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Perfusion Imaging and Clinical Outcome in Acute Minor Stroke With Large Vessel Occlusion

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BACKGROUND: Whether bridging therapy (intravenous thrombolysis [IVT] followed by mechanical thrombectomy) is superior to IVT alone in minor stroke with large vessel occlusion is unknown. Perfusion imaging may identify subsets of large vessel occlusion-related minor stroke patients with distinct response to bridging therapy.

METHODS: We conducted a multicenter international observational study of consecutive IVT-treated patients with minor stroke (National Institutes of Health Stroke Scale score ≤ 5) who had an anterior circulation large vessel occlusion and perfusion imaging performed before IVT, with a subset undergoing immediate thrombectomy. Propensity score with inverse probability of treatment weighting was used to account for baseline between-groups differences. The primary outcome was 3-month modified Rankin Scale score 0 to 1. We searched for an interaction between treatment group and mismatch volume (critical hypoperfusion–core volume).

RESULTS: Overall, 569 patients were included (172 and 397 in the bridging therapy and IVT groups, respectively). After propensity-score weighting, the distribution of baseline variables was similar across the 2 groups. In the entire population, bridging was associated with lower odds of achieving modified Rankin Scale score 0 to 1: odds ratio, 0.73 [95% CI, 0.55–0.96]; $P=0.03$. However, mismatch volume modified the effect of bridging on clinical outcome ($P_{\text{interaction}}=0.04$ for continuous mismatch volume); bridging was associated with worse outcome in patients with, but not in those without, mismatch volume <40 mL (odds ratio, [95% CI] for modified Rankin Scale score 0–1: 0.48 [0.33–0.71] versus 1.14 [0.76–1.71], respectively). Bridging was associated with higher incidence of symptomatic intracranial hemorrhage in the entire population, but this effect was present in the small mismatch subset only ($P_{\text{interaction}}=0.002$).

CONCLUSIONS: In our population of large vessel occlusion-related minor stroke patients, bridging therapy was associated with lower rates of good outcome as compared with IVT alone. However, mismatch volume was a strong modifier of the effect of bridging therapy over IVT alone, notably with worse outcome with bridging therapy in patients with mismatch volume ≤ 40 mL. Randomized trials should consider adding perfusion imaging for patient selection.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

Key Words: incidence ■ odds ratio ■ perfusion imaging ■ propensity score ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

IVT	intravenous thrombolysis
LVO	large vessel occlusion
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
sICH	symptomatic intracranial hemorrhage

Mainly owing to good leptomeningeal collaterals, a sizeable fraction of patients with acute stroke and large vessel occlusion (LVO) present with only mild neurological deficit. In the 4.5-hour window, international guidelines recommend intravenous thrombolysis (IVT) in the context of disabling ischemic minor stroke in general,^{1,2} while an expert consensus statement from the European Stroke Organisation suggests using IVT in nondisabling minor stroke with large vessel occlusion.² Although mechanical thrombectomy (MT) added on best medical management (including IVT if indicated) is currently recommended in LVO stroke patients with National Institutes of Health Stroke Scale (NIHSS) score >5 ,^{1,3} whether it is also beneficial in less-severe LVO-related strokes is unknown because only few patients with NIHSS score ≤ 5 were randomized in the pivotal MT trials.³ Discrepant results have emerged from the observational studies that compared clinical outcomes following MT added on medical treatment versus medical treatment alone in unselected LVO-related minor strokes,^{4–11} although the majority suggested no benefit from MT.^{4,5,7–11} Consequently, uncertainty remains about which patients with LVO-related minor stroke may benefit, or might even derive harm, from MT.

Recent studies from our consortium suggested that occlusion site is a strong modifier of the effect of bridging therapy (ie, IVT followed by MT) on functional outcome, with bridging being associated with higher odds of good outcome in occlusions of first segment of the middle cerebral artery or of the basilar artery, but with lower odds for more distal occlusions.^{4,12} A further major candidate for identifying responders to MT among LVO-related minor stroke patients is advanced imaging (ie, including computed tomography [CT]- or MR-based perfusion imaging), which provides maps of the irreversibly injured tissue (core) and the critically ischemic but salvageable tissue (penumbra), 2 markers of clinical response to endovascular reperfusion in LVO-related stroke with moderate-to-severe presentation.^{13–17} However, whether perfusion imaging-derived data also modify the clinical response to MT in minor stroke with LVO has been little studied. A single-center retrospective study comparing medical treatment alone versus MT in LVO-related minor strokes with significant core-perfusion mismatch volume

found no benefit from MT,¹¹ but its small sample size and exclusion of patients without significant mismatch weaken this conclusion.

