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Research Article

Clinical Benefits of Bridging Therapy for Acute Ischemic Stroke: A Real Life Study from the French Riviera

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Abstract

Background: The proof of the efficacy of the bridging associating intravenous thrombolysis and mechanical thrombectomy (IVTMT) *vs.* intravenous thrombolysis (IVT) alone has been recently introduced changing our practices in the management of ischemic stroke. We present here a multicenter study in "real life" to evaluate efficacy and safety of IVTMT.

Methods: A multicenter study was carried out from 2012 to 2016 in the stroke units of Marseille, Toulon and Nice. Consecutive patients treated in acute phase of ischemic stroke due to proximal occlusion arteries (MCA M1-M2 and/or IC) were included. Patients treated with IVTMT were compared with patients treated with IVT alone before systematic use of IVTMT proposed by the recommendations. The primary efficacy endpoint was the mRS≤2 at 3 months. The safety was apprehended by the mortality and the symptomatic intracranial haemorrhage (SIH) rate.

Results: 557 patients were included, 269 (48.3%) in the IVTMT group and 288 (51.7%) in the IVT control group. At 3 months, 136/269 (50.6%) patients in the IVTMT group had mRS≤2 *vs.* 123/288 (42.7%) patients in the control group. After adjustment (age, sex, NIHSS and tandem occlusion), the odds ratio calculated was 1.95[1.29-2.95]. The recanalization rate at 24H was significantly higher in the IVTMT group (85.8% *vs.* 56.9%). The mortality (aOR: 0.63 [0.38-1.06]) and the SIH rate (aOR: 2.12[0.79-5.63] were not significantly different in both groups. In subgroup analysis, tandem occlusions were be in favor of IVTMT strategy (aOR: 5.31[2.06-13.67]), whereas the moderate clinical severity (NIHSS <10) was in favour of IVT alone (aOR: 0.35[0.13-0.93]).

Conclusion: This study confirms in « real life » the efficacy and the safety of the bridging therapy demonstrated by the previous randomized trials. Our results discuss the inhomogeneity of IVTMT depending of the arterial occlusion site and the initial clinical severity.

Keywords: Ischemic stroke; Acute stroke; Acute therapy; Endovascular treatment; Thrombolysis

Introduction

Ischemic stroke is a devastating condition with a high risk of neurologic disability and death. Since 1995, the gold standard therapy for ischemic stroke in acute phase was intravenous administration of Alteplase, a tissue plasminogen activator (rt-PA), within 4.5 hours of stroke onset, so called intravenous thrombolysis (IVT) [1,2]. Effectiveness of IVT is reduced in case of large proximal vessel occlusion due to a poor rate of early recanalization (one third of cases) with thrombolysis in this condition [3-5]. Then, intra-arterial therapy has been developed in addition to IVT, so called the bridging therapy. First randomized control studies trials (RCTs), as IMS III in 2013, failed to demonstrate clinical benefits of bridging therapy. In 2015, new randomized controlled trials (RCTs) with more performing mechanical devices and more restricted inclusion criteria [6-12], have strongly demonstrated the significant clinical benefit of combination therapy. In line with these results, new guidelines by European Stroke Organisation (ESO) now recommend (13) that MT, in addition to IVT within 4.5h when eligible, must be performed routinely to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 h after symptom onset. Medico-economic approaches were carried out, based on RCTs and Meta-analyzes [14] but these results have not been yet confirmed in real world setting. The purpose of our study performed in the in the south of France, was to assess the clinical benefits of bridging therapy demonstrated by RCTs, through a real life multicenter controlled study.

Methods

Patient's selection and procedure

Three academic hospitals were involved in this retrospective but controlled multicenter observational study: University Hospital of Marseille, University Hospital of Nice and Sainte Anne Military Teaching Hospital of Toulon. In "Provence Alps Côte d'Azur" region (5 million inhabitants), these three centres alone have a comprehensive stroke unit and are entitled to deliver endovascular treatment in acute phase of stroke. We included in the study the consecutive patients aged over 18 years, who underwent a recanalization treatment in stroke units from January 2012 to December 2016, with a documented stroke and a proximal

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Table 1: Baseline characteristics. * p<0.05.

