**Brain imaging abnormalities and outcome after acute ischaemic stroke: the ENCHANTED trial**

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**ABSTRACT**

**Objective:**To test the hypothesis that imaging signs of ‘brain frailty’ and acute ischaemia predict clinical outcomes and symptomatic intracranial haemorrhage (sICH) after thrombolysis for acute ischaemic stroke (AIS) in the alteplase-dose arm of ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED).

**Methods:**Blinded assessors coded baseline images for acute ischaemic signs (presence, extent, swelling and attenuation of acute lesions; and hyper-attenuated arteries) and pre-existing changes (atrophy, leukoaraiosis and old ischaemic lesions). Logistic regression models assessed associations between imaging features and death at 7 and 90 days; good recovery (modified Rankin scale scores 0-2 at 90 days) and sICH. Data are reported with adjusted odds ratios (OR) and 95% confidence intervals (CI).

**Results:**2916 patients (67±13 years, National Institutes of Health Stroke Scale 8 [5-14]) were included. Visible ischaemic lesions, severe hypoattenuation, large ischaemic lesion, swelling and hyper-attenuated arteries were associated with 7 day-death (OR [95% CI]: 1·52 [1·06-2·18]; 1·51 [1·01-2·18]; 2·67 [1·52-4·71]; 1·49 [1·03-2·14] and 2·17 [1·48-3·18]) and inversely with good outcome. Severe atrophy was inversely associated with 7 day-death (0·52 [0·29-0·96]). Atrophy (1·52 [1·08-2·15]) and severe leukoaraiosis (1·74 [1·20-2·54]) were associated with 90 day-death. Hyper-attenuated arteries were associated with sICH (1·71 [1·01-2·89]). No imaging features modified the effect of alteplase dose.

**Conclusions:** Non-expert defined brain imaging signs of brain frailty and acute ischaemia contribute to the prognosis of thrombolysis-treated AIS patients for sICH and mortality.

However, these imaging features showed no interaction with alteplase dose.

**INTRODUCTION**

Findings from the third International Stroke Trial (IST3) suggest that acute brain imaging signs of acute ischaemia and markers of ‘brain frailty’ individually, and in combination, predict clinical outcome and sICH[1]. Key findings were that acute ischaemic tissue hypoattenuation, lesion swelling and hyperattenuated artery sign, and pre-existing signs of cerebrovascular disease (“brain frailty”) including leukoaraiosis and cerebral atrophy, predicted poor functional outcome, while tissue hypoattenuation, hyperattenuated artery and previous infarction, increased the risk of sICH. We aimed to confirm or refute these findings in the international, ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) with three important differences: a broader sociodemographic mix of patients; an opportunity to identify whether dose of alteplase influenced the findings; and whether a less experienced brain imaging analysis team, more representative of everyday clinical practice, would lead to similar findings. The latter being particularly important for the potential generalisability of the findings. We also recognise that replication is an important mechanism to reduce waste in biomedical research[2]. Herein, we report our prospectively designed study of the prognostic value of acute brain imaging signs, individually and combined, and their interaction with alteplase dose in the ENCHANTED trial.

**METHODS**

**Study design**

ENCHANTED was an international, multicentre, 2x2 quasi-factorial prospective, randomised, open-label, blinded-endpoint assessed trial that evaluated a lower dose of alteplase[3](#_ENREF_6) and more intensive blood pressure lowering in thrombolysis-eligible acute ischaemic stroke (AIS) patients[3,4]. These results are based on participants contributing to the alteplase arm of the trial[3]. Key demographic and clinical characteristics were recorded at the time of enrolment, where clinical severity was defined according to the National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, and at Day 7 (or earlier, on discharge from hospital). The primary efficacy clinical outcome of this imaging study was good outcome, defined by scores 0-2 on the modified Rankin scale (mRS) at 90 days post-randomisation. Secondary safety outcomes were any sICH according to standard criteria on brain imaging adjudicated centrally, by an adjudication panel of experts[5]. The study protocol was approved by the appropriate ethics committee at each participating centre, and written informed consent was obtained from each patient or an appropriate surrogate. The study is registered with clinicaltrials.gov (number NCT01422616).