Here, we tested the hypothesis that the amount of salvageable tissue on perfusion imaging would influence the clinical effects of bridging therapy over IVT alone in LVO-related minor stroke. To this end, we compared LVO-related minor stroke patients intended for bridging therapy or IVT alone as a function of baseline core-perfusion mismatch volume, and specifically assessed the interaction between mismatch volume and functional outcome for bridging therapy versus IVT alone. We focus our hypothesis on mismatch volume because a modifying treatment effect of core volume on response to MT would not be expected given the small ischemic core in this population.¹⁸

METHODS

Study Design and Data Sources

The MINOR-STROKE-PERFUSION international collaboration retrospectively collected the data from all consecutive acute stroke patients admitted to 19 stroke centres (France, $n=13$; Switzerland, $n=3$; US, $n=2$ and Germany, $n=1$) between 2010 and 2019 (inclusion date varied among centers) who fulfilled the following criteria: (1) baseline admission NIHSS score ≤ 5 ; (2) admission imaging showing LVO of the anterior circulation (internal carotid artery, first [M1] or second [M2] segment of middle cerebral artery); (3) available perfusion imaging, systematically obtained in all participating centers except specific circumstances; and (4) treated with IVT (alteplase 0.9 mg/kg), with or without intended additional MT. Patients not receiving IVT were not included, as they were not recorded in the majority of participating centers.

The requirement for local ethics approval differed across centers and was obtained if required. According to French legislation, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required. Each patient was informed of their participation in this study and was offered the possibility to withdraw, if required by the local legislations. Our analysis was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria for observational studies. The data supporting the study findings are available upon reasonable request.

Study Treatment Groups

Patients were assigned to 2 treatment groups, according to an intention-to-treat analysis: (1) bridging therapy: patients immediately intended for additional MT following IVT start, including those who eventually did not receive MT (eg, because of early post-IVT recanalization or distal thrombus migration) and (2) IVT alone: patients intended for IVT alone, including those who eventually received rescue MT because of early neurological deterioration. This approach was deliberate, to reflect the real-world dilemma facing the clinician in-charge.⁴ For each patient, the intended treatment group was determined based on careful analysis of admission medical notes.

Clinical Data

The following variables were collected: age, sex, vascular risk factors, prestroke antithrombotic medication, MT facility in the admission center, time between symptom onset and start of IVT, NIHSS score on admission and at 24 hours, and prestroke and 3-month modified Rankin Scale (mRS) score. For patients receiving MT we additionally collected time between (1) symptom onset and groin puncture; (2) IVT start and groin puncture; and (3) groin puncture and reperfusion, as well as the device used for MT.

Radiological Data

All included patients underwent either CT, CT-angiography and CT-perfusion or MRI with perfusion-weighted imaging before IVT, and follow-up MRI or CT within ~24 hours following admission. To optimize homogeneity in radiological evaluation, 1 stroke neurologist with clinical expertise in acute stroke imaging (P.S.) reviewed all pre-IVT and follow-up imaging using a structured form, blinded to clinical and radiological outcomes, from 15 of the 19 participating centers. For the remaining 4 centers (n=103 patients), imaging variables were reviewed locally again blinded to outcome, according to prespecified criteria. The following variables were collected: (1) ischemic core (defined on MRI as an apparent diffusion coefficient $<620 \times 10^{-6} \text{ mm}^2/\text{s}$ or on CT-perfusion as relative cerebral blood flow $<30\%$ of normal brain) and time-to-maximum (Tmax) >6 second volumes, automatically processed using the RAPID software (iSchemaView); (2) mismatch volume, defined as Tmax >6 second volume—core volume; (3) occlusion site, divided into the following 6 categories: proximal M1, distal M1, M2, tandem ICA+proximal M1, tandem ICA+distal M1 and tandem ICA+M2 occlusions; the M1 segment being defined as the first portion of the middle-cerebral artery up to the main bifurcation and dichotomized as proximal or distal based on the middle-cerebral artery origin-to-clot interface distance (<10 and ≥ 10 mm, respectively)^{4,19}; (4) thrombus length measured either on MRI (ie, susceptibility vessel sign), CT (hyperdense middle cerebral artery sign), or CT-angiography¹⁹; and (4) intracranial haemorrhage on follow-up imaging, according to the European Cooperation Acute Stroke Study. For patients receiving MT, recanalization was evaluated on the final intracranial run using the modified Thrombolysis in Cerebral Infarction scale, with 2b-3 considered as successful recanalization.

Study Outcomes

Taking into account the mild initial deficit, 3-month excellent functional outcome (mRS score 0–1 or return to baseline mRS) was elected as primary outcome.^{4,20} Good functional outcome (mRS score 0–2 or return to baseline mRS) was used as secondary outcome. Safety outcome was symptomatic intracranial hemorrhage (sICH) according to the European Cooperative Acute Stroke Study-II definition, namely any ICH associated with clinical worsening ≥ 4 points on the NIHSS score within the first 36 hours.

