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Functional and radiological outcomes after bridging therapy versus direct thrombectomy in stroke patients with unknown onset: Bridging therapy versus direct thrombectomy in unknown onset stroke patients with 10-point ASPECTS

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Title: Functional and radiological outcomes after bridging therapy versus direct thrombectomy in stroke patients with unknown onset.

Bridging therapy versus direct thrombectomy in unknown onset stroke patients with 10-Point ASPECTS.

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ABSTRACT

Background: We aimed to assess functional and radiological outcomes after bridging therapy (intravenous thrombolysis plus mechanical thrombectomy, MT) vs direct MT in unknown onset stroke patients.

Methods: We conducted a cohort study on prospectively collected data from unknown onset stroke patients who received endovascular procedures ≤6 hours from symptom recognition or awakening time.

Results: Of the 349 patients with 10-Point ASPECTS, 248 received bridging and 101 received direct MT. Of the 134 patients with 6-9-Point ASPECTS, 123 received bridging and 111 received direct MT. Each patient treated with bridging was propensity score matched with a patient treated with direct MT for age, sex, study period, pre-stroke disability, stroke severity, type of stroke onset, symptom recognition (or awakening)-to-groin time, ASPECTS, and procedure time. In the two matched groups with 10-Point ASPECTS (n=73 vs n=73), bridging was associated with higher rates of excellent outcome (46.6% vs 28.8%; OR: 2.302, 95% CI: 1.010-5.244) and

successful recanalization (83.6% vs 63%; OR: 3.028, 95% CI: 1.369-6.693) compared with direct MT; no significant association were found between bridging and direct MT as regards rate of sICH (0 vs 1.4%). In the two matched groups with 6-9-Point ASPECTS (n=45 vs n=45), no significant associations were found between bridging and direct MT as regards rates of excellent functional outcome (44.4% vs 31.1%), successful recanalization (73.3% vs 76.5%), and sICH (0

vs 0).

Conclusions: Bridging ≤6 hours of symptom recognition or awakening time was associated with better functional and radiological outcomes in unknown onset stroke patients with 10-Point ASPECTS.

INTRODUCTION

Mechanical thrombectomy (MT) has revolutionized care for ischemic stroke patients with intracranial internal carotid artery (ICA) or M1-segment middle cerebral artery (MCA) occlusion and Alberta Stroke Program Early CT Score (ASPECTS) ≥6.1 Bridging therapy (intravenous thrombolysis, IVT with Alteplase within 4.5 hours of known symptom onset plus MT) is recommended within 6 hours of known symptom onset,2 while direct MT is recommended in patients with contraindications for IVT.2,3

DEFUSE-3 and DAWN trials provided evidence for effectiveness of direct MT between 6 hours and respectively 16 and 24 hours after the time the patient was last known to be well, according to strict selection criteria based on perfusion imaging and mismatch between clinical severity and infarct size.4,5 WAKE-UP trial provided evidence for effectiveness of IVT in patients with unknown onset stroke and DWI/FLAIR-MRI mismatch,6 while EXTEND trial provided evidence for effectiveness of IVT between 4.5 and 9 hours after known stroke onset or awakening in patients with salvageable penumbra based on PWI/CBF-CT or PWI/DWI-MRI and infarct core volume.7

Intracranial ICA, M1-MCA, or M2-MCA occlusion was reported in one third of patients enrolled in the WAKE-UP trial6 and in more than two thirds of patients enrolled in the EXTEND trial7, but no patient received bridging therapy. At this point, some issues should be addressed. First, there are no data from the trials about possible differences in effectiveness between bridging

therapy and direct MT in patients with wake-up or unwitnessed stroke. Second, clinical and radiological criteria do not overlap across the trials for IVT alone and direct MT. Third, radiological selection according to trial protocols was based on the use of an automated software,

which is not currently available everywhere, especially in the smaller community and rural hospitals.

Non-contrast CT is available in all hospitals and is considered the reference standard for patients with suspected acute ischemic stroke who are candidates for IVT to exclude an acute intracranial hemorrhage and to detect early signs of ischemia in the MCA territory. Presence of early ischemic changes on CT scan within 6-10-Point ASPECTS is listed in the current guidelines as a

criterion for providing a strong recommendation in favor of bridging therapy ≤6 hours of known symptom onset.2 However, if the risk of sICH can be increased in patients with early ischemic changes on CT scan remains a controversial topic even within conventional time window for IVT.8 A recent clinical series reflecting routine practice reported that patients with wake-up stroke and normal brain CT scan (10-Point ASPECTS) treated with IVT alone ≤4.5 hours from awakening time had similar safety and efficacy outcomes to stroke patients with known onset stroke.9 Instead, to the best of our knowledge, no data are available as regards safety and efficacy of bridging therapy in stroke patients with unknown symptom onset and normal CT scan.

AIMS

The aim of this study was to assess functional and radiological outcomes after bridging therapy (vs direct MT) in unknown onset stroke patients with 10-Point and 6-9-Point ASPECTS.

