Interaction of Recanalization, Intracerebral Hemorrhage and Cerebral Edema after Intravenous thrombolysis

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Abstract:

Background and Purpose: Both intracerebral hemorrhage (ICH) and brain edema, have been attributed to reperfusion after IV thrombolysis. We explored the interaction of recanalization, and core size for imaging outcomes (ICH and vasogenic brain edema).

Methods: In patients with anterior circulation occlusion given IV thrombolysis <4.5h and imaged with CT perfusion (CTP) and CT angiography (CTA), we defined volumes of core (relative Delay Time [rDT]>2s, relative cerebral blood flow<40%) and penumbra (rDT>2s). CT and CTA at 24h were reviewed for ICH (ECASS-2 definition), early vasogenic edema (IST-3 criteria), and recanalization (TIMI 2-3). Independent effects of recanalization, core volume and potential interactions on edema, ICH and day 90 outcomes were estimated by logistic regression.

Results: In 123 patients, there was a trend for recanalization to be associated with H1/2 ICH, but not with PH1/2 ICH (OR 1.7 (0.33-8.8); p=0.5), any edema or Significant Brain Edema (SBE; OR 1.45 (0.4-4.9); p=0.55). Ischemic core (>50ml) was associated with any ICH (OR 4.0 (1.6-9.5); p=0.003), edema (OR 5.4 (2-14); p<0.01), and SBE (OR 17.4 (5.3-57); p<0.01), but not PH1/2 ICH (OR 1.2 (0.23-6.5); p=0.8), after controlling for recanalization. There was no significant interaction of recanalization and large core for any adverse outcomes.

Conclusions: Large ischemic core was associated with poorer outcomes and both early vasogenic brain oedema and ICH, but recanalization on 24h CTA was associated with clinically favourable outcome. There was no significant interaction of recanalization and large core volume for any outcomes. The association of haemorrhage or brain edema with post-thrombolysis reperfusion is unclear.

Introduction:

Intravenous (IV) thrombolysis <4.5h after onset significantly improves outcome , but carries increased risk of intracerebral hemorrhage (ICH).[1, 2] Reperfusion is proposed to be necessary both for ICH [3] and vasogenic brain edema[4], the other major cause of early neurological deterioration after stroke.

Both the third International Stroke Trial (IST-3), and subsequent pooled analysis of alteplase trials [5], indicated slight excess of fatal symptomatic ICH (SICH) within 7 days of treatment (2.7% compared to 0.4% in IST-3)[6]. IST-3[7] also reported a small excess risk of fatal brain swelling (approximately 1.5%) within 7 days, and the Alteplase Summary of Medicinal Product Characteristics (https://www.medicines.org.uk/emc/medicine/308 section 4.4) states that "reperfusion of the ischemic area may induce cerebral oedema in the infarcted zone." Vasogenic edema was associated with increased blood-brain barrier permeability after reperfusion in a rodent transient global cerebral ischemia model[8, 9], but complex interactions of severity and duration of ischemia, and timing of reperfusion confound this possible relationship[10]. Space-occupying cerebral edema is clinically associated with large artery occlusions that recanalize rarely with IV rtPA[11, 12], and no excess risk of brain edema was reported in previous trials[2, 13].

Different types of hemorrhage may have different mechanisms and clinical implications: hemorrhagic infarction (HI1 or HI2 in the ECASS-2 classification[13]) may be an epiphenomenon of reperfusion with no adverse clinical implications, while, in contrast, parenchymal hematomas with independent mass effect (PH1 or PH2 [13]) are linked with clinical worsening and may be related to blood-brain barrier breakdown after reperfusion[14].

Imaging features may interact with treatment. The Diffusion and perfusion Imaging evaluation for understanding stroke evolution (DEFUSE)[15]study and combined analysis of DEFUSE and the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) studies [16]found increased risk of PH1 or PH2 ICH when reperfusion occurred in patients with "large core" (large volumes of severely hypoperfused tissue on

MRI). Interaction of early reperfusion with other indices of severe ischemia (large DWI volumes, [17, 18], very low cerebral blood volume on perfusion imaging[19] or poor collaterals[20]) has been reported for SICH after IV thrombolysis. The extent of vasogenic edema may also interact with ischemic core volume (>50% hypodensity on CT was associated clinically with malignant brain edema [21])., and in an animal model reperfusion of large volumes of severely ischemic tissue (CBF <40%) led to malignant edema[22] .

