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Benefit from successful recanalization in an Italian cohort of stroke patients receiving endovascular treatments according to the DIRECT-MT trial criteria

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Abstract

Introduction: To identify predictors of 3-month mRS score and to estimate the benefit from successful recanalization across baseline subgroups of Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) cohort of stroke patients receiving endovascular treatments according to the DIRECT-MT criteria.

Methods: Using a model of propensity score matching, we retrospectively identified an IRETAS cohort of 137 patients receiving bridging who were matched with 137 patients receiving MT alone according to the DIRECT-MT criteria.

Results: Differences were found between DIRECT-MT and IRETAS cohorts for 3-month mRS score 0 to 1 (23.5% vs. 33.1%) and 0 to 2 (36.7% vs. 47.1%), successful (82% vs. 76.7%) and complete recanalization (32.3% vs. 58.8%). Among unfavorable predictors for 3-month mRS shift, diabetes mellitus (18.9% vs. 13.9%) and asymptomatic intracerebral hemorhage (ICH) (34.8% vs. 25.5%) were more frequent in the DIRECT-MT, whereas age ≥80 years (23.7% vs. 15.3%) and pre-stroke mRS score >0 (16.1% vs. 7.8%) were more frequent in the IRETAS.

The direction of effect on the 3-month mRS shift (6 to 0) favored successful recanalization across all strata. Greatest benefit from successful recanalization was observed in patients with most severe strokes (NIHSS ≥20, OR:4.002; 16–19, OR:3.292; 2–5, OR:2.470) and most proximal occlusion site (intra-cranial ICA, OR:4.092; M1-MCA, OR:3.705; M2-MCA, OR:2.001), in younger patients (18–59 years, OR:3.677; 60–79, OR:3.267; ≥80, OR:1.993), and in patients who started the treatment earlier (onset-to-groin time ≤205 min, OR:4.361; onset-to-groin time >205, OR:2.326).

Conclusions: The benefit from successful recanalization for 3-month mRS shift in the direction of favorable outcome was different across baseline subgroups.

Keywords

Thrombectomy, thrombolysis, stroke, modified Rankin Scale, DIRECT-MT trial

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Introduction

Five randomized controlled clinical trials (RCTs) evaluated whether mechanical thrombectomy (MT) alone in ischemic stroke with large vessel occlusion (LVO) is sufficient in patients who were eligible to intravenous thrombolysis (IVT) with standard dose of Alteplase (0.9 mg/kg) prior MT (bridging therapy) within 4.5 h from symptom onset.[1–5] Despite successful recanalization remains the therapeutic mechanism behind clinical benefit, all RCTs had clinical outcomes as primary endpoints. This has often led to the observation that the success of the treatment itself did not match with the 3-month clinical success assessed by the RCT.

Already in the first published RCT on this topic – the Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large

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Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial (DIRECT-MT) – the 5.1% increase in successful recanalization from the addition of IVT (84.5% vs. 79.4%) did not translate into increased clinically benefits on primary endpoint (OR for a mRS shift at 3 months).[1] Similarly, in the MR CLEAN-NO IV trial, difference in successful recanalization between bridging and MT alone (78.7% vs. 83.1%) did not lead to differences in the primary endpoint (OR for a mRS shift at 3 months).[2]

From another point of view, the proportion of mRS score of 0-2 at 3 months (primary endpoint) was higher after MT alone than bridging (54.3% vs. 46.6%) in the DEVT trial, despite similar rates of successful recanalization between the two study groups (88.5% vs. 87.2%).[3] Instead, similar rates of successful recanalization were observed between the two study groups (89% vs. 88.8%) in the DIRECT-SAFE trial (World Stroke Congress, 28–29 October 2021),[4] but the proportion of mRS score of 0-2 at 3 months (primary endpoint) was higher after bridging than MT alone (60.5% vs. 54.8%).

Only the SWIFT-DIRECT trial (European Stroke Organization Conference, 1–3 September 2021)[5] showed a concordance between successful recanalization and clinical benefit; specifically, higher successful recanalization rate in the bridging cohort (96.6% vs. 90.5%) translated into increased benefits on the proportion of mRS score of 0-2 at 3 months (primary endpoint, 65.2% vs. 56.7%).

Furthermore, it's not completely clear why the overall percentage of DIRECT-MT patients with a favorable outcome at 3 months was modest (mRS score 0-2, 36.7%) when compared with previous trials,[6] although successful recanalization occurred in more than 80% of the patients and proportion of intracranial atherosclerotic disease – more common in Asians – was unusually low (6.9%).

The main aim of this study was to identify the significant predictors in the direction of favorable outcome on mRS shift at 3 months in a cohort of stroke patients receiving endovascular treatments according to the DIRECT-MT criteria. In addition, we assessed if the clinical benefit on mRS shift at 3 months from successful recanalization was different across prespecified baseline subgroups.

Methods

Study design, participants, and procedures

We conducted a study on prospectively collected data of patients treated with bridging therapy or MT alone and included between January 2011 and December 2017 in the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS), a multicenter, observational internet-based registry (Supplemental Tables 1). Participating centers were required to accept the rules of the IRETAS, including consecutive registration of all stroke patients receiving endovascular procedures.

We retrospectively applied to the entire IRETAS cohort the inclusion and exclusion criteria per DIRECT-MT trial protocol (NCT03469206).

