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Susceptibility vessel sign on MRI predicts better clinical outcome in patients with anterior circulation acute stroke treated with stent retriever as first-line strategy

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ABSTRACT

Background Susceptibility vessel sign (SVS) can be a useful MRI biomarker of an occlusion but its relationship with clinical outcomes of acute ischemic stroke (AIS) is yet to be fully elucidated.

Objective To investigate SVS in relation to the clinical outcomes after mechanical thrombectomy using a stent retriever (SR) as first-line approach in patients with AIS.

Material and methods We included patients with a first-line SR approach for anterior AIS from the *Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER)* and *THRombectomy des Artères Cerebrales (THRACE)* trials when both baseline imaging of SVS and 90-day modified Rankin Scale (mRS) scores were available. Patients were assigned to two groups based on the presence of an SVS (independent core laboratory), and the overall distributions of the mRS score at 90 days (shift analysis) and clinical independence (mRS score ≤ 2) were compared.

Results 217 patients were included and SVS was diagnosed in 76.0% of cases ($n=165$, 95% CI 70.4% to 81.7%). After adjustment for potential confounders, SVS+ was significantly associated with 90-day mRS improvement (adjusted common OR=2.75; 95% CI 1.44 to 5.26) and favorable outcome (adjusted common OR=2.76; 95% CI 1.18 to 6.45).

Conclusion Based on results for patients of the ASTER and THRACE trials receiving first-line SR treatment, SVS was associated with lower disability at 3 months. Large prospective studies using MRI-based thrombus evaluation are warranted.

(THRACE) trials are large multicenter prospective randomized control studies that included patients who were treated with MT for AIS.^{3,4} In these trials, most of the patients were selected for treatment and inclusion with MRI, allowing thrombus characteristics to be evaluated using the MRI susceptibility vessel sign (SVS).⁵ The SVS can be identified on T2* gradient recalled echo (GRE) sequences and corresponds to a localized hypointense signal at the site of the thrombus, exceeding the diameter of the contralateral artery.^{5,6} Retrospective monocentric studies have shown that qualitative evaluation of SVS could help predict reperfusion and clinical outcome after MT.^{7–11} The presence of a SVS (SVS+) is probably related to a larger amount of red blood cells within the thrombus that can favourably interfere with the stent retriever (SR) struts during retrieval.^{12–15} Conversely, its absence (SVS–) has been related to the presence of fibrin-rich thrombi, typically harder to extract with conventional MT using a SR.^{15–18} A SR is the most commonly used technique and, moreover, was the strategy used to show the efficacy of endovascular thrombectomy compared with IV thrombolysis (IVT) alone. Thus, the purpose of our study was to investigate whether SVS+ is associated with better clinical and angiographic outcome after MT with SR first-line SR treatment in patients presenting with anterior AIS.

MATERIAL AND METHODS

The designs of the two trials from which our study population is derived have been already reported.^{3,4,19}

ASTER examined the question of which first-line strategy for MT (contact aspiration (CA) or SR) leads to higher revascularization rates at the end of the procedure. In line with the recommendations of the American Stroke Association and European Stroke Organization, enrolled patients were given IVT (if eligible) and transferred quickly to the catheter laboratory for urgent MT.² CA or SR techniques were conducted in accordance with good practice recommendations (minimum of three passes before switching to another strategy; use of a

INTRODUCTION

After demonstration of the superiority of mechanical thrombectomy (MT) over standard medical management alone, the current challenges in the field of acute ischemic stroke (AIS) focus on reducing time to reperfusion, optimizing imaging methods for patient selection, and evaluating the best technical approach.^{1,2} The *Contact Aspiration vs Stent Retriever for Successful Revascularization (ASTER)* and the *THRombectomy des Artères Cerebrales*



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proximal occlusion balloon with the SR). The CA approach has been previously reported.^{20,21} The ASTER protocol was registered with ClinicalTrials.gov (Identifier NCT02523261) and the consent forms were approved by an independent institutional review board (Comité de Protection des Personnes Ile de France VI (ID 2015- A00830 –49)).

THRACE aimed to compare IVT alone with IVT plus MT using SR to determine their effects on clinical independence at 3 months in patients with AIS. Patients were included within 4 and 6 hours of symptom onset, respectively, in the THRACE and ASTER trials. The THRACE protocol was approved by an independent institutional review board (Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers). All patients or their legal representatives provided written informed consent. For both trials, practitioners had to show proof of performance of at least five MT procedures before the trial.

