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Endovascular therapy in patients with a large ischemic volume at presentation: An aggregate patient-level analysis

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ABSTRACT

Introduction: Recently, four randomized controlled trials (RCTs) have demonstrated the benefits of mechanical thrombectomy (MT) in patients with acute ischemic stroke (AIS) caused by anterior large vessel occlusion (LVO) and a large ischemic core at baseline (LIC). The purpose of this study was to investigate the features influencing the clinical outcome and the benefits of mechanical thrombectomy in this subgroup.
Methods: We conducted a multicenter retrospective aggregate cohort study of patients with AIS-LVO and a LIC, assessed with quantitative core volume measures, treated with MT between 2012 and 2019. The data were queried through four registries, including patients with core volumes ≥50cc. Multivariable logistic regression models were employed to determine factors independently associated with clinical outcomes in patients with successful recanalization (modified-Thrombolysis-in-Cerebral-Infarction-score, mTICI=2b-3) and unsuccessful recanalization group (mTICI=0–2a). The primary endpoint was a favorable functional outcome at day-90, defined as a modified Rankin scale (mRS) of 0–3, accounting for the inherent severity of AIS with baseline LIC. Secondary outcomes included functional independence (mRS 0–2) at day-90, mortality, and symptomatic Intracranial Hemorrhage (sICH).
Results: A total of 460 patients were included (mean age 66±14.2 years; 39.6 % females). The mean baseline NIHSS was 20±5.2, and the core volume was 103.2±54.6 ml. Overall, 39.8 % (183/460) of patients achieved a favorable outcome at day-90 (mRS 0–3). Successful recanalization was significantly associated with a more frequent favorable outcome (aOR, 4.79; 95 %CI, 2.73–8.38; P<0.01) and functional independence (P<0.01). This benefit remained significant in older patients and in patients with cores above 100cc. At 90 days, 147/460 patients (32 %) were deceased, with successful recanalization significantly associated with less frequent mortality (OR, 0.34; 95 %CI, 0.22–0.53; P<0.01). The rate of sICH was 17.4 % and did not differ significantly between groups.

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Conclusions: In this large, pooled-cohort study of AIS-LVO patients with infarct cores over 50cc at baseline, we demonstrated that successful recanalization was associated with a better functional outcome, lower mortality, and similar rates of symptomatic intracranial hemorrhage for a wide spectrum of patients.

Subject Terms: Ischemic stroke –Cerebrovascular Procedures–Imaging–Vascular Disease

1. Introduction

In the first randomized controlled trials that validated the benefits of mechanical thrombectomy (MT) on clinical outcomes for patients with acute ischemic stroke due to large vessel occlusion (AIS-LVO), participants were selected based on the likelihood of benefiting from swift revascularization. This led to the exclusion of patients with poor prognostic factors at baseline [1]

A large ischemic core (LIC; e.g., Alberta Stroke Program Early CT -ASPECT- scores below 6, or an ischemic core above 70cc) was among these factors. Consequently, only a few patients with such imaging profiles were finally included in early endovascular trials, preventing the drawing of strong conclusions in this subgroup regarding the treatment effect of MT on clinical outcomes [1–4].

Yet, converging results suggest that, despite a deemed unfavorable imaging profile, a subset of these patients might still benefit from revascularization [5–14].

Recently, the RESCUE-Japan LIMIT trial (NCT03702413), followed by the ANGEL-ASPECT (NCT04551664), the SELECT2 (NCT03876457) and the TENSION (NCT03094715) trials, demonstrated that patients with a large ischemic core at baseline achieved more favorable clinical outcomes when they underwent mechanical thrombectomy (MT) in addition to best medical management, despite experiencing higher rates of hemorrhagic transformation [15–17]. New randomized data from ongoing clinical trials, such as, IN EXTREMIS-LASTE (NCT03811769), and TESLA (NCT03805308), are expected to become available soon. While awaiting significant updates to the American and European recommendations for this subgroup, our aim is to investigate the clinical and imaging features influencing clinical outcomes and the benefits of mechanical thrombectomy in a large pooled-sample study of AIS-LVO patients with a quantitatively assessed large ischemic core.

