Endovascular treatment improves cognition after stroke. A secondary analysis of REVASCAT trial

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Endovascular treatment improves cognitive function after ischemic stroke. A secondary analysis of REVASCAT trial

Abstract

Objective: We aimed to investigate the effect of endovascular treatment on cognitive function as a pre-specified secondary analysis of the REVASCAT trial. **Methods:** REVASCAT (NCT01692379) randomized 206 patients with anterior circulation proximal arterial occlusion stroke to Solitaire® thrombectomy or best medical treatment alone. Patients with established dementia were excluded from enrollment. Cognitive function was assessed in person with Trail Making Test (TMT) parts A and B at three months and one year after randomization, by an investigator masked to treatment allocation. Test completion within 5 minutes, time of completion(seconds)and number of errors were recorded. **Results:** From November 2012 to December 2014, 206 patients were enrolled in REVASCAT trial. TMT was assessed in 82/84 thrombectomy and in 86/87 control patients alive at three months and in 71/79 thrombectomy and in 72/78 control patients alive at one year. Rates of timely TMT-A completion were similar in both treatment arms although thrombectomy patients required less time for TMT-A completion and had higher rates of error-free TMT-A performance; thrombectomy was also associated with higher probability of timely TMT-B completion (adjusted OR, 95% CI; 3·17[1·51, 6·66] at three months and 3·66[1·60-8·35] at one year) and shorter time for TMT-B completion. Differences in TMT completion times among treatment arms were significant in patients with good functional outcome, but not in those functionally dependent (modified Rankin Scale>2). Poorer cognitive outcomes were significantly associated with larger infarct volume, higher modified Rankin scores and worse quality of life. **Conclusions**: Thrombectomy improves TMT performance after stroke, especially among patients who reach good functional recovery. **Classification of Evidence**: This study provides Class I evidence that for patients with stroke from acute anterior circulation proximal arterial occlusion, thrombectomy improves performance on the Trail Making Test at 3 months.

Introduction:

Cognitive impairment is a common consequence of stroke, [1ï3]even in survivors with successful functional recovery,[4] and it is closely related to disability and dependency. [2] Cognitive impairment and dementia following stroke may involve multiple domains, attention and executive functioning being particularly affected.[1, 3]Altered executive functioning early after stroke has been reported as a predictor of long-term cognitive impairment. [5]

Because cognitive outcome has traditionally not been considered as outcome measure in randomized trials investigating the benefit of intravenous t-PA in acute stroke, little knowledge exists with regards to any potential benefit intravenous t-PA may have on cognition. In a recent post-hoc analysis based on pooled data from the VISTA trials, Cog-4 scale (based on four items of NIH stroke scale) was used as an indicator of cognitive function at three months after stroke. It was noted that the distribution of Cog-4 scores was better in patients who received intravenous rTPA compared to those that were not thrombolysed, although this scale did not provide additional information beyond the modified Rankin Scale (mRS) assessment. [6]

Endovascular treatment has recently demonstrated benefit in physical disability and functional outcome after acute stroke [7] but the effect on cognitive outcomes has not been established yet. REVASCAT (RandomizEd trial of reVasculArization with SOLITAIRE FR® device (Covidien-Medtronic, Minneapolis, USA) versus best mediCal therapy in the treatment of Acute stroke due to anTerior circulation large vessel occlusion presenting within eight-hours of symptom onset) randomized acute stroke patients either to medical therapy plus endovascular treatment thrombectomy or to medical treatment alone. Analysis of the third month primary outcome consisting of ordinal mRS score analysis revealed that thrombectomy was beneficial.[8]

A pre-specified secondary outcome of REVASCAT [9] was to evaluate the effect of endovascular treatment on cognitive functioning at three months and one year after stroke as measured by the Trail Making Test. We also aimed to study the relationship among cognitive outcomes and other stroke relevant outcomes (infarct volume, mRS and health-related quality of life). In order to assess if the influence of endovascular treatment on Trail Making Test performance was relevant beyond physical disability, as a post-hoc analysis, cognitive outcome was evaluated separately in patients with good/poor functional outcome (mRSÒ2/>2).

