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Relationship of White Matter Lesions to Intracerebral Hemorrhage Expansion and Functional Outcome: MISTIE II and CLEAR III

Björn M Hansen, MD^{1,*}, Natalie Ullman, MD^{2,*}, John Muschelli, PhD³, Bo Norrving, MD¹, Rachel Dlugash, MSPH⁴, Radhika Avadhani, MS⁴, Issam Awad, MD⁵, Mario Zuccarello, MD⁶, Wendy C Ziai, MD⁴, Daniel F Hanley, MD⁴, Richard E Thompson, PhD^{3,†}, Arne Lindgren, MD^{1,†} MISTIE and CLEAR Investigators

¹.Department of Clinical Sciences Lund, Neurology, Lund University; Department of Neurology, Skåne University Hospital, Lund, Sweden

².Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA.

³.Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁴.Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, MD, USA

⁵.Department of Neurosurgery, University of Chicago, Chicago, IL, USA

⁶.Department of Neurosurgery, University of Cincinnati, Cincinnati, OH, USA

Abstract

Background/Objective: Intracerebral hemorrhage (ICH) patients commonly have concomitant white matter lesions (WML) which may be associated with poor outcome. We studied if WML affects hematoma expansion (HE) and post-stroke functional outcome in a post hoc analysis of patients from randomized controlled trials.

Methods: In ICH-patients from the clinical trials MISTIE II and CLEAR III, WML grade on diagnostic CT scan (dCT, <24 hours after ictus) was assessed using the van Swieten scale (vSS, range 0–4). The primary outcome for hematoma expansion (HE) was >33% or >6 mL ICH volume increase from dCT to the last pre-randomization CT (<72 hours of dCT). Secondary HE outcomes were: absolute ICH expansion, >10.4 mL total clot volume increase, and a subgroup analysis including patients with dCT <6 hours after ictus using the primary HE definition of >33% or >6

Corresponding author Natalie Ullman M.D. M.P.H., Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA. Telephone: 301-758-2172, nullman@gmail.com.

*† Authors contributed equally

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DETAILS

1) We confirm that the manuscript complies with all instructions to authors

2) We confirm that authorship requirements have been met and the final manuscript was approved by all authors

3) We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal

4) We confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate, please see initial paragraph of the Methods section for further detail

5) Include Conflict of Interest statement for all authors

6) We confirm the use of the STROBE Statement—checklist for reports of observational studies (appended).

mL ICH volume increase. Poor functional outcome was assessed at 180 days and defined as modified Rankin Scale (mRS) ≥ 4 , with ordinal mRS as a secondary endpoint.

Results: Of 635 patients, 55% had WML grade 1–4 at dCT (median 2.2 hours from ictus), and 13% had subsequent HE. WML at dCT did not increase the odds for primary or secondary HE endpoints ($P = 0.05$) after adjustment for ICH volume, IVH volume, warfarin/INR > 1.5 , ictus to dCT time in hours, age, diabetes mellitus, and thalamic ICH-location. WML increased the odds for having poor functional outcome (mRS ≥ 4) in univariate analyses (vSS 4; OR 4.16; 95% CI, 2.54–6.83; $P < 0.001$) which persisted in multivariable analyses after adjustment for HE and other outcome risk factors.

Conclusions: Concomitant WML does not increase the odds for hematoma expansion in patients with ICH but increases the odds for poor functional outcome.

Clinical Trial Registration: <http://www.clinicaltrials.gov> trial-identifiers: NCT00224770 and NCT00784134.

Keywords

Cerebral Hemorrhage; Stroke; Leukoencephalopathies; Leukoaraiosis; Cerebral Small Vessel Diseases; Prognosis

INTRODUCTION

The overall short- and long-term prognosis after intracerebral hemorrhage (ICH) is poor. (1,2) The short-term prognosis after ICH is affected by several factors including ICH volume and location, intraventricular hemorrhage (IVH)(1) but also hematoma expansion (HE), a potentially modifiable risk factor.(3,4)

Prognostic models for HE have included warfarin therapy, time from ictus, ICH volume, IVH, and spot sign.(4–7) Another potential contributing cause for HE is the mechanical ability of the brain tissue to withstand damage which might decrease in cerebrovascular small vessel disease (SVD) as described below.

