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Combined intravenous and endovascular treatment versus primary mechanical thrombectomy. The Italian Registry of Endovascular Treatment in Acute Stroke

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Abstract

Background: Whether mechanical thrombectomy alone may achieve better or at least equal clinical outcome than mechanical thrombectomy combined with intravenous thrombolysis is a matter of debate.

Methods: From the Italian Registry of Endovascular Stroke Treatment, we extracted all cases treated with intravenous thrombolysis followed by mechanical thrombectomy or with primary mechanical thrombectomy for anterior circulation stroke due to proximal vessel occlusion. We included only patients who would have qualified for intravenous thrombolysis. We compared outcomes of the two groups by using multivariate regression analysis and propensity score method.

Results: We included 1148 patients, treated with combined intravenous thrombolysis and mechanical thrombectomy therapy (n = 635; 55.3%), or with mechanical thrombectomy alone (n = 513; 44.7%). Demographic and baseline clinical characteristics did not differ between the two groups, except for a shorter onset to groin puncture time ($p < 0.05$) in the mechanical thrombectomy group. A shift in the 90-day modified Rankin Scale distributions toward a better outcome was found in favor of the combined treatment (adjusted common odds ratio = 1.3; 95% confidence interval: 1.04–1.66).

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*For details on The Italian Registry of Endovascular Treatment in Acute Stroke, see Supplementary Material. [AQ2]

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Multivariate analyses on binary outcome show that subjects who underwent combined treatment had higher probability to survive with modified Rankin Scale 0–3 (odds ratio = 1.42; 95% confidence interval: 1.04–1.95) and lower case fatality rate (odds ratio = 0.6; 95% confidence interval: 0.44–0.9). Hemorrhagic transformation did not differ between the two groups.

Conclusion: These data seem to indicate that combined intravenous thrombolysis and mechanical thrombectomy could be associated with lower probability of death or severe dependency after three months from stroke due to large vessel occlusion, supporting the current guidelines of treating eligible patients with intravenous thrombolysis before mechanical thrombectomy.

Keywords
Stroke, thrombectomy, intravenous thrombolysis, ischemic stroke, acute stroke therapy, cerebral infarction

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Introduction

Several randomized controlled trials[1–7] demonstrated the efficacy of mechanical thrombectomy (MT) in patients with acute ischemic stroke caused by a proximal intracranial occlusion in the anterior circulation. A meta-analysis confirmed that, compared with intravenous thrombolysis (IVT) alone, endovascular thrombectomy as add-on to IVT increased the probability of good outcome, without increasing the risk of symptomatic hemorrhage, after large vessel ischemic stroke in the anterior circulation.[8] Therefore, current guidelines recommend to treat eligible patients with IVT before MT. However, the added value of IVT treatment before MT is still under debate.

Observational retrospective analyses gave conflicting results: while some of them suggested a benefit of IVT pretreatment,[9–13] in terms of higher rate of recanalization, shorter duration of the endovascular procedure, lower number of passes of the thrombectomy device per patient, or better clinical outcome, others did not find significant differences between the two approaches.[14–22]

A pooled analysis[23] of the STAR[24] and SWIFT[25] trials suggested that treatment with IVT before MT does not add any clinical benefit as compared to MT alone. Conversely, two meta-analyses carried out on subgroups of patients included in the available randomized clinical trials,[26] and on available observational and randomized studies[27] showed that bridging therapy leads to a lower probability of death or serious disability as compared to MT alone.

However, a significant proportion of patients included in the above studies and treated with MT alone, were not eligible for IVT, thus representing a group of patient inherently different from those who qualified for IVT.

The aim of this study was to compare the outcome of patients with acute ischemic stroke due to proximal intracranial artery occlusion in the anterior cerebral circulation, eligible for IVT according to current guidelines, treated with combined therapy with those who underwent primary MT, included in the Italian Registry of Endovascular Stroke Treatments.[28]

Materials and methods

We retrieved data from The Italian Registry of Endovascular Stroke Treatments,[28] a multicenter, prospective, observational internet-based registry (http://www.registroendovascolare.it). The purposes, organization, and structure of the Registry were described in more details elsewhere.[28]

All patients who underwent endovascular treatment in the participating centers were consecutively recorded: for each patient, demographics, stroke risk factors, personal history, stroke severity, laboratory findings, any contraindication for IVT (and the reasons for exclusion from IVT), time from symptom onset to diagnosis and treatment, baseline neuroimaging data, treatment details, and outcome information were prospectively collected.