Inclusion criteria (per DIRECT-MT trial protocol): age of 18 years or older, onset-to-groin time ≤4.5 h after stroke onset, intracranial ICA or M1- or proximal M2-segment MCA occlusion, NIHSS score ≥2, pre-stroke mRS score ≤2.

Exclusion criteria (per DIRECT-MT trial protocol): blood pressure > 185/110 mmHg, blood glucose < 2.7 or > 22.2 mmol/L, **c**erebral infarction <6 weeks with residual neurological deficit or signs of recent infarction on neuro-imaging, **s**erious head trauma <3 months, major surgery or serious trauma <2 weeks, gastrointestinal or urinary tract hemorrhage <3 weeks, previous intracerebral hemorrhage, use of anticoagulant with INR >1.7, known thrombocyte count <100 × 109 /L, treatment with direct thrombin or factor X inhibitors, treatment with heparin (APTT exceeds the upper limit of normal value) <48 h. As the DIRECT-MT trial, we included also patients with tandem occlusion (ipsilateral extra-cranial ICA occlusion plus or intra-cranial ICA occlusion or M1- or proximal M2-segment MCA). According to the DIRECT-MT trial protocol, intra-arterial (IA) fibrinolysis was accepted as rescue therapy at the discretion of the treating physician.

From the entire IRETAS cohort, we identified patients receiving bridging and those receiving MT alone. Since recruitment in the IRETAS largely preceded the publication of DIRECT-MT trial, bridging was the standard treatment for patients with ischemic stroke resulting from an LVO within the first 4.5 h after symptom onset if there were no contraindications to IVT. Nevertheless, the choice of endovascular procedure type was at the discretion of the neurologist and neuroradiologist.

Data collection

Details on data collection are provided in the online-only Data Supplement.

Outcome

According to the DIRECT-MT trial,[1] the prespecified primary outcome of this study was the degree of disability on the modified Rankin Scale (mRS) at 3 months. The score on mRS ranges from normal (0) to death (6). The degree of revascularization at the end of the endovascular procedure was assessed with the Thrombolysis in Cerebral Infarction (TICI) scale.[7] In particular, grade 0 was defined as penetration with minimal perfusion, grade 1 as partial perfusion, grade 2a as <67% perfusion of the entire vascular territory, grade 2b as 67% to 99% perfusion, and grade 3 as complete perfusion. Successful recanalization was defined as TICI 2b/3. Procedural complications were: distal embolization, vessel dissection, asymptomatic intracerebral hemorhage (ICH) and symptomatic ICH (defined according to the Heidelberg criteria[8] as in the DIRECT-MT trial). Secondary functional outcomes were excellent outcome (mRS score 0-1), favorable outcome (mRS score 0-2), and death at 3 months.

Statistical analysis

We performed statistical analyzes using SPSS 22.0 statistical package and STATA-16 software. Since endovascular treatment was not randomly assigned in the study population, we used a propensity score matching model to reduce the risk of bias. Propensity score matching with a logistic regression for each patient was based on age, sex, hypertension, diabetes mellitus, previous stroke/TIA, atrial fibrillation, pre-stroke mRS score, NIHSS score, ASPECT score, occlusion site, general anesthesia, onset-to-groin time, and additional intra-arterial fibrinolysis. Due to the high number of missing values, the degree of collateral circulation status defined using Careggi Collateral Score (CCS)[9] and the type of procedure (i.e. aspiration alone, stent retriever alone, or combination of aspiration and stent retriever) did not enter the model of propensity score matching. Each patient receiving bridging was matched with a patient receiving MT alone with a 1:1 ratio without replacement using a caliper width of 0.01. Standardized difference <0.1 was considered to support the assumption of balance between the groups.

First, we used $\chi 2$ test to compare proportions of the subgroups of patients enrolled in the DIRECT-MT trial with those of the patients in the IRETAS cohort. Subgroups were defined as reported in the Supplementary Appendix of the DIRECT-MT trial.[1] Specifically, age was categorized into 18 to 59, 60 to 79, and ≥80 years, NIHSS score into 2 to 15, 16 to 19, and ≥20; pre-stroke mRS score, ASPECT score, stroke onset-to-groin time and stroke onset-to-end procedure time were categorized according to median values reported from the DIRECT-MT cohort. To assess the degree of collateral circulation status and revascularization at the end of the endovascular procedure, Collateral Score (CS) and extended TICI (eTICI) scale were used in the DIRECT-MT cohort,[1] respectively. Data for stroke causes and stroke onset-to-needle time for IVT were not available in the IRETAS cohort for comparison with the DIRECT-MT cohort.

Second, we looked for the significant predictors of 3-month mRS score in the direction of favorable outcome (6 to 0) in the IRETAS cohort using a first multivariate ordinal regression model including only clinical variables with a probability value <0.10 in the univariate model and a second multivariate ordinal regression model including only radiological variables. Statistical significance was established at two-tailed 0.05 level ($p < 0.05$).

Third, we estimated the effect of successful recanalization in the direction of favorable outcome on the 3-month mRS score (6 to 0) across prespecified subgroups using an ordinal logistic regression analysis calculating the OR with two-sided 95% confidence intervals (CI) after adjustment for the following predefined covariates: age, pre-stroke mRS score, diabetes mellitus, NIHSS score, ASPECT score, occlusion site, and stroke onset-to-groin time. We tested heterogeneity of successful recanalization effect by subgroups on the primary outcome using a multiplicative interaction term (successful recanalization* variable). We reported graphically using forest plot for stratum-specific successful recanalization effects along with the p value for the interaction term.