METHODS

Study design, participants, and procedures. We conducted a cohort study on prospectively collected data of patients enrolled in the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) between January 2011 and December 2017 for acute ischemic stroke with intra-cranial ICA, M1-MCA, or M2-MCA occlusion and ASPECTS ≥6. The IRETAS is a multicenter, observational internet-based registry (Supplement Table 1). Participating centers were required to accept the rules of the IRETAS, including consecutive registration of all stroke patients receiving endovascular procedures irrespective of whether treatment was according to guidelines.

We included unknown onset stroke patients without absolute exclusion criteria for IVT according to the Italian Stroke Organisation (ISO)-SPREAD guidelines,3 who received bridging therapy or direct MT ≤6 hours of symptom recognition (for unwitnessed stroke) or awakening time (for wake-up stroke). Similar to the time for treatment used by Armona et al.,9 patients treated with bridging therapy were included if they received IVT ≤4.5 hours of symptom recognition or awakening time. Patients treated with additional intra-arterial fibrinolysis were excluded.

Recruitment largely preceded the evidence for MT in unknown onset strokes,4-7 and the choice of

type of endovascular procedure was at the discretion of the neurologist and neuroradiologist. Measures of salvageable penumbra based on PWI/CBF-CT or PWI/DWI-MRI and infarct core volume were not collected. Selection of patients for the present study was exclusively according to presence of early ischemic changes in CT scan within the range for which the recommendations are strong in favor of endovascular treatment ≤6 hours of known symptom

onset (6-10-Point ASPECTS):2 We divided the entire cohort into two group of patients: 10-Point

ASPECTS group (i.e., normal CT scan) and 6-9-Point ASPECTS group.

Data collection. Data collection is provided in the Supplementary Material.

Outcome. Functional outcome measures were: a) excellent functional outcome, defined as mRS score 0-1), b) favorable functional outcome, defined as mRS score 0-2, and c) death at 3 months. Radiological outcome measures: a) complete recanalization, defined as thrombolysis in cerebral infarction (TICI) grading system 3 and b) successful recanalization, defined as TICI grading system 2b/3, at the end of procedure; c) any type of ICH (hemorrhagic infarction, parenchymal hematoma [PH], or subarachnoid hemorrhage), d) PH, and e) symptomatic intracerebral

hemorrhage, defined as PH with increase of ≥4 NIHSS score points from baseline or death within 24 hours.

Statistical analysis. We performed statistical analyses using SPSS 22.0 statistical package. Normally distributed continuous variables were presented as means and standard deviation (SD) and were compared using Student's t-tests. Not normally distributed continuous variables were presented as median and interquatile range (IQR) and were compared using Mann-Whitney U- test. Categorical variables were expressed as frequency and percentage and were compared using $\chi 2$ test. Proportions were calculated for categorical variables, dividing the number of events by the total number excluding missing/unknown cases.

Endovascular treatment was not randomly assigned in the study population, so to reduce the risk of bias because of confounding, three models of propensity score matching was used for both 10- Point ASPECT and 6-9-Point ASPECTS groups. Using logistic regression, the first model of propensity score was calculated for each patient based on age, sex, study period, pre-stroke mRS score ≤1, NIHSS score, type of stroke onset, symptom recognition (or awakening)-to-groin puncture time, and procedure time. ASPECT score entered only the models for 6-9-Point ASPECTS group. The second model of propensity score was calculated for each patient based on covariates of the first model plus medical history (hypertension, diabetes mellitus, previous stroke/TIA, atrial fibrillation, antiplatelet, and anticoagulant), occlusion site, and general anesthesia. Among the covariates with large amounts of missing values (i.e., execution/or not of perfusion CT or MRI, Careggi collateral score, and type of procedure), the availability (or not) of advanced imaging is of utmost importance for choice of treatment and for predicting outcome; therefore, the third

model of propensity score was calculated for each patient based on covariates of the second model plus execution (or not) of perfusion CT or MRI. Each patient treated with bridging therapy was propensity score matched with a patient treated with direct MT. We matched in a 1:1 ratio without replacement using a caliper width of 0.1. Standardized difference

<0.1 was considered to support the assumption of balance between the groups. We estimated the association of bridging therapy (vs direct MT) with outcome measures by calculating the unadjusted odds ratio (OR) with two-sided 95% confidence interval (CI) and the adjusted OR (aOR) with 95% CI after adjustment for pre-defined covariates (age; study period; NIHSS score; pre-stroke mRS score ≤1; symptom recognition (or awakening)-to-groin puncture time).

ASPECT score entered only the adjustment models for 6-9-Point ASPECTS group. Statistical significance was established at two-tailed 0.05 level (P <0.05).

Standard Protocol Approvals, Registrations, and Patient Consents

Need for ethical approval or patient consent for participation in the IRETAS varied among participating hospitals. Ethical approval and informed consent were obtained when required.

Data Availability Statement

Anonymized data will be shared by request from any qualified investigator.