Population study

We included, from the ASTER trial, patients (between October 2015 and October 2016) who received MT with first-line SR treatment and from the THRACE trial, patients (between June 2010 and February 2015) who received IVT plus MT with SR as first line strategy.

Patients with posterior circulation and tandem occlusion were excluded, as were patients for whom baseline SVS information or the 3-month modified Rankin Scale (mRS) scores were not available. The inclusion flowchart is presented in figure 1.

Baseline characteristics, including sex, age, gender, history of hypertension, systolic and diastolic blood pressure, diabetes mellitus, hyperlipidemia, glycemia, smoking habits, initial National Institutes of Health Stroke Scale (NIHSS) score, baseline Alberta Stroke Program Early CT Score (ASPECTS), site of occlusion (either M1/M2 or intracranial carotid artery), IVT use and time between onset and imaging, groin puncture and thrombus contact, were also recorded.

Imaging analysis

SVS was classified as present (SVS+) or absent (SVS–), according to the definition of Rovira *et al*,⁵ by independent core laboratories, on the admission T2* MRI sequence. Inter-reader agreement was assessed using un-weighted kappa and 95% CI in each trial.

Outcomes

The primary outcome was global disability, assessed by overall distribution of the mRS score at 90 days (shift analysis combining

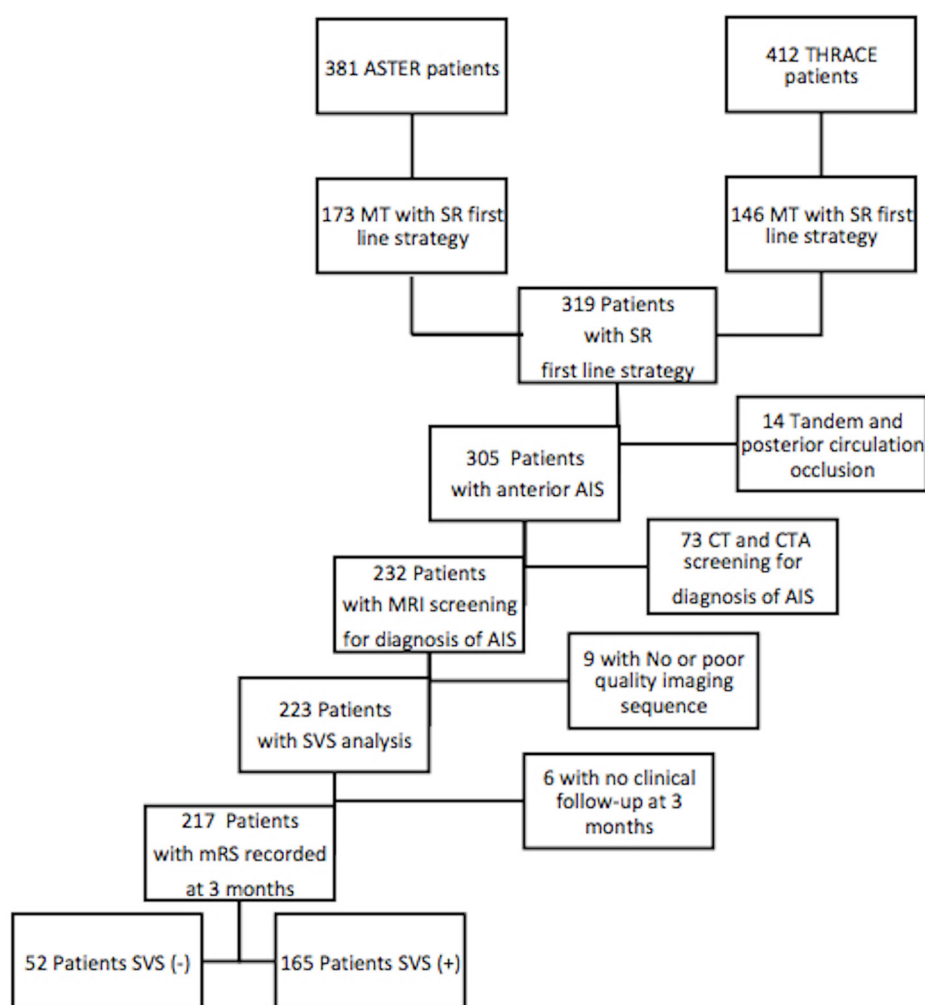


Figure 1 Inclusion flowchart. AIS, anterior ischemic stroke; ASTER, Contact Aspiration versus Stent Retriever for Successful Revascularization; CTA, CT angiography; mRS, modified Rankin Scale; MT, mechanical thrombectomy; SR, stent retriever; SVS, susceptibility vessel sign; THRACE, THrombectomie des Artères Cerebrales.