**Imaging analyses**

Uncompressed digital images of baseline and follow-up CT, MRI, and angiography, were uploaded into the study brain imaging database in Digital Imaging and Communications in Medicine (DICOM) format identified only by the patient's unique study identification number. Where multiple baseline scans were available for a patient, we identified one of these assessments for analysis based on the following rules: non-contrast CT in preference to the plain CT images from CT angiogram or perfusion studies (N[scans excluded]=27); plain CT images from CT angiogram in preference to that from CT perfusion (N[scans excluded]=7); CT scan with thick slices (N[scans excluded]=3); scanning time closest to time of randomisation (N[scans excluded]=7) and MRI when only MRI was conducted at baseline (N[scans included]=100’). Assessment of intracranial haemorrhage was assessed visually by an adjudication panel using the MIStar imaging analysis software (MIStar™ Apollo Inc, Melbourne, Australia), blind to all clinical data. The brain imaging assessment of haemorrhage (Appendix 1) and clinical event reporting were taken from the main trial database.

Our analysis of the non-haemorrhagic components of the brain imaging was established in August 2016. We created a research team with a background in stroke but not necessarily imaging interpretation expertise (one neuroradiologist, 8 stroke neurologists, and 2 stroke neurology trainees) who received standardised training whereby each reader completed the ACCESS training module of recognised acute and pre-existing imaging features ([www.ed.ac.uk/edinburgh-imaging/access](http://www.ed.ac.uk/edinburgh-imaging/access)), as well as in-house training on the MIStar software and data forms. Depending on availability, each reader assessed a median of 265 scans (range 8 to 873 scans), and most (7/11) assessed >100 scans. Interobserver agreement and accuracy in a randomly selected sample of scans was assessed using Krippendorff’s Alpha[6]. For inter-observer agreement, we compared the results from 285 scans that were double read by at least two readers. For reader accuracy, we compared results from 53 scans with an expert gold standard (consensus opinion of two neuroradiologists specialising in stroke imaging, each with >10 years’ experience). The Landis and Koch methods were used to interpret these agreement as ‘slight’ (0.00-0.20), ‘fair’ (0.21-0.40), ‘moderate’ (0.41-0.60), ‘substantial’ (0.61-0.80), and ‘almost perfect agreement’ (0.81-1.00)[7]. Inter-observer agreement was fair-moderate (0.36-0.44) for acute brain changes, and moderate-substantial (0.49-0.62) for chronic brain changes. Accuracy was moderate-substantial for all imaging features assessed (0.50-0.64).

Our imaging assessment was largely derived from the IST3 methodology[8], and included information from a systematic review of acute ischaemic signs[9], a large observer validity study[10-13], and advice from experts. All components used validated scales[14]. We defined the presence and degree of hypoattenuated tissue as either mild (grey matter attenuation equal to normal white matter) or severe (grey and white matter attenuation less than normal white matter)[9]. The extent of acute ischaemic lesions was classified in two ways: with the IST3 method, which includes the whole brain where the score for infarct extent includes all arterial territories[15]; and with the Alberta Stroke Program Early CT Score (ASPECTS)[14]which focuses only on the middle cerebral artery (MCA) territory; although, the version of ASPECTS used in IST3 and for our study, allowed additional scoring of abnormal anterior cerebral artery (ACA) and posterior cerebral artery (PCA) territories. Thus, we used the IST3 score as the primary measure of ischaemic lesion size in analyses, condensing the full IST3 lesion extent score into four groups: small lesions, as lacunar, small cortical, small cerebellar, less than half of brainstem, or less than half of the ACA or PCA territory; medium lesions, classified as striatocapsular, the anterior or posterior half of the peripheral MCA territory, or more than half the ACA or PCA territory; large lesions, defined as the whole of the peripheral MCA territory or all the MCA territory; and very large lesions, which comprised the whole MCA and PCA territory, all the MCA and ACA territory, or all three territories. For ischaemia within the ACA circulation, the corresponding scores on ASPECTS were 8-10, 5-7 and 0-4, for small, medium, and large or very large lesions on the IST3 score[11]. We graded ischaemic lesion swelling on a widely validated 7-point ordinal scale[15] but due to small numbers in categories 4 to 6, these were group into a single category of ‘severe effacement’. The presence or absence, and location of any, hyperattenuated artery[16], the location of old infarcts (ie cortical, lacunar, border zone, and brainstem or cerebellar)[15], and the presence and severity of leukoaraiosis on CT[17] or MRI[18], were also recorded using validated scales. We classified cerebral atrophy as none, moderate, or severe, when compared against standard examples as used previously[19].

