Perfusion imaging and clinical outcome in acute minor stroke with large vessel occlusion

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Abstract

Background: Whether bridging therapy (intravenous thrombolysis [IVT] followed by mechanical thrombectomy) is superior to IVT alone in minor stroke with large vessel occlusion (LVO) is unknown. Perfusion imaging may identify subsets of LVO-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 (NIHSS≤5) who had an anterior circulation LVO and perfusion imaging performed prior to 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 score 0-1. 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). Following propensity-score weighting, the distribution of baseline variables was similar across the two groups. In the entire population, bridging was associated with lower odds of achieving mRS 0-1: OR=0.73, 95%CI 0.55-0.96, P=0.03. However, mismatch volume modified the effect of bridging on clinical outcome ($P_{interaction}$=0.04 for continuous mismatch volume); bridging was associated with worse outcome in patients with, but not in those without, mismatch volume <40ml (OR [95%CI] for mRS 0-1: 0.48 [0.33-0.71] *vs.* 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 ($P_{interaction}$=0.002).

Conclusions: In our population of LVO-related minor stroke patients, bridging therapy was associated with lower rates of good outcome as compared to 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 ≤40ml. Randomized trials should consider adding perfusion imaging for patient selection.

NON-STANDARD ABBREVIATIONS AND ACRONYMS

ASMD: absolute standardized mean differences

IVT: intravenous thrombolysis

LVO: large vessel occlusion

MT: mechanical thrombectomy

INTRODUCTION

Mainly owing to good leptomeningeal collaterals, a sizeable fraction of patients with acute stroke and large vessel occlusion (LVO) present with only mild neurological deficits. In the 4.5hr 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 non-disabling 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] though 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 (*i.e.*, 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 (*i.e.*, including CT- or MR-based perfusion imaging), which provides maps of the irreversibly injured tissue ("core") and the critically ischemic but salvageable tissue ("penumbra"), two 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 *vs.* 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 in bridging therapy *vs*. 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; USA, n=2 and Germany, n=1) between 2010 and 2019 (inclusion date varied among centres) who fulfilled the following criteria: (1) baseline admission NIHSS score ≤5; (2) admission imaging showing LVO of the anterior circulation (internal carotid artery [ICA], 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 (*e.g.*, 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, in order 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, pre-stroke anti-thrombotic medication, MT facility in the admission centre, time between symptom onset and start of IVT, NIHSS score on admission and at 24h, and pre-stroke 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 ~24hrs following admission. To optimize homogeneity in radiological evaluation, one stroke neurologist with clinical expertise in acute stroke imaging (PS) 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 pre-specified criteria. The following variables were collected: (1) ischemic core (defined on MRI as an apparent diffusion coefficient <620 $X10^{-6}$ mm^2/s or on CT-perfusion as relative cerebral blood flow <30% of normal brain) and time-to-maximum (Tmax)>6s volumes, automatically processed using the RAPID software (iSchemaView); (2) mismatch volume, defined as Tmax>6sec volume - core volume; (3) occlusion site, divided into the following six 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 (*i.e.*, susceptibility vessel sign), CT (hyperdense middle cerebral artery sign), or CT-angiography;[19] 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, three-month excellent functional outcome (mRS 0-1 or return to baseline mRS) was elected as primary outcome.[4,20] Good functional outcome (mRS 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 36hrs.

Statistical analysis

Continuous variables were described as mean±standard deviation or median (interquartile range, IQR), as appropriate, and categorical variables as numbers and percentages. In order 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 two treatment groups was assessed before and after propensity-score weighting by calculation of absolute standardized mean differences (ASMD). An absolute standardized mean difference ≤10% was considered acceptable. The association between treatment group and each outcome was estimated through odds ratios (OR) and theirs 95%