2. Methods

2.1. Study design, ethics and participants

The analysis utilized data from a multicenter, retrospective cohort study of patients with acute ischemic stroke due to large vessel occlusion (AIS-LVO) and a large ischemic core (LIC) at baseline. This cohort was derived from the amalgamation of data collected between January 2012 and December 2019 through four prospective registries of AIS-LVO treated with mechanical thrombectomy: (I) The Endovascular Treatment in Ischemic Stroke (ETIS Registry), ClinicalTrials.gov: NCT03776877, is an ongoing, prospective, observational study conducted in 18 comprehensive stroke centers in France. (II) The Japanese National Cerebral and Cardiovascular Center Stroke (NCVC Registry), ClinicalTrials.gov: NCT02251665, is an ongoing, prospective, observational study conducted in the academic comprehensive stroke center of Osaka, Japan. (III) The cohort resulted from the collaborative work of the trainee-led research network (Jeunes en Neuroradiologie Interventionnelle, JENI-research Collaborative) [18], which retrospectively gathered data on patients with AIS-LVO, large ischemic core and pretreatment MRI perfusion [13,14]. (IV) The Lille recanalization registry, which is an ongoing observational registry in the academic comprehensive stroke center of Lille in France [19,20]. We retrospectively queried these registries to identify adult patients with anterior AIS-LVO defined as occlusion of the intracranial internal carotid artery or of the M1 or M2 segments of the middle cerebral artery, an available volumetric measurement of the ischemic core on MR-DWI or CT-Perfusion, a large pretreatment ischemic core volume defined as 50 ml or more, treated with mechanical thrombectomy and with a modified Ranking scale (mRS) available at 90 days. Only patients treated with second and third-generation stroke thrombectomy devices (stent retriver, contact aspiration and combined technique) were included. Patients without available Thrombolysis in Cerebral Infarction (mTICI) score and patients with preexisting handicap (defined as mRs >2) were excluded. The study was approved by the Institutional Review Boards (IRBs) of the participating registries, which established that informed consent was not necessary for this retrospective analysis and the report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [21].

2.2. Treatment groups

Patients were subdivided based on the success of endovascular treatment (EVT), using the mTICI score into two groups: the successful recanalization group (defined by an mTICI score of 2b, 2c, or 3) and the unsuccessful recanalization group (defined by an mTICI score of 0, 1, or 2a).

2.3. Imaging analysis

Ischemic core volumes were assessed quantitatively for all included patients using automated processing of diffusion-MR or CT-perfusion. Olea-Sphere version 3.0 software (Olea Medical, La Ciotat, France) was employed for the JENI and Lille Cohorts, iSchemaView RAPID (Menlo Park, CA, USA) for the NCVC registry, and a noncommercial software specially developed for the ETIS registry [10]. Ischemic core segmentation was calculated using consistent pre-specified thresholds across all software: cerebral blood flow <30 % of that in normal tissue on CTP or apparent diffusion coefficient $<0.6\times10{-}3$ mm2/sec on MRI. As mentioned earlier, recanalization success was assessed locally using the mTICI score.

2.4. Study endpoints

The primary endpoint was a favorable functional outcome at 90 days, defined as a modified Rankin scale (mRS) of 0–3, taking into account the inherent severity of AIS with baseline LIC, and aligns with recent literature [12]. Secondary endpoints included the 24-hour NIHSS and 24-hour Early Neurological Improvement (ENI), defined as an improvement of at least four points in the NIHSS score assessed 24 hours after recanalization therapy [22], day-90 functional independence (mRs of 0–2), day-90 Utility-Weighted Modified Rankin Scale Scores (UW-mRS) [23] a patient centered outcome derived by assigning a mean utility weight to each mRS category based on the valuation of various disability health states [24], day-90 mortality and the rate of symptomatic intracranial hemorrhage (sICH) as per the Second European and Australasian Acute Stroke Study (ECASS II) criteria [25].

2.5. Statistical analysis

Continuous variables were summarized using means (SDs) or medians (interquartile ranges [IQRs]) where appropriate, and discrete variables were summarized using counts (percentages). For univariate analysis, we employed the Chi-square test, Fisher exact test, t-test, and Mann-Whitney test as appropriate. A p-value < 0.05 (2-tailed) served as the threshold for statistical significance.

Multivariable logistic regression models were utilized to identify factors independently associated with clinical outcomes. Variables associated with the outcome in univariate analysis (p≤0.01) were entered into nominal logistic models, and backward elimination was then used to remove non-significant variables (p>0.05).

To address potential heterogeneity between the four mother-registries and its impact on treatment effect for clinical endpoints, we employed mixed-effects modeling with fixed and random effects in dedicated models.

Furthermore, we conducted tests and presented graphically, using a forest plot, the potential impact of relevant prespecified subgroups on treatment effect for the primary endpoint (mRS 0–3). These subgroups were selected from common predictors of outcome in AIS LVO patients, including core volume (50–80; 81–100; 101–150; >150 ml), age (18–55; 56–65; 66–79; >80 years old), intravenous thrombolysis, occlusion site (ICA; M1; M1), NIHSS (≤15; 16–20; >21), Gender (female; male), tandem occlusion, unwitnessed stroke, time from onset to imaging (< or > 4 hours and 30 minutes), time from onset to groin (< or > 6 hours), thrombectomy technique (Stent-retriever; contact aspiration; combination), number of passes (single pass; ≥2 passes), ASPECT score (0–2; 3; 4; 5), mother registry (ETIS; JENI; Lille; NCVS), and anesthesia (local or general).

All analyses were performed using JMP Pro 14 (SAS Institute Inc. 2015. JMP® Pro 14. Cary, NC: SAS Institute Inc) software.