Methods:

Primary research question: Does thrombectomy improve Trail Making Test performance at 3 months after acute ischemic stroke due to an anterior large vessel occlusion?. **Classification of Evidence**: This randomized interventional study provides Class I evidence that for patients with stroke from acute anterior circulation proximal arterial occlusion, thrombectomy improves performance on the Trail Making Test at 3 months, when compared to best medical treatment alone. From November 2012 to December 2014, REVASCAT enrolled 206 patients with stroke of anterior circulation within 8 hours from onset that were randomized to receive thrombectomy (with Solitaire® device, Medtronic,) or best medical treatment (both including intravenous rTPA). The trial was conducted in four comprehensive stroke centers of Catalonia, Spain. Patients with established dementia were excluded from enrollment. Detailed protocol and main results have been previously published. [8, 9] The trial was registered at Clinicaltrials.gov (NCT01692379) and funded by an unrestricted grant from the manufacturer of the device (Covidien, now Medtronic). Primary outcome of REVASCAT trial was distribution of functional outcome expressed as modified Rankin

scale (mRS) at 90 days. A pre-specified secondary objective was to test thrombectomy effects on cognitive function at three months and one year after randomization [9]. Cognitive function was assessed in person by an investigator masked to treatment arm using Trail Making test (TMT) parts A and B. TMT measures attention, processing speed, working memory, visuospatial ability and set shifting [10]. TMT-A requires the patient to draw lines sequentially connecting 25 encircled numbers distributed on a sheet paper. In TMT-B the patient must alternate between numbers and letters (e.g., 1-A-2-B-3-Cé L-13). Before each test trial, a practice trial of six items was administered to ensure task understanding. Tests must be completed in a maximum of 5 minutes. During performance, each error was immediately corrected by the examiner and the patient was asked to continue the task. For each TMT-A and TMT-B cognitive outcome was evaluated by means of: 1) Percentage of patients that completed the tests in the requested time (5 minutes); 2) Time of completion of each test (in seconds); and 3) Number of errors made (none versus one or more errors).

Infarct volumes (ml) at 24 hours on CT or MRI were adjudicated blinded to clinical data by an independent imaging core lab [8]. Functional ability and health-related quality of life were evaluated at three months and one year after enrollment by masked certified assessors using mRS and EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) 3L, respectively. EQ-5D was analyzed using utility index adapted to Spanish population (range -0·3 to 1) and visual analogue scale (range 0 to 100), with higher values corresponding to better quality of life. Language impairment and right upper limb paresis were evaluated with the specific NIH stroke scale items at three months after stroke. This specific data was not available at 1 year.

Standard Protocol Approvals, Registrations, and Patient Consents: REVASCAT trial received approval from ethical committees on human experimentation at the four

recruiting centers; written informed consent was obtained from all patients (or relatives) participating in the study; REVASCAT trial was registered at Clinicaltrials.gov (NCT01692379).

Statistical analysis

Main analyses were in the complete case population. The primary objective was to evaluate the effect of treatment arm on executive cognitive outcome at three months and one year after randomization. Differences in TMT completion on requested time (yes versus no) and presence of errors (0 versus Ó1) among treatment arms were assessed using logistic regression models, expressing the effect as odds ratio and 95% confident interval (CI). Difference in times of completion of TMT (seconds) among treatment arms was assessed using multivariate linear regression models, expressing the effect as the mean difference (B coefficient and 95% CI for B). To avoid missing data, maximum time of completion (300 seconds) was considered in those patients who could not complete the tests in the requested time. Multivariable analyses were adjusted by treatment arm, age, baseline stroke severity (NIHSS) and side of stroke. Association of Trail Making Test performance (completion times) with other outcome measures (infarct volume, mRS, EQ-5D) was assessed using Spearman Correlation coefficients.

In order to assess if the influence of endovascular treatment on Trail Making Test performance was relevant beyond physical disability, differences in time of completion of TMT among treatment arms were evaluated separately in patients with mRS Ò2 and those with mRS >2. In this stratified analysis, differences were assessed using linear regression analysis.