Previous studies have not investigated the relationship of imaging characteristics (e.g. ischemic core volume), reperfusion, and their interaction with brain edema and ICH after IV thrombolysis. We hypothesised that recanalization of large core (large ischemic area) would be associated with significant haemorrhage, and persistent occlusion with significant brain edema.

Methods:

We selected data from subjects treated with IV rtPA <4.5 hours after onset recruited at a single centre to one of three multimodal imaging studies during 2008-2013. Two studies were observational and one was a trial comparing aleplase and tenecteplase (ATTEST: NCT01472926)[22, 23]. In the two observational studies (one investigating feasibility of complex imaging, one investigating pathophysiology of acute hyperglycemia), all ischemic stroke patients aged >18 years and presenting < 6 hours after onset were eligible. Exclusion criteria were contraindications to iodinated contrast (allergy or estimated Glomerular Filtration Rate <30ml/min). In all studies, patients underwent CT, CT angiography and CT perfusion at baseline (<6h after onset) with follow-up brain CT and CTA (if occlusion was present on baseline imaging) approximately 24h later . Favourable outcome was defined as modified Rankin scale (mRS) 0-2 at final review (30 or 90 days, depending on individual study). Endovascular treatment was not used.

Scans were acquired on a Philips Brilliance 64 multidetector scanner. Whole brain NCCT (5 mm slice thickness FOV 218 x 218 mm, 120 kv, 171 mA or 0·9 mm slice thickness, FOV 250x250 mm, 120 kV, 404 mA) was followed by CTP with 40 mm slab coverage from the basal ganglia (8x5 mm slices, FOV 25 cm, 80 kVp, 476 mA, 2 second cycle time, 30 cycles) using a 50 ml contrast bolus administered at 5 mls per second (350 Xenetix) via a large-gauge cannula. CTA covering aortic arch to the top of the lateral ventricles (0·67 mm slice thickness, 120 kV, 475 mA) was acquired during the first arterial passageof contrast (Xenetix 350, 60 mls, followed by 30 mls of saline bolus, both given at 5 ml per second)

Imaging processing and analysis:

Anonymised imaging studies were analysed independently by two researchers (BC, XH). CTP was processed offline using MiStar (Apollo Medical Imaging Technology, Melbourne, Australia). Deconvolution of tissue enhancement curves and arterial input function (AIF) selected from the anterior cerebral artery was performed using modified singular value decomposition (SVD) with compensation for the effects of arterial delay and dispersion. Delay time (DT) was determined by a delay-corrected SVD deconvolution by applying a series of delay time (DT) values, with actual delay time being minimum DT value, which produces Tmax=0[24]. Delay time and Tmax are related but are not identical, and since delay time is derived from a vascular transport model correcting for arterial delay and dispersion, thresholds are smaller than Tmax[23]. Delay Time has demonstrated superior correlation with tissue at risk in recent studies[25]. Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV) were calculated from the peak height and area under tissue enhancement curves respectively, and Mean Transit Time (MTT) = CBV/CBF.

Ischemic core was defined as tissue with relative CBF <40% of contralesional hemisphere and relative DT >2 sec; penumbra was defined as tissue with relative DT >2 sec but relative CBF e 40% of contralateral[23].

To account for limited z axis coverage of CTP, we reduced the 70ml threshold used by EXTEND-IA[23] and DEFUSE-2[26] proportionately, by dividing the mean of (Coregistered Infarct volume over 4cm/Total Infarct volume from whole brain NCCT) in the non-recanalized group: pproximately 70% of the total infarct was covered by the CTP slab, therefore we considered large core to be >50ml.We evaluated baseline NCCT for ASPECT scores[27].

CTA collaterals were graded if retrograde flow was seen on CTP source images, [28] and defined as good (vessels reconstitute distal to the occlusion), moderate (vessels seen partially in ischemic territory), or poor (contrast opacification seen only in distal superficial branches).We modified Miteff's classification to incorporate terminal ICA, M1, or M2 occlusion, (the original classification excluded M2 occlusion)[28].