3. Results

3.1. Patients and stroke characteristics at the acute phase

Among the 8550 patients in the original registries at the time of mutualization, 509 patients were screened, and 460 met the inclusion criteria (182/460 39.6 % females, mean age 66±14.2 years, baseline NIHSS 20±5.2, ischemic core volume 103.2±54.6 ml) (See Table 1 for baseline clinical-imaging characteristics and Supplemental Figure 1 for the flowchart). The vast majority of baseline imaging was MRI (448/460).

Successful recanalization was encountered in 349 out of 460 patients (75.8 %). Patients with successful or unsuccessful recanalization did not differ in baseline parameters (age, baseline NIHSS, ischemic core volume) except for tandem occlusions (53/349 15.2 % vs. 30/111 27 %, P<0.01) and a previous history of AIS or Transient Ischemic Attack (10/160 6.3 % vs. 7/45 15.6 %, P=0.045).

Table 1
baseline clinical-imaging characteristics.

	Patients, % (No./total No.)			
	mTICI 2b-3. n=349	**mTICI 0–2a. n=111**	**Total. n= 460**	**p**
Patients characteristics				
Age, mean±SD, No., yr	66±15 N=349	66.6±13.4 N=111	66.3±14.2 N=460	0.714
Sex, female	40.1 (140/349)	37.8 (42/111)	39.6 (182/460)	0.738
Hypertension	57.9 (202/349)	66.4 (73/110)	59.9 (275/459)	0.119
Diabetes Mellitus	14 (49/349)	16.2 (18/111)	14.6 (67/460)	0.571
Blood glucose,mean±SD, No., mmol/L	7.6±3.3 N=236	8±2.9 N=79	7.8±3.1 N=315	0.326
Dyslipidemia	38.1 (133/349)	38.7 (43/111)	38.3 (176/460)	0.911
Tobacco use (current or past)	34.4 (120/349)	38.7 (43/111)	35.4 (163/460)	0.426
Prior TIA or Stroke	6.3 (10/160)	15.6 (7/45)	8.3 (17/205)	0.045
Atrial Fibrillation	40.4 (59/146)	38.9 (14/36)	40.1 (73/182)	0.867
Stroke characteristics and management				
Unwitnessed onset	23.9 (74/310)	24.3 (25/103)	24 (99/413)	0.934
Baseline NIHSS, mean±SD, No.,	19.7±5.3 N=347	20.3±5.2 N=110	20±5.2 N=457	0.278
Overall Core volume, mean±SD, No., ml	99.5±43.6 N=349	106.9±65.5 N=111	103.2±54.6 N=460	0.263
ASPECTS, median (IQR), No.	4 [3–5] N=349	3 [2–5] N=111	4 [2–5] N=460	0.058
Left sided stroke	45.5 (45/99)	42.9 (12/28)	44.9 (57/127)	0.807
IVT	56.7 (198/349)	45.9 (51/111)	54.1 (249/460)	0.049
Occlusion site				
ICA	28.1 (98/349)	22.5 (25/111)	26.7 (123/460)	0.433
M1	63.6 (222/349)	70.3 (78/111)	65.2 (300/460)	
M2	8.3 (29/349)	7.2 (8/111)	8 (37/460)	
Tandem	15.2 (53/349)	27 (30/111)	18 (83/460)	0.007
General Anesthesia	19.4 (60/310)	29.4 (30/102)	21.8 (90/412)	0.033
Thrombectomy procedure				
Combined	31 (102/329)	32 (32/100)	31.2 (134/429)	0.335
Stent retriever alone	37.7 (124/329)	44 (44/100)	39.2 (168/429)	
Contact aspiration	31.3 (103/329)	24 (24/100)	29.6 (127/429)	
Number of passes, median (IQR), No.	2 [1–3] N=195	3 [2–5] N=74	2 [1–4] N=269	0.006
Time metrics				
Symptom-onset* to imaging, mean±SD, No., min	145.9±105.5 N=342	169.1±140.4 N=105	157.5±122.9 N=447	0.121
Symptom-onset* to IVT, mean±SD, No., min	151.9±52.5 N=114	160.5±39 N=30	156.2±45.7 N=144	0.836
Symptom-onset* to groin, mean±SD, No., min	241.3±101.9 N=338	276.8±143.9 N=106	259±122.9 N=444	0.019
Symptom-onset* to TICI max, mean±SD, No., min	287.4±103.3 N=324	359.9±148.5 N=85	323.6±125.9 N=409	<0.001
Stroke etiology				
Large-artery atherosclerosis	13.7 (36/263)	14.1 (13/92)	13.8 (49/355)	0.033
Cardioembolism	49.4 (130/263)	35.9 (33/92)	45.9 (163/355)	
Other specific	4.2 (11/263)	10.9 (10/92)	5.9 (21/355)	
Unknown	32.7 (86/263)	39.1 (36/92)	34.4 (122/355)	

Values are displayed as absolute values (percentage of column total), unless stated otherwise.
Abbreviations: SD= Standard deviation; IQR=Interquartile range; mTICI=modified Thrombolysis in Cerebral Infarction score, (mTICI 2b-3=successful recanalization and mTICI 0–2a=unsuccessful recanalization); TIA=Transient Ischemic Attack, NIHSS=National Institutes of Health Stroke Scale; ASPECTS= Alberta Stroke Program Early Computed Tomography Score; IVT=intravenous thrombolysis; ICA=internal carotid artery; M1=first segment of the middle cerebral artery; M2=second segment of the middle cerebral artery.
* or last-seen well