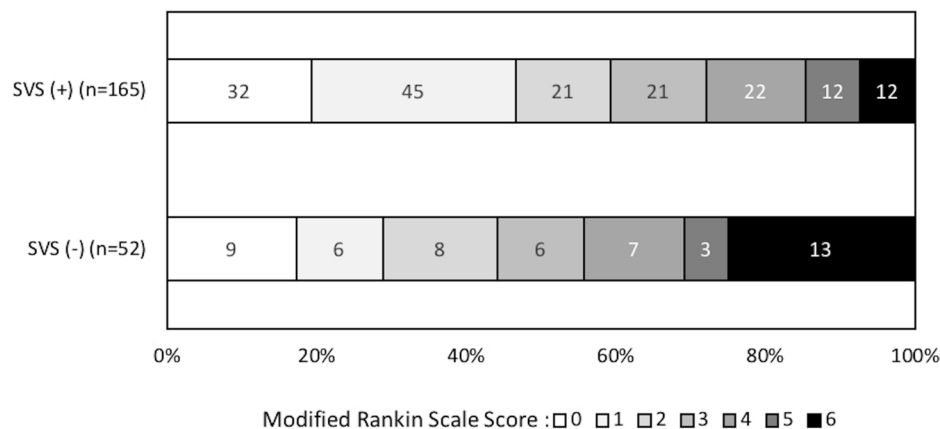


Figure 2 Distribution of modified Rankin Scale score at 90 days according to susceptibility vessel sign (SVS) on MRI.

scores of 5 and 6), and clinical independence as defined by a favorable outcome (90-day mRS score ≤ 2).²²

The secondary efficacy outcomes included successful reperfusion rate (defined as a modified Thrombolysis In Cerebral Infarction (mTICI) score of 2b or 3 at the end of the MT procedure),²³ complete reperfusion rate (defined as mTICI 3 at the end of the MT procedure), and the change in NIHSS score at 24 hours.

Safety outcomes included distal emboli in other territories and overall radiological (CT or MRI) intracranial hemorrhage on imaging at 24 ± 12 hours.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Quantitative variables were expressed as means (SD), or medians (IQR) for non-normal distribution. Normality of distributions was assessed graphically and by the Shapiro-Wilk test. Inter-reader agreement for determination of SVS was assessed using the simple Cohen's kappa coefficient. Baseline characteristics were compared between patients with and without SVS using logistic regression adjusted for the study (ASTER or THRACE) using SVS status as an independent variable. Comparisons of angiographic and clinical outcomes between patients with and without SVS were performed after adjustment for the study using logistic regression models for binary outcomes, an ordinal logistic regression model for overall 90-day mRS score (shift analysis after combining scores 5 and 6), and a covariance analysis for 24-hour NIHSS adjusted on baseline values. We assessed the between-study heterogeneity for each outcome by including the corresponding interaction term in previous models. Finally, between-group comparisons of outcomes were further adjusted for prespecified confounding factors (study, age, and admission NIHSS) and baseline differences (at $P < 0.10$ in bivariate analyses). Using patients without SVS as reference, effect sizes for binary outcomes were calculated as odds ratios (ORs), for overall distribution of mRS scores as a common OR for one point in improvement, and for quantitative outcomes as mean between-group differences.

All statistical tests were two-sided and $P < 0.05$ was considered as significant. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Of the 793 patients randomized in the ASTER and THRACE trials, 319 patients were treated with a SR and 217 of them were eligible for inclusion in this study (figure 1). Reasons for exclusion were posterior or tandem occlusion ($n=14$), absence

or poor, non-diagnostic quality of admission brain MRI ($n=82$), and missing 90-day follow-up ($n=6$). Main baseline characteristics and outcomes of the study population are available in the online supplementary table.