Standard protocol approvals, registrations, and patient consents

The present study was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Need for ethical approval or patient consent for participation in the IRETAS varied among participating hospitals. Informed consent to use of anonymized and aggregated data for participation in the IRETAS was obtained in all patients of each center.

Data availability statement

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

Results

Fulfilling the DIRECT-MT trial criteria, we identified 516 patients enrolled in the IRETAS cohort who were treated with bridging and 213 with MT alone (Supplemental Table 2). Using a model of propensity score matching, we identified an IRETAS cohort of 274 patients: 137 patients receiving bridging were matched with 137 receiving MT alone (Table 1). Absolute standardized difference (ASD) was <10% for all covariates. No significant difference was found between bridging and MT alone groups as regard outcome measures.

A thourough comparison of baseline characteristics and outcomes of patients included in the DIRECT-MT cohort ($n = 656$) and in the IRETAS cohort ($n = 274$) is provided in Table 2. Patients in the DIRECT-MT cohort were more frequently in the 60 to 79-year-old age group (62% vs. 50%; $p < 0.001$), while the IRETAS patients belonged more frequently to the age ≥80 group (23.7% vs. 15.3%; $p = 0.002$). The female prevalence was higher in the IRETAS cohort (49.3% vs. 43.6%; $p = 0.008$) as was the frequency of subjects with pre-stroke disability (mRS score >0, 16.1% vs. 7.8%; $p = 0.004$). While the DIRECT-MT cohort included more patients with diabetes mellitus (18.9% vs. 13.9%; $p = 0.007$), atrial fibrillation (45.9% vs. 32.1%; $p < 0.001$), and previous ischemic stroke/TIA (13.7% vs. 2.2%; $p < 0.001$). Intra-cranial ICA occlusion was more frequent in the DIRECT-MT cohort (35.3% vs. 21.8%; $p = 0.003$), while IRETAS patients had more frequently M1-segment MCA occlusion (66% vs. 52.5%; $p < 0.001$) and tandem occlusion (25.5% vs. 10.8%; $p < 0.001$). The IRETAS cohort included more patients who started endovascular procedure ≤205 min of stroke onset (60.9% vs. 51%; $p = 0.006$) and who received additional IA fibrinolysis (11.3% vs. 2.1%; $p < 0.001$). Successful recanalization

Table 1. Characteristics of the entire IRETAS cohort and of patients treated with bridging and direct MT after propensity score matching.

	All patients (n = 274)	Bridging (n = 137)	Direct MT (n = 137)	p value
Demographics				
Age (years), median (IQR)	72 (61-80)	71 (60-79)	72 (61-80)	0.929
Female sex, n (%)	135 (49.3)	66 (48.2)	69 (50.4)	0.809
Medical history				
Hypertension, n (%)	163 (59.5)	79 (57.7)	84 (61.3)	0.623
Diabetes mellitus, n (%)	38 (13.9)	19 (13.9)	19 (13.9)	1.000
Atrial fibrillation, n (%)	88 (32.1)	43 (31.4)	45 (32.8)	0.897
Previous ischemic stroke/TIA, n (%)	6 (2.2)	3 (2.2)	3 (2.2)	1.000
Baseline data				
Pre-stroke mRS score, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.313
NIHSS score, median (IQR)	18 (13-21)	17 (13-21)	18 (13-21)	0.797
ASPECT score, median (IQR)	10 (8-10)	10 (8-10)	10 (8-10)	0.376
Occlusion site				0.841
Intra-cranial ICA, n (%)	30 (10.9)	17 (12.4)	13 (9.5)	
M1-segment MCA, n (%)	144 (52.6)	70 (51.1)	74 (54)	
M2-segment MCA, n (%)	30 (10.9)	14 (10.2)	16 (11.7)	
Tandem, n (%)	70 (25.5)	36 (26.3)	34 (24.8)	
General anesthesia, n (%)	104 (38)	52 (38)	52 (38)	1.000
Onset-to-groin time (minutes), median (IQR)	190 (152-230)	190 (149-235)	190 (155-229)	0.718
Additional IA fibrinolysis, n (%)	31 (11.3)	15 (10.9)	16 (11.7)	1.000
Onset-to-end procedure time (minutes), median (IQR)	270 (224-319)	265 (220-320)	270 (230-318)	0.507
TICI 3, n (%)	161 (58.8)	79 (57.7)	82 (59.9)	0.806
TICI 2b/3, n (%)	210 (76.6)	105 (76.6)	105 (76.6)	1.000
Radiological complications				
Distal embolization, n (%)	28 (10.2)	18 (13.1)	10 (7.3)	0.162
Vessel dissection, n (%)	3 (1.1)	2 (1.5)	1 (0.7)	1.000
Asymptomatic ICH, n (%)	70 (25.5)	39 (28.5)	31 (22.6)	0.332
Symptomatic ICH, n (%)	17 (6.2)	9 (6.6)	8 (5.8)	1.000
Functional outcomes				
3-month mRS score, median (IQR)	3 (1-4)	3 (1-4)	3 (1-4)	0.277
3-month mRS score 0-1, n (%)	88 (32.1)	45 (32.8)	43 (31.4)	0.897
3-month mRS score 0-2, n (%)	129 (47.1)	66 (48.2)	63 (46)	0.809
3-month death, n (%)	40 (14.6)	19 (13.9)	21 (15.3)	0.864