Confidence Intervals (95%CI), 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 cut-off value in our population, was assessed in logistic models with calculation of *P* values for interaction ($P_{interaction}$). We used mismatch volume rather than mismatch ratio (Tmax>6sec 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 (**Supplemental Table I**). Mean age was 69±15yrs, median NIHSS score was 3 (IQR: 2-4), and median core and mismatch volumes were 0ml (0-8) and 38ml (21-65), respectively. MRI and CT-perfusion were performed in 391 (69%) and 178 (31%) patients, respectively. Using the EXTEND-IA definition (mismatch volume>10ml, mismatch ratio>1.2, core volume<70ml), target mismatch was present in 502/569 (88%) patients. Mismatch volume increased with NIHSS increments: 29ml (IQR: 20-47), 30ml (14-49), 35ml (22-60), 35ml (23-59), 46ml (25-69) and 47ml (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 two treatment groups. Before propensity-score weighting several meaningful differences (ASMD>10%) were observed, which were effectively

reduced following propensity-score weighting (Table 1), with ASMDs now ≤10% for all baseline variables, indicating satisfactory balance between the two 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 0-1)

In the entire population, bridging therapy (as compared to IVT alone) was associated with lower odds of achieving mRS 0-1: OR=0.73, 95%CI 0.55-0.96, *P*=0.03. However, as depicted in **Figure 2A**, which shows the probability of mRS 0-1 as a function of continuous mismatch volume and treatment group, there was a significant treatment group*mismatch interaction ($P_{interaction}$=0.04 for continuous mismatch volume). Using 40ml as cut-off (*i.e.*, the rounded median mismatch volume across the entire cohort), bridging therapy was associated with lower odds of mRS 0-1 in patients with, but not in those without, mismatch volume <40ml (**Figure 2B**; OR [95%CI] for mRS 0-1: 0.48 [0.33-0.71] *vs*. 1.14 [0.76-1.71], respectively, $P_{interaction}$=0.003).

Secondary outcome (mRS 0-2)

In the entire population, bridging therapy (as compared to IVT alone) was associated with lower odds of achieving mRS 0-2: 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 0-2 in patients with, but not in those without, mismatch volume <40ml (OR [95%CI]: 0.37 [0.22-0.61] *vs*. 0.74 [0.42-1.28], respectively, $P_{interaction}$=0.07).

Exploratory subgroup analysis according to occlusion site for primary outcome (mRS 0-1)

There was no significant interaction between continuous mismatch volume and bridging therapy effect in the M1 occlusion subgroup ($P_{interaction}$=0.43), while a trend was found in the M2 occlusion subgroup ($P_{interaction}$=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**, 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 ($P_{interaction}$=0.002 for continuous mismatch volume): bridging therapy was associated with higher sICH incidence in patients with, but not in those without, mismatch volumes <40ml (OR [95%CI] for sICH: 4.77 [2.00-11.37] *vs*. 0.69 [0.30-1.58], respectively, $P_{interaction}$=0.002, **Figure 3B**). Out of the 10 (6%) sICH occurring in the bridging therapy group, 3 were due to endovascular procedural complications (*i.e*., 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 with LVO patients 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 two-fold smaller in our population than in unselected LVO populations (roughly 40ml *vs*. 80ml),[15] with ~90% of patients in our cohort fulfilling the EXTEND-IA 'target mismatch' definition, as opposed to ~70% in a non-minor LVO population.[15] Together with

the lack of benefit from bridging therapy as compared to 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, 40ml). 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 to IVT alone in patients with small (<40ml) mismatch, with no significant effect in case of large (≥40ml) 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 two 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 one

study,[18] though not in others.[19,21] Last, and most notably, MT-induced complications may have greater clinical impact in patients with small, as compared to 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 outweighted 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 -*e.g*. atherosclerotic- occlusion, also implying higher procedure-related risks. Of note, core volume did not appear 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.

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 two ongoing randomized trials are comparing MT + best medical management *vs.* best medical management alone in this population (ENDO-LOW – NCT04167525 and In Extremis/MOSTE -

NCT03796468). As mismatch volume is not considered for patient selection in these two 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 (*i.e.*, without perfusion imaging) patients had similar baseline characteristics (Supplemental Table), 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 successful recanalization, in turn reflecting current daily practice. Third, the central reading of the imaging datasets (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. Even though 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 (*i.e.*, disabling *vs.* non-disabling), the occurrence of clinical fluctuations or the topography of mismatch (*i.e.*, 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 even though the medical records were carefully reviewed to determine 'intention to treat' at the individual level (*i.e.*, 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 4.5hrs 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 ≤40ml, in part due to higher sICH rates, with no significant effect with larger mismatch. Thus, future randomized trials testing MT *vs*. medical treatment alone in LVO-related minor stroke should consider adding perfusion imaging for patient selection.