SVD is often associated with arteriosclerosis and cerebral amyloid angiopathy, and is linked to aging, stroke, and dementia.(8) White matter lesions of presumed vascular origin (WML), also known as leukoaraiosis or white matter hyperintensities (WMH on magnetic resonance imaging, MRI), may indicate SVD(9) and loss of vascular and blood-brain barrier integrity, demyelination, arteriosclerosis, myelin loss, gliosis, and spongiosis.(10, 11) The hypothesis that WML/SVD impact HE risk is supported by a retrospective study ($N=35$) which showed a trend towards increased risk for HE with increasing severity of WMH.(12) However, one CT-based study (13) and one MRI-based study have shown conflicting results.(14) WML have also been associated with ICH and IVH occurrence(15,16) and are commonly seen among patients with ICH.(17)

WML have been related to worse functional outcome(13, 17–21) and increased case fatality(17,22) after ICH. Potential causes may be loss of integrity in compensatory

networks,(23) reduced brain plasticity and cognitive reserves.(8,24) Another possible reason is that WML might increase the risk for acute-phase HE.

WML could be an important risk factor for deterioration related to HE, and decreased post-stroke function although studies have shown inconsistent results.(12–14) To explore this further, standardized radiological follow-up, and functional outcome assessments are required, and possible confounding comorbidities need to be assessed. We therefore utilized two large clinical trial cohorts to study if ICH-patients with concomitant WML at initial diagnostic CT (dCT) had increased risk for (A.) HE and (B.) poor functional outcome, after adjustment for HE.

METHODS

Subjects

Patients with ICH, IVH, or both, were included from two international multicenter randomized clinical trials: (A.) Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation phase II (MISTIE II)(25) including the sub-study on Intraoperative Stereotactic CT-Guided Endoscopic Surgery (ICES –with identical eligibility criteria as the MISTIE II study and henceforth, in this study, included in the MISTIE II abbreviation);(26) and (B.) Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage phase III (CLEAR III).(27) Patients were enrolled in MISTIE II from February 2, 2006–April 8, 2013, and in CLEAR III from September 18, 2009–January 13, 2015. Written informed consent was obtained for all patients. The trials were approved by local Institutional Review Boards of participating sites. This secondary analysis was separately approved by the Johns Hopkins Institutional Review Board, Baltimore, MD.

MISTIE II patients were included, either as pilot or randomized subjects, and treated with: (a) minimally invasive surgery with surgical aspiration of ICH (MIS) and post-surgery infusion of alteplase, (b) endoscopic stereotactic CT-guided clot evacuation, or (c) standard medical care. CLEAR III patients had IVH that required EVD and were randomized to receive either intraventricular infusions with (a) rtPA (experimental) or (b) saline (placebo), in addition to standard medical care.(27) Additional inclusion criteria for these trials have been previously described.(25–27)

Screening for image based clot stability was required for randomization in both studies.(25–27) If stability was not initially met, patients could be screened with subsequent CT-scans up to 48/72 hours (MISTIE II/CLEAR III) after dCT as long as other inclusion criteria continued to be met. To ensure that early expansion was not being missed in the HE analyses, a subgroup analysis was conducted which excluded all patients with more than 6 hours from ictus to dCT. Analyses of additional subgroups with shorter times from ictus to dCT would not yield meaningful results given small numbers.

Clinical and Radiological Characteristics

Baseline and follow-up clinical and radiological characteristics assessments have been previously described.(25–27) Assessments using the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) were completed at randomization. Warfarin

therapy and international normalized ratio (INR) >1.5 at baseline was combined into a dichotomous variable in our study. Baseline platelet count was dichotomized at <100,000/ μ L.

HE was determined by comparing baseline clot volumes at dCT to volumes at the subsequent last pre-randomization CT (i.e. before active trial treatment). Hemorrhage volume measurements were done at the MISTIE II/CLEAR III study center with semi-automated segmentation and Hounsfield thresholds using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland).