Statistical Analysis

Continuous variables were described as mean \pm SD or median (interquartile range), as appropriate, and categorical variables as numbers and percentages. To account for imbalance in

potential confounders for the associations between treatment group and outcomes, we chose a priori to use a propensity-score weighted approach as main analysis.^{4,12} All baseline clinical and radiological variables, including occlusion site and core volume, were included in the logistic model used to estimate the propensity score of each patient to be intended for bridging therapy. Balance of baseline characteristics between the 2 treatment groups was assessed before and after propensity-score weighting by calculation of absolute standardized mean differences. An absolute standardized mean difference $\leq 10\%$ was considered acceptable. The association between treatment group and each outcome was estimated through odds ratios (OR) and their 95% CIs, calculated in univariable binary logistic regression with inverse probability of treatment weighting. Potential heterogeneity in treatment effect depending on mismatch volume, either as a continuous variable or dichotomized using the median mismatch volume cutoff value in our population, was assessed in logistic models with calculation of *P* for interaction (*P*_{interaction}). We used mismatch volume rather than mismatch ratio (Tmax >6 second volume/core volume) considering the very small core volumes in this particular population of minor stroke, resulting in spuriously high or even infinite mismatch ratio in the vast majority of the population. Last, because occlusion site has been reported as a modifier of bridging therapy effect on functional outcome in our minor stroke LVO cohort,⁴ we performed exploratory analyses assessing heterogeneity in treatment effect as a function of mismatch volume separately in the M1 and M2 subgroups. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc). Two-tailed *P* <0.05 was considered significant.

RESULTS

Study Population

Of 841 patients screened, 569 were included in the present study: 172 (30%) and 397 (70%) in the bridging therapy and IVT alone groups, respectively (Figure 1). Included and excluded patients had similar baseline characteristics (Table S1). Mean age was 69 \pm 15 years, median NIHSS score was 3 (interquartile range: 2–4), and median core and mismatch volumes were 0 mL (0–8) and 38 mL (21–65), respectively. MRI and CT-perfusion were performed in 391 (69%) and 178 (31%) patients, respectively. Using the EXTEND-IA definition (mismatch volume >10 mL, mismatch ratio >1.2 , core volume <70 mL), target mismatch was present in 502/569 (88%) patients. Mismatch volume increased with NIHSS increments: 29 mL (interquartile range: 20–47), 30 mL (14–49), 35 mL (22–60), 35 mL (23–59), 46 mL (25–69) and 47 mL (23–82) for NIHSS 0, 1, 2, 3, 4 and 5, respectively (*P* for trend <0.0001). In the subset of patients intended for IVT alone, 39/397 (10%) patients underwent rescue MT because of early neurological deterioration, whereas MT was eventually not performed in 29/172 (17%) patients in the bridging therapy group (Figure 1).

Table 1 summarizes baseline patients' characteristics in the 2 treatment groups. Before propensity-score