Imaging Outcome Variables:

On 24h NCCT, we classified ICH as per ECASS 2 criteria,[13] and SICH as any ICH with increase in NIHSSe 4 points[13]. Any PH1 or PH2 were considered significant haemorrhage. Early vasogenic brain edema was classified as per IST-3[29] as no swelling (0), effacement of lateral ventricle (1), effacement of lateral plus 3rd ventricles (2), or midline shift (3): we defined grades 2-3 as Significant Brain Edema (SBE). Recanalization was defined as Thrombolysis in Myocardial Infarction (TIMI)[30] grading 2- 3 at 24 hour follow up CT angiogram[31].

As an exploratory analysis, early major neurological improvement (NIHSS 0 or 1, or improvement by e8 points by 24h) was taken as a biomarker of early reperfusion, and outcomes were compared among three groups – i) no recanalization on 24h CTA; ii) recanalization on 24h CTA but no early improvement (presumed late recanalization); and iii) recanalization on 24h CTA and early improvement, (presumed early recanalization).

Statistical Analysis:

We compared groups by recanalization and ischemic core volume, using chi-squared tests or Fisher's exact tests for categorical variables, and Mann-Whitney tests for continuous variables. We evaluated the independent effect sizes of recanalization, core volume and their interaction on imaging and clinical outcomes using logistic regression. Analyses used IBM SPSS Statistics (version 22).

Results:

Of 263 subjects, 159 had anterior circulation stroke with vessel occlusion pre-treatment; we excluded 24 subjects presenting >4.5h after onset, and 12 in whom 24h CTA was not evaluable, leaving 123 subjects. Baseline collateral grading was available in a subset of 106 subjects.

Median age was 74 years (IQR 62-80), median NIHSS 15 [IQR 9-20], and median symptom onset to treatment time 180min (IQR 151-210). Occlusion site was ICA or M1 in 84 (68%). Recanalization on 24h CTA was seen in 80 (66%) overall, with recanalization in 30%, Tandem or proximal ICA, 74% of M1, 87% of M2 and 50% of M3 occlusions (online supplementary Table I). Mean time interval from treatment to follow up imaging was 27.5 hrs (SD ±7). Detailed baseline characteristics are presented in Table.1. Tenecteplase was used in 31 patients and alteplase in 92.

Most hemorrhages were HI1 or HI2 (28 (23%)) and there were few PH1 or PH2 (8 (6%)). There was a trend for recanalization to be associated with ICH of any class (28 (35%) v 8 (18%); p=0.06), predominantly HI1/HI2 (22 (27.5%) v 6 (14%); p=0.08), while incidence of PH1/PH2 did not differ (6 (7.6%) v 2 (4.6%); p=0.5. Figure.1). Edema of any grade was less frequent with 24h recanalization,

although not significantly (32 (40%) v 23 (53%); p=0.15) and significant brain edema was not related to recanalization (12 (15%) v 6 (12%); p=0.8. See figure. 2).

Neither significant edema (12/92 alterplase-treated versus 6/31 tenecteplase-treated , OR 0.6, 95% CI 0.2-1.8; p=0.4), nor significant haemorrhage (8/92 alteplase-treated versus 0/31 tenecteplase-treated, p=0.2; odds ratio not calculable) was associated with thrombolytic agent.

After adjusting for 24h recanalization, large core (>50ml) was associated with both hemorrhage and edema, most notably with SBE, although no significant relationship with PH1/PH2 ICH or SICH was evident. Recanalization was also associated with a trend towards any ICH, particularly HI1/2 ICH, but not to edema (Table 2). Regression analysis did not identify significant interaction of large core and 24h recanalization for any outcome (Table 2). Recanalization was associated with significantly reduced odds of death or dependence (mRS 3-6) at day 30 or 90, while large core volume was associated with increased odds of these outcomes.

Early major improvement occurred in 36 patients: 45 had recanalized by 24h CTA but did not exhibit early major improvement, and 38 showed no recanalization and no early improvement. Edema and hemorrhagic outcomes were generally lower and day 90 excellent recovery better, in the group with presumed early recanalization but did not differ significantly between the late recanalizers and those with no recanalization (Table 3 and online Supplementary Table II).

Discussion:

Recent focus on potential hazards of IV rtPA highlights limited data on the interaction of patient characteristics, especially ischemic tissue volumes, reperfusion and the pathophysiology of hemorrhage and brain edema. Few patients have been studied with detailed brain imaging[16], only a proportion of whom

have received thrombolytic therapy; animal models[22, 32] may not recapitulate the human situation, and other data derive from series of late endovascular intervention[33].