WML at dCT were evaluated by two independent reviewers (NU and BMH) using the van Swieten Scale (vSS) which ranges from 0 (no WML) to 4 (severe WML) and was developed for CT and MRI.(28) Both readers are experienced in evaluating ICH-patients' CT scans and were blinded to clinical information. If the area of interest for vSS grading was directly affected by the hematoma or prior brain damage, only the contralateral side was used for grading to minimize the risk of misinterpreting perihematomal edema or old brain damages as WML. A consensus decision was formed if WML assessments differed by more than one vSS grade or if one reader identified presence of WML while the other did not. A third adjudicator (DFH) was consulted when consensus could not be reached. If performed, the vSS grade from the consensus/adjudicated decision was used in outcome analyses; otherwise, when the reader's assessments differed but were within one vSS grade, the higher grade was used.

Endpoints

In the primary analysis we defined HE as an ICH volume increase of >33% or >6 mL, a combination of frequently used cutoffs for ICH expansion.(7,29) Secondary HE outcomes were: the abovementioned analysis of HE defined as >33% or >6 mL ICH volume increase including only patients with dCT <6 hours after ictus, total ICH volume increase as a continuous measure, and total clot volume (ICH+IVH) increase of >10.4 mL, a recently suggested limit to minimize impact of measurement error.(30) Poor functional outcome was assessed 180 days after ICH and primarily defined as modified Rankin Scale(31) (mRS) 4–5 or death; and secondarily as mRS as an ordinal scale; and lower severe disability, vegetative state on the extended Glasgow Outcome Scale (eGOS)(32) or death.

Statistics

Univariate and multivariable logistic regression tests were used to analyze the dichotomized primary and secondary HE endpoints, and the pre-defined covariates: vSS, age, ICH volume, IVH volume, warfarin/INR>1.5 at baseline, time between ictus and dCT, diabetes mellitus, and thalamic ICH location. Linear regression with and without adjustment for the previously mentioned risk factors was used to analyze the relationship between vSS grades and continuous HE.

We performed logistic regression for binary poor functional outcome. In addition to the previously mentioned factors used in HE analyses (except ictus to dCT time), functional outcome models also included: sex, GCS, experimental therapy (MISTIE II: MIS plus alteplase, and ICES; CLEAR III: EVD plus alteplase), and HE (ICH volume increase

>33%/>6 mL). We also performed univariate and multivariate ordinal logistic analyses to evaluate shifts in outcomes according to mRS assuming proportional odds. Patients were stratified by trial in secondary exploratory functional outcome analyses. Multicollinearity between age, vSS, diabetes mellitus, ICH volume, and IVH volume, was tested with pairwise correlations, and by calculating variance inflation factors using linear regress for the logistic outcome of HE and mRS 4–6. Backwards stepwise logistic regression models were performed to confirm the results from the main multivariable logistic regression analyses for the primary HE and functional outcome endpoints. Additional multivariable logistic regressions were conducted to assess for interactions between WML, HE, outcome, and treatment assignment.

Patients with missing clot volume measurements or 180-day follow-up were excluded from HE and functional outcome analyses, respectively. Pearson's χ^2 -test, Mann–Whitney U-test and two-sample *t*-test were used for descriptive statistics. Interrater agreement of vSS-scores was analyzed with intraclass correlation coefficient (ICC) statistics. STATA version 13.0 (STATA Corp, College Station, TX) was used for statistic calculations. Two-sided P-values <0.05 were considered significant.

RESULTS

Study Population

Of 641 patients included in MISTIE II and CLEAR III, 6 patients were excluded due to dCT performed >24 hours from ictus, 7 lacked HE outcomes, and 16 were missing 180-day mRS assessment (Figure 1). Thirteen patients were therefore excluded from the primary HE analysis and 22 from primary functional outcome analyses. An additional 112 patients were excluded from the secondary HE analysis for dCT >6 hours from ictus. Mean age for the 635 patients with dCT performed <24 hours of symptom onset was 59.1 years (SD $\pm$ 11.3), baseline characteristics and outcomes for these patients are shown in Table 1.