Results

Executive cognitive function was assessed in 82/84 thrombectomy and in 86/87 control patients alive at three months and in 71/79 thrombectomy and in 72/78 control patients alive at one year (see flow diagram on Figure 1). The percentage of patients that was able to complete TMT-A in due time (five minutes) was similar among treatment arms but thrombectomy increased around three folds the odds of timely TMT-B completion at three months and at one year after stroke (Table 1). Furthermore, patients assigned to thrombectomy required less time for tests completion and made fewer errors on TMT-A compared to those on medical arm (Table 1).

Longer times to complete TMT were significantly associated with larger infarct volume, higher mRS scores and worse quality of life (Table 2).

Among those patients who reached functional independency at three months (mRS Ò2), all except one completed TMT-A in the requested time in both treatment arms. TMT-B was completed in due time by around 69% of patients in thrombectomy arm and only in 48% of patients in best medical treatment (Table 3). Differences in TMT completion times in favor of endovascular treatment were only significant in those patients who achieved a good functional outcome (mRSÒ2) (Table 3 and Figure 2) and remained significant after adjustment for aphasic symptoms and paresis of right upper limb (among patients with a mRSÒ2 at 3 months, only 9 had aphasic symptoms and only one patient had right hand paresis).

Discussion

Our study demonstrates that in patients with acute stroke due to a proximal large vessel occlusion, treatment with thrombectomy improves Trail Making Test performance, a measure of cognitive functioning, at three months and one year after stroke. These findings are important because they demonstrate that the benefit derived from

thrombectomy, only shown so far to affect disability and health related quality of life, also encompasses the cognitive domain.

Because executive dysfunction is frequently found after stroke,[1] we decided to evaluate this specific cognitive domain in REVASCAT. Trail Making Test is one of the most commonly used neuropsychological tests; it is easy and fast to administer and measures multiple executive functions simultaneously: attention, processing speed, set shifting, visuospatial ability and working memory.[10] We found that the proportion of patients able to complete part A was similar among treatment arms, although patients treated with thrombectomy were less prone to make errors than control patients in this specific test and required shorter times for completion. These findings suggest less pronounced differences in processing speed and more substantial differences in attention and visuospatial abilities between thrombectomy patients and those patients assigned to medical treatment. Furthermore, thrombectomy also improves the completion of part B on requested time, a more complex task related to cognitive flexibility.[11] Regarding time employed to complete the tests, linear regression analyses revealed significant differences in favor of thrombectomy in both tests. It is important to note that in our study, percentage of completion of part B in the requested time was low, so a high proportion of patients received the maximum time score (300 seconds). Although this is a usual practice in administering Trail Making test, it masks performance variability among severely impaired patients who cannot complete the task. Therefore, some authors have tried to find scores that take into account not only time but also errors and correct moves.[12] Because errors and moves were not collected in those patients who did not complete the test in the required time we were not able to investigate this aspect of cognitive performance which should be incorporated in future trials assessing the effect of reperfusion on the Trail Making Test.

In line with previous reports, we found that infarct volume was negatively correlated with executive functioning.[13] Other relevant stroke outcome measures were significantly and directly correlated with poor cognitive status, such as health-related quality of life and disability status.

In the stratified analysis by functional independence status, differences in TMT performance among treatment arms were only significant in those patients functionally independent (mRS Ò2). These findings may therefore justify the evaluation of cognitive outcomes in future stroke trials as it seems to provide relevant information beyond the widely used modified Rankin scale.

There are several limitations to this study. First of all, sample size is smaller than projected because REVASCAT trial was stopped after first interim analysis, and the present study may be underpowered. Although established dementia was an exclusion criterion for enrollment in REVASCAT (because patients enrolled had to score 0 to 1 in mRS), we do not have precise information on pre-stroke cognitive functioning of included patients; therefore we cannot assure that the only factor influencing TMT performance was stroke itself. Analyses were adjusted for other co-variates that may influence understanding and ability to perform cognitive tasks (e.g age, stroke severity and side of stroke). However, data on education level, a factor known to significantly affect cognitive function, was not collected. We do not believe that this limitation may alter conclusions since education level accounted only for 3% and 6% of the variance of TMA and TMB in a sample of 911 healthy volunteers.[14] Also, symptoms of depression/anxiety were only collected indirectly by EQ-5D and not included in multivariable models. Although we cannot assure the correct balance of pre-stroke cognitive status, educational level or depressive symptoms among treatment arms, the randomized nature of REVASCAT trial makes it at least possible. Finally, cognitive

outcome was evaluated only with two cognitive tests focused on executive functioning and therefore we cannot draw conclusions regarding other cognitive domains; we chose the Trail Making Test to evaluate cognition in REVASCAT due to its simplicity in administration and its established correlation with multiple cognitive dimensions. Furthermore, consensus regarding optimal measurement tools for post-stroke cognitive impairment is lacking. Major strengths of this study include its prospective nature, the randomized cohort of patients studied and the high rate of patients available for follow-up.