Our cohort allowed the study of interactions between 24h recanalization, perfusion characteristics and incidence of both ICH and early brain edema. We found ICH incidence comparable to previous literature, for example ICH of all kinds in 34% (36/123) compared to 48% in ECASS-II, and SICH in 5.7% (7/123) compared to7.7% in meta-analysis of thrombolysis trials[6]. Our incidence of early vasogenic brain edema of any degree was 45% (55/123) and of SBE 6.8% (18/123) are comparable to reported figures for edema[8] and for SBE (4% in tPA and 3% in control groups of IST-3)[7] that used similar definitions, although other definitions yield variations in incidence [34]. Our recanalization rate on 24h CTA (66% overall) was almost identical to that reported in the IMS-3 rtPA treated group, as were recanalization rates by occlusion site.[35] The major predictor of ICH and SBE in our study was the presence of a large "core", defined by CTP thresholds and adjusted for limited z-axis coverage of our CTP protocol. This is consistent with a rodent study in which infarct volume, but not reperfusion, was associated with edema[36]. Older literature on reperfusion and post-ischemic edema in non-human primates examined only early time points (< 6 hours) of unclear clinical relevance[22, 37, 38]. Recanalization in our study, in contrast, was associated only with a trend towards HI1/2 ICH. Neither recanalization, large core nor their interaction was associated with clinically relevant PH1/2 ICH. DEFUSE[12] reported potential interaction of large core and early reperfusion in provoking SICH, and defined the "malignant profile" based on MRI features similar to the CTP features in our study. Of 6 DEFUSE subjects with the "malignant profile," 3 experienced (uniformly fatal) SICH. The combined EPITHET and DEFUSE studies[13] included only 27 "malignant profile" patients, of whom 6/9 who reperfused developed PH1/2 ICH, compared to 2/18 without reperfusion. Despite similar patient numbers, we were unable to replicate this interaction. Since perfusion characteristics may better define ICH risk than diffusion-weighted MRI[19], it seems unlikely that this is due to a difference between MRI and CT-based tissue viability assessment methods.

As an exploratory analysis we assessed major early clinical improvement as a biomarker of early reperfusion. This group had significantly fewer ICH or edema events and greater probability of favourable day 90 outcome. The incidence of significant ICH or edema did not differ between those with presumed late recanalization and those without recanalization, but it is not possible to exclude a relationship between late recanalization and adverse imaging outcomes.

Good clinical outcome was strongly associated with 24h recanalization (OR 2.8 (1.2-6.8); p=0.02) and was less likely with large core (OR 0.15 (0.04-0.5); p=0.03), consistent with previous observations[39], but there was no significant interaction between these variables in predicting good 90 day outcome. This is consistent with the known prognostic value of both variables [39, 40], but also with the lack of interaction between endovascular treatment effect and CTP features.[41]

Our study has limitations**.** As a single centre, retrospective analysis, independent replication in other settings is desirable. The small number of clinically significant hemorrhagic and brain swelling outcomes inevitably lead to wide confidence intervals around the effect estimates, encompassing the possibility that recanalization may be related to either significant edema or ICH, and means that conclusions must be cautious: nonetheless, with a larger number of outcome events we were unable to replicate earlier reports of an association with ICH, as discussed above. No classification of brain edema has been reported consistently in clinical studies, and different classification methods may yield different incidence. The timing of brain imaging for outcome assessment in our dataset (mean 27.5h after IV thrombolysis) is too early to detect maximal brain swelling, but while this might underestimate the severity of brain edema, it seems unlikely to underestimate the incidence of significant brain edema based on data that indicate that 95% of cases progressing to malignant MCA infarction were identifiable on 24h CT[34]. CTP analysis was based on validated thresholds, but standardisation is not yet agreed[42]. Since we had access to angiographic outcome data only at approximately 24h, we could not discriminate early from late recanalization, which

may carry different risks of ICH,[43, 44] although we undertook exploratory analyses using early clinical improvement as a biomarker for this. In addition, recanalization does not necessarily lead to tissue reperfusion[45], which is the more important parameter at tissue level[46]. We used TIMI 2-3 (partial or complete recanalization) since even partial restoration of flow might be expected to impact on adverse complications, whereas TIMI 3 would be more strongly related to favourable clinical outcomes, which was an endpoint of secondary interest in this study. The overall recanalization rate at 24h in our study (66%) matches that reported by the IMS-3 trialists (65%) based on a 24h CTA endpoint, with comparable individual occlusion site recanalization rates ,[35] offering further reassurance about external validity.