SVS+ was observed in 76.0% of cases ($n=165$, 95% CI 70.4% to 81.7%) with a significant difference between the two trials (67.2% ($n=84$) in ASTER vs 88.0% ($n=81$) in THRACE, $P < 0.001$). Inter-reader agreements for determination of SVS were 0.83 (95% CI 0.80 to 0.86) and 0.88 (95% CI 0.81 to 0.94), respectively, in the THRACE and ASTER trials.

At the end of the MT procedure, a successful reperfusion rate was observed in 80.6% ($n=175$, 95% CI 75.3% to 85.9%), favourable outcome in 55.8% ($n=121$; 95% CI 49.1% to 62.4%), distal emboli in other territories in 3.2%, only present in the SVS+ group ($n=7$; 95% CI 1.0% to 6.0%), and any intracranial hemorrhage in 40.6% ($n=88$; 95% CI 34.0% to 47.1%).

As shown in table 1, patients with SVS were more often men, non-diabetic, and had an M1/M2 occlusion, and a longer onset-to-MRI time than patients without SVS, although none of the differences reached significance.

shows the distributions of mRS scores at 90 days according to the presence or absence of SVS. In study-adjusted analysis, we found a significant difference in distribution of 90-day mRS scores, with lower scores in the SVS+ group than in the SVS- group, with a common OR for one-point improvement of 2.26 (95% CI 1.27 to 4.03). Compared with SVS- patients, those from the SVS+ group had a significantly higher favorable outcome rate (OR=2.03; 95% CI 1.06 to 2.91) and a greater 24-hour NIHSS score decrease (mean between-group difference, -3.2 ; 95% CI -6.1 to -0.3). There was no difference in reperfusion rates (complete or successful) or incidence of intracranial hemorrhage within 24 hours (table 1). No significant heterogeneity in association with SVS for each study outcome was found (all $P > 0.20$).

After adjustment for potential confounding factors, SVS remained significantly associated with an improvement in 90-day mRS score (adjusted common OR=2.75; 95% CI 1.44 to 5.26) and favorable outcome (adjusted common OR=2.76; 95% CI 1.18 to 6.45). However, the association of SVS with 24 hours decrease in NIHSS was no longer significant (table 2).

DISCUSSION

Using aggregate data from two randomized controlled trials dedicated to endovascular treatment of AIS with first-line SR, we demonstrated that SVS+, assessed on pretreatment brain MRI, is a strong predictor of favorable clinical outcome.

Table 1 Baseline characteristics according to susceptibility vessel sign (SVS) on MRI

| Characteristics | SVS– (n=52) | SVS+ (n=165) | P values† |
|--|------------------|-------------------|-----------|
| Demographics | | | |
| Age, years, mean (SD) | 65.7 (14.1) | 64.5 (15.4) | 0.98 |
| Men | 21/52 (40.4) | 91/165 (55.2) | 0.095 |
| Medical history | | | |
| Hypertension | 33/52 (63.5) | 79/161 (49.1) | 0.17 |
| Diabetes | 13/52 (26.5) | 17/163 (10.4) | 0.066 |
| Hypercholesterolemia | 19/49 (38.8) | 60/155 (38.7) | 0.89 |
| Current smoking | 8/45 (17.8) | 33/143 (23.1) | 0.49 |
| Coronary artery disease | 9/51 (17.6) | 21/161 (13.0) | 0.78 |
| Current stroke event | | | |
| Systolic blood pressure, mmHg, mean (SD)‡ | 142.1 (26.1) | 142.1 (22.9) | 0.85 |
| Diastolic blood pressure, mmHg, mean (SD)‡ | 81.0 (17.4) | 81.0 (15.1) | 0.86 |
| Glycemia, median (IQR)§ | 6.6 (5.6 to 7.7) | 6.7 (5.9 to 8.2) | 0.071 |
| NIHSS score, mean (SD)¶ | 16.2 (6.0) | 16.7 (5.6) | 0.91 |
| ASPECTS, median (IQR)** | 7 (5 to 8) | 7 (5 to 8) | 0.66 |
| Site of occlusion | | | 0.082 |
| M1/M2 | 40/52 (76.9) | 144/165 (87.3) | |
| ICA | 12/52 (23.1) | 21/165 (12.7) | |
| Intravenous rt-PA | 35/52 (67.3) | 141/165 (85.5) | 0.15 |
| Etiology | | | |
| Atherothrombotic | 8/51 (15.7) | 17/161 (10.6) | |
| Cardioembolic | 17/51 (33.3) | 72/161 (44.7) | |
| Other or unknown causes | 26/51 (51.0) | 72/161 (44.7) | |
| Favorable collaterality | 10/42 (23.8) | 26/139 (18.7) | 0.56 |
| Intervals times, min, median (IQR) | | | |
| Onset to groin puncture time†† | 220 (165 to 296) | 215 (180 to 255) | 0.57 |
| Onset to imaging‡ | 102 (72 to 135) | 115 (88.5 to 141) | 0.089 |
| Onset to clot‡‡ | 252 (200 to 325) | 248 (210 to 285) | 0.57 |