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Supplemental Materials:

- STROBE Checklist
- Supplementary Table

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 gender	98 (57.0)	194 (48.9)	0.16	0.00
mRS 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 mellitus	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

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

†: An ASMD ≤10% corresponds to a small difference (*i.e.*, 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).

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

Table 2. Characteristics of endovascular procedures in both treatment groups*

	Bridging therapy N=172	**IVT alone† 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)
Intra-arterial thrombolysis	4 (2.3)	0 (0.0)
None‡	29 (16.8)	6 (15.3)
mTICI 2b-3	145 (84.3)	33 (84.6)

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

†: 39 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.

Abbreviations: ICA indicates internal carotid artery; IVT, intravenous thrombolysis; mTICI, modified thrombolysis in cerebral infarction.

Figure legends

Figure 1. Study flow chart.

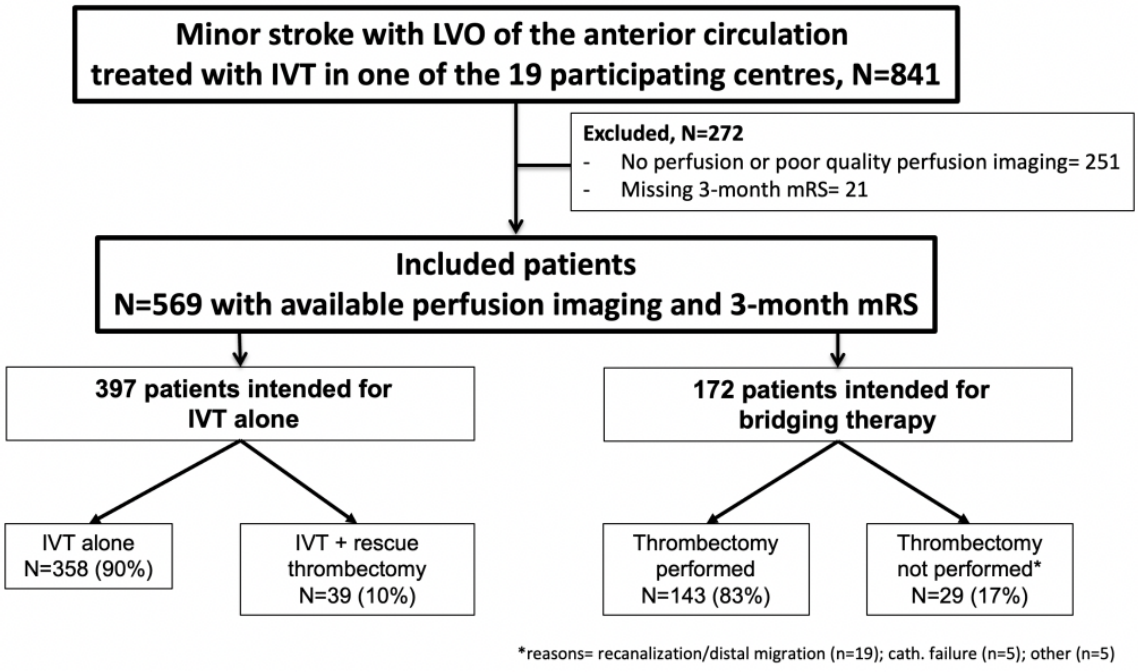
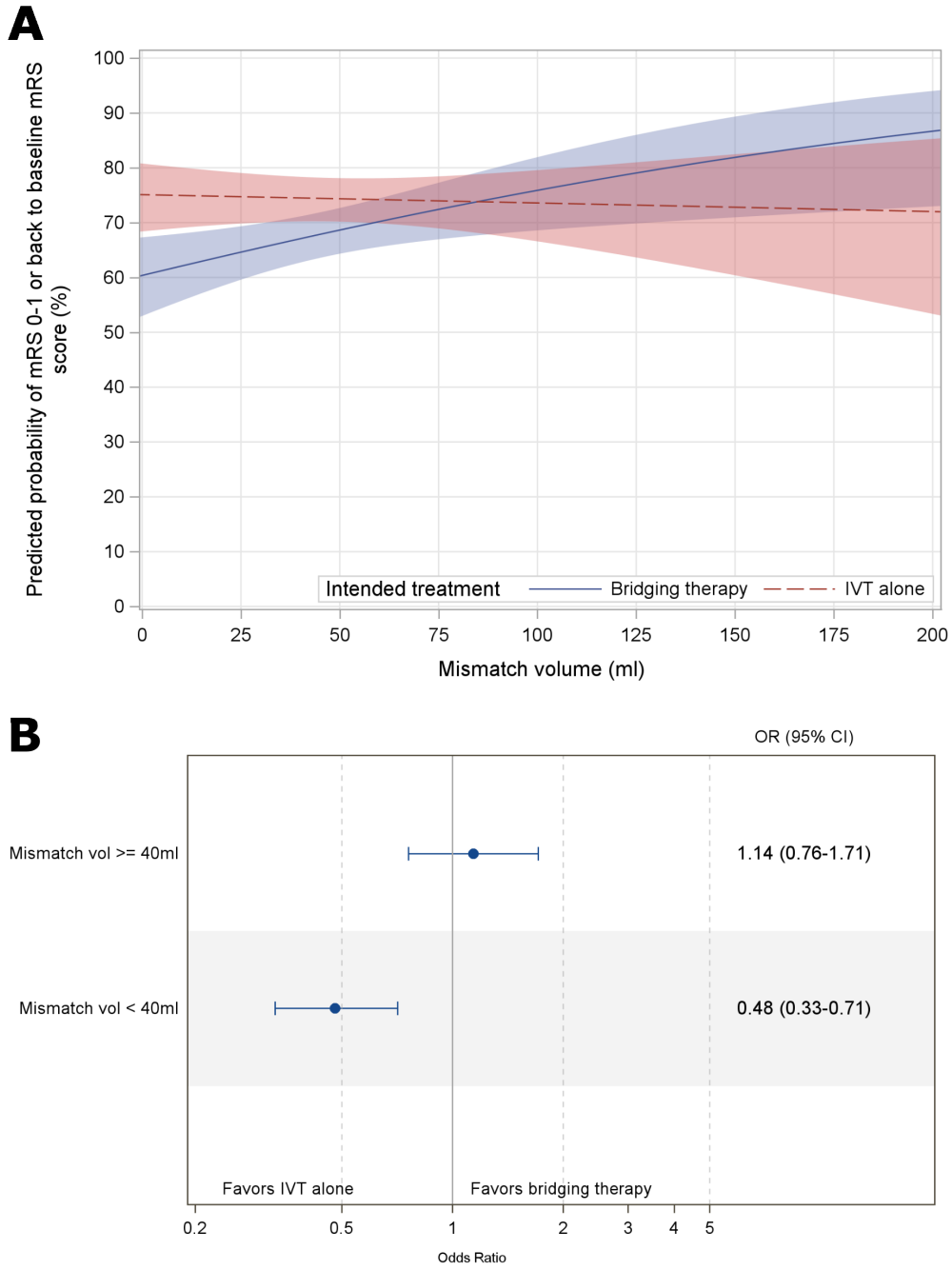