The interrater agreement for pre-adjudication vSS assessments was good (ICC=0.76). A consensus/adjudicated decision was reached for 145 (23%) patients where the original vSS assessments were outside the abovementioned limits for acceptable interrater difference. The distribution of vSS grades was similar between CLEAR III and MISTIE II (Table 1; *P*=0.88).

The median ictus to dCT-time was 2.19 hours (IQR 1.30–4.69) and HE was assessed 39 hours (median; IQR 22.50–54.51) after symptom onset. The time from symptom onset to dCT was <6 hours for 516 (82%) of the patients included in HE analyses.

Among 628 patients included in expansion analyses, HE (primary definition) occurred in 83 (13%) and was more common in MISTIE II than in CLEAR III (*N*=48 versus 35; 34% versus 7%; *P*<0.001). Patients with HE had larger baseline ICH volumes (mean 21.0 mL; 95% CI: 17.3–24.7) compared with patients without HE (14.9 mL; 95% CI: 13.5–16.3 mL; *P*=0.002) but smaller IVH volumes (mean 10.1 versus 25.8 mL; 95% CI: 6.5–13.6 versus 23.9–27.7 mL; *P*<0.001).

WML was associated with higher age, thalamic ICH location and lower GCS at baseline (Supplemental Table I). There were no indications of multicollinearity between abovementioned variables included in the multivariable analyses.

WML and Hemorrhage Expansion

WML severity did not affect the odds for HE in univariate analysis ($P = 0.05$). Age, vSS grade 2, baseline IVH volume, and time between ictus and dCT were associated with the primary definition of HE in multivariable analyses ($P < 0.05$), as shown in Table 2. Similar results were obtained with backwards stepwise regression (not shown). There was no consistent correlation between vSS and HE according to absolute change in ICH volumes (Supplemental Table II); vSS and HE using total hematoma volume with a 10.4 mL cut-off (Supplemental Table III), or vSS and HE among the patients with dCT < 6 hours from ictus (Supplemental Table IV).

WML and Poor Functional Outcome

Of the 619 patients with available mRS, 351 (55%) had poor functional outcome. In the univariate analysis vSS grades 2, 3, and 4 were associated with increased odds for poor functional outcome ($P < 0.05$, Table 3). After adjustment for other potential risk factors for poor functional outcome, vSS 4 remained an independent predictor of poor functional outcome ($P = 0.003$), whereas the vSS grades 2 and 3 crossed unity ($P = 0.05$, Table 3). As illustrated by Figure 2, patients with more WML had a trend toward worse functional outcomes ($P < 0.05$ for vSS 2 and 4; ordinal logistic regression; see Supplemental Table V for effect sizes). Similar results were obtained with backwards stepwise regression (not shown).

In the secondary univariate analysis of functional outcome, using eGOS, vSS grades 2, 3, and 4, were associated with poor functional outcome ($P < 0.05$). However, in multivariable analyses this association only remained for vSS grades 2 and 4 ($P < 0.05$; Supplemental Table VI).

In the trial stratified analyses, there was no association between poor functional outcome (mRS 4) and WML in MISTIE II patients (Supplemental Table VII); while the CLEAR III patients had similar results as the total cohort (Supplemental Table VIII). Furthermore, no significant interaction was observed between WML and treatment assignment for either functional outcome measures (mRS or eGOS). Interestingly, there was a significant interaction between HE (primary definition) and treatment assignment on both mRS and eGOS, with HE having a bigger effect on mRS and eGOS in the control group compared to the treatment group.

DISCUSSION

In contrast to some previously reported data⁽¹²⁾ we did not detect any association between more severe WML and increased odds for HE. We did, however, find that WML severity is associated with poor functional outcome 180 days after ICH, supporting findings of previous studies.^(13, 17–19) This association remained after adjustment for HE and other important clinical risk factors, suggesting that worse functional outcomes among ICH-patients with severe concomitant WML might be mediated by other mechanisms, such as decreased

compensatory networks, brain plasticity and cognitive reserves. Two recent studies, using CT-based vSS and MRI-based Fazekas scale, found similar results for both expansion and functional outcome.(13, 14) Our study confirms these findings in a larger cohort of patients from both the placebo and active therapy arms of two multi-center clinical trials. That HE had a bigger effect on functional outcome in the control group compared to the treatment group may suggest that clot removal strategies may mitigate some of the detrimental effects of HE.