Continuous variables are presented as median and interquartile range (IQR) and were compared using Mann-Whitney U-test Categorical variables are expressed as frequency and percentage and were compared using $\chi 2$ test.
Careggi collateral score (CCS) was known in 147 patients. CCS was 0 (flow in both ACA and MCA territory) in 22 patients (13 MT alone and 9 bridging), 1 (flow in ACA territory) in 23 (10 MT alone and 13 bridging), 2 (flow in MCA territory until the suprainsular segment) in 41 (24 MT alone and 17 bridging), 3 (flow in MCA territory until the insular segment) in 38 (22 MT alone and 16 bridging), and 4 (flow in MCA territory until the alar segment) in 23 (12 MT alone and 11 bridging).
Type of procedure was known in 216 patients. Aspiration alone was used in 72 patients (35 MT alone and 37 bridging), stent retriever alone in 107 (54 MT alone and 53 bridging), and combination of aspiration and stent retriever in 37 (18 MT alone and 19 bridging).

was more often observed in the DIRECT-MT cohort (eTICI 2b/2c/3, 82% vs. TICI 2b/3, 76.7%; p = 0.006); in particular, eTICI 2b/2c (defined as 50–99% reperfusion) versus TICI 2b (defined as 67–99% reperfusion) was in favor of the DIRECT-MT cohort (49.7% vs. 17.9%; p < 0.001), while complete recanalization was more often reported in the IRETAS cohort (58.8% vs. 32.3%; p = 0.006). Asymptomatic ICH was more frequent in the DIRECT-MT cohort (34.8% vs. 25.5%; p = 0.006). Overall, patients in the IRETAS cohort had a better outcome: 3-month mRS score 0 to 1 (33.1% vs. 23.5%; p = 0.007), 0 to 2 (47.1% vs. 36.7%; p = 0.003); while an unfavorable outcome was more common in the DIRECT-MT cohort, i.e., 3-month mRS score 5 (16.7% vs. 5.8%; p < 0.001) and 6 (18.3% vs. 14.6%). From the comparison with 147 patients with available CCS in the IRETAS cohort, good collateral circulation was more frequent in the IRETAS cohort (CCS 2 to 4, 69.4% vs. CS 2 to 3, 23%; p < 0.001). Distribution of 3-month mRS score for each TICI grade in the IRETAS cohort is provided in Figure 1.

Univariate and multivariate models to identify clinical and radiological predictors for 3-month mRS score in the direction of favorable outcome (6 to 0) are provided in Table 3. In the first multivariate ordinal regression including clinical variables (age categories, hypertension, diabetes mellitus, pre-stroke mRS score >0, and NIHSS score categories), favorable predictors for a 3-month mRS score were age 18 to 59 years (OR: 2.091, 95% CI: 1.069–4.089) and age 60 to 79 years (OR: 1.752, 95% CI: 1.043–3.084) compared with age ≥80 years, NIHSS score 2 to 15 (OR: 3.598, 95% CI: 2.155–6.008) and NIHSS score 16 to 19 (OR: 2.130, 95% CI: 1.239–3.663) compared with NIHSS score ≥20, while

Table 2. Comparison of the patient characteristics between DIRECT-MT and IRETAS cohort.

	DIRECT-MT cohort No. (%)	IRETAS cohort No. (%)	p value
Clinical variables			
Age			
18–59 years	149/656 (22.7)	72/274 (26.3)	0.244
60–79 years	407/656 (62)	137/274 (50)	<0.001
≥80 years	100/656 (15.3)	65/274 (23.7)	0.002
Female sex	286/656 (43.6)	135/274 (49.3)	0.008
Hypertension	394/656 (60.1)	163/274 (59.5)	0.871
Diabetes mellitus	124/656 (18.9)	38/274 (13.9)	0.007
Atrial fibrillation	301/656 (45.9)	88/274 (32.1)	<0.001
Previous ischemic stroke/TIA	90/656 (13.7)	6/274 (2.2)	<0.001
Pre-stroke mRS score >0	51/656 (7.8)	44/274 (16.1)	0.004
NIHSS score			
2–15	265/653 (40.6)	101/274 (36.9)	0.290
16–19	162/653 (24.8)	69/274 (25.2)	0.914
≥20	226/653 (34.5)	104/274 (38)	0.317
Radiological variables			
Intra-cranial occlusion site			
Intra-cranial ICA	226/646 (35)	68/274 (21.8)	0.003
M1-segment MCA	339/646 (52.5)	206/274 (66)	<0.001
M2-segment MCA	75/646 (11.6)	38/274 (12.2)	0.340
Tandem occlusion	71/656 (10.8)	70/274 (25.5)	<0.001
Good collateral circulation (CS 2–3 vs. Careggi CS 2–4)	151/656 (23)	102/147 (69.4)	<0.001
General anesthesia	207/639 (32.4)	104/274 (38)	0.104
Onset-to-groin time ≤205 min	324/636 (51)	167/274 (60.9)	0.006
Additional IA fibrinolysis	14/656 (2.1)	31/274 (11.3)	<0.001
Onset-to-end procedure time ≤273 min	319/636 (50)	149/274 (54.4)	0.242
eTICI versus TICI			
0-1 versus 0-1	39/622 (6.3)	22/274 (8)	0.336
2a (TICI 2a49) versus 2a (TICI 2a66)	73/622 (11.7)	42/274 (15.3)	0.139
2b (TICI 2b50) versus 2b (TICI 2b67)	189/622 (30.4)	49/274 (17.9)	<0.001
2c	120/622 (19.3)	-	
2b/2c (TICI 2b50/2c) versus 2b (TICI 2b67)	309/622 (49.7)	49/274 (17.9)	<0.001
3 versus 3	201/622 (32.3)	161/274 (58.8)	<0.001
Successful recanalization	510/622 (82)	210 (76.7)	0.006
Vessel dissection	13/656 (2)	3/274 (1.1)	0.343
Distal embolization	66/656 (10)	28/274 (10.2)	0.942
Asymptomatic ICH	228/656 (34.8)	70/274 (25.5)	0.006
Symptomatic ICH	34/656 (5.2)	17/274 (6.2)	0.533
3-month mRS score			
0-1	154/654 (23.5)	88/274 (33.1)	0.007
0-2	240/654 (36.7)	129/274 (47.1)	0.003
3	111/654 (17)	42/274 (15.3)	0.538
4	74/654 (11.3)	47/274 (17.2)	0.016
5	109/654 (16.7)	16/274 (5.8)	<0.001
6	120/654 (18.3)	40/274 (14.6)	0.168