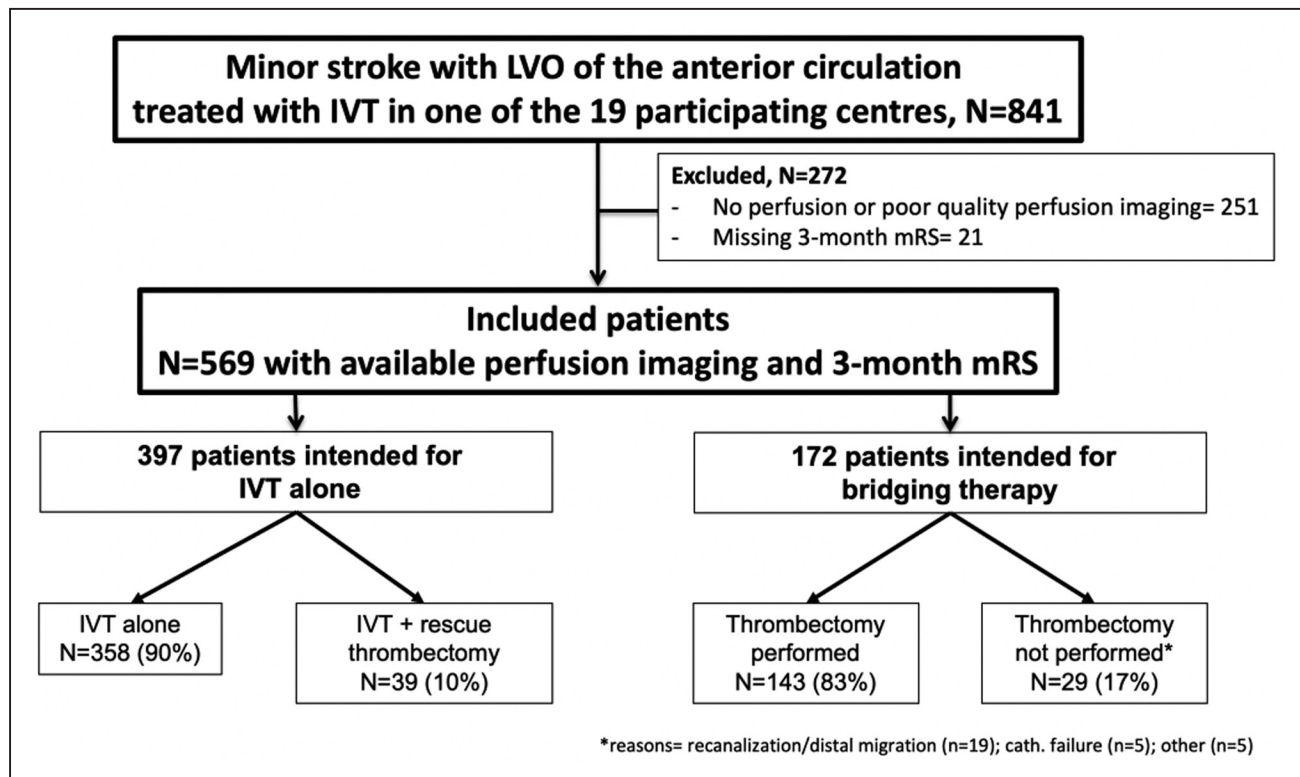


Figure 1. Study flow chart.

IVT indicates intravenous thrombolysis; LVO, large vessel occlusion; and mRS, modified Rankin Scale.

weighting several meaningful differences (absolute standardized mean difference >10%) were observed, which were effectively reduced following propensity-score weighting (Table 1), with absolute standardized mean differences now ≤10% for all baseline variables, indicating satisfactory balance between the 2 groups.

Data regarding the endovascular procedure for all patients who received groin puncture are presented in Table 2. Successful recanalization was obtained in 145/172 (84.3%) and 33/39 (84.6%) patients in the bridging therapy and rescue MT groups, respectively.

Association Between Treatment Group and Efficacy Outcomes According to Mismatch Volume

Primary Outcome (mRS Score 0–1)

In the entire population, bridging therapy (as compared with IVT alone) was associated with lower odds of achieving mRS score 0 to 1: OR=0.73 [95% CI, 0.55–0.96]; $P=0.03$. However, as depicted in Figure 2A, which shows the probability of mRS score 0 to 1 as a function of continuous mismatch volume and treatment group, there was a significant treatment group*mismatch interaction ($P_{\text{interaction}}=0.04$ for continuous mismatch volume). Using 40 mL as cut-off (ie, the rounded median mismatch volume across the entire cohort), bridging therapy was associated with lower odds of mRS score 0 to 1 in patients with, but

not in those without, mismatch volume <40 mL (Figure 2B; OR [95% CI] for mRS score 0–1: 0.48 [0.33–0.71] versus 1.14 [0.76–1.71], respectively, $P_{\text{interaction}}=0.003$).

Secondary Outcome (mRS Score 0–2)

In the entire population, bridging therapy (as compared with IVT alone) was associated with lower odds of achieving mRS score 0 to 2: OR=0.50 [95% CI, 0.35–0.73]; $P=0.0003$. However, there was a trend for a treatment group*mismatch volume interaction, bridging being associated with lower odds of mRS score 0 to 2 in patients with, but not in those without, mismatch volume <40 mL (OR [95% CI]: 0.37 [0.22–0.61] versus 0.74 [0.42–1.28], respectively; $P_{\text{interaction}}=0.07$).

Exploratory Subgroup Analysis According to Occlusion Site for Primary Outcome (mRS Score 0–1)

There was no significant interaction between continuous mismatch volume and bridging therapy effect in the M1 occlusion subgroup ($P_{\text{interaction}}=0.43$), while a trend was found in the M2 occlusion subgroup ($P_{\text{interaction}}=0.10$).

Association Between Treatment Group and Safety Outcomes

In the entire population, bridging therapy was associated with higher incidence of sICH (OR=1.93 [95% CI, 1.11–3.36]; $P=0.02$). However, as depicted on Figure 3A,