As HE was not associated with WML, a possible surrogate for reduced brain tissue density, our results may indicate that HE is rather affected by factors affecting hemostasis, such as coagulation and hypertension.(33) However, since histopathological studies have identified both tissue rarefaction and gliosis in areas affected by WML,(10) it is possible that WML on CT represents a mix of areas with different density and would thereby be a poor surrogate for brain density.

Our cohort's size and high quality, prospectively gathered and well-defined imaging and clinical features and outcomes enabled an evaluation of whether WML affects two important outcomes after ICH. This high level of standardized radiological and clinical follow-up is difficult to achieve outside a clinical trial setting using a purely observational study design. Additionally, the two trials in our study represent two different ICH-patient subgroups: the CLEAR III patients with no/small ICH and large IVH, and the MISTIE patients with large ICH and no/small IVH, thus increasing the representativeness of the total cohort even though the CLEAR-III patients constitutes a majority of included subjects in our study. However, this study consists of a subset of ICH-patients from clinical trials data, which may limit the generalizability of our results.(34) External validation of our results in population-based cohorts would therefore be valuable. Despite our large sample size, the post-hoc study design influences the interpretation of negative findings since a basis for statistical power estimates did not exist prior to the study.

In comparison to other trials using CT-based vSS, the WML frequency and age distribution in our study (55%; mean age 59) was similar to three other studies(17,18,20) (where 50%, 58%, and 59% had WML, respectively; mean age 63, 61 and 67 years), but differed from two other cohorts where 81% and 87% of the ICH-patients had WML (mean age 67 and 75 years).(13,22) MRI is the preferred modality for WML assessments(33) and when using CT, we might have underestimated the WML burden and its relation to HE. However, MRI is rarely used in the acute-phase after ICH due to cost and limited accessibility compared to CT, and our results are therefore potentially more clinically applicable than if they had been derived from MRI assessments.

Both MISTIE II and CLEAR III required pre-randomization stability and approximately 3% of the patients screened for eligibility were ineligible due to hematoma instability. This may have resulted in a lower HE prevalence compared to a general ICH-patient population. Additionally, all CLEAR III patients had an EVD placed before the last pre-randomization CT, (used for HE assessment in our study), which may have reduced post-EVD IVH volumes and led to a falsely low frequency of HE according to the total clot volume (ICH

+IVH) endpoint. This, in addition to studying a selected patient sample,(34) may explain why we did not see any effect of WML on HE.

Despite eventual stabilization, 13% of our patients had pre-randomization HE (ICH >33%/>6 mL) which is similar to expansion rates in the cohorts used to develop and validate two recent HE prediction scores (with 19% and 12% HE using the <6 mL HE definition;(7) and 19% and 16% when using the >33%/>6 mL HE definition⁵), but substantially lower compared to the development cohort of another HE score (32% using the >33%/>6 mL definition).(6) The abovementioned differences in CLEAR III and MISTIE II patient selection may have caused the observed differences in HE rates between the two trials, which in turn may have affected the outcome analyses. We might have missed HE occurring very early after ICH-onset despite our short median ictus to dCT time (2.19 hours; IQR 1.30–4.69). Nonetheless, the majority of our patients (82%) had dCT within 0–6 hours after ictus when the risk of HE is highest.(33) As edema evolves gradually after ICH(36) our short total ictus to dCT-time reduces the risk of periventricular and perihematomal edema being misinterpreted as WML. Nevertheless, since we lacked MRI and absolute CT-scan attenuation thresholds for WML, we cannot rule out the possibility that our WML assessments were affected by edema in the small subset of patients with longer ictus to CT-time which consequently might have affected our outcome analyses.