In these analyses, we used the ENCHANTED blinded haemorrhage assessment for the secondary outcome, and chose the IST3 definition of symptomatic haemorrhagic transformation of infarction as our primary outcome. This definition encompasses either significant ICH (local or distant from the infarct) or significant haemorrhagic transformation of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment[8]; other recognised definitions of sICH were assessed in sensitivity analyses (See appendix for definitions)[5].

**Statistical analysis**

Absolute probability of associations between individual imaging signs and primary and secondary outcomes were presented unadjusted.

Multivariable stepwise logistic regression with age, NIHSS score, and time from symptom onset to randomisation forced into the model, was used to identify whether any combinations of imaging variables were independently associated with sICH and mRS score 0-2 at Day 90. The same analysis was conducted by adding history of diabetes mellitus and baseline systolic blood pressure to the model. Treatment effects of low-dose versus standard-dose alteplase on functional status and sICH were determined using logistic regression models, with the heterogeneity of alteplase dose effect across subgroups estimated by adding an interaction term. Data are reported as adjusted odds ratios (OR) and 95% confidence intervals (CI). Two-sided P values are reported, with P<0·05 considered statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for analyses.

**Role of the funding source**

The sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to the study data. The corresponding author had final responsibility for the decision to submit the paper for publication.

**Data availability**

Individual de-identified participant data used in these analyses will be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health, Australia.

**RESULTS**

Among the 3310 participants in the alteplase-dose arm of ENCHANTED, 2916 had brain imaging (2816 brain CT scans and 100 brain MRI) and outcome data available for these analyses (Figure 1). The absolute percentages of outcomes were 2.6%, 4.6%, 9.4% and 61% for sICH, day 7-death, day 90-death and mRS 0-2 at day 90 respectively (Table S3). Table 1 shows the baseline characteristics of these participants. Most patients (59.6%) were randomised within 3 hours from the onset of symptoms, and approximately one third had completely normal brain imaging at baseline. Approximately one third had an acute ischaemic lesion which was most often of moderate size (85% had an ASPECT score 8-10), with swelling and hyperattenuated arteries present in fewer than 40% and 20%, respectively. Pre-existing signs of cerebrovascular disease were common: two thirds showed some degree of cerebral atrophy and one third each had old infarcts or some leukoaraiosis.

Increasing NIHSS score, but not age, was associated with a higher frequency of early ischaemic changes, with several signs (visible infarct, severe versus mild hypoattenuation) also becoming more frequent with increasing delay from stroke onset to baseline imaging. Increasing age was associated with a higher frequency of pre-existing brain imaging signs of atrophy, leukoaraoisis and/or previous infarction (adjusted for stroke severity), but not the severity of acute ischaemia. Delay in treatment was associated with pre-existing infarction (Table 2).

Individually, only hyperattenuated arteries predicted IST3-defined sICH. The acute signs of visible ischaemic lesion, severe versus mild hypoattenuation, large lesion, swelling and hyperattenuated arteries, each predicted early death, with one pre-existing sign (severe atrophy) suggesting protection. However, all pre-existing signs were highly significant in predicting less favorable 90-day functional outcome (Table 3). Similar findings were found when the analysis was adjusted for additional variables (Table S2). Atrophy predicted sICH, according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) and National Institute of Neurological Disorders and Stroke (NINDS) criteria, while severe hypoattenuation, hyperattenuated arteries and severe leukoaraiosis predicted any ICH and any adjudicated ICH (Table S1).

In the multivariable logistic regression, only hyperattenuated arteries and standard-dose (compared to low-dose) alteplase predicted sICH. However, many variables predicted poor functional outcome (increasing age, stroke severity, swelling, hyperattenuated arteries, old infarct and severe leukoaraoisis) (Table 4).

A similar pattern was seen in stepwise logistic regression (Table 5).

There was no significant interaction between low-dose and standard-dose, and early or pre-existing signs (Figures S1 and S2).

**DISCUSSION**

In these prospectively-planned secondary analyses of the alteplase-dose arm of the ENCHANTED trial, both pre-existing (‘brain frailty”) and acute ischaemic brain imaging signs were shown to have prognostic significance in terms of functional outcome, and to a lesser extent sICH, in AIS patients treated with intravenous alteplase. Specifically, acute brain ischaemic changes were associated with short term death at 7 days and sICH and brain frailty was associated with death at 90 days but atrophy reduced early mortality.