RESULTS

Among 2556 acute ischemic stroke patients with ICA, M1-MCA, and M2-MCA occlusion and ASPECTS ≥6 who were registered in the IRETAS cohort by 44 centers (Supplemental Table 2), 583 unknown onset stroke patients received endovascular procedures ≤6 hours of the symptom recognition or awakening in absence of absolute exclusion criteria for IVT. Flow diagram of patient inclusion and exclusion is provided in Figure 1.

The characteristics in the entire cohort (unwitnessed strokes, n=429; wake-up strokes, n=154) and in the 10-Point ASPECTS (n=349) and 6-9-Point ASPECTS (n=134) groups are provided in Table 1. In the 10-Point ASPECTS group, 248 patients (unwitnessed strokes, n=214; wake-up strokes, n=34) received bridging therapy and 101 patients (unwitnessed strokes, n=60; wake-up strokes, n=41) received direct MT. In the 6-9-Point ASPECTS group, 123 patients (unwitnessed strokes, n=109; wake-up strokes, n=14) received bridging therapy and 111 patients (unwitnessed strokes, n=46; wake-up strokes, n=65) received direct MT. Data for execution (or not) of perfusion CT or MRI were collected in 346/583 patients. In the 10-Point ASPECTS group, perfusion CT or MRI was performed in 81 (70.4%) patients treated with bridging therapy and 47 (72.3%) patients treated with direct MT. In the 6-9-Point ASPECTS group, perfusion CT or MRI was performed in 69 (81.2%) patients treated with bridging therapy and 69 (85.2%) patients treated with direct MT.

In the 10-Point ASPECTS group, diabetes mellitus (p=0.020), wake-up stroke (p<0.001), good collateral circulation (p=0.006) were more frequent in patients treated with direct MT. In the 6-9- Point ASPECTS group, patients treated with bridging therapy were more often enrolled during the 2016-2017 study period (p=0.045) and underwent general anesthesia (p=0.040), while antiplatelet use (p=0.040) and wake-up stroke (p<0.001) were more frequent in patients treated with direct MT; distribution of type of procedure was different between the groups (p=0.002). In the 10-Point ASPECTS group, rates of excellent (43.1% vs 26.6%, p=0.006) and favorable functional outcome (54.8% vs 39.4%, p=0.015) were higher in patients treated with bridging therapy. Any ICH was reported in the 67 patients treated with bridging therapy (HI-1, n=32; HI- 2, n=11; PH-1, n=15; PH-2, n=7; SAH alone, n=2; SAH plus HI or PH, n=5;) and in 21 patients

treated with direct-MT (HI-1, n=7; HI-2, n=4; PH-1, n=3; PH-2, n=4; SAH alone, n=3; SAH plus HI or PH, n=1). In the 6-9-Point ASPECTS group, no significant difference on functional and radiological outcome measures were found. Any ICH was reported in the 35 patients treated with bridging therapy (HI-1, n=9; HI-1, n=17; PH-1, n=5; PH-2, n=3; SAH alone, n=1; SAH plus HI or PH, n=3) and in 34 patients treated with direct-MT (HI-1, n=15; HI-1, n=8; PH-1, n=7; PH-2, n=4).

After the first model of propensity score matching, the characteristics of the patients treated with bridging and direct MT in the 10-Point-ASPECTS (n=73 vs n=73) and 6-9-Point ASPECTS (n=45 vs n=45) groups are provided in Supplemental Table 3. An absolute standardized difference (ASD) was <10% for all covariates. In the 10-Point ASPECTS group, bridging therapy was associated with higher rates of excellent functional outcome (46.6% vs 28.8%; OR: 2.159, 95% CI: 1.089-4.279; aOR: 2.302, 95% CI: 1.010-5.244) and successful recanalization

(83.6% vs 63%; OR: 2.984, 95% CI: 1.367-6.511; aOR: 3.028, 95% CI: 1.369-6.693) (Table 2).

No significant association were found between bridging therapy and direct MT as regards rate of favorable functional outcome (54.8% vs 41.1%), death (17.8% vs 19.2%), complete

recanalization (17.8% vs 19.2%), any ICH (27.4% vs 21.9%), PH (8.2% vs 6.8%), and sICH (0 vs 1.4%) (Table 2). In the 6-9-Point ASPECTS group, no significant associations were found between bridging therapy and direct MT as regards rates of excellent functional outcome (44.4% vs 31.1%), favorable functional outcome (60% vs 53.3%), death (15.6% vs 13.3%), complete

recanalization (57.8% vs 55.6%), successful recanalization (73.3% vs 76.5%), any ICH (33.3%

vs 24.4%), PH (2.2% vs 6.7%), and sICH (0 vs 0) (Table 2).