Our findings indicate that 24h recanalization itself is not significantly associated with early vasogenic edema, or significant hemorrhage, questioning the widespread attribution of these outcomes to "reperfusion injury." The association of large core with both significant edema, and also poor outcome in spite of recanalization, is consistent with recent clinical trial strategies that have sought to exclude such patients from reperfusion therapies. Observational data cannot define risk: benefit ratio, however, and it is important to bear in mind that excluding "large core" patients might represent an efficient clinical trial strategy, but that risk: benefit balance in this group remains to be determined: treatment in this group may still be associated with net benefit.

Conclusions: Among patients treated with IV rtPA, 24h recanalization was not independently associated with significant early (24h) vasogenic edema or significant hemorrhage, although incidence of hemorrhagic infarction types 1 and 2 was higher. Large ischemic core was associated with both significant brain edema and poor outcome. There was no interaction of recanalization and large core lesions for any imaging outcomes. Early major clinical improvement as a marker of probable early reperfusion, was associated with lower incidence of both significant hemorrhage and edema.

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Tables & Figures:

Table1. Baseline characteristics of study population (n=123)

Variables	Recanalized (n=80)	Occluded (n=43)	P*
Age (median (IQR), years)	73 (63-81)	74 (62-79)	0.8
Male (n, %)	48 (60%)	21 (48.8%)	0.1
NIHSS baseline(median, IQR)	15(9-19)	14(9-20)	0.6
Onset to treatment time(median , IQR, min)	175(145-210)	190(165-206)	0.6
ASPECT score (median, IQR)	7(5-9)	7(5-9)	0.9
Occlusion Site:			<0.01
ICA/tandem (n, %) †	9 (11.3%)	21 (48.8%)	
M1 (n, %) †	40 (50%)	14 (32.6%)	
M2 (n, %) †	27 (33.8%)	4 (9.3%)	
M3 (n, %) †	4 (5%)	4 (9.3%)	
Cardioembolic (n, %) Â	34(47.9%)	16 (39%)	0.7
TACI (n, %) §	54 (67.5%)	30 (69.8%)	0.7
Atrial Fibrillation (n, %)	35 (47.9%)	14 (33.3%)	0.17
Diabetes (n, %)	8 (10%)	5 (11.6%)	0.7
History of Stroke or Transient Ischemic attack (n, %)	14 (18%)	7 (16.3%)	1.0
Hypertension (n, %)	45 (56.3%)	26 (62%)	0.5
Smoker (n, %)	23 (28.8%)	14 (32.6%)	0.3
On anti platelets (n, %)	42 (52.5%)	24 (55.8%)	0.8

Imaging outcomes in relation to recanalization within small or large core groups (n=122)Á

	Core small(<50ml) (n=95)			Core large(>50ml) (n=27)		p
ICA or M1 occlusion†	57(69%)			26(96%)		<0.001
Poor (vs. good or moderate) collaterals	9/78(11.5%)			12/22(54.5%)		<0.01
Poor outcome (mRS 3-6 at 30 or 90 days)	51(54%)			24(89%)		0.001
	Recanalized (n=63)	Occluded(n=32)	P value	Recanalized (n=16)	Occluded(n=11)	P value
Any ICH (n, %)	19 (30%)	4 (12%)	0.06	8 (50%)	4 (36%)	0.5
HI1 or HI2 (vs. no ICH, PH1, PH2)	14 (22%)	3 (9.4%)	0.16	7 (44%)	3 (27%)	0.4
Type of hemorrhage						0.25

#						
No ICH (n, %) #	44 (70%)	28 (87%)	0.35	8 (50%)	7 (63.6%)	
HI1 (n, %) #	5 (8%)	2 (6%)		3 (19%)	3 (27%)	
HI2 (n, %) #	9 (14%)	1 (3%)		4 (25%)	0 (0%)	
PH1 (n, %) #	1 (1.6%)	0 (0%)		0 (0%)	1 (9%)	
PH2 (n, %) #	4 (6%)	1 (3%)		1 (6%)	0 (0%)	
Any edema (n, %)	19 (31%)	15 (47%)	0.13	12 (75%)	8 (73%)	0.9
Edema type**						0.38
No edema (n, %)**	44 (70%)	17 (53%)	0.17	4 (25%)	3 (27%)	