These results largely confirm those from IST3, despite major differences in the study population characteristics of the two studies. Our ENCHANTED participants were over a decade younger than those in IST3, were assessed earlier in the course of their illness (mean time from symptoms onset to treatment, 170 vs. 252 min) and had less severe stroke (median NIHSS score, 8 vs. 13). Despite these baseline differences and for IST3 to have included patients outside of the conventional time window and regulatory criteria for thrombolysis, our results confirm the prognostic significance of certain brain imaging markers despite nearly three times as many patients had a normal baseline scan in ENCHANTED compared to IST3. In addition, consistent with the younger age of the ENCHANTED cohort, we found less atrophy, leukoaraiosis and old infarcts than in IST3. Despite these important differences, indicating that the ENCHANTED cohort had less brain “frailty”, the prognostic factors were remarkably similar, thus providing new evidence of the robustness of these findings.

The importance of AIS signs are well recognised but these results emphasise that pre-existing brain frailty signs provide important additional prognostic value. Interestingly, whilst atrophy might provide protection from an early death (perhaps by allowing greater tolerability to brain swelling), its presence reduces the chances of good functional outcome (perhaps through loss of neuronal plasticity and recovery). Leukoaraiosis and old infarcts similarly reduced the chance of good functional outcome.

Replication of research findings is increasingly recognised as an important part of scientific progress[2], and replication of the IST3 results was a pre-specified goal of ENCHANTED.

Importantly, the prognostic information obtained in ENCHANTED was derived by a less expert imaging team (stroke neurologists) than utilised in IST-3 (mainly neuroradiologists), further strengthening the external validity of these data for clinical practice.

We recognise, however, that we were also able to identify some differences with the previous IST3 results, where we found no association between the frequency of early ischaemic change and increasing age. Previous studies have shown that pre-existing age-related signs can mask acute imaging signs, but the younger age of those in ENCHANTED may explain why we did not see any association with less evidence of atrophy (63% in ENCHANTED vs. 77% in IST3), leukoaraiosis (33% vs. 51%) and previous cerebral infarction (35% vs. 44%). Even so, and as reported in IST3, increasing atrophy and leukoaraiosis were still related to ageing in our younger cohort. Worsening neurological severity increased the likelihood of identifying acute ischaemic imaging signs (such as visible lesion, severe hypoattenuation, brain swelling and a large lesion), and a delay from the onset of symptoms increased the likelihood of observing a visible lesion, severe hypoattenuation and brain swelling, thus providing internal validity. In addition, ENCHANTED showed that old infarcts alone or in combination, were not associated with sICH, whilst hyperattenuated arteries were predictive of sICH in both ENCHANTED and IST3; and the presence of old infarction was only predictive of sICH in IST3. It is possible that the lower proportion of the ENCHANTED cohort in this later category (35% vs. 44%) is one part of the explanation, but the younger age is another explanation.

There was no heterogeneity of alteplase dose, treatment effect, on functional outcome (mRS 3-6) according to imaging characteristics, but these analyses had low statistical power. These results confirm that whilst the imaging signs can provide useful prognostic information, they should not on their own be used to inform alteplase dose treatment decisions. The observed statistically significant increased risk of sICH with standard-dose versus low-dose alteplase provides further reassuring internal validity for our results, being consistent with the overall clinical findings of the ENCHANTED trial[3].

The strengths of our analysis include the prospective design, with an aim to replicate or refute previous findings from an earlier trial, the common use of imaging definitions and study data forms; the large number of participants in a completely different independent cohort; the generalisability across many nations and regions of the world; and the consistency of the results, despite a less expert imaging panel of readers. This latter point may reflect consistent training and expertise gained through a high volume of scans assessed by each reader. However, there are some weaknesses, as some members of the study team were also part of the IST3 study group (RIL and JMW), and the less expert imaging panel may have under-estimated the prognostic value of some imaging features. The assessment of acute ischaemic signs had only fair to moderate reproducibility, as shown by the mid-range coefficient for agreement between raters. However, similar levels of agreement were found in IST-3 despite the reader panel comprising greater neuroradiological expertise[20]. Caution should applied when brain CT scan signs are used to discuss individual patient management. Although some of the relative effects of the imaging factors appeared large in our analysis; in absolute terms, the incidences of outcomes and differences caused by the presence of imaging signs are too small to alter the decision to thrombolyse. Finally, the large and very heterogenous number of scanners utilised in the study may have reduced prognostic power but adds real-world relevance.