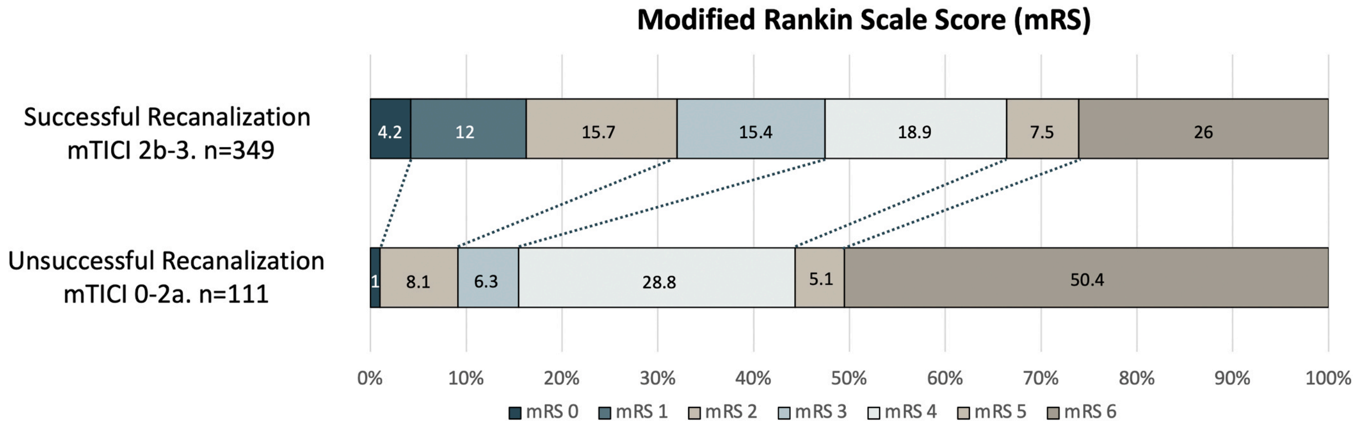

Fig. 1. Modified Rankin Scale (mRS) distribution in patients with successful recanalization and those with unsuccessful recanalization. Values are displayed as percentage of row total; Abbreviations: mTICI=modified Thrombolysis in Cerebral Infarction score, (mTICI 2b-3=successful recanalization and mTICI 0–2a=unsuccessful recanalization).

3.2. Revascularization treatments

In the successful recanalization group, the administration of intravenous thrombolysis was more frequent (198/349 56.7 % vs 51/111 45.9 %, P=0.049), MT procedures were more frequently performed without general anesthesia (60/310 19.4 % vs 30/102 29.4 %, P=0.03), and there was a lower number of passes (median IQR: 2 [1–3] vs. 3 [2–5], P<0.01). In this same group, onset-to-groin-puncture delays and onset-to-TICI max were shorter (241.3±101.9 vs. 276.8±143.9 minutes, P=0.019, and 287.4±103.3 vs. 359.9±148.5 minutes, P<0.01, respectively). The rate of MT performed with a combined technique, stent retriever alone, or contact aspiration alone did not differ between successful and unsuccessful recanalization groups (see details in Table 1).

3.3. Outcomes

3.3.1. Primary endpoint: favorable functional outcome (mRS 0–3)

Overall, 183 out of 460 patients had a favorable outcome at day-90 (39.8 %), with a significantly larger proportion in patients with successful recanalization (166/349 47.6 % vs. 17/111 15.3 %, P<0.01). Patients successfully recanalized had five times higher odds of favorable outcomes (OR, 5.02; 95 % CI 2.87–8.76; P<0.01), and the recanalization effect remained consistent after fixed adjustment for the patients' mother registry's origin (adjusted OR, 4.79; 95 % CI 2.73–8.38; P<0.01) and after multivariate adjustment for age, baseline NIHSS, core volume, diabetes, gender, occlusion site, baseline imaging, IVT, number of passes, delay to imaging, and craniectomy (aOR, 4.79; 95 % CI 2.73–8.38; P<0.01). See Table 2 and Supplemental Table I for detailed variables associated with day-90 favorable functional outcome.

3.3.2. Secondary endpoints

The mean NIHSS at 24 hours post-treatment was significantly lower in the successful recanalization group (16 ± 9.9 vs. 23.5 ± 10.2; P<0.01). Similarly, Early Neurological Improvement (ENI) was observed more frequently in the successful recanalization group (148/299 49.5 % vs. 14/87 16.1 %; P<0.01). *See* Table 2.

