Clinical prognosis of FLAIR hyperintense arteries in ischaemic stroke patients: a systematic review and meta-analysis

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ABSTRACT

Objective  We performed a systematic review and meta-analysis to determine the association of fluid-attenuated inversion recovery (FLAIR) hyperintense arteries (FLAIR-HAs) on brain MRI and prognosis after acute ischaemic stroke (AIS).

Methods  We searched Medline, Embase and Cochrane Central Register of Controlled Trials for studies reporting clinical or imaging outcomes with presence of FLAIR-HAs after AIS. Two researchers independently assessed eligibility of retrieved studies and extracted data, including from the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED). Outcomes were unfavourable functional outcome (primary, modified Rankin scale scores 3–6 or 2–6), death, intermediate clinical and imaging outcomes. We performed subgroup analyses by treatment or types of FLAIR-HAs defined by location (at proximal/distal middle cerebral artery (MCA), within/beyond diffusion-weighted imaging (DWI) lesion) or extent.

Results  We included 36 cohort studies (33 prospectively collected) involving 3577 patients. FLAIR-HAs were not associated with functional outcome overall (pooled risk ratio 0.87, 95% CI 0.71 to 1.06), but were significantly associated with better outcome in those receiving endovascular therapy (0.56, 95% CI 0.41 to 0.75). Contrary to FLAIR-HAs at proximal MCA or within DWI lesions, FLAIR-HAs beyond DWI lesions were associated with better outcome (0.67, 95% CI 0.57 to 0.79). FLAIR-HAs favoured recanalisation (1.21, 95% CI 1.06 to 1.38) with increased risk of intracerebral haemorrhage (2.07, 95% CI 1.37 to 3.13) and early neurological deterioration (1.93, 95% CI 1.30 to 2.85).

Conclusions  FLAIR-HAs were not associated with functional outcome overall but were associated with outcome after endovascular therapy for AIS. FLAIR-HAs were also associated with early recanalisation or haemorrhagic complications, and early neurologic deterioration.

INTRODUCTION

Fluid-attenuated inversion recovery (FLAIR) hyperintense arteries (FLAIR-HAs) are a common sign (>45%) on brain MRI in patients with acute ischaemic stroke (AIS).1,2 Although recognised for nearly two decades,3,4 the prognostic significance of FLAIR-HAs has not been well defined despite reflecting the presence of a large ischaemic penumbra and good collateral circulation from slow retrograde flow distal to the occluded vessel (‘clot’) or ischaemic lesion.5–7 Potential reasons for this uncertainty in the literature include the limitations of retrospective design, small sample size, varying assessment of FLAIR-HAs, different treatments administered to patients and heterogeneity of endpoints across studies.5–14

Our previous analyses of thrombolysis-treated AIS patients (n=293) from the alteplase-dose arm of the international Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED)15 showed that presence of FLAIR-HAs was independently associated with a favourable 90-day functional outcome, defined on the modified Rankin scale (mRS) (scores 0–1 (n=144), adjusted OR 4.14, 95% CI 1.63 to 10.50) despite an increased risk of haemorrhagic infarct (adjusted OR 4.77, 95% CI 1.12 to 20.26) after adjusting for baseline covariables (unpublished). Herein, we extended this work through a systematic review and meta-analysis of the association of FLAIR-HAs with early vascular recanalisation or reperfusion, intracerebral haemorrhage (ICH), cerebral infarct growth and clinical outcomes in AIS.

METHODS

Search strategy

The protocol followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement,16 and was registered with PROSPERO international prospective register of systematic reviews. Our search strategy was based on a combination of the following medical subject headings terms or keywords: [‘arterial hyperintensity’ OR ‘hyperintense vessels’ OR ‘vascular hyperintensities’] AND [‘FLAIR’ OR ‘MRI’] AND [‘cerebrovascular disease’ OR ‘stroke’ OR ‘cerebral infarction’] (Methods S1 in the online supplemental material). Medline, Embase and the Cochrane Central Register of Controlled Trials were searched from inception to the end of October 2019. The clinicaltrials.gov website was searched for randomised controlled trials (RCTs) registered as completed but not yet published. There was no language restriction. Reference lists of all retrieved studies and
related review articles were cross-checked for further relevant studies until no further publications were found.