In summary, our analyses have confirmed the important prognostic value of brain imaging signs in patients scanned within a few hours of the onset of AIS, and together with those of IST3, now provide robust evidence to help guide clinicians when considering prognosis in such patients treated with thrombolysis. Certain imaging signs can predict early and delayed death, and functional outcome, but are less useful when trying to identify who has the potential to be harmed from sICH after alteplase.

**Table 1: Baseline clinical and imaging variables by alteplase dose**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Low-doseAlteplase group (N=1465)** | **Standard-doseAlteplase group (N=1451)** |
| Mean age (years) | 67 (13) |  |  |
| Age Categories | ≤80 | 1233/1465 (84.2) | 1234/1451 (85.0) |
|  | >80 | 232/1465 (15.8) | 217/1451 (15.0) |
|  | ≥18 and ≤50 | 148/1465 (10.1) | 140/1451 (9.6) |
|  | >50 and ≤60 | 276/1465 (18.8) | 268/1451 (18.5) |
|  | >60 and ≤70 | 382/1465 (26.1) | 410/1451 (28.3) |
|  | >70 and ≤80 | 427/1465 (29.1) | 416/1451 (28.7) |
|  | >80 and ≤90 | 198/1465 (13.5) | 188/1451 (13.0) |
|  | >90 | 34/1465 (2.3) | 29/1451 (2.0) |
| Baseline NIHSS | 8 [5-14] |  |  |
| NIHSS score categories | 0-5 | 428/1465 (29.2) | 443/1451 (30.5) |
|  | 6-10 | 491/1465 (33.5) | 446/1451 (30.7) |
|  | 11-15 | 276/1465 (18.8) | 280/1451 (19.3) |
|  | 16-20 | 170/1465 (11.6) | 183/1451 (12.6) |
|  | >20 | 100/1465 (6.8) | 99/1451 (6.8) |
| Pre-stroke mRS=1 |  | 280/1462 (19.2) | 297/1447 (20.5) |
| Time to randomisation (hours) | 0 to ≤3 | 858/1443 (59.5) | 848/ 1431 (59.3) |
|  | >3  | 585/1443 (40.5) | 583/1431 (40.7) |
| Assessment of AIC on baseline images by site clinicians | No change & visible lesion | 987/1463 (67.5) | 965/1448 (66.6) |
|  | Visible change | 359/1463 (24.5) | 353/1448 (24.4) |
|  | Visible lesion | 339/1463 (23.2) | 346/1448 (23.9) |
| Assessment of AIC on baseline images centrally | Scan completely normal | 501/1464 (34.2) | 475/1447 (32.8) |
|  | Not normal but no AIC | 461/1464 (31.5) | 486/1447 (33.6) |
|  | Signs of any AIC | 502/1464 (34.3) | 486/1447 (33.6) |
| Early ischaemic lesion/change territory | Indeterminate | 971/1465 (66.3) | 971/1451 (66.9) |
|  | MCA or ACA or border zone | 425/1465 (29.0) | 413/1451 (28.5) |
|  | Posterior | 25/1465 (1.7) | 11/1451 (0.8) |
|  | Lacunar | 44/1465 (3.0) | 56/1451 (3.9) |
| Early ischaemic lesion size | None visible | 994/1454 (68.4) | 994/1439 (69.1) |
|  | Small | 105/1454 (7.2) | 101/1439 (7.0) |
|  | Medium | 298/1454 (20.5) | 285/1439 (19.8) |
|  | Large | 55/1454 (3.8) | 59/1439 (4.1) |
|  | Very large | 2/1454 (0.1) | 0/ 1439 (0.0) |
| ASPECT score | 0-4 | 85/1465 (5.8) | 78/1451 (5.4) |
|  | 5-7 | 133/1465 (9.1) | 146/1451 (10.1) |
|  | 8-10 | 1247/1465 (85.1) | 1227/1451 (84.6) |
| Degree of tissue hypoattenuation | None | 1030/1464 (70.4) | 1035/1447 (71.5) |
|  | Mild | 368/1464 (25.1) | 353/1447 (24.4) |
|  | Severe | 66/1464 (4.5) | 59/1447 (4.1) |
| Degree of swelling | None | 965/1465 (65.9) | 968/1451 (66.7) |
|  | Mild sulcal effacement | 271/1465 (18.5) | 253/1451 (17.4) |
|  | Mild ventricular effacement | 195/1465 (13.3) | 205/1451 (14.1) |
|  | Moderate effacement | 34/1465 (2.3) | 25/1451 (1.7) |
|  | Severe effacement | 0/1465 (0.0) | 0/1451 (0.0) |
| Location of hyperattenuated arteries | None | 1221/1465 (83.3) | 1204/1451 (83.0) |
|  | Only anterior circulation | 230/1465 (15.7) | 229/1451 (15.8) |
|  | Only posterior circulation | 9/1465 (0.6) | 12/1451 (0.8) |
|  | MCA, or ACA, or BA | 243/1465 (16.6) | 244/1451 (16.8) |
|  | MCA, or ACA, or PCA  | 234/1465 (16.0) | 233/1451 (16.1) |
| Pre-existing brain changes | Evidence of atrophy | 934/1465 (63.8) | 915/1451 (63.1) |
|  | Evidence of leukoaraiosis | 488/1465 (33.3) | 465/1451 (32.0) |
|  | Evidence of old infarcts | 488/1465 (33.3) | 533/1451 (36.7) |
|  | Evidence of old haemorrhage | 13/1465 (0.9) | 16/1451 (1.1) |