CONCLUSIONS

ICH-patients with concomitant WML on the initial early diagnostic CT have an increased likelihood of poor post-stroke 180-day functional outcome which is likely not mediated by an increased risk for acute-phase hematoma expansion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Patient selection diagram. *CLEAR III* Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage phase III, *dCT* diagnostic CT scan, *EVD* external ventricular drainage, *h* hours, *ICES* Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *MIS* minimally invasive surgery, *MISTIE II* Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation phase II, *rt-PA* recombinant tissue plasminogen activator, *mRS* modified Rankin Scale.

Figure 2.
Distribution of modified Rankin Scale (mRS) scores between van Swieten Scale (vSS) grades

Table 1.

Baseline and follow-up characteristics of 635 patients from MISTIE II and CLEAR III

		Total (N=635)	CLEAR III (N=495)	MISTIE II (N=140)	Missing N (%)
Age, years (IQR)		59 (51–67)	59 (51–67)	61 (53.5–70.5)	0 (0%)
Female		266 (42%)	219 (44%)	47 (34%)	0 (0%)
Race	White	393 (62%)	302 (61%)	91 (65%)	6 (1%)
	Black	210 (33%)	168 (34%)	42 (30%)	
	All Other	26 (4%)	20 (4%)	6 (4%)	
Diabetes mellitus		90 (14%)	54 (11%)	36 (26%)	1 (0%)
Hypertension		579 (91%)	455 (92%)	124 (89%)	0 (0%)
NIHSS (IQR)		20 (13–31)	19 (11–35)	21 (17–28)	40 (6%)
GCS (IQR)		10 (7–13)	10 (7–13)	10 (8–13)	4 (1%)
Warfarin/INR>1.5		60 (9%)	50 (10%)	10 (7%)	44 (7%)
Platelet count <100,000/ μ L		2 (0%)	1 (0%)	1 (0%)	9 (1%)
Experimental therapy		346 (55%)	247 (50%)	99 (71%)	0 (0%)
Time ictus to dCT, h (IQR)		2.2 (1.3–4.7)	2.3 (1.3–4.8)	2.1 (1.2–4.6)	0 (0%)
Time ictus to last pre-randomization CT, h (IQR)		39.0 (22.5–54.5)	44.8 (29.2–59.9)	21.8 (14.5–30.4)	0 (0%)
vSS	0	286 (45%)	222 (45%)	64 (46%)	0 (0%)
	1	82 (13%)	65 (13%)	17 (12%)	
	2	82 (13%)	66 (13%)	16 (11%)	
	3	65 (10%)	52 (10%)	13 (9%)	
	4	120 (19%)	90 (18%)	30 (21%)	
ICH-location	Thalamus	294 (46%)	290 (59%)	4 (3%)	1 (0%)
	Deep non-thalamic	195 (31%)	102 (21%)	93 (66%)	
	Lobar	47 (7%)	5 (1%)	42 (30%)	
	IVH only	33 (5%)	33 (7%)	0 (0%)	
	Other	65 (10%)	64 (13%)	1 (1%)	
IVH		551 (87%)	495 (100%)	56 (40%)	0 (0%)
Baseline ICH volume, mL (IQR)		10.2 (4.4–20.5)	7.98 (2.9–13.6)	35.4 (24.5–51.3)	6 (1%)
Baseline IVH volume, mL (IQR)		19.1 (6.6–33.5)	24.5 (14.3–39.9)	0 (0–2.5)	6 (1%)
ICH volume, mL (IQR)		0.0 (–1.4;1.9)	–0.1 (–1.4;0.9)	2.2 (–1.3;8.9)	7 (1%)
IVH volume, mL (IQR)		–0.9 (–5.1;1.2)	–2.3 (–6.3;1.2)	0 (0.0;1.1)	7 (1%)
ICH expansion >33%/>6 mL		83 (13%)	35 (7%)	48 (34%)	7 (1%)
Total volume expansion >10.4 mL		80 (13%)	48 (10%)	32 (23%)	7 (1%)
mRS 4 or death		351 (55%)	262 (53%)	89 (64%)	16 (2%)
eGOS Lower severe disability, VS, or death		381 (60%)	309 (62%)	72 (51%)	55 (9%)

Data reported as median (IQR) or frequency (%), unless otherwise specified. *dCT* diagnostic CT scan, *eGOS* extended Glasgow Outcome Scale, *GCS* Glasgow Coma Scale, *h* hours, *ICH/IVH volume* ICH/IVH volume difference between dCT and last pre-randomization CT, *mRS* modified Rankin Scale, *VS* vegetative state, *vSS* van Swieten Scale

Table 2.