Sources of funding

REVASCAT was funded by a local independent Catalan institution (Fundació Ictus Malaltia Vascular, www.fundacioictus.com/es) by means of an unrestricted grant from the manufacturer of the device (Covidien, now Medtronic), who was not involved in the conduct, analysis or report of the trial. This project has been partially supported by a grant from the Spanish Ministry of Health co-financed by FEDER (Instituto de Salud Carlos III, RETICS-INVICTUS, RD 12/0014/008) as well as grant from the Generalitat de Catalunya (SGR 464/2014) to the GRBIO group.

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Figure legends:

Figure 1:
Title: CONSORT flow diagram of patients included in REVASCAT trial
Legend: The diagram shows patient allocation, deaths and missings for cognitive evaluation in each treatment arm and at both times of follow-up (three and 12 months after randomization)

Figure 2:
Title: TMT-A and TMT-B completion times stratified by functional outcome (mRSÒ2 and >2) in both treatment arms.
Legend: Vertical axis represents completion times (seconds). Arrows and lines represent mean and 95% CI of the mean. Grey arrows=endovascular treatment (EVT) and white arrows=best medical treatment (BMT). 3m=3 months; 1y= 1 year. P represents unadjusted mean difference (linear regression analysis) between treatment arms.

Figure 1:

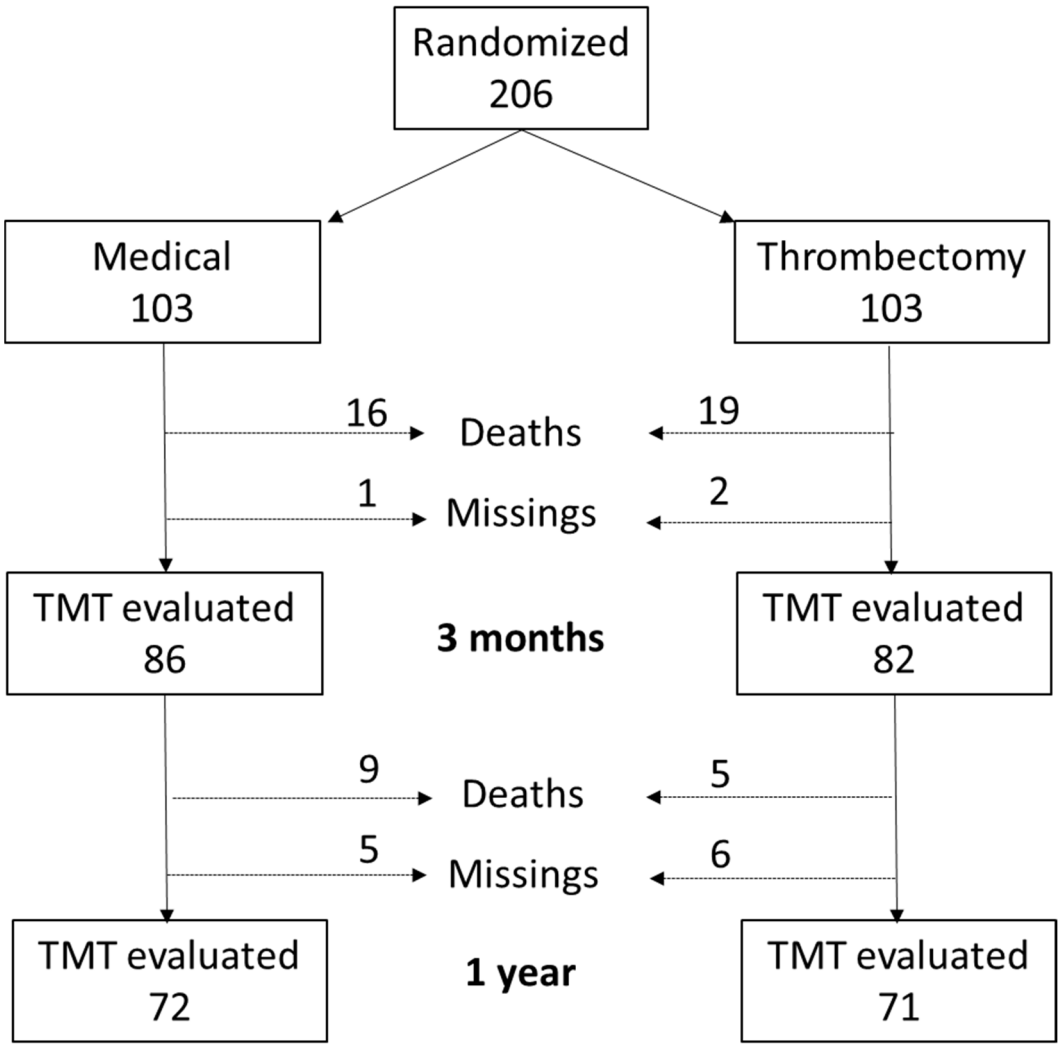
Randomized
206
Medical
103
Thrombectomy
103
16
Deaths
19
1
Missings
2
TMT evaluated
86
3 months
TMT evaluated
82
9
Deaths
5
5
Missings
6
TMT evaluated
72
1 year
TMT evaluated
71