Patients and interventions

In the present analysis, we included all cases treated either with IVT followed by MT (IVT-MT) or with MT alone for anterior circulation stroke due to proximal vessel occlusion (internal carotid artery, and M1 or M2 segment of the middle cerebral artery). We restricted the analysis to patients who would have been eligible for IVT, according to the current guidelines.[29] Patients with IVT contraindications,[29] posterior circulation stroke, treated with intra-arterial thrombolysis, or patients who ultimately did not undergo any endovascular treatment were excluded. We limited the analysis to patients treated between 2011 and 2015 because of the widespread use of next generation devices for thrombectomy since 2011. Moreover, in

2015, new recommendations for IVT in acute stroke were released to relax some of the original exclusion criteria that had proven to be unnecessarily restrictive in real-world clinical practice. These amendments overcame IVT undertreatment due to strict exclusion criteria.[29] In particular, mild deficit or rapid improvement of symptoms, clinically severe stroke, seizure at onset, stroke present upon awakening, history of stroke and concomitant diabetes, history of stroke in the last three months, serum glucose levels <50 or >400 mg/dl, severe arterial hypertension and aggressive treatment required to reduce the blood pressure (BP) to the accepted limits (systolic BP < 185, and diastolic BP < 110 mmHg), arterial aneurysms or arteriovenous malformations, history of central nervous system diseases, and major surgery or severe trauma <3 months are no longer considered absolute exclusion criteria.[29] Many patients who had not been considered eligible for IVT on the basis of previous guidelines or of their too restrictive interpretation would have been treated according to the new recommendations.

Thus, we could include a large sample of patients qualified for IVT, who did not undergo this treatment.

IVT was administered according to the national guidelines within 4.5 h from symptom onset at the usual dosage (0.9 mg/kg body weight, maximum 90 mg).

Endovascular treatment was performed with or without previous IVT within 6 h of symptom onset using stent retrievers and/or aspiration devices.

The final treatment decision was left at the discretion of the neurologist and neurointerventionalist on duty.

All patients underwent CT scan 24 h after therapy or in case of clinical worsening.

Clinical evaluation and outcome measures

Stroke severity was evaluated by the National Institute of Health Stroke Scale (NIHSS), at baseline, after the end of therapeutic procedure and after seven days. [AQ3]

Hemorrhagic transformations were classified according to the ECASS II criteria.[30]

Symptomatic intracranial hemorrhage (SICH) was defined as any intracranial hemorrhage associated with 4 points increase in the NIHSS or leading to death.[30] The primary outcome measure for this study was the mRS score at 90 days (range ± 5 days), as assessed by a local trained neurologist unaware of the treatment given through in-person visit, or through a phone standardized interview when a face to face assessment was not possible.

For efficacy measures, arterial recanalization was rated according to the thrombolysis in cerebral infarction (TICI) score.[31] Successful reperfusion was defined as TICI score 2b or 3. Number of stentriever passes, thrombotic fragmentation, and distal embolization were also recorded.

SICH, procedural adverse events (subarachnoid hemorrhage and vessel dissection), and death rate were considered as safety measures. Need for ethical approval or patient consent for participation in the Italian Registry of Endovascular Treatment in Acute Stroke varied among participating hospitals. Ethical approval and patient consent were obtained where required.

Statistical analysis

Data were presented as absolute number, percentages, mean ± standard deviation or median and interquartile range (IQR) as appropriate. Dichotomous variables were compared using the chi squared test, and continuous variables were compared by Student's t-test or Mann–Whitney U test as appropriate on the basis of data distribution. The functional outcome was evaluated with ordinal logistic regression, taking the whole range of mRS into account as dependent variable to obtain a common odds ratio (OR, and 95% confidence interval (CI)) for a shift in the direction of a better outcome on the mRS. A multivariate model was planned to adjust for age, sex, history of diabetes, atrial fibrillation, hypertension, previous stroke or transient ischemic attack in the previous three months, the presence of carotid stenosis >70%, baseline NIHSS score, wake-up stroke, onset to door time, onset to groin puncture time, site of occlusion, and ASPECTS score. A second model was run to add TICI score as an additional covariate. The mRS at 90 days was also treated as dichotomous variable comparing the proportion of patients surviving with mRS 0–1, mRS 0–2, or mRS 0–3 between the two treatment groups. All dichotomous variables were evaluated by using a logistic regression analysis and adjusting for the above mentioned covariates.