		Control population (IVT) (n= 288)	Intervention population (IVTMT) (n=269)	*p*
Demographic characteristics				
Age (Years)	*	72.97±13.03	66.08±13.60	*<0.001*
Men		139/288 (48.26%)	147/269 (54.65%)	*0.132*
Comorbidities ans risk factors				
Hypertension	*	125/230 (54.35%)	96/126 (44.44%)	*0.037*
Diabetes mellitus		34/231 (14.72%)	23/216 (10.65%)	*0.197*
Smoking (recent or current)	*	41/229 (17.90%)	59/215 (25.44%)	*0.016*
Atrial fibrillation		36/229 (15.72%)	46/217 (21.40%)	*0.124*
Coronary disease		30/232 (12.93%)	30/216 (13.89%)	*0.770*
History of ischemic stroke		26/232 (14.21%)	32/216 (14.81%)	*0.256*
Hypercholesterolaemia		72/231 (31.17%)	58/216 (26.85%)	*0.315*
Anticoagulant therapy	*	12/230 (5.22%)	35/209 (16.75%)	*<0.001*
Clinical characteristics				
Baseline NIHSS score	*	14.76±6.02	16.69±4.97	*<0.001*
Systolic blood pressure (mmHg)		157.34±27.56	154.58±27.51	*0.322*
Diastolic blood pressure (mmHg)		82.46±15.45	83.75±18.29	*0.449*
Blood glucose (g/L)		1.31±0.44	1.31±0.56	*0.934*
Imaging characteristics				
Baseline imaging by MRI		261/288 (90.63%)	249/269 (93.57%)	*0.410*
Occlusion site (MRI 3DTOF and/or CT-angiography)				
Intracranial ICA		17/288 (5.90%)	12/269 (4.46%)	*0.444*
M1 segment middle cerebral artery segment		191/288 (66.32%)	167/269 (62.08)	*0.297*
ICA with involvement of M1 middle cerebral artery segment		80/288 (27.78%)	90/269 (33.46%)	*0.146*
ASPECT Score (DWI)		8[7-9]	7[6-8]	*0.322*
DWI Volume (cm^3)		61.86±5.94	47.91±4.52	*0.062*
Biological characteristics				
Haemoglobin (g/dl)		13.61±1.66	13.59±1.96	*0.948*
Platelets count (G/l)		232.10±70.64	237.17±69.68	*0.454*
HbA1c (%)		6.01±0.97	5.93±1.02	*0.436*
Brain Natriuretic Peptide BNP (pg/ml)		354.21±432.26	292.26±394.57	*0.146*

occlusion of the anterior circulation. Proximal occlusion site had to be documented by vascular imaging such as three-dimensional time of flight (TOF) magnetic resonance (MR) angiography, and/or computed tomography (CT) or MR angiography (MRA) of supra-aortic arteries according to each center habits. We have selected intra- and extra-cranial internal carotid artery (ICA) occlusions, middle cerebral artery (MCA) occlusions from M1 segment until M1-M2 junction and tandem occlusions (ICA and MCA occlusion at once). Two groups of patients were formed: the control group (IVT group), in which were included patients treated with systemic thrombolysis alone in the 4.5h time window; the intervention group (IVTM group) in which were included patients treated since 2015, according to ESO recommendations, with bridging therapy. This group also included patients in whom MT was performed as first-line therapy when systemic thrombolysis was contraindicated because of anticoagulation, recent surgery, recent hemorrhage or coagulation disorder. MT was performed by a trained operator using new devices as retrievable stents or aspiration. Each patient was clinically assessed by neurologist at baseline. We collected radiological data as stroke volume on MRI (DWI), MRI Alberta Stroke Program Early Computed Tomography Score (ASPECTS) [15] and occlusion site using 3DTOF and/or CT angiography and finally mTICI score before and after thrombectomy. Evaluation of the recanalization was done on CT angiography at 24 hours. All neuroimaging studies were reviewed by a neurologist in each center. At 3 months, mRS scale was calculated during a follow-up consultation by certified neurologist. When patients did not honor this consultation, they were contacted by phone using standardized interview. Although collection of initial clinical data was retrospective, it was done from our local stroke registry which is prospectively completed. Only imaging data and mRS were strictly retrospective. We excluded patients with posterior circulation occlusion, differential diagnosis, no clearly defined onset of symptoms, and patients lost to follow-up or with missing data at 3 months. The research was conducted according to the principles

Table 2: Treatment procedure data's.