Table 1. Characteristics and Comparison of Both Treatment Groups*

	Bridging therapy N=172	IVT alone N=397	ASMD before propensity score weighting†	ASMD after propensity score weighting†
Age	66.1±15.1	69.7±14.5	0.24	0.04
Male sex	98 (57.0)	194 (48.9)	0.16	0.00
mRS score before stroke	0 (0–0)	0 (0–1)	0.15	0.06
Medical history				
Hypertension	104 (60.5)	244 (61.5)	0.02	0.05
Diabetes	25 (14.5)	58 (14.6)	0.01	0.06
Current smoking	44 (25.6)	75 (18.9)	0.16	0.07
Antiplatelet therapy	44 (25.6)	141 (35.5)	0.21	0.06
Anticoagulants	6 (3.5)	18 (4.5)	0.05	0.03
Pre-IVT characteristics				
NIHSS	4 (2–5)	3 (2–4)	0.28	0.00
Treated after 2014	164 (95.3)	265 (66.8)	0.77	0.02
On-site MT facility‡	142 (82.6)	362 (91.2)	0.27	0.01
Onset to IVT time, min	153 (120–203)	168 (135–210)	0.02	0.02
Pre-IVT imaging				
MRI	110 (64.0)	281 (70.8)	0.13	0.04
Site of occlusion			0.62	0.06
Proximal M1	18 (10.5)	19 (4.8)		
Distal M1	53 (30.8)	67 (16.9)		
M2	71 (41.3)	269 (67.8)		
Tandem prox. M1+ICA	10 (5.8)	9 (2.3)		
Tandem dist. M1+ICA	13 (7.6)	8 (2.0)		
Tandem M2+ICA	7 (4.1)	25 (6.3)		
Thrombus length,§ mm	9 (7–13)	8 (6–12)	0.21	0.06
Core volume, mL	0 (0–11)	0 (0–6)	0.13	0.02
Mismatch volume, mL	51 (31–85)	34 (17–57)	0.49	0.05

ASMD indicates absolute standardized mean difference; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MT, mechanical thrombectomy; and NIHSS, National Institutes of Health Stroke Scale.

*Categorical variables are expressed as numbers (%) and continuous variables as median (IQR) or mean (SD).

†An ASMD≤10% corresponds to a small difference (ie, well-balanced groups regarding the variable of interest).

‡Baseline imaging performed in a stroke center with on-site thrombectomy capability.

§Available in 495 (87%) patients (bridging therapy, n=147; IVT alone, n=348).

which shows the probability of sICH as a function of continuous mismatch volume and treatment group, this potential deleterious effect of bridging therapy on sICH was significantly modified by mismatch volume ($P_{\text{interaction}}=0.002$ for continuous mismatch volume): bridging therapy was associated with higher sICH incidence in patients with, but not in those without, mismatch volumes <40 mL (OR [95% CI] for sICH: 4.77 [2.00–11.37] versus 0.69 [0.30–1.58], respectively, $P_{\text{interaction}}=0.002$, Figure 3B). Out of the 10 (6%) sICH occurring in the bridging therapy group, 3 were due to endovascular procedural complications (ie, vessel perforation).

DISCUSSION

The aim of this novel study was to compare the rates of both excellent clinical outcome and sICH as efficacy

and safety outcomes, respectively, of bridging therapy versus IVT alone in minor stroke patients with LVO as a function of mismatch volume present on baseline imaging. Two salient findings emerged. First, consistent with our hypothesis, mismatch volume significantly modified the clinical effect of bridging therapy over IVT alone. In dichotomized analysis, this interaction translated as bridging therapy being associated with significantly lower odds of excellent outcome in case of small mismatch, with no significant effect in case of large mismatch. Second, although bridging therapy was associated with higher incidence of sICH in the entire population, this effect was also modified by mismatch volume: bridging therapy was associated with higher sICH incidence in case of small mismatch only.

Median mismatch volume was around 2-fold smaller in our population than in unselected LVO populations

Table 2. Characteristics of Endovascular Procedures in Both Treatment Groups*

	Bridging therapy	IVT alone†
	N=172	N=39
Onset-to-puncture time, min	215 (173–270)	362 (246–519)
IVT-to-puncture time, min	45 (30–73)	168 (110–260)
Puncture-to-reperfusion time, min	42 (26–63)	65 (43–89)
Material used		
Aspiration	26 (15.1)	7 (17.9)
Stentriever	67 (39.0)	18 (46.2)
Aspiration+stentriever	42 (24.4)	8 (20.5)
Angioplasty/stenting of cervical ICA	13 (7.6)	6 (15.3)
Intraarterial thrombolysis	4 (2.3)	0 (0.0)
None‡	29 (16.8)	6 (15.3)
mTICI 2b-3	145 (84.3)	33 (84.6)

ICA indicates internal carotid artery; IVT, intravenous thrombolysis; and mTICI, modified Thrombolysis in Cerebral Infarction.

*Categorical variables are expressed as numbers (%) and continuous variables as median (IQR) or mean (SD).

†Thirty-nine patients who eventually received MT because of early neurological deterioration (Figure 1).

‡These patients were found to have distal thrombus migration or complete recanalization on angiographic first run or had catheterization failure.