Given the observational nature of this study, to address the imbalance of baseline characteristics between the two treatment groups, we adopted a propensity score (PS) analysis with an inverse probability of treatment weighting (IPW) method.[32–34] The individual PS was calculated by logistic regression analysis using treatment as dependent variables and adding, as covariates sex, age, and all additional explanatory variables that differed between the two groups, or that could influence patient assignment or outcome (age, sex, history of hypertension, diabetes, prior stroke or transient ischemic attack, atrial fibrillation, use of oral anticoagulants, known carotid stenosis >70%, wake-up stroke, time interval from symptom onset to hospital arrival, and site of arterial occlusion). This PS was

used in the subsequent analyses with the IPW method, where subjects who received IVT and MT were weighted by an inverse of their PS whereas those who received MT alone were weighted by an inverse of 1 − PS.[33,34]

The IPW created a synthetic sample in which the distribution of measured baseline covariates is independent of treatment assignment. To estimate treatment effect, ordinal and logistic regression models were built to derive IPW ORs.

A two-sided p value <0.05 was considered significant for all tests. Analysis was performed using SPSS statistical package version 23, and R release 3.1.2.

Results

We included 1148 consecutive patients treated with combination of IVT and MT (n = 635; 55.3%), or with MT alone (n = 513; 44.7%), in 13 Italian centers from 2011 through 2015.

Most patients (1043) were directly referred to an endovascular-capable center (ECC), while 105 were sent to the comprehensive stroke center from a hospital capable of assessing the patients and delivering at least IVT: of these latter, 63 underwent combined treatment, and 42 primary endovascular treatment.

The reasons not to treat patients with IVT were exclusion criteria recommended by previous guidelines (and in the summary of product characteristics of Actilyse) and no longer reported in the current ones (331 patients). In many circumstances (152 patients), the treating team decided against IVT thrombolysis and performed direct endovascular treatment because of a time of arrival judged to be too close to the 4.5 h time window (32 patients), concerns regarding the coagulation status or borderline INR, comorbidities such as renal dysfunction or malignancies, leukoaraiosis on CT scan, advanced age, high-burden clot, or proximal clot location. Thirty patients underwent primary endovascular treatment in the setting of a randomized clinical trial.

Demographic data, risk factors distribution, and baseline characteristics were not significantly different between the two groups (Table 1).

Time from symptoms onset to first hospital arrival was similar in the two groups (Table 1) as was the median time from onset to ECC arrival (95 min, IQR 59–143.2 for combined therapy patients, and 96 min, IQR 60–150 for MT patients; p = 0.7), and the time from onset to CT scan. Patients who underwent combined treatment had a significantly (p < 0.05) longer time from onset to groin puncture (230 min, IQR 185–275 versus 210 min, IQR 170–270). Median onset to end of treatment time was slightly higher in IVT-MT patients (315 min, IQR 258–362.5) than in MT patients (300 min, IQR 252.75–360), without statistically significant differences (p = 0.15). Median time from groin puncture to the end of the procedure was shorter (p < 0.05) for patients who underwent combined treatment (55 min, IQR 27.5–90) than for MT patients (60 min, IQR 34.5–90).

The distribution by site of arterial occlusion was similar in the two groups (Table 1). After adjustment by IPW, none of the clinical or procedural characteristics remained significantly different between the two groups (Table 1).

The stacked bar graph (Figure 1) shows 90-day clinical outcome (mRS) for each treatment arm.

A shift in the 90-day mRS distributions toward a better outcome was found in favor of the combined IVT + MT treatment. The common unadjusted OR was 1.45 (95% CI: 1.18–1.78), and it was 1.3 (95% CI: 1.04–1.66), when adjusted to the above possible confounders.