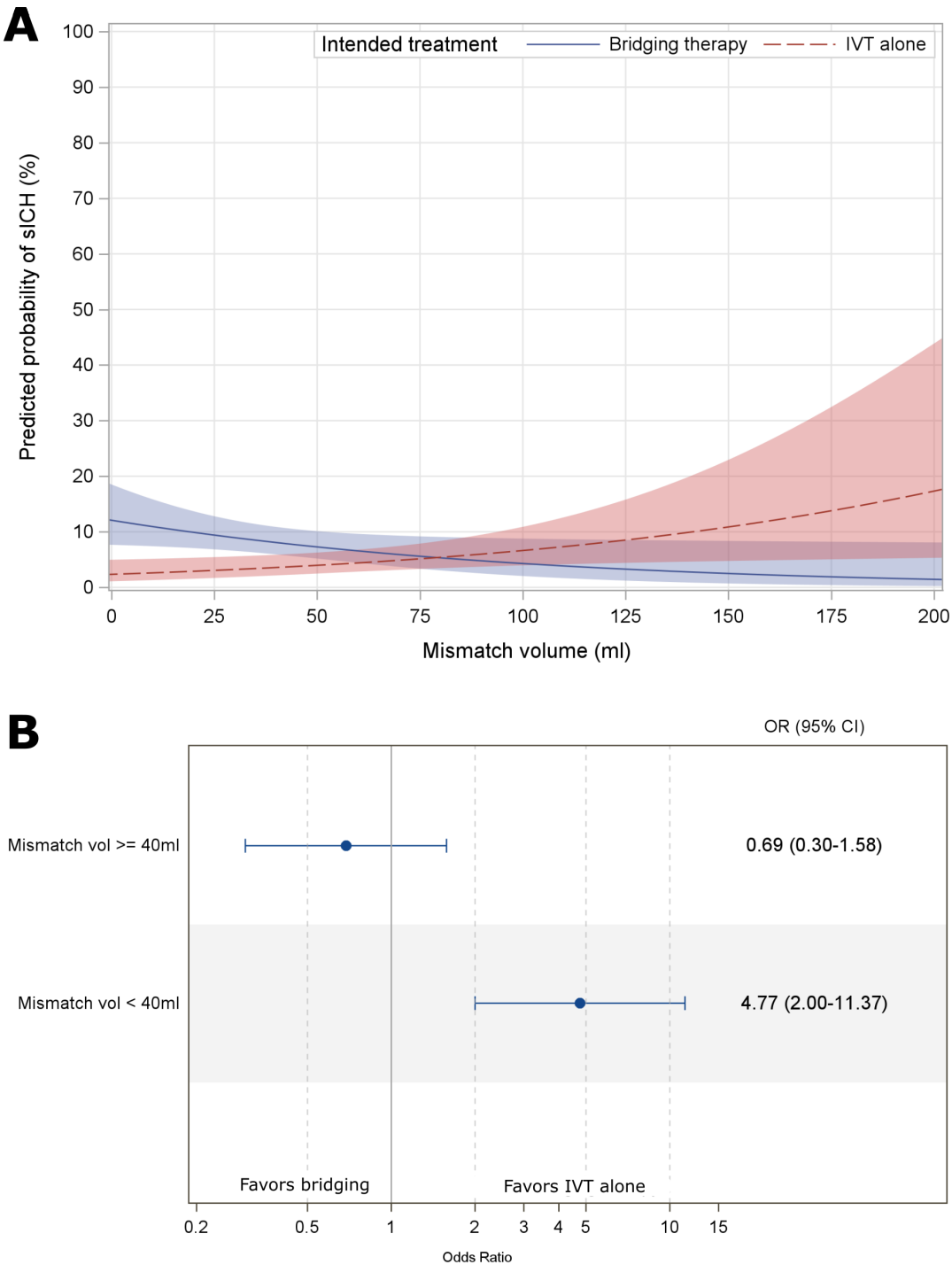
Figure 2. Primary efficacy outcome (mRS 0-1 or back to baseline mRS) according to continuous (A) or dichotomized (B) mismatch volume and treatment group.



A: The blue curve corresponds to the predicted probability of mRS 0-1 in bridging therapy patients, and the red dotted curve to IVT alone patients. The shaded area corresponds to the 95% confidence interval (logistic regression model).

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

Figure 3. Safety outcome (symptomatic intracranial hemorrhage) according to continuous (A) or dichotomized (B) mismatch volume and treatment group.