Data are n (%), mean (SD), median (interquartile range)

ACA denotes anterior cerebral artery, AIC acute ischaemic changes, BA basilar artery, MCA middle cerebral artery, NIHSS National Institutes of Health Stroke Scale, PCA posterior cerebral artery.

**Table 2: Logistic regression analysis of associations between imaging signs and age, NIHSS score, and time to randomization**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Age, adjusted for NIHSS score** | **p value** | **NIHSS score, adjusted for age** | **p value** | **Delay, adjusted for age and NIHSS score** | **p value** |
| Early ischaemic signs |  |  |  |  |  |  |
| Visible ischaemic lesion | 1.00 (0.99-1.00) | 0.1536 | 1.05 (1.04-1.06) | **<0.0001** | 1.09 (1.01-1.17) | **0.0182** |
| Hypoattenuation | 1.00 (0.99-1.00) | 0.3826 | 1.04 (1.03-1.06) | **<0.0001** | 1.08 (1.01-1.16) | **0.0241** |
| Large lesion | 0.99 (0.98-1.01) | 0.4953 | 1.10 (1.07-1.13) | **<0.0001** | 1.06 (0.96-1.18) | 0.2690 |
| Swelling | 1.00 (0.99-1.00) | 0.1836 | 1.05 (1.03-1.06) | **<0.0001** | 1.09 (1.01-1.17) | **0.0180** |
| Hyperattenuated arteries | 1.00 (0.99-1.01) | 0.9289 | 0.91 (0.90-0.93) | **<0.0001** | 1.04 (0.95-1.13) | 0.4044 |
| Pre-existing signs |  |  |  |  |  |  |
| Atrophy | 1.10 (1.09-1.11) | **<0.0001** | 1.01 (1.00-1.02) | 0.1788 | 0.98 (0.92-1.05) | 0.5543 |
| Leukoaraiosis | 1.08 (1.07-1.09) | **<0.0001** | 0.99 (.0.97-1.00) | 0.0598 | .1.07 (1.00-1.15) | 0.0528 |
| Old infarct | 1.03 (1.03-1.04) | **<0.0001** | 0.99 (0.98-1.01) | 0.239 | 1.09 (1.01-1.16) | **0.0174** |

Data are OR (95% CI) and p value.

NIHSS denotes National Institutes of Health Stroke Scale.