After the second model of propensity score matching, the characteristics of the patients treated with bridging and direct MT in the 10-Point-ASPECTS (n=47 vs n=47) and 6-9-Point ASPECTS (n=31 vs n=31) groups are provided in Supplemental Table 4. An absolute standardized difference (ASD) was <10% for all covariates. In the 10-Point ASPECTS group, bridging therapy was associated with higher rates of excellent (44.7% vs 19.1%; OR: 3.410, 95% CI: 1.350-8.614; aOR: 5.816, 95% CI: 1.672-20.228) and favorable functional outcome (63.8% vs

38.3%; OR: 2.843, 95% CI: 1.232-6.563; aOR: 4.094, 95% CI: 1.382-12.131), and successful

recanalization (76.6% vs 57.4%; OR: 2.424, 95% CI: 1.009-5.897; aOR: 2.532, 95% CI: 1.022-

6.275) (Table 3). No significant association were found between bridging therapy and direct MT as regards rate of death (12.8% vs 17%), complete recanalization (53.2% vs 38.3%), any ICH (19.1% vs 21.3%), PH (6.4% vs 4.3%), and sICH (2.1% vs 0) (Table 3). In the 6-9-Point ASPECTS group, no significant associations were

found between bridging therapy and direct MT as regards rates of excellent (41.9% vs 29%) and favorable functional outcome (64.5% vs 61.3%), death (12.9% vs 12.9%), complete (64.5% vs 51.6%) and successful recanalization

(90.3% vs 77.4%), any ICH (25.8% vs 25.8%), PH (6.5% vs 9.7%), and sICH (0 vs 0) (Table 3).

After the third model of propensity score matching, the characteristics of the patients treated with bridging and direct MT in the 10-Point-ASPECTS (n=34 vs n=34) and 6-9-Point ASPECTS (n=23 vs n=23) groups are provided in Supplemental Table 5. An absolute standardized difference (ASD) was <10% for all covariates. In the 10-Point ASPECTS group, bridging therapy was associated with higher rates of excellent (44.1% vs 20.6%; OR: 3.429, 95% CI: 1.176-9.994; aOR: 5.365, 95% CI: 1.57-24.888) and favorable functional outcome (61.8% vs

35.3%; OR: 2.962, 95% CI: 1.104-7.942; aOR: 3.468, 95% CI: 1.023-13.013), and successful

recanalization (85.3% vs 58.8%; OR: 4.060, 95% CI: 1.261-13.072; aOR: 3.879, 95% CI: 1.130-

13.315) (Table 4). No significant association were found between bridging therapy and direct MT as regards rate of death (14.7% vs 17.6%), complete recanalization (55.9% vs 38.2%), any

ICH (20.6% vs 14.7%), PH (5.9% vs 2.9%), and sICH (3% vs 0) (Table 4). In the 6-9-Point ASPECTS group, no significant associations were found between bridging therapy and direct MT as regards rates of excellent (43.5% vs 30.4%) and favorable functional outcome (60.9% vs 65.2%), death (13% vs 8.7%), complete (56.5% vs 52.2%) and successful recanalization (91.3%

vs 82.6%), any ICH (26.1% vs 30.4%), PH (4.3% vs 13%), and sICH (0 vs 0) (Table 4).

DISCUSSION

Our study showed that bridging therapy vs direct MT was associated with better 3-month functional outcomes and a higher rate of successful recanalization in unknown onset stroke patients with ICA, M1-MCA, or M2-MCA occlusion and 10-Point ASPECTS, who received endovascular treatment ≤6 hours of symptom recognition or awakening in absence of absolute exclusion criteria for IVT. Instead, radiological

and functional outcomes were similar in the group of patients with 6-9-Point ASPECTS. Bridging therapy did not increase the risk of intracerebral bleedings.

The raw rates of recanalization are numerically lower in the group of patients with 10-Point ASPECT treated with direct MT as compared with the other three groups. We are unable to investigate whether the group of patients with 10-Point ASPECT treated direct MT could have more adverse conditions for recanalization such as difficult anatomical access, intracranial atherosclerotic stenosis, different thrombus etiology and composition, distal embolization or re- occlusion during the intervention, or different operator skills.

Optimal treatment of stroke patients with unknown symptom onset remains uncertain. Only some patients (11% and 5%, respectively) received bridging therapy in the endovascular treatment-arm of the DEFUSE-3 (11%) and DAWN (5%) trials.4,5 In a different study, bridging therapy (n=19) vs direct IVT (n=21) was associated with 3-month favorable outcome in patients with LVO in the anterior circulation and DWI/FLAIR-MRI mismatch.10

In patients with known symptom onset, a recent meta-analysis showed that bridging therapy provides extra benefits to direct MT on radiological and functional outcomes as compared with direct MT in anterior LVO-related strokes;11 however, direct MT was used more often in patients

contraindicated to receive IVT. On the other side, the DIRECT-MT trial showed recently that direct MT was noninferior to bridging therapy with regard to the primary outcome (adjusted common OR for the 3-month mRS score) in Chinese patients who were eligible for IVT and IAT (<4.5 hours after symptom onset); however, direct MT was associated with lower percentages of patients with successful reperfusion after endovascular procedure.12 Why this improvement in reperfusion from the addition of IVT did not translate into clinical benefits is unclear. However,

the topic is currently being investigated in another ongoing trial (SWIFT DIRECT; NCT03192332) in European and North American Stroke Centers.