Age and NIHSS score were categorized according to Supplementary Appendix of the DIRECT-MT trial; pre-stroke mRS score, ASPECT score, stroke onset-to-groin time, and stroke onset-to-end procedure time were categorized according to median values reported from the DIRECT-MT cohort.
Median ASPECT score was 9 in both DIRECT-MT groups, but number of patients with ASPECT score <10 and number of patients with ASPECT score = 10 were not available in Supplementary Appendix of the DIRECT-MT trial. ASPECT score was <10 in 117/274 (42.7) patients including in the IRETAS cohort.
In the DIRECT-MT cohort, stent retriever was used as first enodvascular procedure in 566/591 (95.8%) patients and aspiration was used as fist endovascular procedure in 12/591 (2%) patients. In the IRETAS cohort, aspiration alone was used in 72/216 (33.3%) patients, stent retriever alone in 107/216 (49.5%) patients, and combination of aspiration and stent retriever in 37/216 (17.2%) patients.

unfavorable predictors for 3-month mRS score were diabetes mellitus (OR: 0.468, 95% CI: 0.265–0.907) and pre-stroke mRS score >0 (OR: 0.490, 95% CI: 0.265–0.907). In the second multivariate ordinal regression including radiological variables (M2-segment MCA occlusion, onset-to-groin time >205 min, onset-to-end procedure time >273 min, TICI 2b/3, TICI 3, asymptomatic ICH, and symptomatic ICH), favorable predictors for a 3-month mRS score were M2-segment MCA occlusion (OR: 2.193, 95% CI: 1.146–4.197) and TICI 2b/3 (OR: 2.782, 95% CI: 1.405–5.506), while unfavorable predictors for 3-month mRS score were asymptomatic ICH (OR: 0.389, 95% CI: 0.237–0.638), and symptomatic ICH (OR: 0.064, 95% CI: 0.021–0.190).

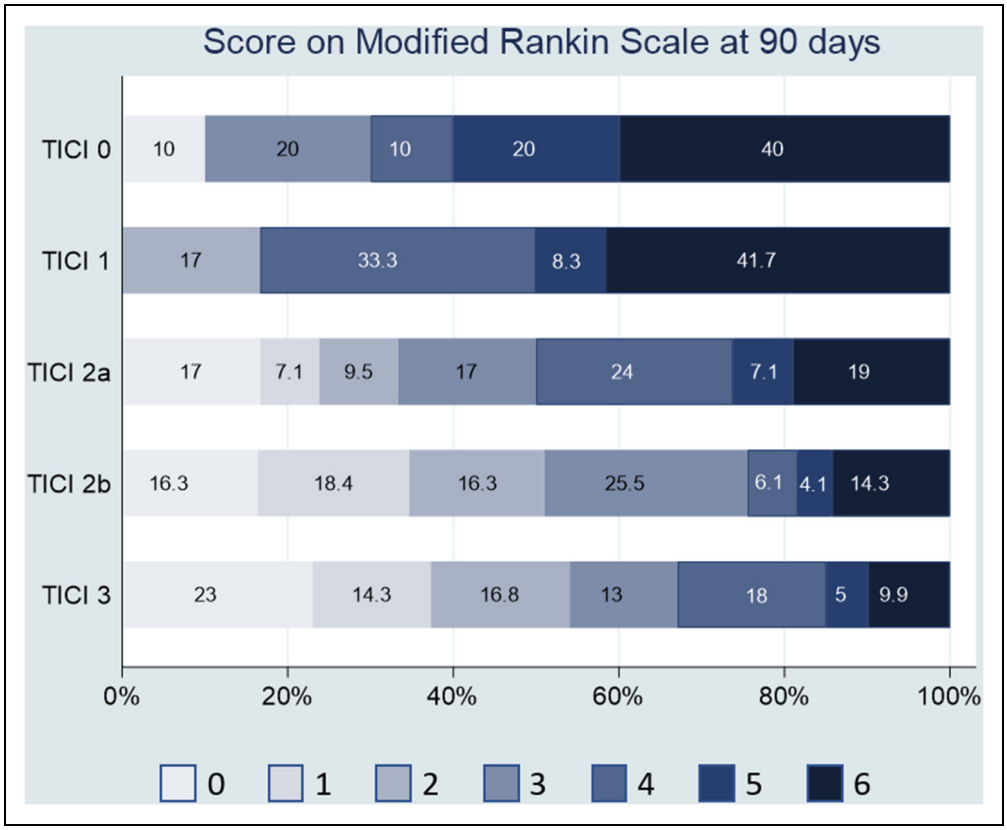

Figure 1. Distribution of 3-month mRS score for each TICI grade.