Multivariate analysis (Figure 2) showed that the proportion of people surviving with mRS 0–3 was significantly higher in the combined treatment group (adjusted OR = 1.42; 95% CI: 1.04–1.95), while the risk of death or very unfavorable outcome (mRS 5–6) was significantly lower in the same arm (adjusted OR = 0.62; 95% CI: 0.45–0.84). The 90-day case fatality rate was lower in patients treated with combined therapy than in those who underwent primary MT (adjusted OR = 0.6; 95% CI: 0.44–0.9). These results retained statistical significance after adjustment for TICI 2b–3 in the multivariate model.

The recanalization rate (TICI 2b–3) was higher in the combined treatment arm (71% versus 66%). Complete recanalization (TICI 3) was achieved in 55% of patients in the combined treatment group and in 49% of patients treated with primary endovascular thrombectomy. These differences lost statistical significance after multivariate comparisons (Figure 2). No differences were found regarding hemorrhagic transformation or procedure complications.

The PS analysis yielded the same results regarding clinical outcomes (Figure 3).

Discussion

The results of this study suggest that IVT treatment before MT procedure can lead to a better outcome, without affecting safety in patients with anterior circulation stroke due to large artery occlusion, and eligible to IVT. There was a significant shift in the distribution of the primary-outcome scores in favor of the combined intervention. Moreover, patients treated with combined therapy had significantly lower rates of death/severe disability as compared with patients undergoing only MT. These results are consistent with those reported

Table 1. Demographic and clinical characteristics of MT and IVT+MT patients. [AQ6]

	Original sample			IPW sample[a]		
	IVT + MT	MT	p value	IVT + MT	MT	p value
Age (years): mean (SD)	67.6 (14.6)	68.8 (13.1)	0.18	68.3 (13.9)	68.5 (13)	0.8
Sex (women)	50.7	51.1	0.9	52.6	52.2	0.97
Hypertension	65.8	63.4	0.43	66.1	66.8	0.84
Atrial fibrillation	27.8	32.3	0.13	30	34.6	0.2
Diabetes mellitus	13	17	0.08	15.4	18.1	0.1
Dyslipidemia	26.2	28.8	0.37	27.1	29.3	0.56
Smoke	23.8	18.9	**0.06**	22.2	19.2	0.38
Previous stroke/TIA[b]	2.7	6.6	< **0.01**	4.4	5.3	0.1
Carotid stenosis > 70%	4.4	5.1	0.6	5.6	6	0.8
NIHSS at entry: median, IQR	18, 14–21	18, 14–22	0.51	18, 14–21	18, 14–22	0.55
Site of vessel occlusion			0.22			0.77
MCA-M1	48.8	44.8	0.18	49.9	48.4	0.68
MCA-M2	14.2	12.5	0.4	14.2	12.1	0.43
Carotid tandem occlusion	19.1	23.4	0.07	18.2	19.8	0.63
Carotid T occlusion	18	19.3	0.56	17.7	19.8	0.95
Process times : median, IQR						
Onset to first hospital admission	73, 46–111	80, 48–128.5	0.08	73, 46–101	80.4, 54.4–134.3	0.32
Onset to CT scan	113, 76–150	110, 75–152	0.6	112, 78–171	110, 77–165	0.9
CT scan to groin puncture	120, 80–165	96, 68.6–140	< 0.01	112, 86–152	98.5, 70–136	0.06
Onset to groin puncture	230, 185–275	210, 170–270	< 0.05	225, 189–270	210, 180–273	0.09
Onset to end of procedure	315, 258–362.5	300, 252.7–360	0.15	315, 260–365	302, 255–360,7	0.12
Groin puncture to recanalization	55, 27.5–90	60, 34.5–90	<0.05	56, 29–92	60, 35–94.1 [AQ7]	0.08

ECC: endovascular-capable stroke center; IQR: interquartile range; IVT: intravenous thrombolysis; MCA: middle cerebral artery; MT: mechanical thrombectomy; NIHSS: National Institute of Health Stroke Scale; TIA: . [AQ8]

Number indicate percentages unless otherwise noted.

[a]IPW: inverse probability weighting (see text for definition).

[b]TIA or stroke in the last three months.

Figure 1. Three-month mRS in IVT+MT versus MT patients.