Values expressed as the no/total no (%) unless otherwise indicated.

P values were computed using logistic regression model adjusted for study (except for Intravenous rt-PA).

†P values calculated after log- transformation of data.

‡Two missing values (one in SVS+).

§Seven missing values (four in SVS+).

¶One missing value in SVS–.

**Four missing values (three in SVS+).

††Three missing values (two in SVS+).

‡‡Five missing values (four in SVS+).

ASPECTS, Alberta Stroke Programme Early CT Score; ICA, internal carotid artery; IQR, IQR range; M1/M2, first or second segment of the middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; SVS, susceptibility vessel sign.

Our findings are in line with a previous smaller retrospective monocentric study, in which SVS+ appeared to be a radiologic biomarker predictive of favorable clinical outcome at 3 months after MT.¹⁰ However, a very large CI precluded any generalization of the results (OR=8.7; 95%CI 1.1 to 69.4; P value 0.04). Our results are in apparent contradiction with those of others,^{7 24} which did not establish SVS+ as a treatment effect

imaging biomarker. In the overall population of the ASTER trial, SR use has recently shown its superiority for recanalization and clinical outcome compared with CA when SVS is present. However, conversely, in this group of patients treated with SR and CA, SVS was not found to be a factor related to clinical outcome. This might be due, in part, to the merging of SR- and CA-treated patients but also because the sample size in the SR group was small (59.0% in SVS+ vs 43.1% in SVS–; adjusted risk ratio (RR), 1.27; 95%CI 0.97 to 1.66).¹⁶ Because SR is the most commonly used technique and, moreover, the strategy used to show the efficacy of endovascular thrombectomy compared with IVT alone, we thought it important to highlight the prognostic significance of SVS. Hence, we collected a large, controlled population of patients treated with SR, and showed that, when treated with SR, the presence of SVS is a prognostic factor related to good outcome. Conversely, the absence of SVS in patients treated with SR is related to unfavorable outcome.

Despite the better clinical outcome in the SVS+ group, mTICI scores did not differ between groups. SVS is observed when red blood cell-dominant clots are present, whereas a lack of SVS is indicative of clots with a higher fibrin content or an underlying atherosclerotic plaque.^{9 14 25 26} In the latter case, one may argue that an SVS– patient might have experienced delayed short-term reocclusion, despite a final mTICI 2b/3.^{27–29} Even if we were unable to assess the vessel patency at 24 or 48 hours after MT, we found a trend towards a higher NIHSS score at 24 hours in the SVS– group, which might reflect such a reocclusion. Furthermore, the observed impact of an SVS– occlusion on clinical outcome may be explained by a higher number of passes required to reach a TICI 2b/3 reperfusion.^{30 31} The thrombus composition and its mechanical properties could explain a more difficult MT procedure, requiring more numerous passes. Indeed, a fibrin-rich thrombus can be difficult to engage in the SR, as it adheres more strongly to the vessel wall,^{15 17} and SVS– is thought to be related to fibrin-rich thrombi. However, we were unable to analyse the number of passes in this study.

Potential limitations should be considered in interpreting the results of this report.