A: The blue curve corresponds to the predicted probability of sICH in bridging therapy patients, and the red dotted curve to IVT alone patients.

B: Forest plot summarizes the odds ratio obtained for comparison of treatment groups on sICH according to dichotomized mismatch ratio.

Appendix

MINOR-STROKE perfusion collaborators: Christophe Cognard, Gaultier Marnat, Patrice Menegon, Sylvain Ledure, Cyril Dargazanli, Tae-Hee Cho, Norbert Nighoghossian, Omer Eker, Sylvain Gouttard, Diogo Haussen, Séverine Debiais, Vladimir Charron, Nicolas Charron, Didier Leys, Canan Ozsancak, Mathilde Delpech, Hervé Brunel, Chrysanti Papagiannaki, Emmanuel Girardin, Sébastien Richard, Benjamin Gory, Martin Zbinden, Tomas Dobrocky, Peter Ringelb, Markus Möhlenbruch.

References:

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B*, et al.* 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46-e110
2. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I-lxii
3. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, Schellinger PD, Toni D, de Vries J, White P*, et al.* European stroke organisation (ESO)- european society for minimally invasive neurological therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;11:535-538
4. Seners P, Perrin C, Lapergue B, Henon H, Debiais S, Sablot D, Girard Buttaz I, Tamazyan R, Preterre C, Laksiri N*, et al.* Bridging therapy or iv thrombolysis in minor stroke with large vessel occlusion. *Ann Neurol*. 2020;88:160-169
5. Goyal N, Tsivgoulis G, Malhotra K, Ishfaq MF, Pandhi A, Frohler MT, Spiotta AM, Anadani M, Psychogios M, Maus V*, et al.* Medical management vs mechanical thrombectomy for mild strokes: An international multicenter study and systematic review and meta-analysis. *JAMA Neurol*. 2020;77(1):16-24.
6. Nagel S, Bouslama M, Krause LU, Kupper C, Messer M, Petersen M, Lowens S, Herzberg M, Ringleb PA, Mohlenbruch MA*, et al.* Mechanical thrombectomy in patients with milder strokes and large vessel occlusions. *Stroke*. 2018;49:2391-2397
7. Sarraj A, Hassan A, Savitz SI, Grotta JC, Cai C, Parsha KN, Farrell CM, Imam B, Ribo M. Endovascular thrombectomy for mild strokes: How low should we go? *Stroke*. 2018;49(10):2398-2405.
8. Manno C, Disanto G, Bianco G, Nannoni S, Heldner M, Jung S, Arnold M, Kaesmacher J, Muller M, Thilemann S*, et al.* Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms. *Neurology*. 2019;93:e1618-e1626

9. Heldner MR, Chaloulos-Iakovidis P, Panos L, Volbers B, Kaesmacher J, Dobrocky T, Mordasini P, El-Koussy M, Gralla J, Arnold M*, et al.* Outcome of patients with large vessel occlusion in the anterior circulation and low NIHSS score. *J Neurol*. 2020;267:1651-1662

10. Volny O, Zerna C, Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R*, et al.* Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. *Neurology*. 2020;95:e3364-e3372

11. Wolman DN, Marcellus DG, Lansberg MG, Albers G, Guenego A, Marks MP, Dodd RL, Do HM, Wintermark M, Martin BW*, et al.* Endovascular versus medical therapy for large-vessel anterior occlusive stroke presenting with mild symptoms. *Int J Stroke*. 2019:1747493019873510

12. Seners P, Dargazanli C, Piotin M, Sablot D, Bracard S, Niclot P, Baron JC, Turc G. Intended bridging therapy or intravenous thrombolysis alone in minor stroke with basilar artery occlusion. *Stroke*. 2021;52:699-702

13. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, Wilder MJ, Lutsep HL, Czartoski TJ, Bernstein RA*, et al.* MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): A prospective cohort study. *Lancet Neurol*. 2012;11:860-867