Functional independence (mRS 0–2) at day-90 was achieved in 122/460 (26.5 %) of cases overall, more frequently in the successful recanalization group (112/349 32.1 % vs. 10/111 9 %; P<0.01). Successful recanalization was an independent predictor of functional independence after both fixed-adjustment for the mother-registry (aOR 4.71; 95 % CI 2.36–9.4; P<0.01) and multivariate adjustment for clinical confounders (aOR 6.44; 95 % CI 2.82–14.68; P<0.01). Refer to Table 2 and Supplemental Table II for aOR of the different predictors of day-90 functional independence.

Similarly, the mean UW-mRS was twofold higher in the successful recanalization group (0.4 ± 0.4 vs. 0.2 ± 0.3; OR 1.12; CI 95 % 1.08–1.16; P<0.01), and the recanalization effect did not change after adjusting for clinical confounders and the mother-registry (fixed and random effect have been tested). *See* Table 2 and Supplemental Tables III and IV.

At 90 days, 32 % (147/460) of patients were deceased overall, and this rate significantly decreased in the successful recanalization group (91/349 26.1 % vs. 56/111 50.5 %; OR 0.34; CI 95 % 0.22–0.53; P<0.01).

The rate of sICH was 17.4 % (79/454) in the overall population and did not differ significantly between groups (See Table 2). Successful recanalization and IVT were not associated with a higher likelihood of sICH in both univariate and multivariate analyses, whereas older age, longer time from onset to IVT, and diabetes were significant factors for sICH. See Supplementary Table V

3.3.3. Heterogeneity of treatment effect across prespecified subgroups

For the subgroup analysis of a favorable functional outcome (mRS 0–3), the benefit of successful recanalization remained significant after multivariable adjustment in all prespecified subgroups, except for patients with a very large core volume (>150 ml), patients with ICA or M2 occlusions, patients with an unwitnessed stroke, patients treated with contact aspiration alone or under general anesthesia, and patients from the NCVS registry. Finally, we observed a significant interaction of two variables on treatment effect for the primary endpoint: iv-tPA (P_interaction = 0.02) and unwitnessed stroke (P_interaction = 0.02). See supplemental table VI for more details on the impact of the different thrombectomy techniques

4. Discussion

In this large, pooled cohort study of patients with AIS-LVO and infarct cores above 50cc before MT, we showed (1) that successful recanalization increased the odds of a favorable functional outcome (mRS 0–3) at 90 days by a factor of 5; (2) that this benefit remained significant in both older patients and those with cores above 100cc; and (3) that successful recanalization was strongly beneficial across all secondary outcome measures, increasing the likelihood of ENI, functional independence, and achieving better UW-mRS scores at 90 days, while decreasing the likelihood of mortality. (4) Finally, in this cohort, neither successful recanalization nor IVT was associated with a higher rate of sICH.

Our results are in line with previous systematic reviews and meta-analyses in various settings, suggesting that MT was highly beneficial in increasing functional independence after AIS with ASPECTS <6. This benefit was found to be of similar magnitude in analyses comparing