Figure 2:

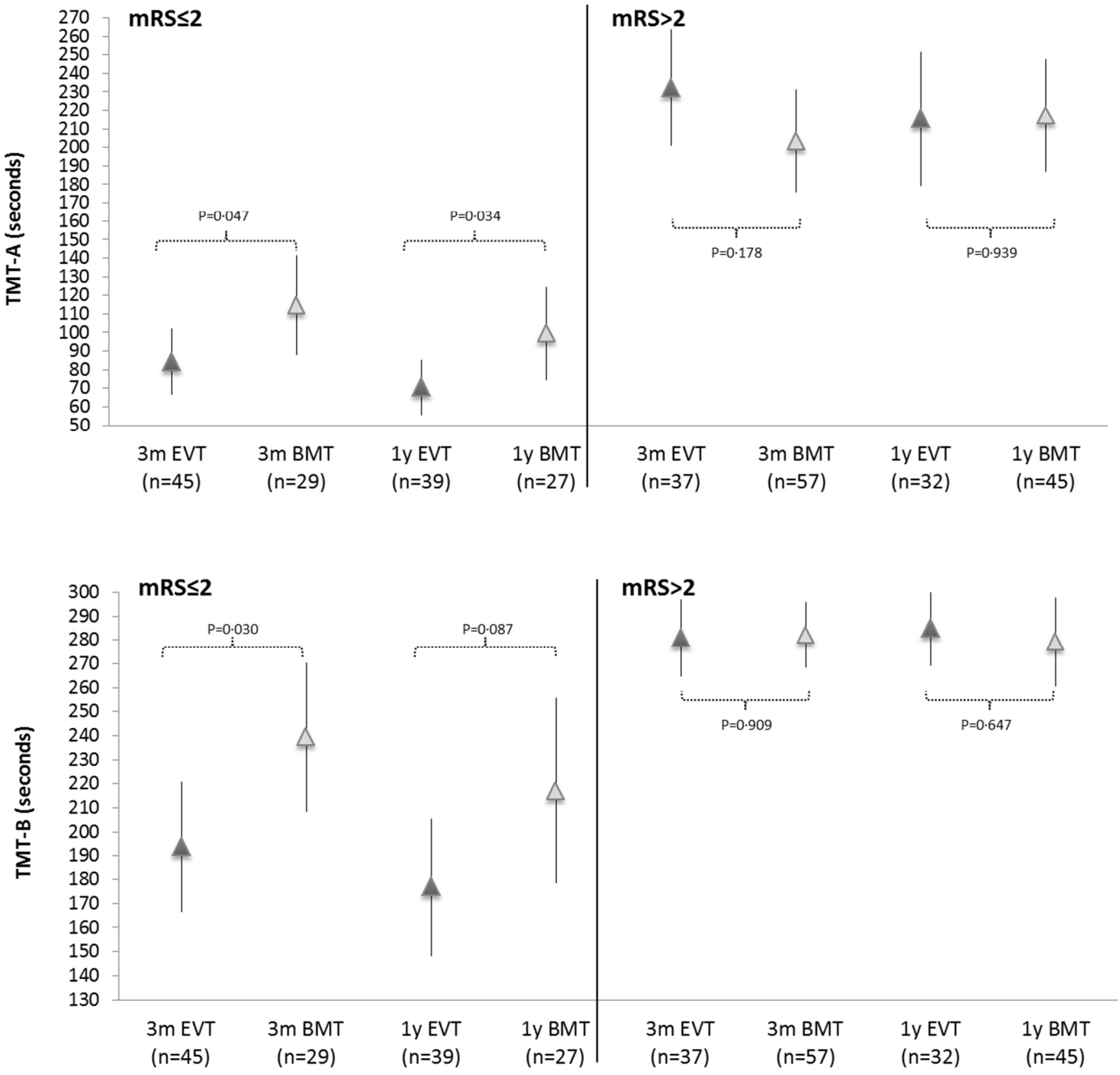
mRS≤2
mRS>2
TMT-A (seconds)
270
260
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
P=0·047
P=0·034
P=0·178
P=0·939
3m EVT (n=45)
3m BMT (n=29)
1y EVT (n=39)
1y BMT (n=27)
3m EVT (n=37)
3m BMT (n=57)
1y EVT (n=32)
1y BMT (n=45)
mRS≤2
mRS>2
TMT-B (seconds)
300
290
280
270
260
250
240
230
220
210
200
190
180
170
160
150
140
130
P=0·030
P=0·087
P=0·909
P=0·647
3m EVT (n=45)
3m BMT (n=29)
1y EVT (n=39)
1y BMT (n=27)
3m EVT (n=37)
3m BMT (n=57)
1y EVT (n=32)
1y BMT (n=45)