14. Sarraj A, Hassan AE, Grotta J, Sitton C, Cutter G, Cai C, Chen PR, Imam B, Pujara D, Arora A*, et al.* Optimizing patient selection for endovascular treatment in acute ischemic stroke (SELECT): A prospective, multicenter cohort study of imaging selection. *Ann Neurol*. 2020;87:419-433

15. Olivot JM, Albucher JF, Guenego A, Thalamas C, Mlynash M, Rousseau V, Drif A, Christensen S, Sommet A, Viguier A*, et al.* Mismatch profile influences outcome after mechanical thrombectomy. *Stroke*. 2021;52:232-240

16. Kerleroux B, Janot K, Dargazanli C, Daly-Eraya D, Ben-Hassen W, Zhu F, Gory B, Hak JF, Perot C, Detraz L*, et al.* Perfusion imaging to select patients with large ischemic core for mechanical thrombectomy. *J Stroke*. 2020;22:225-233

17. Seners P, Oppenheim C, Turc G, Albucher JF, Guenego A, Raposo N, Christensen S, Calvière L, Viguier A, Darcourt J*, et al.* Perfusion imaging and clinical outcome in acute ischemic stroke with large core. *Ann Neurol*. 2021;90:417-427

18. Gwak DS, Kwon JA, Shim DH, Kim YW, Hwang YH. Perfusion and diffusion variables predict early neurological deterioration in minor stroke and large vessel occlusion. *J Stroke*. 2021;23:61-68

19. Seners P, Ben Hassen W, Lapergue B, Arquizan C, Heldner MR, Henon H, Perrin C, Strambo D, Cottier JP, Sablot D*, et al.* Prediction of early neurological deterioration in individuals with minor stroke and large vessel occlusion intended for intravenous thrombolysis alone. *JAMA Neurol*. 2021;78:321-328

20. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN, Jr., Starr M, Mejilla J, Broderick J, Chatterjee A, Jauch EC, Levine SR*, et al.* Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: The prisms randomized clinical trial. *JAMA*. 2018;320:156-166

21. Saleem Y, Nogueira RG, Rodrigues GM, Kim S, Sharashidze V, Frankel M, Al-Bayati A, Bianchi N, Haussen DC. Acute neurological deterioration in large vessel occlusions and mild symptoms managed medically. *Stroke*. 2020;51:1428-1434

22. Mokin M, Fargen KM, Primiani CT, Ren Z, Dumont TM, Brasiliense LBC, Dabus G, Linfante I, Kan P, Srinivasan VM*, et al.* Vessel perforation during stent retriever thrombectomy for acute ischemic stroke: Technical details and clinical outcomes. *J Neurointerv Surg*. 2017;9:922-928

23. Rao NM, Levine SR, Gornbein JA, Saver JL. Defining clinically relevant cerebral hemorrhage after thrombolytic therapy for stroke: Analysis of the national institute of neurological disorders and stroke tissue-type plasminogen activator trials. *Stroke*. 2014;45:2728-2733

Supplementary Table: Baseline comparison of included *vs*. excluded patients

	Included, n=569	**Excluded[a], n=272**	***P* value**
Age (years)	68.6 ±14.8	70.3 ±14.6	0.12
Male gender	292 (51.3)	138 (50.7)	0.87
Hypertension	348 (61.2)	157 (57.7)	0.34
Diabetes	83 (14.6)	39 (14.3)	0.92
NIHSS score on admission	3 (2-4)	3 (2-4)	0.21
MRI	391 (68.7)	178 (65.4)	0.34
Intracranial occlusion			0.77
M1	197 (34.6)	97 (35.7)	
M2	372 (65.4)	175 (64.3)	
Tandem occlusion	72 (12.7)	39 (14.3)	0.50

a: patients were excluded because of no perfusion or poor quality perfusion imaging (n=251) or missing 3-month mRS (n= 21), see Figure 1. Missing mRS were similarly distributed across the two treatment groups: 15/402 (3.6%) and 6/178 (3.4%) in the IVT alone and bridging therapy groups, respectively.

Abbreviations: IVT indicates intravenous thrombolysis; M1; first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MRI, magnetic resonance imaging.
Continuous variables are presented as mean± standard deviation or median (interquartile range).