**Table 3: Logistic regression analysis of associations between individual imaging signs and primary and secondary outcomes, adjusted for age, NIHSS score, and time to randomisation**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **sICH (IST3)** |  | **Death within 7 days** |  | **Death within 90 days** |  | **mRS 0-2** |  |
|  |  | **Adjusted Odds ratio (95%CI)** | **p** | **Adjusted Odds ratio (95%CI)** | **p** | **Adjusted Odds ratio (95%CI)** | **p** | **Adjusted Odds ratio (95%CI)** | **p** |
| Early ischaemic signs | Visible ischaemic lesion | 1.3 (0.82-2.08) | 0.2666 | 1.52 (1.06-2.18) | **0.0243** | 1.27 (0.97-1.68) | 0.0819 | 0.7 (0.59-0.84) | **0.0001** |
| Hypoattenuation | 1.17 (0.72-1.9) | 0.5233 | 1.51 (1.04-2.18) | **0.0287** | 1.27 (0.96-1.68) | 0.0968 | 0.74 (0.62-0.9) | **0.0018** |
| Severe hypoattenuation | 0.9 (0.28-2.91) | 0.8642 | 1.24 (0.52-2.96) | 0.6203 | 0.87 (0.43-1.74) | 0.6908 | 1.16 (0.76-1·78) | 0.4825 |
| Large lesion | 0.83 (0.25-2.7) | 0.5460 | 2.67 (1.52-4.71) | **0.0007** | 1.94 (1.19-3.17) | **0.0078** | 0.52 (0.33-0·81) | **0.0035** |
| Very large lesion | 0 (0-0) | 0.9876 | 12.08 (0.65-223.57) | 0.0942 | 6.88 (0.39-120.4) | 0.1864 | 0 (0-0) | 0.9701 |
| Swelling | 1.24 (0.78-1.99) | 0.3597 | 1.49 (1.03-2.14) | **0.0323** | 1.27 (0.96-1·67) | 0.0886 | 0.7 (0.58-0.84) | **0.0001** |
| Hyperattenuated arteries | 1.71 (1.01-2.89) | **0.0446** | 2.17 (1.48-3.18) | **0.0001** | 1.87 (1.39-2.52) | **0.0000** | 0.63 (0.5-0.79) | **0.0001** |
| Pre-existing signs | Atrophy | 0.88 (0.51-1.52) | 0.5420 | 0.99 (0.64-1.53) | 0.9629 | 1.52 (1.08-2.15) | **0.0178** | 0.83 (0.68-1.01) | 0.0625 |
| Severe atrophy | 1.59 (0.88-2.86) | 0.1246 | 0.52 (0.29-0.96) | **0.0352** | 1.29 (0.9-1.84) | 0.1594 | 0.83 (0.64-1.06) | 0.1327 |
| Leukoaraiosis | 0.84 (0.5-1.4) | 0.4964 | 1.07 (0.71-1.61) | 0.7613 | 1.17 (0.87-1.58) | 0.2881 | 0.71 (0.59-0.86) | **0.0005** |
| Severe leukoaraiosis | 0.78 (0.36-1.69) | 0.533 | 1.2 (0.68-2.11) | 0.5266 | 1.74 (1.2-.2.54) | **0.0037** | 0.68 (0.51-0.89) | **0.0055** |
| Old infarct | 0.95 (0.59-1.54) | 0.838 | 1.24 (0.85-1.81) | 0.2646 | 1.2 (0.91-1.58) | 0.2072 | 0.7 (0.59-0.84) | **0.0001** |

Data are adjusted OR (95% CI), p values. Variable results are shown as yes versus no.

mRS denotes modified Rankin Scale, sICH symptomatic intracerebral haemorrhage;