	Control population (IVT) (n= 288)	Intervention population (IVTMT) (n=269)	*p*
Workflow duration, mn			
From onset to admission	92.88±49.17	91.90±44.14	*0.841*
From onset to clinical examination	100.50±52.13	105.21±58.94	*0.392*
From onset to imaging	124.25±51.78	129.50±56.50	*0.314*
From onset to intraveinous thrombolysis	161.62±51.59	155.49±51.83	*0.262*
From onset to thrombectomy		238.37±68.86	
From onset to end of thrombectomy		304.53±82.64	
Treatment procedure			
Systemic thrombolysis			
Treatment with intravenous alteplase	288/288 (100%)	206/269 (76.58%)	
Intravenous Nicardipine treatment	35/217 (16.13%)	15/130 (11.54%)	*0.239*
Injected dose of alteplase (mg)	64.75±12.90	67.32±12.45	*0.070*
Mechanical thrombectomy			
General anesthesia with intubation		211/217 (97.24%)	
TICI before thrombectomy		0 [0-1]	
TICI at the end of thrombectomy		2b [2b-3]	
Stent retriever system used		128/217 (58.99%)	
Aspiration system used		145/217 (66.82%)	
Number of thrombectomy device used per procedure		2 [1-2]	
Number of thrombectomy device attempts per procedure		2 [1-3]	
Antithrombotic therapy during thrombectomy		32/217 (14.74%)	
Implantation of intracranial stent		2/217 (0.92%)	
Implantation of extracranial stent		30/217 (13.82%)	

Table 3: Efficacy outcomes at 90 days.

	Control population (IVT) n=288	Intervention population (IVTMT) n=269	Unadjusted Odds ratio	Adjusted Odds ratio*
Primary outcome				
mRS ≤ 2 at 90 days	123/288 (42.71%)	136/269 (50.56%)	1.37 [0.98- 1.92]	1.95 [1.29-2.95]
Secondary outcomes				
mRS (Median)	3 [1-5]	2 [1-4]	1.38 [1.03-1.85]	1.80 [1.31-2.49]
mRS 0-1	89/288 (30.90%)	102/269 (37.92%)	1.37 [0.96-1.94]	2.10 [1.37- 3.22]
Arterial recanalization†	127/223 (56.95%)	194/226 (85.84%)	4.58 [2.89-7.74]	7.11 [4.20-12.05]

*Odds ratios were adjusted for age, sex, NIHSS at baseline and ICA occlusion
†No intracranial occlusion on follow-up CT angiography at 24 h

of the Declaration of Helsinki. Ethics approval was obtained from the local institutional review board. The board waived the need for patient consent for this non-interventional study.

Clinical and radiological Outcomes

The primary efficacy outcome was the proportion of patients with a modified Rankin scale score of 0-2, indicating functional independence, at 3 months after the intervention. The primary outcome was assessed at each center. The secondary efficacy outcomes included mRS gradual analysis and imaging outcomes defined by the absence of intracranial occlusion on follow-up CT angiography at 24h. Safety outcomes were represented by death at 3 months (mRS equal to 6) and symptomatic or asymptomatic intracranial haemorrhage (IH) at 24 hours. Haemorrhagic events were classified according to ECASS I [16] definition at 24 hours distinguishing haemorrhagic infarction (HI) and parenchymal haematoma (PH). Symptomatic IH was evaluated at 24 hours and defined as blood at any site in the brain on the CT control scan causing deterioration in the National Institutes of Health Stroke Scale (NIHSS) of 4 or more points.