First, differences in entry criteria and patient characteristics among the trials are a source of potential bias. Second, no thrombus histology data were available to further characterize the relationships between SVS, outcomes, and thrombus composition.^{32–34}

Third, a favorable collateral circulation has been associated with better reperfusion and subsequent more favorable clinical outcomes.³⁵ We did not adjust our analysis for these collaterals since we included M1/M2 but also internal carotid artery occlusions for which presence of collaterals with DSA was not recorded. Fourth, we analysed SVS only as a binary variable (presence/absence),⁵ whereas others distinguished different subtypes of SVS (namely ‘two-layered SVS’) or carried out a quantitative estimation based on the overestimation ratio of SVS.^{36–38}

Finally, although SVS+ identification is reliable and reproducible, with excellent interobserver agreement, SVS evaluation was performed on different MRI machines owing to the multicentric design of both studies. This is a significant limitation, as it was previously reported in an in vitro study that the prevalence of the SVS+ varies significantly among MRI machines.²⁶

CONCLUSION

Basing our study on the ASTER and THRACE trial populations treated with SR as a first-line strategy, we found a higher rate of favourable clinical outcome at 3 months in SVS+ patients. Thrombus MRI examination before MT might be

Table 2 Comparison of main angiographic and clinical outcomes according to susceptibility vessel sign (SVS) on MRI

| Outcomes | SVS– (n=52) | SVS+ (n=165) | Effect size | Study-adjusted | | Fully adjusted | |
|-------------------------------------|----------------------|----------------------|-------------------|------------------------|----------|-----------------------|-----------|
| | | | | Values (95% CI) | P Values | Values (95% CI)* | P Values* |
| Angiographic outcomes | | | | | | | |
| Reperfusion at end of procedure | | | | | | | |
| mTICI 3 | 20/52 (38.5) | 53/165 (32.1) | OR | 0.95 (0.48 to 1.86) | 0.88 | 0.96 (0.45 to 2.06) | 0.92 |
| mTICI 2b/3 | 42/52 (80.8) | 133/165 (80.6) | OR | 1.34 (0.59 to 3.17) | 0.47 | 1.31 (0.51 to 3.38) | 0.58 |
| Clinical outcomes | | | | | | | |
| mRS score at 3 months | 3 (1 to 5)† | 2 (1 to 4)† | Common OR‡ | 2.26 (1.27 to 4.03) | 0.005 | 2.75 (1.44 to 5.26) | 0.002 |
| Favorable outcome at 3 months | 23/52 (44.2) | 98/165 (59.4) | OR | 2.03 (1.06 to 3.91) | 0.034 | 2.76 (1.18 to 6.45) | 0.019 |
| Change in NIHSS at 24 hours§ | −3.1 (−5.6 to −0.6)¶ | −6.3 (−7.7 to −5.0)¶ | Mean difference** | −3.20 (−6.04 to −0.35) | 0.028 | −2.59 (−5.66 to 0.48) | 0.098 |
| Intracranial hemorrhage at 24 hours | 21/51 (41.2) | 67/164 (40.9) | OR | 0.99 (0.51 to 1.92) | 0.98 | 0.98 (0.47 to 2.05) | 0.96 |

Values expressed as the no/total no (%), unless otherwise stated. OR and mean difference were calculated using patients with SVS (–) as the reference group.

*Adjusted for prespecified factors (study, age, admission NIHSS) and baseline between-group difference at $P < 0.10$ in bivariate analysis (gender, diabetes, IVT, glycemia, site of occlusion, onset to MRI time).

†Median (IQR).

‡Common OR of improvement of 1 point in 90-day mRS score.

§13 missing values (five in SVS–).

¶Mean change (95% CI) adjusted for study and baseline values.

**Adjusted mean between-group difference.

IVT, IV thrombolysis; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale;

SVS, susceptibility vessel sign.

useful for choosing a first-line strategy in acute ischemic stroke following large vessel occlusions. Large prospective studies using MRI-based thrombus evaluation are warranted.

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Contributors RB conceived the idea for the study and wrote the manuscript. ON, BL, and WBH wrote the manuscript. SS, PR, MT, CR, RB, MP, ID, GB, CO, HD and SB collected data and made a critical review of the manuscript. JL and MK performed the statistical analysis.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The ASTER protocol was registered with ClinicalTrials.gov (Identifier NCT02523261) and the consent form was approved by the Comité de Protection des Personnes Ile de France VI (ID 2015- A00830 -49). The THRACE trial aimed to compare intravenous thrombectomy (IVT) alone with IVT plus mechanical thrombectomy using SR to determine their effect on clinical independence at 3 months in patients with acute ischemic stroke. Patients were included within respectively 4 and 6 hours of symptom onset in the THRACE and ASTER trial. The THRACE protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent.

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