Univariate and multivariable analyses of hematoma expansion (ICH volume increase >33%/>6 mL)

		Univariate Analyses		Multivariable Analysis	
		OR (95% CI)	P	OR (95% CI)	P
vSS	0	Reference		Reference	
	1	0.64 (0.30–1.37)	0.253	0.55 (0.24–1.25)	0.153
	2	0.41 (0.17–1.00)	0.050	0.38 (0.15–0.99)	0.049
	3	0.84 (0.39–1.82)	0.657	0.71 (0.33–1.54)	0.391
	4	0.62 (0.32–1.20)	0.159	0.52 (0.25–1.09)	0.083
Baseline ICH volume (per mL)		1.02 (1.01–1.03)	0.001	1.00 (0.98–1.01)	0.648
Baseline IVH volume (per mL)		0.94 (0.92–0.97)	<0.001	0.95 (0.92–0.97)	<0.001
Thalamic ICH		0.69 (0.43–1.11)	0.125	0.82 (0.47–1.44)	0.493
Diabetes mellitus		1.52 (0.83–2.76)	0.172	1.28 (0.65–2.50)	0.478
Warfarin/INR>1.5		1.43 (0.71–2.89)	0.315	1.48 (0.66–3.34)	0.335
Age (per year)		1.03 (1.01–1.05)	0.003	1.03 (1.01–1.06)	0.004
Time ICH to dCT (per hour)		0.85 (0.76–0.95)	0.003	0.85 (0.76–0.95)	0.004

dCT diagnostic CT scan, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *vSS* van Swieten Scale

Table 3.

Univariate and multivariable analyses of poor functional outcome (mRS 4 or death)

		Univariate Analyses		Multivariable Analysis	
		OR (95% CI)	P	OR (95% CI)	P
vSS	0	Reference		Reference	
	1	1.11 (0.67–1.82)	0.689	0.98 (0.49–1.95)	0.956
	2	2.24 (1.33–3.78)	0.002	1.52 (0.78–2.97)	0.222
	3	1.81 (1.04–3.16)	0.035	1.39 (0.68–2.84)	0.365
	4	4.16 (2.54–6.83)	<0.001	2.89 (1.44–5.82)	0.003
Baseline ICH volume (per mL)		1.04 (1.02–1.05)	<0.001	1.06 (1.04–1.09)	<0.001
Baseline IVH volume (per mL)		1.01 (1.00–1.02)	0.001	1.03 (1.02–1.05)	<0.001
Thalamic ICH		1.70 (1.23–2.35)	0.001	3.70 (2.31–5.94)	<0.001
Diabetes mellitus		2.00 (1.23–3.27)	0.005	3.06 (1.57–5.98)	0.001
Warfarin/INR>1.5		1.48 (0.85–2.59)	0.168	0.86 (0.39–1.88)	0.713
Age (per year)		1.06 (1.04–1.07)	<0.001	1.06 (1.03–1.08)	<0.001
Sex (female)		0.92 (0.67–1.27)	0.623	1.48 (0.95–2.29)	0.082
Experimental therapy (vs. standard)		0.90 (0.65–1.24)	0.525	1.19 (0.78–1.82)	0.417
GCS (per point)		0.78 (0.73–0.83)	<0.001	0.79 (0.74–0.85)	<0.001
Hematoma expansion *		2.82 (1.62–4.91)	<0.001	5.36 (2.55–11.26)	<0.001

* ICH volume increase >33%/>6 mL. *dCT* diagnostic CT scan, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *mRS* modified Rankin scale, *vSS* van Swieten Scale