Statistical analysis

Statistical analyses were conducted using statistical package STATA SE 10.0. To determine the statistically significant differences between IVT and IVTMT groups, Chi 2 test was assessed for categorical variables and Student's t test for continuous variables. Nonparametric continuous variables were represented by medians and interquartile ranges and medians and standard deviation for parametric variables. Categorical variables are presented by

Table 4: Safety outcomes at 90 days.

	Control population (IVT) n=288	Intervention population (IVTMT) n=269	Unadjusted Odds ratio [95% CI]	Adjusted Odds ratio [95% CI]*
Intracranial hemorrhage (IH)†	60/288 (20.83%)	62/269 (23.05%)	1.14 [0.76-170]	1.07 [0.70-1.65]
Hemorrhagic infarction type 1	14/288 (4.86%)	11/269 (4.09%)	0.83 [0.37-1.87]	0.85 [0.36-2.04]
Hemorrhagic infarction type 2	9/288 (3.13%)	12/269 (4.46%)	1.44 [0.60-3.49]	1.47 [0.57-3.75]
Parenchymal hematoma type 1	20/288 (6.94%)	12/269 (4.46%)	0.62 [0.30-1.31]	0.51 [0.24-1.13]
Parenchymal hematoma type 2	17/288 (5.90%)	27/269 (10.04%)	1.77 [0.95-3.34]	1.79 [0.91-3.49]
Symptomatic IH	8/288 (2.78%)	12/269 (4.46%)	1.63 [0.65-4.06]	2.12 [0.79-5.63]
Mortality	70/288 (24.31%)	42/269 (15.61%)	0.57 [0.37-0.88]	0.63 [0.38-1.06]

*Odds ratios were adjusted for age, sex, NIHSS at baseline and ICA occlusion

†ECASS I Intracranial hemorrhage at 24h

absolute numbers (%). P<0.05 was considered significant. Binary outcomes were analyzed with logistic regression and were reported as odds ratios with 95% confidence intervals. In this real-life non-randomized study unadjusted and adjusted odds ratios. The adjusted common odds ratios were adjusted for potential imbalances in the following major known prognostic variables between IVT and IVMT groups: age, sex, stroke severity (NIHSS at baseline) and tandem ICA/MCA occlusion (yes *vs.* no). According to the definition of secondary clinical outcome, mRS gradual analysis was assessed by ordinal logistic regression. Treatment-effect modification was explored in pre-specified subgroups of patients, defined by centers (Nice, Marseille, Toulon), age (<80, ≥80 y), gender (man, woman), diabetes mellitus (yes, no), arterial occlusion site (MCA, ICA/MCA, ICA alone), baseline NIHSS score (<10, 11-19, ≥20), MRI ASPECT score (<6, ≥6) and onset to imaging time (≤180, >180 mn). Differences between subgroups in the treatment effect were tested with interaction terms. Independent predictive variables of a good outcome (mRS≤2 at 3 months) were assessed by multivariate analysis by backward stepwise logistic regression (p<0.05). The regression model included all non-redundant variables associated to mRS≤2 at 3 months with p<0.1 in univariate analysis.

Results

Baseline characteristics

Between January 2012 to December 2016, 605 patients (281 from Nice, 203 from Marseille, and 121 from Toulon) met the inclusion criteria. 48 (7.93%) patients were excluded of the study according to exclusion criteria mentioned above. Among the remaining 557 stroke patients, 269 received combined therapy (IVTMT group) and 288 patients constituted the control group (IVT group). 510 (91.56%) patients underwent brain MRI at admission (261 in the IVTMT group and 249 in IVT group). Baseline characteristics of studied population are presented in Table 1. IVTMT patients were significantly younger than IVT group (mean age 66.08±13.60 years *vs.* 72.97±13.03 years, p< 0.001). There were 139 men (48.26%) in the IVT group and 147 men (44.44%) in the IVTMT group, with no significant difference between the 2 groups. The NIHSS score at baseline was significantly higher in the IVTMT group compared to the IVT group (16.69±4.97 *vs* 14.76±6.02; p<0.001). The IVT group had a higher proportion of hypertension, and smoking and the IVTMT group had a higher proportion of anticoagulant therapy. The other baselines characteristics did not differ between the two groups.