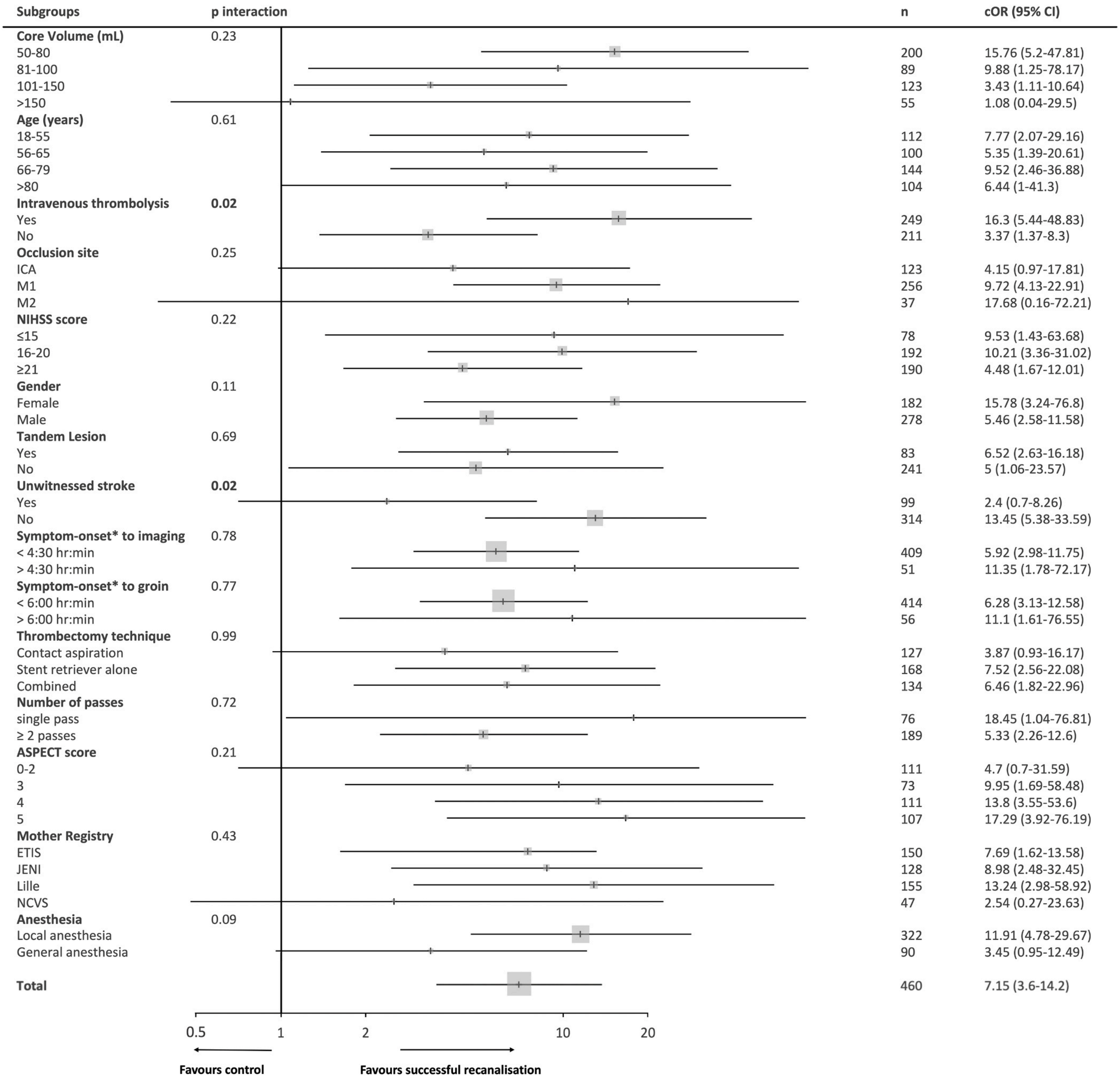

Fig. 2. Forest plot of successful recanalization effect on primary outcome (90 day, mRS 0–3), by prespecified subgroups with p values for multiplicative interaction terms. Abbreviations: cOR (95 CI) = common odds-ratio (95 % confidence interval); ICA=internal carotid artery; M1=first segment of the middle cerebral artery; M2=second segment of the middle cerebral artery; NIHSS=National Institutes of Health Stroke Scale; ASPECTS= Alberta Stroke Program Early Computed Tomography Score; ETIS=the Endovascular Treatment in Ischemic Stroke registry; JENI= Jeunes en Neuroradiologie Interventionnelle reseach collaborative network; Lille= The Lille recanalization registry; NCVC= The Japanese National Cerebral and Cardiovascular Center Stroke; * or last-seen well.

successful vs. unsuccessful recanalization groups (OR 5.3, 95 % CI 2.7–10; P=0.01 for mRS 0–2, Cagnazzo et al. [26]) and in analyses comparing MT on top of best medical management (BMM) versus BMM alone (OR 4.76; 95 % CI 1.3–16.8;; P=0.01 for mRS 0–2 in the work by Cagnazzo et al [26]. and OR, 4.39; 95 % CI, 2.53–7.64; P=0.01 for mRS 0–2 in Sarraj et al. [27]). In a recently published meta-analysis, we also demonstrated at the cohort level that patients treated with MT & BMM versus BMM alone had 5 times the odds of favorable outcomes when a large core was defined using quantitative core volume measures (e.g., 50cc or above) (OR 5.26; 95 % CI 3.03–9.01; P=0.01 for mRS 0–3, Kerleroux et al. [28]), but these results were unadjusted due to the aggregate nature of the data. These previous works, as well as our analyses show a remarkable consistency despite varying settings, definitions of LIC, and statistical approaches.

RESCUE-Japan LIMIT [15] was the first randomized study to validate the benefits of MT in patients with a baseline LIC over BMM alone. In this trial, LIC was defined by an ASPECTS value of 3–5. The rate of patients with a favorable functional outcome (mRS 0–3) at 90-days was 31.0 % in the MT & BMM group and 12.7 % in the BMM group (relative risk (RR) 2.43; 95 % CI, 1.35–4.37; P=0.002).

ANGEL-ASPECT [16] also included patients with ASPECTS value of 3–5, and was stopped early owing to a significant shift in the distribution of scores on the modified Rankin scale in favor of the MT group over the BMM control group (generalized odds ratio, 1.37; 95 % CI 1.11–1.69; P=0.004). In the SELECT2 trial [17], patients with a large ischemic core were defined by an ASPECT value of 3–5 or a core volume of 50 ml and

Table 2
Primary & Secondary outcomes.