Eligibility criteria
We included the ENCHANTED trial and other RCTs or cohort studies that recruited AIS patients (age ≥ 18 years) where baseline brain MRI was performed after admission and before intravenous thrombolysis or endovascular therapy. We aimed to extract data on vascular recanalisation or reperfusion, infarct growth, ICH, short/long-term clinical outcomes (measured by National Institutes of Health Stroke Scale (NIHSS) or mRS score) from reports. We excluded: (i) studies where outcomes were not reported separately for participants who did and did not have FLAIR-HAs; (ii) where the primary aim was to assess the effect of FLAIR-HAs change before and after thrombolysis on clinical prognosis, or to explore the association of FLAIR-HAs with other imaging features such as collateral flow, perfusion status or perfusion-diffusion mismatch; and (iii) reviews, editorials, letters, case or case series reports, guidelines, technical notes and book chapters. Conference abstracts were not excluded if the data could be extracted.

In this report, we also included 220 ENCHANTED participants (198 from alteplase-dose arm and 22 from blood pressure lowering arm) who had middle cerebral artery (MCA) infarct identified on MRI obtained within 4.5 hours of symptom onset with both FLAIR and diffusion-weighted imaging (DWI).

Study selection and data extraction
The screen of potentially eligible studies identified by searches was conducted by two authors (ZZ and AM) to select reports for review in full text. Each full text article was reviewed for eligibility by these authors and, for each included study, data were extracted independently using a standardised electronic form; any disagreement was settled by discussion or in consultation with two other authors (SY and CD). Extracted data included: (i) first author, year of publication, publication type, country or region, study design, sample size, inclusion criteria, clinical and imaging characteristics of recruited participants at baseline (age, sex, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation (AF), coronary artery disease, history of stroke, current smoking status, NIHSS score, time from stroke onset to MRI, infarct volume, hypoperfusion volume, proximal arterial or large vessel occlusion and collateral grade); (ii) treatment administered to the study patients (intravenous thrombolysis, endovascular therapy, conservative treatment or mixed treatments); (iii) FLAIR-HAs definition or assessment method by location or extent: at proximal (M1 or M1-2 segment) or distal (M3-6 segment) MCA, within or beyond DWI lesion, FLAIR-HAs score (0–10, calculated by using 10 consecutive axial slices from the first slice with an appearance of the M1 segment of MCA, absence of FLAIR-HAs on one slice rated 0 and ≥1 present rated 1 point), modified Alberta Stroke Program Early CT Score (ASPECTS) grade for FLAIR-HAs (0–7, calculated according to the spatial distribution in seven cortical areas of ASPECTS (insula, M1-M6), absence of FLAIR-HAs in one area rated 0 and present rated 1 point); and (iv) primary and other outcomes in patients who did and did not have FLAIR-HAs on baseline MRI. In cases of missing data, the authors were contacted using details given in articles or identified by internet search. Two authors (ZZ and AM) also judged the quality of each included studies according to the Cochrane Collaboration’s tool for RCT or the Newcastle-Ottawa Scale (NOS) for cohort studies.

Outcomes
The primary outcome of interest was unfavourable functional outcome, defined by mRS scores 2–6 or 3–6. Other outcomes were: 90-day unfavourable functional outcome, any death, intermediate clinical outcomes (early neurological improvement (ENI), early neurological deterioration (END), NIHSS score change before and after treatment), and intermediate imaging outcomes (early vascular recanalisation or reperfusion, ICH, infarct growth).

