difference, CI – confidence interval, CT – computed tomography, mL – milliliter.

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 years), time from onset to randomization (< 3 compared to ≥ 3 hours) and National Institute of Health Stroke Scale (< 15 compared to ≥ 15 points). CT – computed tomography, mL – milliliter, OR – odds ratio, no. – number of participants, CI – confidence interval.