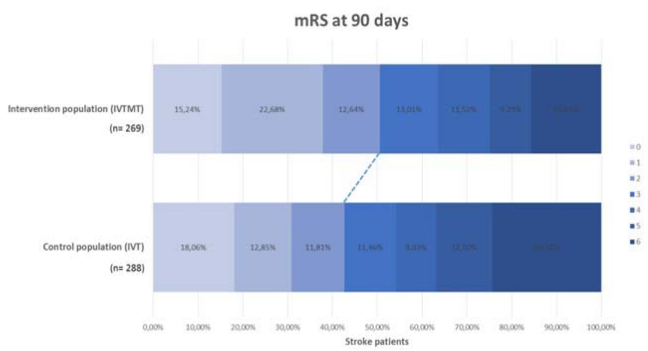

Figure 1: Modified Rankin Scale (mRS) score at 90 days.

Treatment procedure data are shown in Table 2.

Efficacy outcome

The distribution of mRS scores at 3 months in each treatment group is presented in Figure 1. In IVTMT group, 50.56% of patients had a good clinical outcome (mRS≤2) at 3 months *vs.* 42.61% in IVT group (Table 3). This difference was significant (aOR: 1.95 [1.29-2.95] (p=0.001). For 449 patients, CT angiography at 24 hours was available (223 in the control group and 226 in the intervention group). The proportion of patient with intracranial recanalization on follow-up CT angiography at 24h was significantly higher in the IVTMT group (85.84% *vs.* 56.95%).

Safety outcomes

The rate of symptomatic intracranial hemorrhage at 24h was 4.46% in IVTMT group, compared to 2.78% in IVT group, with no significant difference between both groups (Table 4). There was no significant difference between both groups concerning the different subtypes of asymptomatic intracranial hemorrhage defined by imaging at 24 h. At 3 months, mortality rate was not different in both groups (aOR: 0.63 [0.38-1.06]).

Subgroup analysis

Subgroup analysis did not show any appreciable difference between the three stroke units (Figure 2). It did not demonstrate any significant thrombectomy effect modification for sex, age, diabetes mellitus, ASPECT score and onset to imaging time. There was a significant difference in the NIHSS subgroup analysis (p <0.001), with an effect in favor of thrombectomy for the NIHSS ≥ 10 (aOR: 2.30

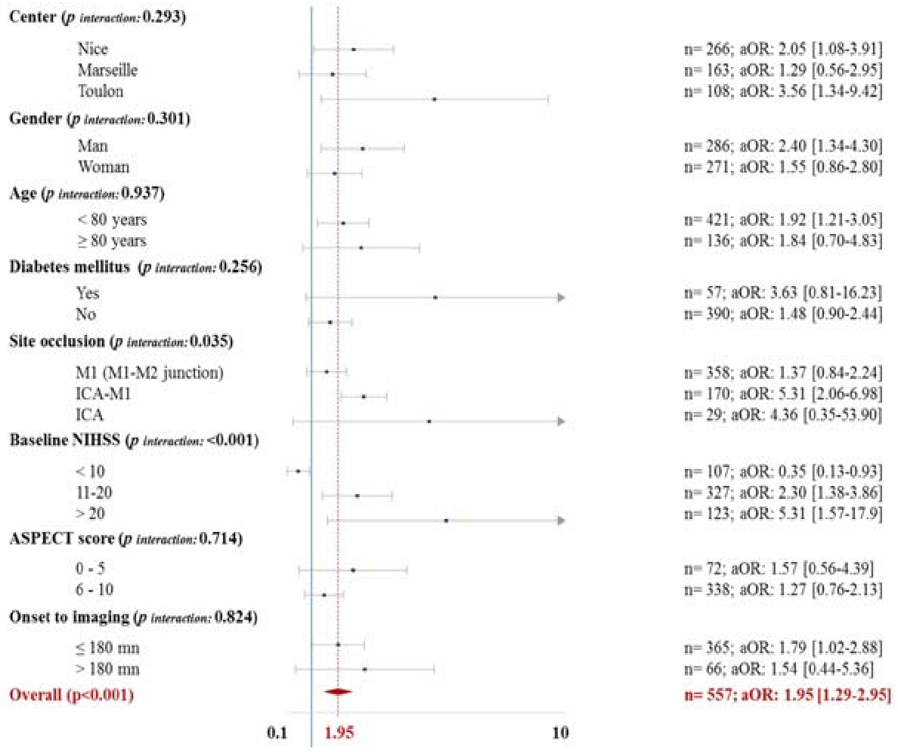

Figure 2: Subgroup analysis (Forest plot showing adjusted treatment effect for mRS at 90 days in pre-specified subgroups).