Since data for CCS were available in 147 patients of the IRETAS cohort, a multivariate ordinal regression including radiological predictors obtained from the univariate ordinal regression was repeated. Compared with CCS 4, CCS 0 to 1 (OR: 0.274, 95% CI: 0.106–0.708), 2 (OR: 0.325, 95% CI: 0.122–0.862), and 3 (OR: 0.377, 95% CI: 0.145–0.980) were unfavorable predictors for 3-month mRS score.

Forest plot showing adjusted effect of successful recanalization for mRS shift (6 to 0) at 3 months in different subgroups with p values for heterogeneity across baseline variables is provided in Figure 2. There was no evidence of heterogeneity of successful recanalization effect across any of the baseline variables. The direction of effect favored successful recanalization across all strata, although the adjusted ORs for TICI 2b/3 were not significant for age ≥80 years, pre-stroke mRS score >0, diabetes mellitus, M2-segment MCA occlusion, general anesthesia, and TICI 2b (vs. TICI 2a). Due to the small sample size of the subgroups, effect of successful recanalization for a mRS shift at 3 months was not estimated along previous ischemic stroke/TIA and additional IA fibrinoliysis.

Discussion

Comparing our results with the DIRECT-MT trial, our study confirms that favorable outcome was modest in the DIRECT-MT cohort[1] and no significant difference was found between bridging and MT alone regarding ORs for a mRS shift at 3 months.[1,2] Rates of successful and complete recanalization were similar between bridging and MT alone. Complete recanalization was more often reported in the IRETAS cohort, while successful recanalization was more frequent in the DIRECT-MT cohort. However, TICI 2b/3, but not TICI 3, remained significant favorable predictor of 3-month mRS score and the forest plot showed that effects of TICI 2b and TICI 3 for mRS shift at 3 months were similar. Despite a direct comparison for successful recanalization was not possible because classification systems to define the degree of revascularization were different in the cohorts, our results are consistent with a recent analysis from HERMES collaboration which suggested that eTICI ≥2b67, equivalent to TICI ≥2b, is optimal to define successful recanalization and generally translates in a better outcome.[10]

Among unfavorable predictors of 3-month mRS score selected by the multivariate model in the IRETAS cohort, diabetes mellitus and asymptomatic ICH according to the Heidelberg criteria were more frequent in the DIRECT-MT cohort, whereas age ≥80 years and pre-stroke mRS score >0 were more often observed in the IRETAS cohort. No significant difference between DIRECT-MT and IRETAS cohorts was found in other predictors of 3-month mRS score including categorized NIHSS score, M2-segment MCA occlusion, and sICH.

While diabetes mellitus is well-known unfavorable outcome predictor after endovascular treatment,[11] the role of asymptomatic ICH in both DIRECT-MT treatment

Table 3. Univariate and multivariate models to identify clinical and radiological predictors of 3-month mRS score.

		Univariate ordinal regression			Multivariate ordinal regression[a]		
	No.	OR	95% CI	P value	OR	95% CI	p value
Clinical variables							
Age							
18–59 years	72	3.350	1.318–3.808	<0.001	2.091	1.069–4.089	0.031
60–79 years	137	2.240	1.318–3.808	0.003	1.752	1.043–3.084	0.048
≥80 years	65	Reference	-		Reference	-	-
Female sex	135	0.939	0.619–1.245	0.768	-	-	-
Hypertension	163	0.634	0.414–0.971	0.036	-	-	NS
Diabetes mellitus	38	0.366	0.196–0.683	0.002	0.468	0.247–0.886	0.020
Atrial fibrillation	88	1.113	0.708–1.747	0.643	-	-	-
Previous ischemic stroke/TIA	6	1.794	0.425–7.571	0.427	-	-	-
Pre-stroke mRS score >0	44	0.288	0.164–0.506	<0.001	0.490	0.265–0.907	0.023
NIHSS score							
2–15	101	4.096	2.473–6.783	<0.001	3.598	2.155–6.008	<0.001
16–19	69	2.211	1.291–3.788	0.004	2.130	1.239–3.663	0.006
≥20	104	Reference	-	-	Reference	-	-
Radiological variables							
ASPECT score <10	117	0.809	0.532–1.232	0.323	-	-	-
Intra-cranial occlusion site							
Intra-cranial ICA	68	0.804	0.496–1.304	0.377	-	-	-
M1-segment MCA	206	0.949	0.582–1.546	0.833	-	-	-
M2-segment MCA	38	1.757	0.940–3.283	0.077	2.193	1.146–4.197	0.018
Tandem occlusion	70	0.766	0.474–1.237	0.275	-	-	-
Careggi collateral score[b]							
0–1	45	0.230	0.092–0.576	0.002	0.274	0.106–0.708	0.008
2	41	0.300	0.120–0.749	0.010	0.325	0.122–0.862	0.024
3	38	0.354	0.142–0.886	0.027	0.377	0.145–0.980	0.045
4	23	Reference	.	.	Reference	-	-
Bridging	137	1.260	0.831–1.910	0.276	-	-	-
General anesthesia	104	0.772	0.501–1.188	0.239	-	-	-
Onset-to-groin time >205 min	107	0.654	0.426–1.003	0.051	-	-	NS
Additional IA fibrinolysis	31	1.294	0.669–2.501	0.444	-	-	-
Onset-to-end procedure time >273 min	215	0.432	0.282–0.661	<0.001	-	-	NS
TICI 2b/3	210	2.978	1.788–4.961	<0.001	2.782	1.405–5.506	0.003
TICI 3	161	1.896	1.236–2.908	0.003	-	-	NS
Radiological complications							
Distal embolization	28	0.950	0.469–1.924	0.887	-	-	-
Asymptomatic ICH	70	0.449	0.281–0.716	0.001	0.389	0.237–0.638	0.001
Symptomatic ICH	17	0.079	0.028–0.218	<0.001	0.064	0.021–0.190	<0.001