(roughly 40 versus 80 mL),¹⁵ with ~90% of patients in our cohort fulfilling the EXTEND-IA target mismatch definition, as opposed to ~70% in a nonminor LVO population.¹⁵ Together with the lack of benefit from bridging therapy as compared with IVT alone across our population, in line with previous observational studies,^{4,5,7–11} our findings suggest that standard definition 'target mismatch' per se may be too prevalent in LVO-related minor stroke to allow identification of a subset that derives benefit or harm from MT. Accordingly, a previous single-center observational study in minor stroke LVO patients with target mismatch found no benefit of MT over medical management alone.¹¹

In the present study, we evaluated the effect of mismatch volume as continuous measure, and then assessed the effect of mismatch volume dichotomized according to the median value in our population (namely, 40 mL). The probability of excellent functional outcome increased in proportion with mismatch volume in the bridging therapy group, but not in the IVT alone group (Figure 2A). Following dichotomization, bridging therapy was associated with worse outcome as compared with IVT alone in patients with small (<40 mL) mismatch, with no significant effect in case of large (≥40 mL) mismatch. These results are in line with previous findings in moderate-to-severe LVO-related stroke,^{13–17} suggesting the amount of mismatch is a generic marker of clinical response to endovascular therapy regardless of baseline stroke severity. However, to our knowledge, our study is the first to report such modifying treatment effect of mismatch volume in LVO-related minor stroke. Further analysis disclosed that this effect was not significant in the M1 or M2 occlusion

subgroups taken separately, likely due to smaller sample size. Importantly, we elected to assign patients to the treatment group in which they were intended on initial decision, which allows a comparison between the 2 treatment paradigms with less selection bias. An interaction between mismatch volume and excellent functional outcome was not found in exploratory analysis based on the treatment that each patient eventually received ('as-treated' analysis, data not shown).

Several factors may explain the significant interaction between mismatch volume and treatment. First, despite mild baseline deficits, MT-induced reperfusion of larger, as opposed to smaller, volumes of salvageable tissue would be expected to result in larger clinical improvements, including cognitive functions. Second, bridging therapy may prevent the occurrence of early neurological deterioration, a serious complication found associated with larger mismatch in medically treated patients in 1 study,¹⁸ although not in others.^{19,21} Last, and most notably, MT-induced complications may have greater clinical impact in patients with small, as compared with large, mismatch volume. In line with the latter idea, we found here that bridging was associated with higher odds of sICH in patients with small mismatch volumes. Three main factors may explain this observation. First, in patients with small mismatch, the detrimental effects of even a medium-size parenchymal hemorrhage on neurological deficit may not be outweighed by beneficial effects from penumbral salvage. Second, smaller mismatch volumes are expected in M2 occlusions, which may be associated with more frequent thrombectomy-related complications potentially leading to sICH.²² Last, a smaller mismatch downstream an LVO may be explained by a more chronic, for example, atherosclerotic occlusion, also implying higher procedure-related risks. Of note, core volume did not seem to account for this observation as the impact of mismatch volume on the association of sICH with bridging therapy remained highly significant after adjustment for core volume in sensitivity analysis (data not shown). Also, we opted to use the ECASSII definition for sICH (any ICH associated with ≥4 NIHSS points deterioration) because it is widely used, straightforward, and robustly predicts 3-month poor outcome.²³ However, this definition does not require a presumed causal relation nor a temporal association between the ICH and the deterioration. As it encompasses minor ICH, sometimes unlikely to cause neurological deterioration, this classification therefore mixes 2 distinct causes of poor outcome, namely true sICH and 'ischemic' worsening associated with asymptomatic hemorrhagic transformation. The raw rates of sICH using a stricter definition (parenchymal type 1 or 2 associated with ≥4 NIHSS points deterioration) were also higher in the bridging therapy group (1/397 and 5/172 in the IVT and bridging therapy groups, respectively), but the small numbers impeded meaningful statistical analysis.