[1.38-3.86]), and an effect in favor of rtPA alone for NIHSS < 10 (aOR: 0.35 [0.13-0.93]). Concerning the site of arterial occlusion (p=0.035), we found that there was an effect in favor of thrombectomy for stroke patients with ICA-MCA tandem occlusion (aOR: 5.31 [1.57-17.9]).

Factors associated with good outcome

Independent factors associated at baseline of a good outcome (mRS≤2 at 3 months) were: NIHSS score (/4 pts, OR: 0.40 [0.28-0.58]), systolic blood pressure (/10 mmHg, OR: 0.83 [0.73-0.96]), blood glucose (/1g/L, OR: 0.21 [0.06-0.73]), ICA/MCA occlusion (y/n, 0.31 [0.13-0.75]), MRI ASPECT score (/1 pt, OR: 1.49 [1.15-1.92]), BNP level (/100pg/ml, OR:0.78 [0.68-0.90]) and endovascular treatment (y/n, OR: 2.23 [1.04-4,79]).

Discussion

The main result of the present study is that bridging therapy, namely intravenous thrombolysis followed by mechanical thrombectomy, performed in real life setting, significantly improves functional outcome in patients with acute ischemic stroke caused by proximal occlusion of anterior cerebral arteries, without increasing the risk of serious complication or death. It could be noted that although no statistically significant, there were trends toward lower mortality in IVTMT group what is consistent with RCTs. Recently, published data extracted from stroke-unit registers highlighted the safety and efficacy of bridging therapy [17,18]. Originally, this design allows assessing the clinical benefit of this therapeutic strategy in real life compared to rtPA alone. Indeed, in IVMT group, 50.56% of patients had a good clinical outcome at 3 months *vs.* 42.61% in IVT group (aOR 1.95 [1.29-2.95] in line with the results of the THRACE study performed in whole France (53.0% *vs.* 42.1%; aOR: 1.55[1.05-2.30] [11]. In HERMES, pooled analysis of the five positive RCTs (MRCLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA), 46% of patients were functionally independent at 90 days after bridging therapy against 26.5% in control population (aOR: 2.49[1.76-3.53]) [6-12,14].

Our results also confirm the safety of mechanical thrombectomy combined with IVT. The rate of symptomatic haemorrhages (4.46% in IVTMT group, and 2.78% in IVT group, p=0.131) was consistent with the results of HERMES pooled analysis (4.4% in IVTMT *vs.* 4.3% in control population, p=0.81) (14). There was no statistical difference between the two groups in terms of mortality (15.61% in IVTMT group *vs.* 24.31%, p=0.081) in line with RCT results such as THRACE study (12% *vs.* 13%) or HERMES analysis (15.3% *vs.* 18.9%) [11,14].