Statistical analysis
The number of dichotomous outcomes was summarised. Mean values with SD or median values with ranges or IQRs were collated for continuous outcomes. Pooled risk ratios (RR) with 95% CI were estimated for dichotomous outcomes using the DerSimonian and Laird random-effects model. For changes in NIHSS scores and infarct growth, the extracted data were only tabulated, given their non-normal distribution and it was not common to estimate pooled median differences through meta-analysis. In every case, a two-sided p value ≤0.05 was deemed significant. The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated using the I² statistic, and by calculating the p value for heterogeneity. I² values of 25%, 50% and 75% were regarded as low, moderate and high heterogeneity, respectively. Where there was a high likelihood of heterogeneity in pooled primary outcome, sensitivity analyses were performed by excluding individual studies: those without prospective data collection or studies where participants had late brain MRI (>24 hours after onset). As planned, subgroup analyses were performed for the primary outcome by treatment administered to patients, or types of FLAIR-HAs defined by location or extent. In addition, a random-effects meta-analysis was undertaken to show the association of clinical and imaging factors with the presence of FLAIR-HAs on baseline MRI. Evidence of publication bias was assessed using Egger’s regression test for funnel asymmetry in addition to visual inspection of the funnel plots. All statistical analyses were performed using Stata V.12.0.

RESULTS
Study selection and characteristics
The literature search in April 2019 yielded 219 potentially eligible articles or conference abstracts, of which 44 articles were reviewed in full (figure 1). After search updating by the end of October 2019 and including data from the ENCHANTED trial, a total of 36 cohort studies (33 with prospective data collection, 6 from conference abstracts) involving 3577 AIS patients met the inclusion criteria. Excluded studies included: not original research, no eligible research objectives or outcomes of interest, duplicate cohorts or outcome data not separately obtainable in patients with and without FLAIR-HAs. Included studies were published between 2007 and 2019, and the sample sizes ranged from 3011 to 325, with MCA infarct being the predominant lesion type (online supplementary table 1). Twenty-six studies involving 2681 patients’ with MCA infarct being the predominant lesion type (online supplementary table 1). The number of eligible studies (patients) for meta-analysis of recanalisation or reperfusion at 24–48 hours was 17 (n = 1487), 17 12 13 23 24 25 31 33 35 36 38–44 46 48 49

ICH 7 (n = 1114), 9 15 28 31 40 45 ENI 5 (n = 644), 7 24 30 32 END 4 (n = 738) 40 48 and any death 3 (n = 635), 12 40 Seventeen studies
Cerebrovascular disease

Figure 1 Flow chart of literature search. ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; FLAIR, fluid-attenuated inversion recovery; F-HAs, FLAIR hyperintense arteries.

(n=1677) reported infarct volume on admission or within 5 days after admission, in which six studies (n=705) reported infarct growth. Data from 21 studies\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^12\)\(^3\)\(^7\)\(^8\)\(^9\)\(^10\)\(^12\)\(^13\)\(^23\)\(^25\)\(^29\)\(^31\)\(^33–37\)\(^40\)\(^42\)\(^43\)\(^48\) were pooled for predictors with the presence of FLAIR-HAs. Only one study\(^13\) had low quality, with more than half of the total items (6/9) being assessed as having a high risk of bias (online supplementary table 2).

**Association of FLAIR-HAs with functional outcome**

Prior AF (pooled RR 1.17, 95% CI 1.01 to 1.36; \(p=0.04\)) and proximal arterial occlusion (pooled RR 1.88, 95% CI 1.28 to 2.77; \(p=0.001\)) were significantly associated with the presence of FLAIR-HAs (table 1). Overall, compared with no FLAIR-HAs, the presence of FLAIR-HAs was not associated with poor functional outcome (pooled RR 0.87, 95% CI 0.71 to 1.06; \(p=0.17\)). However, there was a significant association with better functional outcome in patients who had endovascular therapy (pooled RR 0.56, 95% CI 0.41 to 0.75; \(p<0.001\)) (figure 2). Comparable results were observed in sensitivity analyses for 90-day functional outcome (online supplementary figure 1) and after excluding studies without prospective data collection and early brain MRI (online supplementary figure 2). There was high heterogeneity in results pooled for functional outcome \((I^2=86.4\%)\), which persisted in sensitivity analyses. There were diverging associations in subgroup analyses by different types of FLAIR-HAs and functional outcome: being associated with unfavourable outcome for FLAIR-HAs in relation to proximal MCA (pooled RR 2.01, 95% CI 1.39 to 2.89; \(p<0.001\)) and within DWI lesions (pooled RR 1.74, 95% CI 1.05 to 2.88; \(p=0.03\)), and associated with better outcome for FLAIR-HAs beyond a DWI lesion (pooled RR 0.67, 95% CI 0.57 to 0.79; \(p<0.001\)) (figure 3). There was no association with functional outcome for FLAIR-HAs related to distal MCA and with greater extent (FLAIR-HAs scores>4 or FLAIR-HAs ASPECTS grade>4). Heterogeneity for associations was generally high across studies, except in the assessment of FLAIR-HAs in relation to proximal MCA \((I^2=0.0\%)\) or beyond DWI lesion \((I^2=52.7\%)\).