The use of ASPECTS could facilitate an early initiation of IVT for a portion of patients with unknown onset stroke who are transported directly to the nearest non-endovascular capable center and then transferred to the nearest endovascular capable center for MT according to the drip and ship model. A previous study showed that ASPECTS correlated with CBV infarct core volume on CT-perfusion after 180 minutes from known symptom onset, and predicted final infarct volume in patients with complete recanalization and 3-month functional outcome after

endovascular treatment.13 In addition, a recent study reported that the prevalence of mismatch

did not reduce over time (0-24 hours) among ASPECTS groups and higher ASPECTS was an independent predictor of clinical-core mismatch (i.e., clinical deficit out of proportion to infarct volume) in stroke

patients with ICA or M1-MCA occlusion.14 Lack of systematically collected data of mismatch and infarct volume on perfusion imaging is the main limitation of our study, and this does not allow for a comparison with previous studies.13,14

We are aware that our study has some limitations. First, the present study did not randomize patients by treatment, but it is based on a retrospective analysis of prospectively collected data. Second, the number of missing data for outcome measures and pre-defined variables might have influenced the final outcome. Third, reasons for the treatment were not recorded; it is likely that these choices were influenced by unmeasurable factors related to individual physician's decision, which might have influenced our key findings. However, patient recruitment in our study

preceded the evidence for MT in unknown onset and wake-up stroke,3-6 and the choice of

treatment could not be influenced by particular conditions which are listed in the absolute exclusion criteria for IVT. Fourth, lack of data for time last well known or sleep onset does not allow for a comparison with endovascular stroke trials4,5 to estimate the hypothetical onset of stroke. Nevertheless, the identification of possible differences between bridging therapy and

direct MT along an extended therapeutic window was not the aim of the present study. Fifth, imaging analysis to calculate ASPECTS was done locally and the CT images were not reviewed centrally. Finally, we did not use data of collateral circulation and type of procedure because of large amounts of missing values.

CONCLUSIONS

Bridging therapy within 6 hours of symptom recognition or awakening time was associated with better 3-month functional outcomes and a higher rate of successful recanalization in unknown onset stroke patients with ICA, M1-MCA, or M2-MCA occlusion and 10-Point ASPECTS. However, our findings should be considered with caution, and a trial is needed to assess bridging therapy (IVT with Alteplase plus MT) vs direct MT in unknown onset stroke patients.

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REFERENCES

1 Goyal M, Menon BK, van Zwam WH, et al. Endovascular Thrombectomy After Large- Vessel Ischaemic Stroke: A Meta-Analysis of Individual Patient Data From Five Randomised Trials. Lancet. 2016;387:1723-31.

2 Powers WJ, Rabinstein AA, Ackerson T, 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.

3 Toni D, Mangiafico S, Agostoni E, et al. Intravenous thrombolysis and intra-arterial interventions in acute ischemic stroke: Italian Stroke Organisation (ISO)-SPREAD Guidelines. Int J Stroke. 2015;10:1119-29.

4 Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378:708-718.

5 Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378:11-21.

6 Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med. 2018;379:611-622.

7 Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med. 2019;380:1795-1803.

8 IST-3 collaborative group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. Lancet Neurol. 2015;14:485-96.

9 Armona C, Wainsteina J, Goura A, et al. CT-guided thrombolytic treatment of patients with wake-up strokes. eNeurologicalSci. 2019;14:91-97.

10 Mourand I, Milhaud D, Arquizan XC, et al. Favorable Bridging Therapy Based on DWI- FLAIR Mismatch in Patients with Unclear-Onset Stroke. AJNR Am J Neuroradiol. 2016;37:88-93.

11 Mistry EA, Mistry AM, Nakawah MO, et al. Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: A Meta-Analysis. Stroke. 2017;48:2450-2456.

12 Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Engl J Med. DOI:10.1056/NEJMoa2001123.

13 Olive-Gadea M, Martins N, Boned S, et al. Baseline ASPECTS and e-ASPECTS Correlation with Infarct Volume and Functional Outcome in Patients Undergoing Mechanical Thrombectomy. Neuroimaging 2019;29:198-202.

14 Desai SM, Tonetti DA, Molyneaux BJ, et al. Interaction between time, ASPECTS, and clinical mismatch. J Neurointerv Surg. 2020 Apr 3. pii: neurintsurg-2020-015921.

Table 1. Characteristics in the entire cohort and in the 10-Point-ASPECTS and 6-9-Points ASPECTS groups.