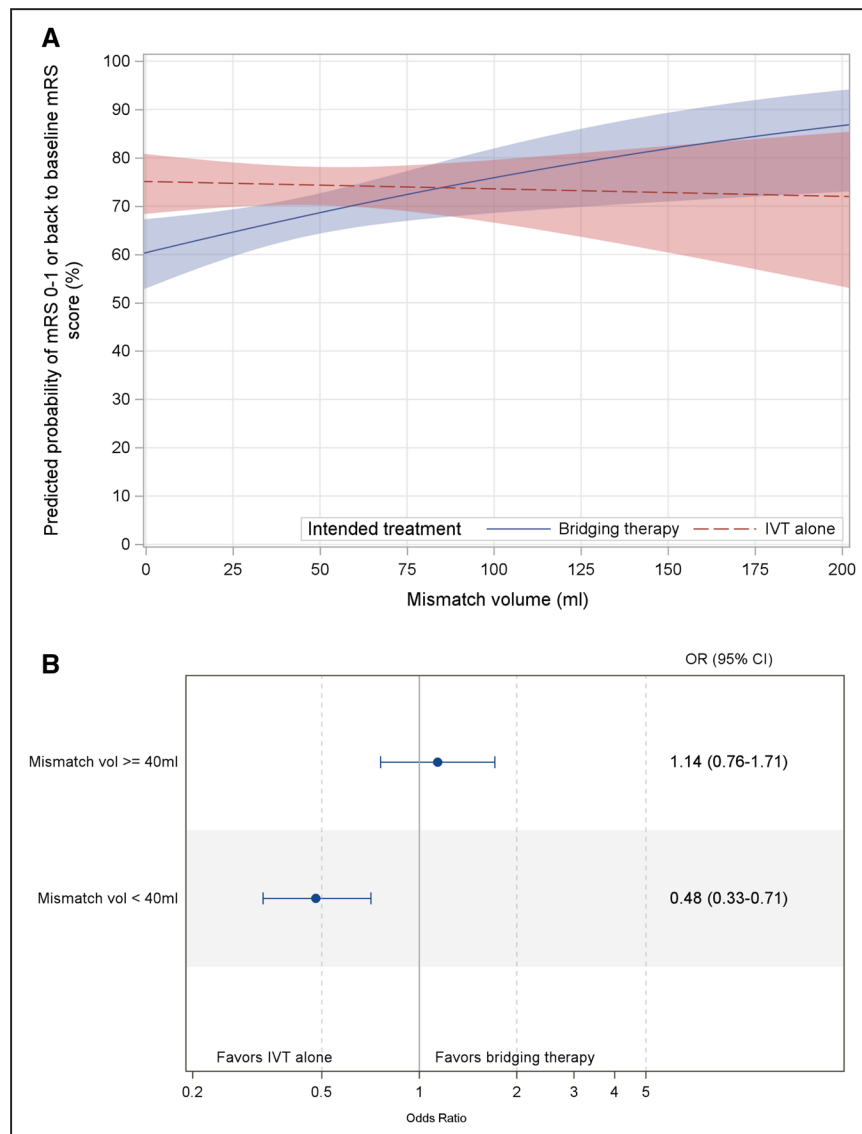


Figure 2. Primary efficacy outcome (modified Rankin Scale [mRS] score 0–1 or back to baseline mRS) according to mismatch volume and treatment group.

A, Continuous mismatch volume: The blue curve corresponds to the predicted probability of mRS score 0 to 1 in bridging therapy patients, and the red dotted curve to intravenous thrombolysis (IVT) alone patients. The shaded area corresponds to the 95% CI (logistic regression model).

B, Dichotomized mismatch volume: Forest plot summarizes the odds ratio obtained for comparison of treatment groups on mRS score 0 to 1 according to dichotomized mismatch ratio (using 40 mL as cutoff, the rounded median mismatch volume across the entire population).

Documenting an influence of mismatch volume on clinical and safety outcomes after reperfusion therapy in minor stroke with LVO sheds new light on current debates regarding the best treatment strategy in this population. Because minor stroke was an exclusion criterion in most of the pivotal MT trials,³ the benefit from MT over medical management alone has remained uncertain in this setting, and 2 ongoing randomized trials are comparing MT+best medical management versus best medical management alone in this population (URL: <https://www.clinicaltrials.gov>; Unique identifier: ENDOLOW-NCT04167527 and In Extremis/MOSTE-NCT03796468). As mismatch volume is not considered for patient selection in these 2 trials, patients with variable perfusion profiles, in turn predicting different responses to MT, will inevitably be pooled together. Consequently, a positive result from these trials would extend indication for MT to patients with small mismatch volume, in whom the benefit/risk profile may be unfavorable. Conversely, a negative result would exclude from MT those patients

with large mismatch who might derive benefit. In the current emerging era of personalized medicine, our data suggest that future trials in LVO-related minor stroke may consider adding mismatch volume as a selection criterion so as to enhance their chance of clinically relevant findings. This warrants further studies.

This study has several strengths. First, although a relatively uncommon clinical presentation, we were able to collect a large sample of LVO-related minor stroke, thanks to the multicenter international design. Furthermore, a large fraction of the sample had undergone baseline perfusion imaging, in turn allowing for the first time a reliable assessment of the impact of mismatch volume on treatment effect. Moreover, included and excluded (ie, without perfusion imaging) patients had similar baseline characteristics (Table S1), suggesting perfusion imaging did not induce a selection bias in our study. Second, almost all (namely, 96%) of the sample in the bridging therapy group were treated after 2015, ensuring the use of efficient endovascular devices and high rates of