**Association of FLAIR-HAs with other outcomes**

Presence of FLAIR-HAs was associated with recanalisation or reperfusion at 24 to 48 hours (pooled RR 1.21, 95% CI 1.06 to 1.38; \(p=0.005\)), increased risk of ICH (pooled RR 2.07, 95% CI 1.37 to 3.13; \(p=0.001\)) and END (pooled RR 1.93, 95% CI 1.30 to 2.85; \(p=0.001\)), all with low to moderate heterogeneity \((I^2 from 21.1\% to 51.8\%)\) (figure 4). There was no significant association with ENI (pooled RR 1.44, 95% CI 0.83 to 2.49; 0.05).

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**Table 1** Meta-analysis of the associations of baseline factors with the presence of FLAIR-HAs

| Factors | No of studies (patients) | Reference number of included studies besides ENCHANTED | Risk ratio or mean difference (95% CI) | Heterogeneity \(I^2\) (%) |
|---------|--------------------------|-------------------------------------------------------|---------------------------------------|--------------------------|
| Clinical factors | | | | |
| Age (year) (with FLAIR-HAs vs without) | 14 (1304) | 6 9 10 23 25 31 34–38 40 42 46 | –0.81 (–3.27 to 1.66) | 61.9 |
| Male vs female | 18 (1950) | 6 7 9 10 12 13 23 25 31 33–38 40 42 43 48 | 0.94 (0.87 to 1.02) | 27.4 |
| With hypertension vs without | 17 (1838) | 6 7 9 10 13 23 29 31 33–38 40 42 43 48 | 0.94 (0.87 to 1.02) | 20.1 |
| With DM vs without | 17 (1839) | 6 7 9 10 13 23 29 31 33–38 40 42 43 48 | 0.97 (0.89 to 1.06) | 0.0 |
| With dyslipidaemia vs without | 15 (1594) | 6 7 9 10 13 23 29 31 33–37 40 42 43 48 | 1.03 (0.93 to 1.13) | 27.0 |
| With AF vs without | 15 (1480) | 6 7 9 10 12 13 23 29 31 33–35 37 40 42 43 48 | 1.17 (1.01 to 1.36) | 64.7 |
| With CAD vs without | 6 (775) | 10 31 33 42 43 | 1.06 (0.87 to 1.29) | 42.3 |
| With prior stroke/TIA vs without | 6 (694) | 13 23 31 43 48 | 0.87 (0.64 to 1.19) | 54.2 |
| Smoking vs no | 14 (1608) | 6 7 9 10 23 29 33–37 40 42 43 48 | 0.94 (0.85 to 1.03) | 17.2 |
| Imaging factors | | | | |
| With proximal arterial occlusion vs without | 12 (1564) | 7 10 12 13 23 34 38 40 42 43 48 | 1.88 (1.28 to 2.77) | 91.3 |

AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; FLAIR-HAs, fluid-attenuated inversion recovery hyperintense arteries; TIA, transient ischaemic attack.
Cerebrovascular disease

Figure 2  Meta-analysis of associations between FLAIR-HAs and unfavourable functional outcome, by type of treatment administered to the study patients: ASPECTs, Alberta Stroke Program Early CT Score; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; FLAIR-HAS, FLAIR hypointense arteries; mRS, modified Rankin scale; SE/GRE, spin echo/gradient recalled echo sequence. *mRS scores 2–6 were regarded as unfavourable functional outcome (mRS scores 3–6 for other studies).