It is noteworthy to point out that the clinical benefit of bridging therapy in the present study appeared only after adjustment. Indeed, no significant differences were found between 2 groups through non-adjusted analysis (unadjusted ratio 1.37 [0.98-1.92], p=0.064). One might supposed that the inclusion in the IVTMT of patients with more severe stroke (baseline NIHSS 14.7±6.02 *vs.* 16.69±4.97) and the non-randomized design of our study could explain this result. Therefore, it was already suspected that the clinical benefit of bridging therapy depends on the characteristic of the studied population. Indeed, it was one of the more relevant explanation for failure of the first RCTs published in 2013 (IMS III, Synthesis, MR RESCUE) in contrast with recent RCTs [19-21]. To answer this question, a subgroup analysis has been carried out with the aim to determine sub group(s) more likely to benefit from each treatment modality. First, this analysis didn't show any significant difference between the three centres reflecting same practices and same patient recruitment. Secondly, we identified two pertinent parameters influencing the results: initial NIHSS score (p=0.001) and occlusion site (p=0.035). Discussion of bridging therapy when NIHSS is low is currently debated in the literature but data remains scarce and would justify dedicated RCTs [22-24]. Our study provides a part of answer since here, there is a benefit of IV thrombolysis alone in low NIHSS score (<10) (aOR: 0.35 [0.13-0.93]) whereas the benefit is in favor of bridging therapy for high NIHSS score. The analysis also identifies the initial arterial occlusion site as pertinent parameter. Clearly, ICA/MCA occlusions have a frank benefit in favor to bridging therapy (OR= 5.31 [2.06-3.67]), which is not true for M1 or isolated ICA occlusions. This result reflects the recanalization failure in ICA/MCA occlusions with intravenous rt-PA alone as it has been already reported in older studies [3-5, 25]. In IMS III for instance, the rate of partial or complete recanalization at 24 hours was 81% for an occlusion in the ICA after combined treatment against 35% in the intravenous t-PA group [19]. In contrast, the rates of recanalization in IV thrombolysis alone group were 68% for an M1 occlusion, and 77% for an M2 occlusion. These results lead us to discuss a management strategy simplification in tandem occlusions. That means that, in case of high NIHSS score and/or tandem occlusion, patients should be sent as soon as possible to thrombectomy centers.

As in most trials, the other analyzed subgroups did not show any differences between the two strategies especially for the initial volume, as assessed by the MRI ASPECT score, and the DWI volume. DWI volume and MRI ASPECT score were well correlated in our study (data not shown), and we chose to select the score used in our clinical practice for presented analysis. This result does not seem surprising because the DWI volume at baseline, which is the preponderant element allowing penumbra evaluation, must be considered as a predictor of functional independence whatever the method of recanalization. Thus, this parameter was found to be inversely associated with the good functional outcome in multivariate analysis. Our multivariate analysis identified some other parameters associated with the good functional outcome, among which the use of thrombectomy. Unsurprisingly, and regardless of the recanalization type, we found predictive factors already known and reported in initial works about intravenous thrombolysis [13]. Of note, the delay did not appear in the proposed predictive model, apparently replaced by the initial volume. As described in the first negative trials (IMS III, Synthesis and MR RESCUE), we identified also the paradox that there is no linear correlation between the rate of 24 hours recanalization and clinical outcome [19-21]. In line with these findings, IVTMT was associated in our study with an increase of 30% of recanalization rate at 24H and an increase of 8% in proportion of good clinical outcome. This makes us highlight again the importance of patient's selection before recanalization procedure on the basis of a penumbra imaging as proposed in MR RESCUE [21]. The initial volume, correlated with infarcted area growth rate, seems to take a major place in decision-making. Penumbra evaluation, based on the volume measure, and/or control of this penumbra called "freezing penumbra", are probably the key for the therapeutic decision and for functional prognosis improvement [26-30].

Conclusion

This study based on real life data confirms benefit and safety of the mechanical thrombectomy for ischemic stroke due to proximal occlusion of cerebral anterior arteries. We can conclude that benefit of MT observed in RCTs is also found in real world setting. However, adjustment has been necessary to demonstrate the benefit of combined strategy in our non-randomized population. These points out the importance of patient selection in order to improve medico-economic cost of these new strategies avoiding some futile procedures. For example, we highlighted the major benefit of IVTMT in ICA/MCA occlusion (cervical or intracranial), suggesting that IV Alteplase* is probably less useful in this situation. Subgroup analysis also shows that IVTMT benefit is expressed only in more severe patients, with high NIHSS scores, independently of occlusion site. Finally, for both strategies, outcome prediction model underlines the importance of the MRI ASPECT score (or DWI volume) which appears more determinant than time. This result reinforces the major role of patient's selection based on ischemic penumbra derived from initial volume. It supports the concept of changing the face of stroke stopwatch [31].

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