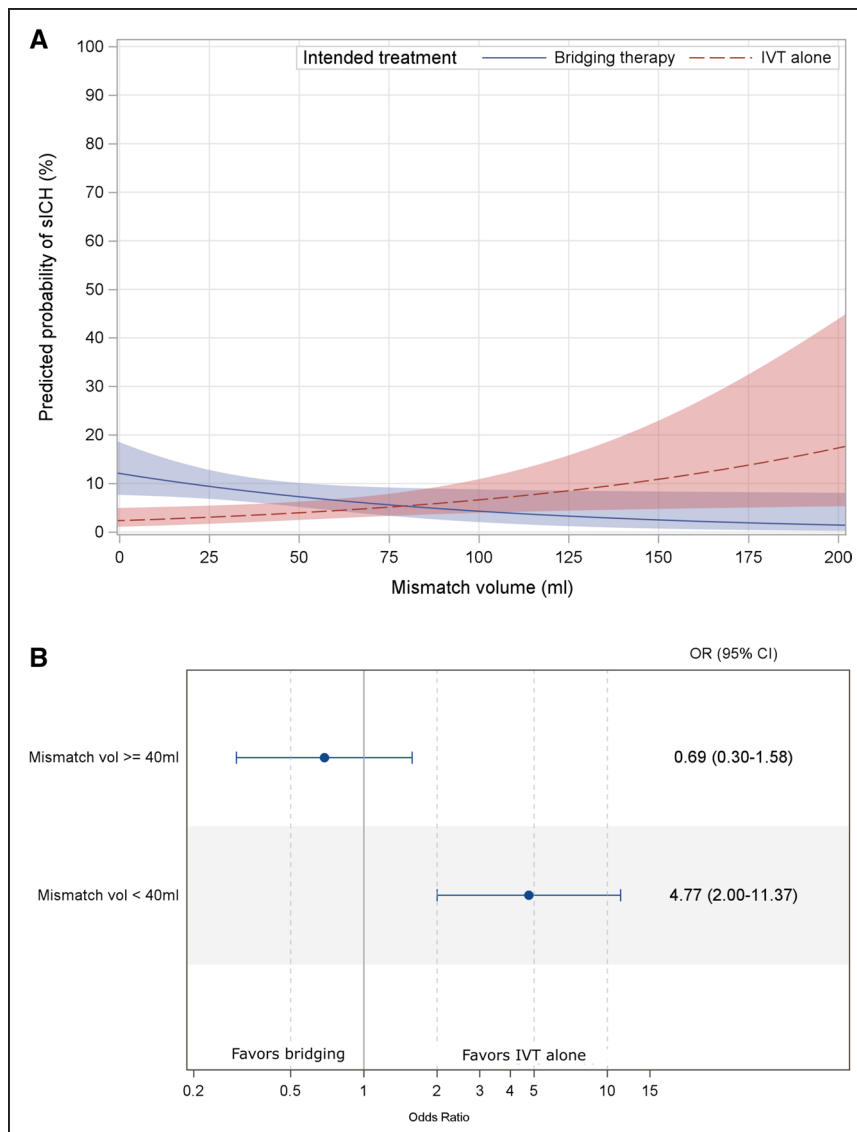


Figure 3. Safety outcome (symptomatic intracranial hemorrhage) according to mismatch volume and treatment group

A, Continuous mismatch volume: the blue curve corresponds to the predicted probability of symptomatic intracranial hemorrhage (sICH) in bridging therapy patients, and the red dotted curve to intravenous thrombolysis (IVT) alone patients. **B**, Dichotomized mismatch volume: forest plot summarizes the odds ratio (OR) obtained for comparison of treatment groups on sICH according to dichotomized mismatch ratio.

successful recanalization, in turn reflecting current daily practice. Third, the central reading of the imaging data-sets (performed for over 80% of the sample) ensured a uniform assessment of key variables such as occlusion site, recanalization and intracranial hemorrhage for the majority of the population. Finally, the same validated software was employed for automatic perfusion post-processing across the sample, ensuring uniform assessment of perfusion parameters.

Our study has limitations. The main limitation is the observational design leading to the possibility of confounding by indication. In particular, the results of perfusion imaging likely influenced individual treatment choice, including IVT use. Although propensity-score weighting analysis dramatically reduced between-group differences in baseline characteristics—including core and mismatch volumes—unmeasured or unknown confounding factors affecting both treatment decision and functional outcome may have been overlooked. For instance, the type of neurological deficit (ie, disabling versus nondisabling), the

occurrence of clinical fluctuations or the topography of mismatch (ie, involving potentially eloquent areas) could impact both decision-making and the effect of bridging therapy, but these data were not available. The associations observed here may, therefore, not necessarily be causative, and accordingly our findings should be interpreted with caution pending randomized trials. Second, this study was retrospective, and although the medical records were carefully reviewed to determine ‘intention to treat’ at the individual level (ie, bridging therapy or IVT alone), misclassification might have affected a minority of patients. Last, only IVT-treated patients were included in this study, so our results do not apply to populations ineligible to IVT, in particular, those admitted beyond 4.5 hours from stroke onset.

CONCLUSIONS

In our population of minor strokes with LVO, bridging therapy was associated with lower rates of good functional

outcome than IVT alone. However, mismatch volume was a strong modifier of the effect of bridging therapy over IVT alone. Bridging therapy was associated with worse outcome in patients with mismatch volume ≤ 40 mL, in part due to higher sICH rates, with no significant effect with larger mismatch. Thus, future randomized trials testing MT versus medical treatment alone in LVO-related minor stroke should consider adding perfusion imaging for patient selection.

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Supplemental Material

STROBE Checklist

Table

APPENDIX

MINOR-STROKE Perfusion Collaborators

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