p=0.19) or death (pooled RR 3.60, 95%CI 0.65 to 19.81; p=0.14). Funnel plots and Egger’s regression tests identified no strong evidence of publication bias for all dichotomous outcomes except recanalisation or reperfusion (p=0.01) (online supplementary figure 3). Data from the ENCHANTED trial as well as several other studies had shown that patients with FLAIR-HAs had greater NIHSS scores at baseline and early follow-up than those without, but there was no apparent imbalance in the level of NIHSS scores according to FLAIR-HAs beyond a DWI lesion (online supplementary table 3). Moreover, compared with those without FLAIR-HAs, those with FLAIR-HAs had greater reduction in NIHSS scores between baseline and early follow-up and were more likely to have larger initial and subsequent growth in infarct volumes (online supplementary table 4).

DISCUSSION

In this systematic review and meta-analysis, we have identified the key determinants of FLAIR-HAs on MRI after AIS as prior AF and proximal arterial occlusion. While overall, FLAIR-HAs were not associated with functional outcome, it is associated with favourable recovery when endovascular therapy is performed.
FLAIR-HAs were also associated with early recanalisation or haemorrhagic complications, and early neurologic deterioration.

We did not identify a significant association of FLAIR-HAs with functional outcome, but there was an apparent benefit in those with MCA AIS who received endovascular therapy, where the FLAIR-HAs was located beyond a DWI lesion, and when there was no proximal FLAIR-HAs or FLAIR-HAs within the DWI lesion. FLAIR-HAs were more likely to be seen with proximal arterial occlusion, suggesting they indicate retrograde filling in the ischaemic territory by leptomeningeal collateral flow. This explanation also provides a plausible mechanism for improved outcome in such patients treated with thrombectomy. Data from ENCHANTED showed a possibility that proximal arterial occlusion status mediated the association of FLAIR-HAs with 90-day functional outcome. FLAIR-HAs, if present, are also more likely to be assessed as within rather than beyond the DWI lesions in cases where proximal arterial occlusion tends to cause a large ischaemic lesion on DWI. This may explain the variable associations of FLAIR-HAs within versus beyond the DWI lesion with the functional outcome.

We also found the presence of FLAIR-HAs favoured early recanalisation or reperfusion after reperfusion treatment,