**Table 4: Full multivariable logistic regression models for symptomatic intracerebral haemorrhage and functional outcome at 3 months**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **sICH**  | **p** | **mRS 0-2** | **p** |
|  | **OR (95%CI)\*** | **OR (95%CI)\*** |
| Age (years) | 1.01 (0.99-1.03) | 0.4557 | 0.98 (0.97-0.99) | **<0.0001** |
| NIHSS score | 1.03 (0.99-1.07) | 0.1038 | 0.86(0.85-0.88) | **<0.0001** |
| Time to randomisation (hours) | 0.97 (0.77-1.21) | 0.7652 | 0.99 (0.92-1.06) | 0.7068 |
| Treatment group (standard vs. low) | 1.63 (1.00-2.64) | **0.0487** | 1.08 (0.90-1.29) | 0.3983 |
| Antiplatelet (Yes vs. No) | 1.35 (0.80-2.29) | 0.2606 | 0.95 (0.77-1.17) | 0.6415 |
| Lesion size (large or very large vs. others) | 0.65 (0.19-2.23) | 0.4898 | 0.56 (0.34-0.9) | **0.0178** |
| Swelling | 0.87 (0.22-3.48) | 0.8492 | 0.56 (0.32-0.97) | **0.0379** |
| Hyperattenuated arteries | 1.81 (1.03-3.17) | **0.0380** | 0.70 (0.55-0.9) | **0.0043** |
| Old infarct | 0.93 (0.56-1.56) | 0.7969 | 0.78 (0.64-0.94) | **0.0090** |
| Hypoattenuation (mild vs. none) | 1.44 (0.35-5.9) | 0.6091 | 1.31 (0.74-2.31) | 0.3472 |
| Hypoattenuation (severe vs. none) | 0.91 (0.13-6.45) | 0.9276 | 1.94 (0.96-3.89) | 0.0631 |
| Atrophy (mild vs. none) | 0.95 (0.51-1.76) | 0.8707 | 0.81 (0.64-1.01) | 0.0599 |
| Atrophy (severe vs. none) | 1.73 (0.78-3.86) | 0.1802 | 0.74 (0.54-1.03) | 0.0708 |
| Leukoaraiosis (mild vs. none) | 0.76 (0.39-1.48) | 0.4260 | 0.80 (0.63-1.01) | 0.0657 |
| Leukoaraiosis (severe vs. none) | 0.67 (0.29-1.54) | 0.3409 | 0.64 (0.47-0.87) | **0.0043** |

Data are adjusted for age, NIHSS and time to randomisation.

CI denotes confidence interval, NIHSS National Institutes of Health Stroke Scale, mRS modified Rankin Score, sICH symptomatic intracerebral haemorrhage according to IST3 definition

**Table 5: Multivariable logistic regression models selected by stepwise logistic regression for sICH (IST3 definition) and functional outcome at 90 days**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **sICH** | **p** | **mRS 0-2** | **p** |
|  | **OR (95%CI)** | **OR (95%CI)** |
| Age (years) | 1.01(0.99-1.03) | 0.1947 | 0.98(0.97-0.99) | **<0.0001** |
| NIHSS score | 1.03(0.99-1.07) | 0.1130 | 0.86(0.85-0.88) | **<0.0001** |
| Time to randomisation (hours) | 0.95(0.76-1.2) | 0.6755 | 0.99(0.92-1.06) | 0.7505 |
| Treatment group (standard vs. low-dose) | 1.60(0.99-2.59) | 0.0545 | 1.08(0.91-1.29) | 0.3887 |
| Lesion size (large or very large vs. others) |  |  | 0.57(0.35-0.92) | **0.0207** |
| Swelling |  |  | 0.79(0.65-0.97) | **0.0256** |
| Hyperattenuated arteries | 1.86(1.09-3.17) | **0.0227** | 0.68(0.54-0.87) | **0.0018** |
| Old infarct |  |  | 0.76(0.63-0.91) | **0.0038** |
| Hypoattenuation (mild vs. none) |  |  |  |  |
| Hypoattenuation (severe vs. none) |  |  |  |  |
| Leukoaraiosis(mild vs. none) |  |  | 0.78(0.62-0.99) | **0.0369** |
| Leukaraiosis (severe vs. none) |  |  | 0.61(0.46-0.82) | **0.0011** |

Data are adjusted for age, NIHSS and time to randomisation.

CI denotes confidence interval, NIHSS National mRS denotes modified Rankin Score, NIHSS National Institutes of Health Stroke Scale, sICH symptomatic intracerebral haemorrhage according to IST3 definition

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**CONTRIBUTORS**

Candice Delcourt designed and conceptualized study, had a major role in the acquisition of data, analyzed the data, interpreted the data, drafted the manuscript for intellectual content, revised the manuscript for intellectual content and takes responsibility for the overall content.

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Richard Lindley designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content, revised the manuscript for intellectual content and takes responsibility for the overall content.

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**FIGURE LEGEND**

**Figure 1: Trial flowchart**

Footnote: a There was only enhanced image of CTA or reconstructed MRA available at baseline.

bIn participants with multiple baseline CT scans, we choose only one scan for analysis based on following priority: (1) non-contrast CT is prior to the plain CT images in CTA or CTP; (2) CT scan with thick slices is prior to CT scan with thin slices; (3) scanning time closest to the randomisation. Other baseline CT scans are excluded for analysis.

cThe scan was received repeatedly or different CT images/MRI sequences of one scan were received separately and stored as individual scans.