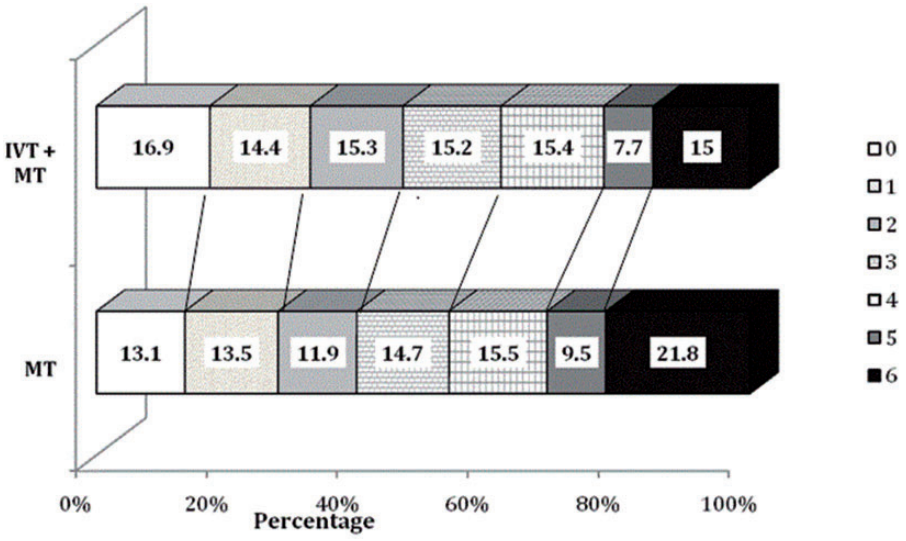
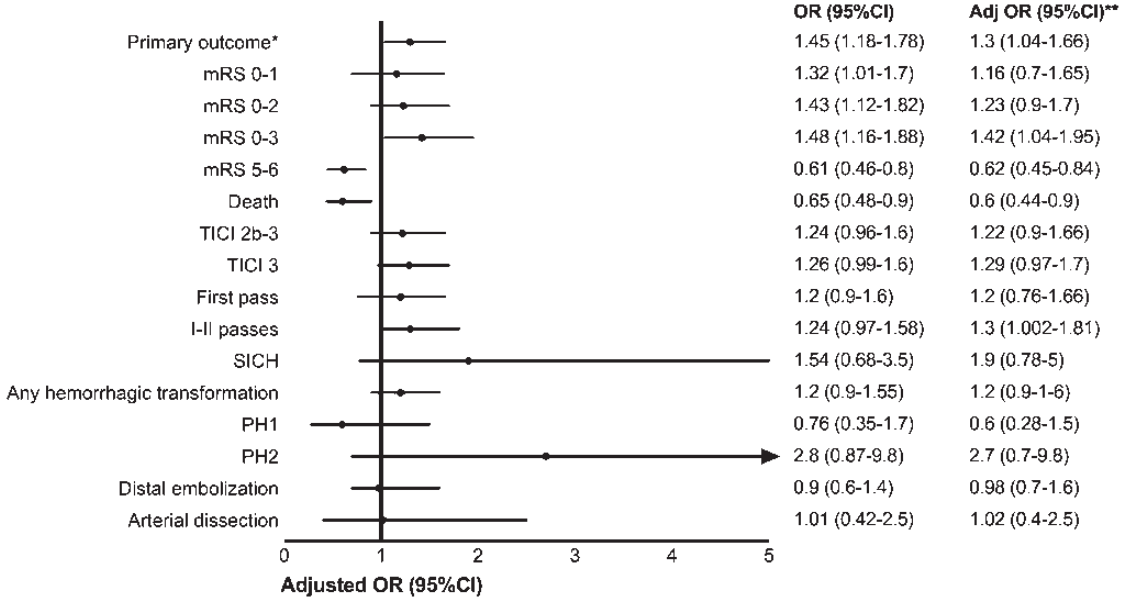
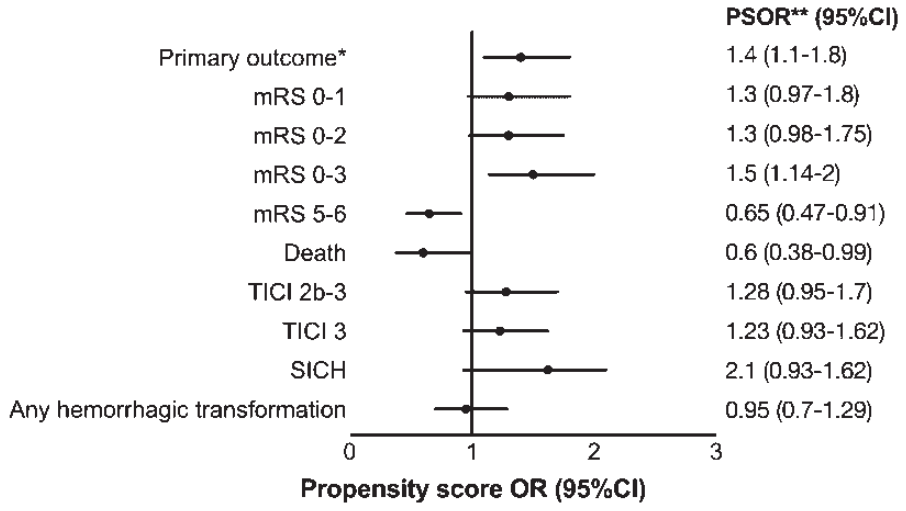