| Source (treatment administered to patients) | Favour with FLAIR-HAs | Risk ratio (95% CI) | n/N | Without FLAIR-HAs | n/N | Weight |
|--------------------------------------------|----------------------|--------------------|-----|-------------------|-----|--------|
| With distal FLAIR-HAs vs. without          |                      |                    |     |                   |     |        |
| Ebinger et al 2012 (intravenous thrombolysis) |                      | 1.90 (1.17, 3.10)  | 25/42 | 15/48            | 9.87 |        |
| Cai et al 2014 (intravenous thrombolysis)   |                      | 3.26 (1.61, 6.58)  | 33/55 | 7/38             | 9.10 |        |
| Kim et al 2019a (intravenous thrombolysis)* |                      | 0.77 (0.36, 1.62)  | 10/26 | 6/12             | 8.94 |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 1.68 (1.11, 2.54)  | 59/134 | 21/80          | 10.09 |        |
| Miura et al 2016 (endovascular therapy)    |                      | 0.35 (0.19, 0.63)  | 9/29  | 8/9              | 9.53 |        |
| Girot et al 2007a (conservative treatment)  |                      | 10.90 (1.56, 70.89) | 12/16 | 1/4               | 6.66 |        |
| Huang et al 2012 (conservative treatment)   |                      | 0.34 (0.21, 0.56)  | 12/42 | 27/32            | 9.83 |        |
| Song et al 2016 (conservative treatment)    |                      | 0.45 (0.33, 0.62)  | 27/65 | 21/23            | 10.34 |        |
| Nam et al 2017 (conservative treatment)     |                      | 2.04 (1.41, 2.94)  | 74/152 | 27/113         | 10.21 |        |
| Li et al 2018 (conservative treatment)      |                      | 0.86 (0.53, 1.39)  | 13/22 | 11/16            | 8.99 |        |
| Kim et al 2019b (conservative treatment)*   |                      | 2.90 (1.00, 8.77)  | 24/54 | 3/20             | 7.54 |        |
| Subtotal (I-squared = 91.4%, p = 0.000)     |                      | 1.17 (0.88, 2.03)  | 298/637 | 147/405      | 100.00 |        |
| With proximal FLAIR-HAs vs. without         |                      |                    |     |                   |     |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 2.19 (1.45, 3.29)  | 58/117 | 22/97            | 79.13 |        |
| Girot et al 2007b (conservative treatment)  |                      | 1.40 (0.68, 3.24)  | 5/9  | 8/21             | 20.87 |        |
| Subtotal (I-squared = 0.0%, p = 0.371)     |                      | 2.01 (1.39, 2.89)  | 63/126 | 30/118         | 100.00 |        |
| With FLAIR-HAs beyond DWI lesion vs. without|                      |                    |     |                   |     |        |
| Legrand et al 2016 (intravenous thrombolysis) |                      | 0.67 (0.53, 0.84)  | 64/121 | 34/43            | 17.73 |        |
| Ichioji et al 2017 (intravenous thrombolysis)* |                      | 0.63 (0.43, 0.95)  | 18/39 | 24/33            | 10.42 |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 0.75 (0.52, 1.09)  | 29/92 | 51/122           | 11.48 |        |
| Liu et al 2016a (endovascular therapy)      |                      | 0.74 (0.61, 0.90)  | 36/52 | 46/49            | 19.53 |        |
| Jiang et al 2016b (endovascular therapy)    |                      | 0.48 (0.28, 0.81)  | 13/39 | 14/20            | 7.10  |        |
| Legrand et al 2016 (endovascular therapy)   |                      | 0.82 (0.51, 1.33)  | 34/79 | 11/21            | 8.15  |        |
| Song et al 2019 (conservative treatment)    |                      | 0.81 (0.67, 0.97)  | 47/66 | 39/43            | 19.91 |        |
| Yuan et al 2019 (conservative treatment)    |                      | 0.28 (0.15, 0.52)  | 9/41  | 21/27            | 5.68  |        |
| Subtotal (I-squared = 52.7%, p = 0.039)     |                      | 0.67 (0.57, 0.79)  | 250/529 | 239/358       | 100.00 |        |
| With FLAIR-HAs inside DWI lesion vs. without |                      |                    |     |                   |     |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 2.33 (1.69, 3.22)  | 36/62 | 41/152           | 33.92 |        |
| Liu et al 2016b (endovascular therapy)      |                      | 1.29 (1.09, 1.52)  | 35/37 | 47/84            | 37.90 |        |
| Addia et al 2013b (mixed treatment)         |                      | 1.83 (1.10, 3.03)  | 36/59 | 12/36            | 28.28 |        |
| Subtotal (I-squared = 87.2%, p = 0.000)     |                      | 1.74 (1.05, 2.88)  | 110/158 | 100/252       | 100.00 |        |
| FLAIR-HAs scores>4 vs. ≤4                    |                      |                    |     |                   |     |        |
| Ollondo et al 2012 (intravenous thrombolysis) |                      | 0.53 (0.39, 0.72)  | 31/71 | 28/34            | 25.97 |        |
| Kuhner et al 2015 (intravenous thrombolysis) |                      | 1.84 (1.03, 3.20)  | 19/31 | 10/30            | 22.93 |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 2.09 (1.45, 3.00)  | 50/95 | 30/119           | 25.43 |        |
| Vural et al 2016 (mixed treatment)          |                      | 1.01 (0.72, 1.41)  | 23/31 | 14/19            | 25.67 |        |
| Subtotal (I-squared = 92.5%, p = 0.000)     |                      | 1.18 (0.59, 2.34)  | 123/228 | 82/202         | 100.00 |        |
| FLAIR-HAs ASPECT grade>4 vs. ≤4            |                      |                    |     |                   |     |        |
| ENCHANTED (intravenous thrombolysis)       |                      | 1.82 (1.41, 2.38)  | 25/47 | 55/167           | 31.80 |        |
| Nave et al 2018 (endovascular therapy)      |                      | 0.84 (0.48, 0.98)  | 36/74 | 31/41            | 33.38 |        |
| Mahdoub et al 2018 (mixed treatment)        |                      | 0.88 (0.69, 1.12)  | 82/161 | 48/83           | 34.83 |        |
| Subtotal (I-squared = 87.7%, p = 0.000)     |                      | 0.96 (0.60, 1.55)  | 143/282 | 134/261       | 100.00 |        |