	ASPECTS 10			ASPECT 6-9		
	All patients (n=583)	Bridging therapy (n=248)	Direct thrombectomy (n=101)	P value	Bridging therapy (n=123)	Direct thrombectomy (n=111)	P value
Demographics							
Age (years), mean (SD)	70 (13)	70 (14)	72 (14)	0.372	71 (12)	69 (13)	0.238
Male sex, n (%)	268 (46)	120 (48.4)	50 (49.5)	0.357	48 (39)	50 (45)	0.906
Years							

2016-2017, n (%)	346 (59.3)	147 (59.3)	58 (57.4)	0.811	82 (66.7)	59 (53.2)	0.045
Medical history							
Hypertension, n (%)	334 (66.4) [80]	138 (63.6) [31]	49 (65.3) [26]	0.889	80 (71.4) [11]	67 (67.7) [12]	0.653
Diabetes mellitus, n (%)	69 (13.7) [80]	24 (11.1) [31]	17 (22.7) [26]	0.020	14 (12.5) [11]	14 (14.1) [12]	0.839
Previous stroke/TIA, n (%)	25 (5) [80]	8 (3.7) [31]	5 (6.7) [26]	0.330	5 (4.5) [11]	7 (7.1) [12]	0.554
Atrial fibrillation, n (%)	128 (25.4) [80]	57 (26.3) [31]	27 (36) [26]	0.138	19 (17) [11]	25 (25.3) [12]	0.174
Antiplatelet, n (%)	205 (35.2)	88 (35.5)	36 (35.6)	1.000	35 (28.5)	46 (41.4)	0.040
Anticoagulant oral with INR ≤1.7, n (%)	23 (3.9)	7 (2.8)	5 (5)	0.339	5 (4.1)	6 (5.4)	0.760
Baseline data							
Pre-stroke mRS score ≤1, n (%)	458 (90.5) [77]	200 (90.9) [28]	77 (89.5) [15]	0.671	94 (94) [23]	87 (87) [11]	0.146
NIHSS score, median (IQR)	18 (13-21) [7]	17 (12-20)	16 (12-20) [4]	0.656	18 (14-21) [2]	19 (15-23) [1]	0.100
Wake-up stroke, n (%)	154 (26.4)	34 (13.7)	41 (40.6)	<0.001	14 (11.4)	65 (58.6)	<0.001
ASPECT score				0.605			
6, n (%)	36 (6.2)	-	-	17 (13.8)	19 (17.1)		
7, n (%)	45 (7.7)	-	-	21 (17.1)	24 (21.6)		
8, n (%)	71 (12.2)	-	-	41 (33.3)	30 (27)		
9, n (%)	82 (14.1)	-	-	44 (35.8)	38 (34.2)		
Occlusion site	0.478			0.302			
Intra-cranial ICA, n (%)	68 (11.7)	24 (9.7)	14 (13.9)	18 (14.6)	12 (10.8)		
M1-segment MCA, n (%)	409 (70.2)	175 (70.6)	66 (65.3)	83 (67.5)	85 (76.6)		

M2-segment MCA, n (%) 106 (18.2) 49 (19.8) 21 (20.8) 22 (17.9) 14 (12.6)

Good collateral circulation, n (%) 240 (65.2) [215] 95 (56.2) [79] 37 (78.7) [54] 0.006 64 (70.3) [32] 44 (72.1) [50] 0.857

Execution of perfusion CT or MRI, n (%) 266 (76.9) [237] 81 (70.4) [133] 47 (72.3) [36] 0.865 69 (81.2) [38] 69 (85.2) [30] 0.539

General anesthesia, n (%) 238 (44.8) [52] 86 (37.7) [20] 31 (36) [15] 0.896 72 (62.6) [8] 49 (48) [9] 0.040

Symptom recognition (or awakening)-to- 240 (190-286) 240 (194-280) 241 (180-297) 0.850 240 (200-290) 233 (169-300) 0.309

groin puncture time (min), median (IQR)

Type of procedure 0.750 0.002

Aspiration alone, n (%) 212 (47) [132] 82 (43.4) [59] 30 (38.5) [23] 62 (63.9) [26] 38 (43.7) [24]

Stent retriever alone, n (%) 172 (38.1) [132] 79 (41.8) [59] 36 (46.2) [23] 19 (19.6) [26] 38 (43.7) [24]

Combination of aspiration and stent 67 (14.9) [132] 28 (14.8) [59] 12 (15.4) [23] 16 (16.5) [26] 11 (12.6) [24]

retriever, n (%)

Procedure time (min), median (IQR) 65 (44-93) [4] 68 (45-100) [1] 77 (41-100) [1] 0.995 58 (35-90) [2] 64 (45-84) 0.183

Functional outcome measures

mRS score 0-1, n (%) 207 (37.4) [30] 103 (43.1) [9] 25 (26.6) [7] 0.006 44 (37.6) [6] 35 (34) [8] 0.673

mRS score 0-2, n (%) 286 (51.7) [30] 131 (54.8) [9] 37 (39.4) [7] 0.015 63 (53.8) [6] 55 (53.4) [8] 1.000