Figure 2. Outcome data: comparison between IVT + MT and in MT patients. *Common OR for a shift toward better outcome. **AdjOR: ORs were adjusted for age, sex, history of diabetes, atrial fibrillation, hypertension, previous stroke or transient ischemic attack in the previous three months, the presence of carotid stenosis > 70%, baseline NIHSS score, baseline ASPECTS score, onset to ECC arrival time, onset to groin puncture time, site of occlusion. PH1: parenchymal hematoma occupying less than 30% of the infarct zone, with some mass effect; PH2: parenchymal hematoma occupying less than 30% of the infarct zone, with significant mass effect; SICH: symptomatic hemorrhagic transformation.



from observational studies[9–13,35,36] and available meta-analyses.[26,27] A recent post hoc analysis of the ASTER trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization) showed a lower 90-day mortality rate in the IVT+MT group than after MT alone, and a better functional outcome, recanalization rate, and reduced mortality in a subgroup of patients.[37]

Figure 3. Outcome data: comparison between IVT + MT and in MT patients. Multivariate analysis using inverse probability of treatment weight. *Common OR for a shift toward better outcome. **AdjOR: ORs were adjusted for age, sex, history of diabetes, atrial fibrillation, hypertension, previous stroke or transient ischemic attack in the previous three months, the presence of carotid stenosis > 70%, baseline NIHSS score, baseline ASPECTS score, onset to ECC arrival time, onset to groin puncture time, site of occlusion. **PSOR: propensity score (PS) analysis with inverse probability of treatment weighting method. PH1: parenchymal hematoma occupying less than 30% of the infarct zone, with some mass effect; PH2: parenchymal hematoma occupying over 30% of the infarct zone, with significant mass effect; SICH: symptomatic hemorrhagic transformation.



It has been suggested that preceding IVT thrombolysis could facilitate and shorten the endovascular procedure, by partially lysing the clot, thus making easier its detachment from the vessel wall. Recanalization of distal thrombi that are not accessible to endovascular devices could be another, at least partial, explanation.

In this study, while the onset to groin puncture time was significantly longer in combined therapy patients, the onset to end of procedure time was similar in the two groups, because of the shorter duration of the procedure with fewer stentriever passes.

Moreover, the recanalization rate was higher in patients receiving combined treatment as compared with subjects who underwent primary MT, and this could at least in part explain the differences in clinical outcome between the two groups although the association between combined treatment and better functional outcome retained statistical significance after adjustment for TICI 2b–3 in the multivariate model.

As in other similar studies,[14–18,21,22] we found that the proportion of patients with hemorrhagic complications was higher in the combined treatment group although the difference was not statistically significant due to the small number of events in both group. However, the combined treatment could increase the chances of acceptable recovery and reduce mortality.