NOTE: Weights are from random effects analysis.
which is consistent with prior studies reporting good leptomeningeal collateral flow being associated with recanalisation or reperfusion after either intravenous thrombolysis or endovascular therapy.50–53 Good leptomeningeal collaterals have been shown to be associated with permeable thrombus, which is easier to lyse based on larger contact surface area between the thrombus and alteplase for use of intravenous thrombolysis or ease of thrombectomy with stent retrievers due to reduced wall tension.54–57 Association between FLAIR-HAs and ICH could be supported by the concept that reperfusion can lead to haemorrhagic infarct (HI): Miller Fisher found petechial HI around infarcts (mainly occipital lobe) in a small post-mortem study in

Figure 4  Meta-analysis of associations between FLAIR-HAs and death, intermediate clinical and imaging outcomes. ASPECTs, Alberta Stroke Program Early CT Score; CT, conservative treatment; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; DWI, diffusion-weighted imaging; ET, endovascular therapy; FLAIR, fluid-attenuated inversion recovery; FLAIR-HAs, FLAIR hyperintense arteries; ICH, intracerebral haemorrhage; IT, intravenous thrombolysis; MT, mixed treatment; SE/GRE, spin echo/gradient recalled echo sequence.
the 1950s,58 or that HI is more common with proximal arterial occlusion: another small contemporaneous post-mortem study reported worse HI with proximal arterial occlusion and peripheral collaterals replicated in primates.59 Our prior analysis of ENCHANTED participants showed that a significant increase in the risk of ICH after intravenous thrombolysis was driven by HI (adjusted OR 4.77, 95% CI 1.12 to 20.26; p=0.03) rather than parenchymal haemorrhage (adjusted OR 0.78, 95% CI 0.21 to 2.91; p=0.71) after adjustment of baseline covariables, which may explain why the clinical prognosis is not influenced even after haemorrhagic complications occur in those with FLAIR-HAs.

It is interesting that the pooled results for ENI and END were contradictory. The small number of studies included in our meta-analysis, and the different definitions of ENI or END across studies (online supplementary table 3), limits the robustness of these results and raises the potential influence of the play of chance. The consistent results from the ENCHANTED data were that FLAIR-HAs were associated with an increased risk of END, and a decrease in ENI, which may be related to a greater likelihood of ICH after reperfusion in those with FLAIR-HAs versus without, but this needs further confirmation in the future.

A key limitation of the study is the low number of studies and participants to allow examination of associations in subgroups and for some intermediate outcomes, raising the potential for chance finding. While caution is warranted over the interpretation of the findings in relation to FLAIR-HAs in patients who received endovascular therapy, early recanalisation or haemorrhagic complications, and early toward producing an individual participant data meta-analysis in the ENCHANTED trial and varied according to types of therapy warrants future investigation. Another issue is that we of stroke patients with DWI-FLAIR mismatch for endovascular as an additional imaging marker to select these and other types outcomes, raising the potential for chance finding. Evidence on the use of MRI in wake-up stroke patients has been provided recently.60 Whether FLAIR-HAs may serve as an additional imaging marker to select these and other types of stroke patients with DWI-FLAIR mismatch for endovascular therapy warrants further investigation. Another issue is that we were not able to provide a strong estimate of the relation with NIHSS score change or infantar growth, which were undertaken in the ENCHANTED trial and varied according to types of FLAIR-HAs defined by location or extent. A future collaboration towards producing an individual participant data meta-analysis could provide more insights.

In summary, FLAIR-HAs were not associated with functional outcome overall but were associated with outcome after endovascular therapy for AIS. FLAIR-HAs were also associated with early recanalisation or haemorrhagic complications, and early neurologic deterioration.

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