	Patients, % (No./total No.)				OR (95 % CI)	
	mTICI 2b-3. n=349	mTICI 0–2a. n=111	Total. n= 460	p	Unadjusted	Adjusted
Primary outcome						
90 day, mRS 0–3	47.6 (166/349)	15.3 (17/111)	39.8 (183/460)	<0.001	5.02 (2.87–8.76)	6.57 (3.4–12.68)
Secondary outcomes						
24 h - NIHSS, mean±SD, No.	16±9.9 N=299	23.5±10.2 N=88	19.8±10.1 N=387	<0.001	NA	NA
ENI	49.5 (148/299)	16.1 (14/87)	42 (162/386)	<0.001	5.11 (2.84–9.81)	NA
sICH	16.5 (57/346)	20.4 (22/108)	17.4 (79/454)	0.383	0.77 (0.45–1.35)	0.85 (0.46–1.54)
90 day, mRs 0–2	32.1 (112/349)	9 (10/111)	26.5 (122/460)	<0.001	4.77 (2.4–9.49)	6.44 (2.82–14.68)
90 day, mRS, median (IQR), No.	4 (2–6) N=349	6 (4–6) N=111	4 (2–6) N=460	<0.001	2.2 (1.74; 2.8)	NA
90 day, UW mRS, mean±SD, No.	0.4±0.4 N=349	0.2±0.3 N=111	0.3±0.3 N=460	<0.001	1.12 (1.08; 1.16)	1.11 (1.07; 1.15)
90 day, Mortality	26.1 (91/349)	50.5 (56/111)	32 (147/460)	<0.001	0.34 (0.22; 0.53)	NA
Craniectomy	12.1 (25/206)	22.2 (12/54)	14.2 (37/260)	0.078	NA	NA

Values are displayed as absolute values (percentage of column total), unless stated otherwise.
Abbreviations: SD= Standard deviation; IQR=Interquartile range; OR (95 CI) = odds-ratio (95 % confidence interval); mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; ENI=Early Neurological Improvement; sICH=symptomatic intra-cerebral hemorrhage (ECASS II)

larger. The trial was stopped after intermediate analyses due to a significantly higher rate of favorable outcomes in the MT group (generalized odds ratio, 1.51; 95 % CI 1.20–1.89; P<0.001). Likewise, the TENSION trial [29] was prematurely for efficacy. It demonstrated, in the MT group, a shift in the distribution of scores on the mRS towards better outcome (adjusted odds ratio 2.58; 95 % CI 1.60–4.15; P=0·0001) with no significant increase in sICH.

In all recent randomized trials comparing the benefit of mechanical thrombectomy (MT) over best medical management (BMM) for this subgroup of patients with a large ischemic core, the magnitude of the benefit seemed more modest (ORs or RRs around 1.4–2.43) compared to meta-analyses of retrospective studies (ORs or RRs around 5). This difference could be at least partially explained by the fact that patients undergoing thrombectomy with unsatisfactory recanalization (mTICI 0–2a) fare significantly worse than those not undergoing thrombectomy (BMM group) [30]. We can also hypothesize that a conscious or unconscious preselection of patients with a more favorable profile may have been done in retrospective studies, selecting criteria such as younger age, earlier time of onset to presentation or the presence of a salvageable penumbra on initial imaging [28]. While ASPECTS has been shown to correlate with quantitative ischemic core volumes, each ASPECTS point corresponds to a wide range of volumes, and decreased performances have been reported in lower score ranges [31]. This explains our choice to limit inclusions for this analysis to patients with a quantitatively assessed core volume. Volumetric approaches have been facilitated in clinical practice by the development of multiple dedicated post-processing software such as iSchemaView RAPID (Menlo Park, CA, USA) and Olea-Sphere version 3.0 (Olea Medical, La Ciotat, France), which were used in this study. It is important to note, however, that several studies have highlighted significant variability in the segmentation of ischemic lesions between different software tools in both MRI and CTP [32–36].

Gathering nearly 500 patients with LIC, this study allowed for the adjustment of prespecified prognostic variables at the individual participant's level, which had not been previously done in aggregate analyses [28]. The sample size of the present study and the stability of the statistical association between recanalization and better functional outcome strongly suggest that the benefits of recanalization persist even in patients with more severe presentations and characteristics typically associated with poor outcomes. We note that in our sample, revascularization was not significantly associated with a better outcome in octogenarians. The width of the confidence interval in this subgroup likely reflects a higher degree of uncertainty and is in line with the demonstration that the maximal admission lesion volume compatible with a subsequent favorable outcome is lower in octogenarians [37].

In line with previous studies [2,3,10,12,38], our analysis suggests that the benefit of recanalization decreases as core volume increases. Although this study is not adequately powered to conclude for the very large core (e.g., ≥150 ml) groups, it is very likely that demonstrating a benefit in this population will be challenging. True equipoise with regards to the offset of potential benefits of MT, the risk of increased sICH following revascularization, and futility due to the extremely high rates of poor outcomes in this group will be hard to resolve.

Stratifying by occlusion site, the benefit of recanalization was significant in our analyses only in patients with M1 occlusion. Neutral results in ICA and M2 groups regarding clinical outcomes might be due to insufficient power. In the ICA group, statistical heterogeneity in recanalization effect was particularly high, precluding us from drawing conclusions. Only 37 patients with LIC and M2 occlusion were included in the analyses, making it impossible to address the benefit of recanalization in this group. Future studies using a patient-centered approach to evaluate the eloquent salvageable tissue in M2 occlusions with a baseline LIC may help elucidate this question.