Death, n (%) 81 (14.6) [30] 36 (15.1) [9] 18 (19.1) [7] 0.409 16 (13.7) [6] 11 (10.7) [8] 0.542

Radiological outcome measures

TICI 3, n (%) 0.894	325 (56.2) [5]	142 (57.5) [1]	48 (48) [1]	0.122	71 (57.7)	64 (59.3) [3]
TICI 2b/3, n (%) 1.000	435 (75.3) [5]	185 (74.9) [1]	67 (67) [1]	0.145	97 (78.9)	86 (79.6) [3]
Any ICH, n (%) 0.773	157 (27.7) [17]	67 (27.5) [4]	21 (21.9) [5]	0.336	35 (29.4) [4]	34 (31.8) [4]
PH, n (%) 0.235	48 (8.5) [17]	22 (9) [4]	7 (7.3) [5]	0.393	8 (6.7) [4]	11 (10.3) [4]
sICH, n (%) 0.660	11 (2) [42]	6 (2.5) [12]	1 (1.1) [6]	0.335	2 (1.8) [14]	2 (2) [10]

Data are n (%) or mean (SD) or median (IQR). Numbers within square brackets indicate number of missing values.

Table 2. Associations of bridging therapy versus direct thrombectomy with outcome measures after the first model of propensity score matching.

	ASPECTS 10		ASPECTS 10		ASPECTS 6-9		ASPECTS 6-9
N (%) P	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	N (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI) P value
mRS score 0-1								

Bridging	34 (46.6)	2.159 (1.089-4.279)	0.028	2.302 (1.010-5.244)	0.047	20 (44.4)	1.771 (0.748-4.197)	0.194	1.534 (0.554-4.249)	0.411
Direct MT	21 (28.8)	1.000		1.000		14 (31.1)				
mRS score 0-2										
Bridging	40 (54.8)	1.737 (0.902-3.347)	0.099	1.795 (0.793-4.062)	0.161	27 (60)	1.312 (0.569-3.028)	0.524	1.012 (0.375-2.736)	0.981
Direct MT	30 (41.1)	1.000		1.000		24 (53.3)				
Death										
Bridging	13 (17.8)	0.913 (0.396-2.107)	0.831	0.838 (0.338-2.081)	0.704	7 (15.6)	1.197 (0.369-3.890)	0.764	1.341 (0.371-4.852)	0.655
Direct MT	14 (19.2)	1.000		1.000		6 (13.3)				
TICI 3										
Bridging	42 (57.5)	1.642 (0.854-3.159)	0.137	1.690 (0.862-3.314)	0.126	26 (57.8)	1.095 (0.475-2.521)	0.832	0.971 (0.406-2.321)	0.947
Direct MT	33 (45.2)	1.000		1.000		25 (55.6)				
TICI 2b/3										
Bridging	61 (83.6)	2.984 (1.367-6.511)	0.006	3.028 (1.369-6.693)	0.006	33 (73.3)	0.890 (0.345-2.296)	0.809	0.786 (0.287-2.152)	0.639
Direct MT	46 (63)	1.000		1.000		34 (76.5)				
Any ICH										
Bridging	20 (27.4)	1.344 (0.631-2.864)	0.443	1.266 (0.574-2.795)	0.559	15 (33.3)	1.545 (0.616-3.878)	0.354	2.252 (0.769-6.599)	0.139
Direct MT	16 (21.9)	1.000		1.000		11 (24.4)				
PH										
Bridging	6 (8.2)	1.218 (0.355-4.183)	0.754	1.146 (0.324-4.058)	0.832	1 (2.2)	0.318 (0.032-3.181)	0.330	0.028 (0.005-2.905)	0.131
Direct MT	5 (6.8)	1.000		1.000		3 (6.7)				
sICH										
Bridging	0	-	NA	-	NA	0	-	NA	-	NA

Direct MT	1 (1.4)	-	-	0	-	-

ORs were adjusted for pre-defined variables (age; study period; pre-stroke mRS score ≤1; NIHSS score; symptom (or awakening)- recognition-to-groin puncture time). ASPECT score entered the adjustment model for 6-9-Points ASPECTS groups.

Table 3. Associations of bridging therapy versus direct thrombectomy with outcome measures after the second model of propensity score matching.

	ASPECTS 10		ASPECTS 10		ASPECTS 6-9			ASPECTS 6-9
	N (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	N (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI) P value
mRS score 0-1									
Bridging	21 (44.7)	3.410 (1.350-8.614)	0.009	5.816 (1.672-20.228)	0.006	13 (41.9)	1.765 (0.615-5.064)	0.290	1.840 (0.603-5.614) 0.284

Direct MT 9 (19.1) 1.000 1.000 9 (29)

mRS score 0-2

Bridging 30 (63.8) 2.843 (1.232-6.563) 0.014 4.094 (1.382-12.131) 0.011 20 (64.5) 1.148 (0.409-3.221) 0.793 0.933 (0.291-2.991) 0.907

Direct MT 18 (38.3) 1.000 1.000 19 (61.3)