The benefit of combined therapy versus MT alone is still a matter of debate. Many studies, in fact, did not reveal any difference between the two treatments.[14–22]

On the whole the available studies are based on small samples of patients, the larger study being the Catalonia analysis, including 1166 patients.[18] On the basis of data from a recent meta-analysis,[26] assuming an alpha of 0.05 and beta of 0.2, a total sample of 408 patients would be needed to detect a 12% absolute difference in 90-day death or severe dependency, and 962 patients to detect a 9.7% absolute difference in functional independence at three months. Thus, most of the above studies have a low statistical power, and the failure to reject the null hypothesis could be due to a type II error due to the small sample size. On the other hand, some studies reporting negative results showed a non-significant trend toward a better outcome in patients treated with bridging therapy.[14,16,19,20]

All but five[16,18,20,21,36] studies did not account for their observational nonrandomized nature, which carries potential selection biases resulting from assignment to bridging treatment or primary endovascular thrombectomy on the basis of pretreatment baseline data rather than randomization.

Moreover, the main shortcoming of most of the above comparisons was to include both IVT eligible and not IVT eligible patients in the MT group or to compare eligible IVT patients treated with combined

therapy to ineligible patients treated with MT alone. Only four studies, in fact, compared patients who would have been eligible for IVT.[16,17,20,21] These studies, on the whole did not find significant differences.

We analyzed a large real-world sample of IVT eligible patients and we could observe a significant reduction of mortality and serious disability in patients treated with bridging therapy. These results retained statistical significance after PS modeling, to account for the nonrandomized nature of the study.

This study has several limitations: First, a weakness of the study was the lack of random allocation of patients to either treatment group: since the therapeutic option was left to the discretion of the attending physician, factors that have influenced treatment selection also could have influenced outcomes, leading to bias. PS approaches attempt to correct this problem by ensuring that the treatment groups under study are balanced with respect to measured covariates, but they cannot balance unmeasured characteristics and confounders.

Second, while the onset to door time (as well as the door to CT scan time) was acceptably short as a result of strategies implemented in early 2000s for timely delivery of IVT, the in-hospital process times were quite long, mostly due to a delay in the CT to groin puncture time. In should be noted that the enrollment of the majority of our study population predated the publication of trials demonstrating the benefit of endovascular recanalization treatment over IVT alone among patients with acute stroke due to large vessel occlusions. These trials prompted stroke centers, including ours, to plan and implement further system strategies to shorten in-hospital processes (prenotification of the neurointerventional team, expediting consent acquisition, and transfer to angiography suite), to minimize time from qualifying imaging to groin puncture. On the other hand, the workflow times in our study did not differ from that reported in some randomized clinical trials carried out in the same period (median time from onset to groin puncture: 238 min, IQR 180–302; and from onset to reperfusion: 301 min, IQR 226–384),[38] a remarkable exception being represented by the SWISS PRIME trial that was designed to include an intensive program of workflow acceleration.[39]

Another limitation is that patients treated with IVT who had achieved recanalization before MT were not included in this analysis because their data are not systematically recorded in the Registry.

It is known that pretreatment with systemic thrombolysis in patients with stroke due to large vessel occlusion results in successful reperfusion before the onset of endovascular procedure in about 10% of cases obviating the need for additional intervention.[40,41]

Conclusions

Our results suggest that current practice of administering IVT thrombolysis in eligible patients eventually followed by MT remains the standard approach, although an increased risk of symptomatic hemorrhage should be taken into account.

However, evidence can be definitely established only by a randomized controlled trial.[42]

Authors' contribution

All authors gave their substantial contributions to the conception and design of the Registry, the acquisition, and interpretation of data, critically revised the manuscript for important intellectual content, and approved the final version of the paper. In addition, IC and GP preformed the statistical analysis. IC wrote the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article Alessandro De Vito has received consulting fees from Boehringer-Ingelheim; Domenico Inzitari has received research grants and speaker honoraria from Shire Italia; Andrea Zini has received speaker and consulting fees from Boehringer-Ingelheim and Medtronic, and serves as advisory board of Boehringer-Ingelheim; Salvatore Mangiafico acts as a consultant for Johnson & Johnson; Danilo Toni received honoraria as a member of speaker bureau and as advisory board of Boehringer Ingelheim and Bayer, Pfizer-BMS, and Daiichi Sankyo. The other authors declare no potential conflicts of interest.

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