Among the key findings of this report is the absence of a demonstrated higher rate of sICH in patients with successful recanalization. We did find a significant interaction between receiving IVT and the effect of recanalization regarding the clinical outcome, further complicating the issue [39,40]. Indeed, while patients with LIC are at inherently higher risk for hemorrhagic transformation [2,41–43], the question of the role of both thrombolysis and MT in increasing this risk in patients with LIC remains poorly determined. Since determinants of ischemic volume are strongly intertwined with those of hemorrhagic transformation risk (collaterals, delay until revascularization, glucose levels, etc.), especially in the LIC population, a definite conclusion will require randomized studies. Recently, the RESCUE-Japan LIMIT trial [15] demonstrated higher rates of hemorrhage in the MT group (58.0 % vs. 31.4 % in the non-MT group, p<0.001). However, the rates of symptomatic hemorrhages were similar across groups, and the prognosis remained more than two times more frequently favorable in patients treated with MT. This suggests that the higher rate of ICH in the MT group does not counterbalance the benefit of mechanical thrombectomy. These findings regarding the rate of hemorrhage were consistent in the ANGEL ASPECT and the SELECT2 Trial [16,17].

Surprisingly, in our study, the core volume does not appear to be an independent predictor for sICH after multivariate adjustment. Our first hypothesis to explain this discrepancy with the literature [2,42,43] is the specific subgroup of included patients (only patients with LIC defined as ischemic core above 50cc), in whom the relevance of the NIHSS score is probably limited by a 'ceiling effect'. It is likely that the relevance of the sICH variable defined by the ECASS II criteria (+4pts of NIHSS) is consequently decreased to detect clinical worsening in relation to bleeding transformation, as patients with LIC typically have a high baseline NIHSS. This 'ceiling effect' was already apparent in the study of Gilgen et al [9]. where sICH rates were of similar magnitude between patients with an ischemic core volume ≥70cc and those with an ischemic core volume ≥100cc (19.7 % and 17.9 %, respectively).

Finally, in this cohort, and in line with previous studies [41,42] receiving IVT does not appear to be an independent predictor of sICH after multivariate adjustment, while the likelihood of sICH increases with the time from symptom-onset/last-seen well to IVT.

Strengths and limitations: The strengths of our study included (1) international recruitment from four registries of patients with AIS-LVO treated with MT; (2) the large sample size allowing adjustment for prespecified prognostic variables at the individual participant's level; (3) the quantitative measurement of ischemic core volume. The limitations are (1) inherent to the retrospective design of the study including missing data, selection bias (particularly with younger patients being included and managed within shorter time frames compared to the majority of RCTs on this patient subgroup), and heterogeneity of the population; (2) the registries did not consistently record the number or characteristics of patients with large core LVO who did not undergo EVT; (3) the lack of an untreated control group (BMM only); (4) the use of different software for ischemic core measurements; and (5) the vast majority of baseline imaging was MRI (rather than CTP), making our results less generalizable.

5. Conclusion

Successful recanalization could significantly increase the odds of a favorable functional outcome in patients with a large ischemic core at baseline. Neither successful recanalization nor intravenous thrombolysis appears to be associated with a higher rate of symptomatic hemorrhage in this large retrospective sample. This study provides encouraging data on the safety and efficacy of recanalization therapies for a wide spectrum of patients with acute ischemic stroke and a large ischemic core at baseline.

Informed consent and ethical approval

none

The study was approved by the Institutional Review Boards (IRBs) of the participating registries, which established that informed consent was not necessary for this retrospective analysis and the report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Contributorship

BK, JFH, ON and GB researched literature and conceived the study. BK, JFH, BL, NB, FZ, MI, KJ, CD, JK, AR, GF, HG, JB, TY, AC, WBH, HH, ON and GB made data acquisition.

BK wrote the first draft of the manuscript. BK, JBZ and GB made the data analysis and the statistics. JFH, BL, NB, FZ, MI, KJ, CD, JK, AR, GF, HG, JB, TY, AC, WBH, HH, ON and GB improve the draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript

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Takeshi Yoshimoto: Writing – review & editing, Data curation. **Bertrand Lapergue:** Writing – review & editing, Data curation. **Joseph Benzakoun:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jean-François Hak:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Wagih Ben Hassen:** Writing – review & editing, Data curation. **Arturo Consoli:** Writing – review & editing, Data curation. **Aymeric Rouchaud:** Writing – review & editing, Data curation. **Johannes Kaesmacher:** Writing – review & editing, Data curation. **Hugo Gortais:** Writing – review & editing, Data curation. **Basile Kerleroux:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Géraud Forestier:** Writing – review & editing, Data curation. **Olivier Naggara:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Hilde Henon:** Writing – review & editing, Data curation. **Grégoire Boulouis:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Manabu Inoue:** Writing – review & editing, Data curation. **François Zhu:** Writing – review & editing, Data curation. **Cyril Dargazanli:** Writing – review & editing, Data curation. **Kévin Janot:** Writing – review & editing, Data curation. **Nicolas Bricout:** Writing – review & editing, Data curation.

Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2024.108452.

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