Age and NIHSS score were categorized according to Supplementary Appendix of the DIRECT-MT trial; pre-stroke mRS score, ASPECT score, stroke onset-to-groin time, and stroke onset-to-end procedure time were categorized according to median values reported from the DIRECT-MT cohort.

[a]ORs with 95% CIs were calculated after a first multivariate ordinal regression including clinical variables with a probability value <0.10 in the univariate model and after a second multivariate ordinal regression including radiological variables.

[b]ORs with 95% CIs of CCS were calculated after repeating the multivariate ordinal regression including radiological predictors obtained from the univariate ordinal regression.

groups (33.3% for MT alone and 36.2% for bridging) deserves a particular consideration to explain why the overall percentage of DIRECT-MT patients with a favorable outcome was modest. A recent study reported that, after endovascular treatment, patients with asymptomatic ICH according to the Heidelberg criteria had a lower ratio of independent outcome than without ICH; poor collateral status was a strong independent predictor for asymptomatic ICH.[12] In this regard, the DEVT trial recently confirmed how the highest rate of asymptomatic ICH according to to the Heidelberg criteria could have penalized the 3-month mRS score after bridging compared to MT alone (25.6% vs. 15.7%).[3] However, it's unclear why the rate of asymptomatic ICH was unusually lower in DEVT patients treated with MT alone compared with the IRETAS and DIRECT-MT cohorts, despite off-labe use of intra-arterial tirofiban in 16.4% of patients.[3] Future studies will be needed to better understand the underlying mechanisms.

Our study shows that a better circulation collateral status assessed by CCS improved the 3-month mRS score. This finding is consistent with what reported by previous studies.[13–14] Interestingly, the rate of good collaterals in DIRECT-MT cohort was