Effacement of lateral ventricle (n, %)**	16 (25%)	13 (40%)		3 (19%)	4 (36%)	
Effacement of lateral ventricle and 3rd ventricle (n, %)**	2 (3%)	0 (0%)		6 (37.5%)	1 (9%)	
Midline shift (n, %)**	1 (1.6%)	2 (6.3%)		3 (19%)	3 (27%)	
SICH (ECASS-2) (n, %) #	4 (6%)	1 (3%)	0.5	0	2(18%)	0.07
Significant ICH (n, %)	5 (8%)	1 (3%)	0.36	1 (6%)	1 (9%)	0.8
SBE (n, %) ††	3 (5%)	2 (6%)	0.7	9 (56%)	4 (36%)	0.3
Poor	20 (47%)	22 (69%)	0.04	13 (81%)	11	0.13

outcome at 30 d or 90d (mRS>2) (n, %)					(100%)	

* Chi-square test or Fisher test for categorical variables, Mann-whitney U test for continuous variables

ASPECT score: Alberta stroke Early CT Score

† ICA-Internal Carotid artery, M1,M2,M3- branches of Middle cerebral artery

ÂCardio embolic versus other aetiologies (large artery atherosclerosis, lacunar stroke, unknown cause)

§ Total anterior circulation Infarction(TACI) versus other stroke types (Oxford stroke classification)

Áone subject out of total study population (n=123)did not have core size available

#Hemorrhage classification according to ECASS-2 criteria

** Brain edema classification by Wardlaw&Sellar criteria

††SBE: Significant Brain Edema

Table 2: Regression for association of large core and recanalization, and their interaction, for imaging and clinical outcomes

	Any ICH*	HI1 or HI2†	Significant ICH*	SICHÂ	Any edema	SBE§	Good 90d mRS (0-2)
Large core (OR (95% CI); p)	4 (1.6-9.5); p=0.003	2.9 (1.13-7.8); p=0.03	1.2 (0.23-6.5); p=0.8	1.6 (0.3-8.5); p=0.6	5.4 (2-14); p<0.01	17.4 (5.3-57); p<0.01	0.15 (0.04-0.5); p=0.03
Recanalization (OR (95% CI); p)	2.3 (0.97-5.5); p=0.06	2.5 (0.9-6.9); p=0.08	1.7 (0.33-8.8); p=0.5	0.8 (0.17-3.8); p=0.8	0.5 (0.27-1.18); p=0.13	1.45 (0.4-4.9); p=0.55	2.8 (1.2-6.8); p=0.02
Large core * Recanalization (OR (95%CI);	0.34 (0.05-2.2); p=0.26	0.7 (0.09-6); p=0.8	0.25 (0.007-9); p=0.45	p=1Á	1.7 (0.2-11); p=0.56	3(0.2-34) p=0.37	p=0.99#

p)							

* ICH Intracerebral hemorrhage, Hemorrhagic infarction type 1 or 2, ÂSymptomatic Intracerebral hemorrhage, § Significant Brain Edema, ÁSince 0% of recanalized group in large core has SICH, the corresponding odds ratios cannot be calculated,# since 100% of occluded group in large core have poor 90dmRS, the corresponding odds ratios cannot be calculated.

Table.3: Comparison of early improvers with non-early improvers

	Early improvement (n=36)	No early improvement/Recanalized (n=45)	No early improvement/Non-recanalized (n=38)	P value§
Any ICH	5 (14%)	19 (42%)	9 (24%)	0.014
Significant ICH	1 (3%)	5 (11%)	2 (5%)	0.3
SICH*	0	3 (7%)	3 (8%)	0.25
Any edema	7 (19%)	24 (53%)	21 (55%)	0.002
SBE	2 (5.6%)	10 (22%)	6 (16%)	0.11
Good 90d mRS	22 (63%)	12 (27%)	10 (26%)	0.001

ICH: Intracerebral hemorrhage

*SICH as per ECASS-2 criteria

SBE: Significant brain edema

§ chi-square values