Table 1. Cognitive outcomes in each treatment arm

	EVT+BMT	BMT alone	Effect measure	Unadjusted value [95% CI]	Adjusted value [95% CI] [1]
TMT-A 3 months (N)	82	86			
Completion on due time, n(%)	60 (73·2)	58 (67·4)	Odds ratio	1·32[0·68,2·56]	1·48[0·71,3·11]
Without errors, n(%)	47 (78·3)	34 (58·6)	Odds ratio	2·55[1·14,5·71]	2·45[1·05,5·70]
Time of completion (raw)	96·5±65·0	112·7±63·7	Mean diff	16·2[-7·3,39·7]	15·6[-6·3,37·6]
Time of completion (imputed)	151·1±106·3	173·7±102·5	Mean diff	22·6 [-9·2, 54·4]	21·0 [-6·1,48·1]
TMT-A 1 year (N)	71	72			
Completion on due time, n(%)	54 (76·0)	48 (66·7)	Odds ratio	1·59[0·76,3·30]	2·00[0·87,4·61]
Without errors, n(%)	44 (81·5)	30 (62·5)	Odds ratio	2·64[1·07,6·50]	3·50[1·25,9·77]
Time of completion (raw)	84·2±54·5	109·7±66·3	Mean diff	23·3 [0·4, 46·1]	23·4 [1·1, 45·8]
Time of completion (imputed)	135·9±104·1	173·1±105·2	Mean diff	37·2 [2·6,71·8]	35·3 [4·5, 66·2]
TMT-B 3 months (N)	82	86			
Completion on due time, n(%)	38 (46·3)	22 (25·6)	Odds ratio	2·51[1·31,4·81]	3·17[1·51,6·66]
Without errors, n(%)	15 (39·5)	8 (36·4)	Odds ratio	1·14[0·39,3·38]	1·05[0·33,3·38]
Time of completion (raw)	155·6±68·7	173·9±71·7	Mean diff	18·3[-19·1,55·7]	22·9[-12·0,58·9]
Time of completion (imputed)	233·1±86·0	267·7±65·8	Mean diff	34·6 [11·4,57·9]	32·1[11·9,52·3]
TMT-B 1 year (N)	71	72			
Completion on due time, n(%)	36 (50·7)	19 (26·4)	Odds ratio	2·87[1·42,5·78]	3·66[1·60,8·35]
Without errors, n(%)	17 (47·2)	8 (42·1)	Odds ratio	1·23[0·40,3·78]	0·93[0·28,3·09]
Time of completion (raw)	153·4±71·4	132·9±70·3	Mean diff	-20·5[-60·9,19·9]	-18·0[-59·9,23·8]
Time of completion (imputed)	225·6±89·5	255·9±82·2	Mean diff	30·2[1·9,58·6]	30·3[4·0,56·6]