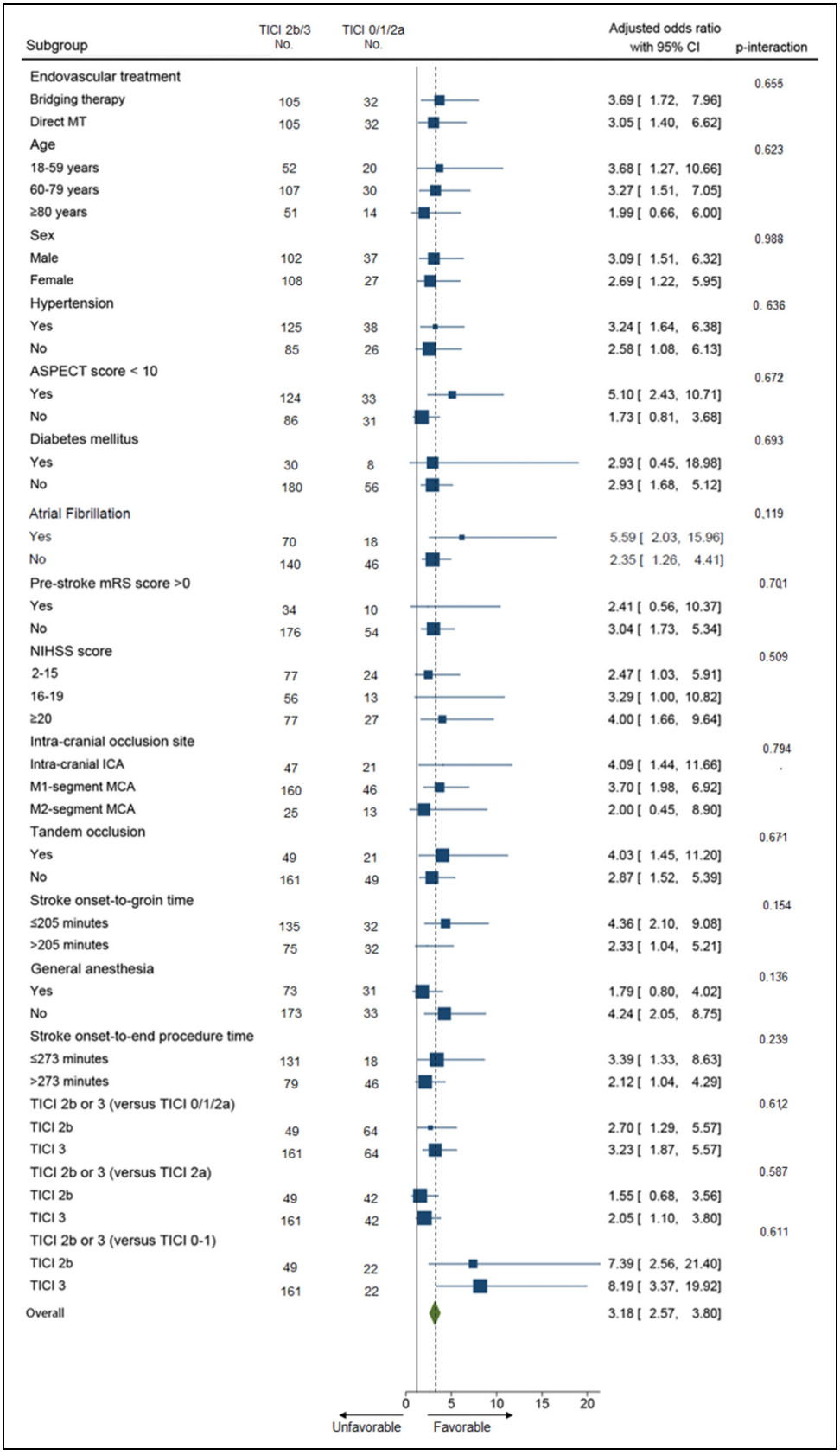

Figure 2. Forest plot showing adjusted effect of successful recanalization for mRS shift (from 6 to 0) at 3 months in subgroup with p values for heterogeneity across different variables.

significantly lower than in the IRETAS cohort (CS 2–3, 23% vs. CCS 2–4, 69.4%) and was also unsually low in comparison with the results of previous trials.[4] This is crucial to explain why the overall percentage of DIRECT-MT patients with 3-month functional independence was modest.

Forest plot shows that benefit from successful recanalization was observed across all baseline subgroups of the IRETAS patients. Similar effects were found along different endovascular treatments (bridging and MT alone). Although no statistical heterogeneity was found in successful recanalization effect, our analysis does not have power to fully confirm clinical benefit in some patient subgroups including age ≥80 years, pre-stroke mRS score >0, diabetes mellitus, ASPECT score <10, general anesthesia, M2-segment MCA occlusion, and TICI 2b versus TICI 2a. The greatest benefit from successful recanalization was observed in patients with most severe strokes (NIHSS ≥20: OR 4.002; NIHSS 16 to 19: OR 3.292; NIHSS 2 to 5: OR 2.470) and most proximal occlusion site (intracranial ICA: OR 4.092; M1-MCA: OR 3.705; M2-MCA: OR 2.001), in younger patients (18 to 59 years: OR 3.677; 60 to 79 years: 3.267; ≥80 years: OR 1.993), in patients who started the treatment earlier (onset-to-groin puncture time ≤205 min: OR 4.361; onset-to-groin time puncture >205 min: OR 2.326) and ended the treatment earlier (onset-to-end procedure time ≤273 min: OR 3.394; onset-to-end procedure time >273 min: OR 2.116), and in patients with atrial fibrillation (presence: OR 5.696; absence: OR 2.354).

As well as the clinical benefit from endovascular treatments over standard medical care was lower in some subgroups of patients included in previous trials,[6] our study shows that the benefit from successful recanalization after bridging or MT alone for 3-month mRS shift in the direction of favorable outcome was lower in several patient subgroups. Thus, this might explain why the increased rate of successful recanalization from bridging over MT alone did not translate into clinical benefits on 3-month mRS shift in the DIRECT-MT trial, if a significant proportion of successful recanalization occurred in those subgroups with unfavorable charcteristics. The same reason could explain why similar rates of successful recanalization between bridging and MT alone were associated with different proportion of 3-month functional independence in the DEVT trial[3] and in the DIRECT-SAFE trial,[4] and why different rates of successful recanalization between the two groups were associated with no differences in 3-month mRS shift in the MR CLEAN-NO IV trial[2] and in the SWIFT-DIRECT trial.[5]

Since successful recanalization remains the therapeutic mechanism behind clinical benefit, our study shows that the inclusion of patients with different clinical benefit from successful recanalization is crucial when primary analysis asses the between group difference in the distribution of the 3-month mRS scores.

We are aware that our study has several limitations. First, the present study did not randomize patients by treatment, but it is based on a retrospective analysis of prospectively collected data. However, all analyzes were conducted on the IRETAS cohort identified after propensity score matching of patients receiving and MT alone. Second, lack of systematic data collection of CCS remains the main limitation of the present study. Third, a direct comparison for successful recanalization was not possibile due to use of different classification systems to define the degree of revascularization in DIRECT-MT and IRETAS cohorts. Fourth, stroke onset-to-needle time for IVT was not available; however, all patients started the endovascular procedure ≤4.5 h of stroke onset and occlusion site was assessed on baseline angiogram. Lastly, aspiration alone was often used in our cohort, whereas aspiration devices were used only as a secondary option in the DIRECT-MT trial.

Conclusions

Among unfavorable predictors for 3-month mRS score in the IRETAS cohort, diabetes mellitus, asymptomatic ICH according to the Heidelberg criteria, and poor collateral circulation were more frequent in the DIRECT-MT, whereas age ≥80 years and pre-stroke mRS score >0 were more often observed in the IRETAS cohort. In the IRETAS cohort, the benefit from successful recanalization for 3-month mRS shift in the direction of favorable outcome was lower in several patient subgroups.

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Authors' contributions

Manuel Cappellari: concept and design of the study, acquisition of data, analysis and interpretation of data, and drafting the manuscript for intellectual content. All authors: acquisition of data, interpretation of data, revising the manuscript for intellectual content.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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