Death

Bridging 6 (12.8) 0.713 (0.227-2.243) 0.563 0.709 (0.195-2.571) 0.601 4 (12.9) 1.000 (0.226-4.415) 1.000 1.071 (0.228-5.030) 0.931

Direct MT 8 (17) 1.000 1.000 4 (12.9)

TICI 3

Bridging 25 (53.2) 1.831 (0.805-4.161) 0.149 1.944 (0.836-4.521) 0.123 20 (64.5) 1.705 (0.616-4.720) 0.305 1.836 (0.608-5.546) 0.281

Direct MT 18 (38.3) 1.000 1.000 16 (51.6)

TICI 2b/3

Bridging 36 (76.6) 2.424 (1.009-5.897) 0.049 2.532 (1.022-6.275) 0.045 28 (90.3) 2.722 (0.633-11.701) 0.178 2.971 (0.584-15.113) 0.189

Direct MT 27 (57.4) 1.000 1.000 24 (77.4)

Any ICH

Bridging 9 (19.1) 0.876 (0.320-2.401) 0.797 0.876 (0.307-2.502) 0.805 8 (25.8) 1.000 (0.321-3.120) 1.000 1.089 (0.318-3.734) 0.892

Direct MT 10 (21.3) 1.000 1.000 8 (25.8)

PH

Bridging 3 (6.4) 1.534 (0.244-9.629) 0.648 1.509 (0.204-11.183) 0.687 2 (6.5) 0.644 (0.100-4.147) 0.643 1.725 (0.080-37.046) 0.728

Direct MT 2 (4.3) 1.000 1.000 3 (9.7)

sICH

Bridging 1 (2.1) - NA - NA 0 - NA - NA

Direct MT 0 - - 0 - -

ORs were adjusted for pre-defined variables (age; study period; pre-stroke mRS score ≤1; NIHSS score; symptom recognition (or awakening)-to-groin puncture time). ASPECT score entered the adjustment model for 6-9-Points ASPECTS groups.

Table 4. Associations of bridging therapy versus direct thrombectomy with outcome measures after the third model of propensity score matching.

	ASPECTS 10		ASPECTS 10		ASPECTS 6-9		ASPECTS 6-9
	N (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	N (%)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI) P value
mRS score 0-1									
Bridging	21 (47.1)	3.429 (1.176-9.994)	0.024	5.365 (1.157-24.888)	0.032	10 (43.5)	1.758 (0.523-5.907)	0.361	2.055 (0.497-8.489) 0.320
Direct MT	9 (20.6)	1.000		1.000		7 (30.4)			
mRS score 0-2									

Bridging	30 (61.8)	2.962 (1.104-7.942)	0.031	3.648 (1.023-13.013)	0.046	14 (60.9)	0.830 (0.250-2.752)	0.760	0.625 (0.138-2.837)	0.543		
Direct MT	18 (35.3)	1.000		1.000		15 (65.2)						
Death												
Bridging	5 (14.7)	0.805 (0.220-2.939)	0.742	0.923 (0.205-4.158)	0.917	3 (13)	1.575 (0.238-10.437)	0.638	1.500 (0.187-12.064)	0.703		
Direct MT	6 (17.6)	1.000		1.000		2 (8.7)						
TICI 3												
Bridging	25 (55.9)	2.046 (0.777-5.386)	0.147	2.130 (0.750-6.051)	0.156	13 (56.5)	1.192 (0.373-3.807)	0.767	1.243 (0.340-4.539)	0.742		
Direct MT	18 (38.2)	1.000		1.000		12 (52.2)						
TICI 2b/3												
Bridging	36 (85.3)	4.060 (1.261-13.072)	0.019	3.879 (1.130-13.315)	0.031	21 (91.3)	2.211 (0.363-13.470)	0.390	3.203 (0.309-33.224)	0.329		
Direct MT	27 (58.8)	1.000		1.000		19 (82.6)						
Any ICH												
Bridging	7 (20.6)	1.504 (0.426-5.310)	0.526	1.482 (0.396-5.556)	0.559	6 (26.1)	0.807 (0.223-2.920)	0.744	0.749 (0.180-3.104)	0.690		
Direct MT	5 (14.7)	1.000		1.000		7 (30.4)						
PH												
Bridging	2 (5.9)	2.062 (0.178-23.882)	0.562	2.709 (0.199-36.834)	0.454	1 (4.3)	0.303 (0.029-3.155)	0.318	1.265 (0.043-36.978)	0.891		
Direct MT	1 (2.9)	1.000		1.000		3 (13)						
sICH												
Bridging	1 (3)	-	NA	-	NA	0	-	NA	-	NA		
Direct MT	0	-	-	0	-	-						

ORs were adjusted for pre-defined variables (age; study period; pre-stroke mRS score ≤1; NIHSS score; symptom recognition (or awakening)-to-groin puncture time). ASPECT score entered the adjustment model for 6-9-Points ASPECTS groups.

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