EVT: endovascular treatment. BMT: best medical treatment. TMT=Trail Making Test. Completion on due time refers to those that completed the test in less than 5 minutes. Time of completion is shown in seconds. Imputed times (300 sec) in those patients not able to complete the tests in requested time. Values are expressed as number (percentage), and mean±standard deviation. [1]Adjusted by age, affected hemisphere and baseline stroke severity (NIHSS).

Table 2. Spearman Correlation coefficients between TMT performance (completion times) and other outcome measures: infarct volume, functional outcome (mRS) and health-related quality of life (EQ-5D)

	TMT-A 3m (n=168)	TMT-A 1y (n=143)	TMT-B 3m (n=168)	TMT-B 1y (n=143)
Infarct Volume (ml)	0·24 (0·002)	0·31 (<0·001)	0·35(<0·001)	0·29(<0·001)
mRS	0·56 (<0·001)	0·60(<0·001)	0·53(<0·001)	0·51(<0·001)
EQ-5D (VAS)	-0·25(0·003)	-0·32(0·001)	-0·25(0·003)	-0·17(0·074)
EQ-5D (UI)	-0·50(<0·001)	-0·57(<0·001)	-0·48(<0·001)	-0·47(<0·001)

Values are expressed as Spearman correlation coefficients (p). TMT=Trail Making Tests. 3m=3 months. 1y=1 year. Imputed values for completion times of TMT were used to avoid missing data in those participants that did not completed the tests on requested time. EQ-5D: EuroQoL Group 5-Dimension Self-Report Questionnaire 3L. VAS: visual analogue scale. UI: utility index. mRS: modified Rankin Scale score

Table 3. TMT performance in each treatment arm stratified by functional outcome (mRSÒ2 and >2)

	Functionally independent (mRSÒ2)			Functionally dependent (mRS>2)		
	EVT+BMT	**BMT alone**	**Effect**	**SEVT+BMT**	**BMT alone**	**Effect**
TMT-A 3 months (N)	45	29		37	57	
Completion on due time,n(%)	44 (98·7)	29 (100)		16(43·2)	29(50·9)	
Time of completion (sec±SD)	84·3±59·0	114·8±69·8	30·5[0·4,60·6], 0·047	232·3±93·9	203·6±104·0	-28·7[-70·7,13·3] 0·178
TMT-A 1 year (N)	39	27		32	45	
Completion on due time,n(%)	39 (100)	27 (100)		15 (46·9)	21(46·7)	
Time of completion (sec±SD)	70·6±45·5	99·5±62·7	28·9[2·3,55·5], 0·034	215·5±100·2	217·3±101·1	1·8[-44·6,48·2], 0·939
TMT-B 3 months (N)	45	29		37	57	
Completion on due time,n(%)	31 (68·9)	14 (48·3)		7(18·9)	8(14)	
Time of completion (sec±SD)	193·8±90·6	239·5±81·2	45·7[4·4,87·1], 0·030	280·9±48·5	282·1±51·5	1·2[-19·9,22·3], 0·909
TMT-B 1 year (N)	39	27		32	45	
Completion on due time,n(%)	30 (76·9)	13 (48·1)		6 (18·8)	6 (13·1)	
Time of completion (sec±SD)	176·9±88·3	217·1±97·7	40·2[-6·0,86·3], 0·087	285·0±43·3	279·2±61·4	-5·8[-31,19·3], 0·647

EVT: endovascular treatment. BMT: best medical treatment. Effect is expressed as Mean Difference between treatment arms [95% CI] for completion times. Time of completion (sec=seconds, SD=standard deviation), using imputed values (300 sec) for those that were not able to complete the test on requested time.