Chapter 4.3

Efficacy of early cognitive-linguistic treatment for aphasia due to stroke; a randomized controlled trial (Rotterdam Aphasia Therapy Study – 3)

Nouwens F, Lau LML, Visch-Brink EG, van de Sandt-Koenderman WME, Lingsma HF, Goosen S, Blom DMJ, Koudstaal PJ, Dippel DWJ, on behalf of the RATS-3 investigators (Appendix I).
European Stroke Journal. March 10th 2017, DOI: 10.1177/2396987317698327.

ABSTRACT

Background

One third of patients with acute stroke have aphasia. The majority receive speech and language therapy (SLT). There is evidence for a beneficial effect of SLT on restoring communication, but it is unknown whether and how efficacy of SLT is influenced by timing of treatment. We studied whether SLT early after stroke by way of intensive cognitive-linguistic treatment (CLT) is more effective than no SLT in the Rotterdam Aphasia Therapy Study (RATS) – 3, a multicenter randomized single-blind trial.

Methods

Stroke patients with first-ever aphasia were randomized within two weeks of onset to either four weeks of early intensive CLT (one hour/day) or no language treatment. Hereafter, both groups received regular SLT. Primary outcome was the score on the Amsterdam-Nijmegen Everyday Language Test (ANELT), measuring everyday verbal communication, four weeks after randomization. Secondary outcomes were ANELT at three and six months. The study was powered to detect a clinically relevant difference of four points on the ANELT.

Results

Of the 152 included patients, 80 patients were allocated to intervention. Median treatment intensity in the intervention group was 24.5 hours. The adjusted difference between groups in mean ANELT scores four weeks after randomization was 0.39, 95% CI: -2.70 to 3.47, $p = 0.81$. No statistically significant differences were found at three and six months after randomization either.

Conclusion

Four weeks of intensive CLT initiated within two weeks of stroke is not more effective than no language treatment for the recovery of aphasia due to stroke. Our results exclude a clinically relevant effect of very early CLT on everyday language.

INTRODUCTION

Aphasia occurs in about one third of stroke patients and has severe consequences for verbal communication and quality of life.[1, 2] Several randomized controlled trials (RCT) have reported a benefit of speech and language therapy (SLT) over no treatment for patients with aphasia due to stroke.[3] Hence, most patients receive SLT as part of their rehabilitation program.

The relationship between timing of SLT, i.e. the interval between stroke onset and start of treatment, and its efficacy is unclear.[4] In a meta-analysis comparing studies with different starting points of SLT, the average effect size in studies evaluating treatment initiated in the first three months after stroke was larger than that in studies performed in a later stage.[5] However, this analysis was mainly based on uncontrolled and non-randomized studies. The efficacy of early initiated SLT has been studied in four trials with contradictory findings; two large studies were neutral, but two smaller studies suggested an effect of early treatment.[6-9] The need for more research on the effect of timing of SLT was explicitly accentuated in a Cochrane review on efficacy of SLT for aphasia due to stroke.[10]

In the early phase after stroke, impairment-based cognitive-linguistic treatment (CLT) is often preferred over other types of SLT, as it targets specific linguistic functions, supposedly stimulating functional neural networks.[11-13] As most recovery occurs within the first three months after stroke,[5, 14-16] standard practice early after stroke often comprises CLT.[17] When linguistic performance reaches a plateau, SLT may be continued with compensatory treatment instead of CLT.

There is some evidence suggesting that high-intensity treatment may be more effective than less frequent therapy.[3, 18, 19] However, the feasibility of high-intensity treatment is questionable, as in several trials compliance with treatment was significantly lower in intervention groups with intensive language treatment.[3]

Experts in language rehabilitation suggest a best practice regimen of early initiated intensive CLT.[13, 17] Scientific evidence underpinning this recommendation is frail. The objective of the Rotterdam Aphasia Therapy Study (RATS) – 3 was to study whether early intensive CLT for four weeks is more effective than no language treatment in the first four to six weeks after stroke, and whether this approach generates a long-lasting benefit.

METHODS

Essential elements of the study design are described below. Detailed methods were published elsewhere.[20] RATS-3 is a prospective multicenter controlled clinical trial with randomized treatment allocation, open label treatment and blinded evaluation of the primary outcome measure (PROBE design).[21] Thus, after randomization both patients and therapists were aware of the allocated treatment. Fourteen regional networks for integrated stroke care comprising a total of 23 hospitals and 66 rehabilitation facilities across the Netherlands participated (Appendix I). Within two weeks of stroke onset, patients were randomized to four weeks of either intensive CLT or no language treatment. After the four weeks, both groups received regular SLT.

The study protocol was approved by the Medical Ethical Committee of the Erasmus MC (MEC-2005-347) and the study was registered in the Netherlands Trial Register (NTR3271).

Participants

Speech and language therapists (SL-therapists) from participating centers checked eligibility criteria (Table 1) and requested informed consent from patients and/or their proxy. Information about RATS-3 was provided to patients and their relatives orally and on paper, including simplified information leaflets adapted to people with aphasia.

Patients who were not eligible or who did not consent to participation were not registered.

Table 1. Eligibility criteria for RATS-3

Inclusion criteria:	
1.	Aphasia after stroke, diagnosed by a neurologist or rehabilitation physician and SL-therapist
2.	Aphasia ascertained with shortened Token Test (score<29) or Aphasia Severity Rating Scale (score<5)
3.	Testable with ScreeLing
4.	Treatment can be started within two weeks after stroke onset
5.	Age 18-85 years
6.	Language near-native Dutch
7.	Life expectancy of more than six months
Exclusion criteria:	
1.	Pre-existing aphasia
2.	Subarachnoid/subdural hemorrhage/hematoma
3.	Language therapy is not feasible because of:
	▸ Severe dysarthria
	▸ Premorbid dementia
	▸ Illiteracy
	▸ Severe developmental dyslexia
	▸ Severe visual perceptual disorders
	▸ Recent psychiatric history

Randomization

The trial coordinator verified inclusion criteria and, after written informed consent was obtained, included and randomized participants within two weeks of stroke onset. Independent trial assistants concealed computer-generated allocation sequences in consecutively numbered, opaque, sealed envelopes. Randomization was stratified according to baseline aphasia severity (Aphasia Severity Rating Scale: ASRS score 0 to 2 = severe; ASRS score 3 to 4 = moderate/mild) and including center.

Baseline tests

At baseline, a short test battery was conducted including the ScreeLing, the 36-item Token Test and a semi-standardized interview for eliciting spontaneous speech, which was rated with the ASRS.[20] An experienced SL-therapist blinded to treatment allocation classified the

spontaneous speech samples as fluent or non-fluent. Baseline characteristics and the Barthel Index were recorded, as well as treatment with intravenous alteplase, as this is associated with rapid recovery from stroke.[22]

Intervention

Patients in the intervention group were to receive at least one hour of CLT every day of the week for a period of four weeks. The hour of treatment could be delivered in more than one session per day, if preferable. We chose an intervention period of four weeks for three reasons. First, intervention in the control group had to reflect usual care in the Netherlands, where SLT for aphasia starts on average three to six weeks after onset. Second, we specifically aimed to study the effect of early initiated treatment. With a maximal inclusion period of two weeks and a four-week intervention period this early phase was not exceeded. Lastly, we expected that a longer intervention with high intensity would be too burdensome for many patients.

Treatment was directed at semantics using the therapy program BOX[23] and/or phonology using the therapy program FIKS[24], to improve word finding deficits. Participating SL-therapists had ample experience in using both Dutch therapy programs and carefully selected exercises for face-to-face treatment and homework, registered as part of the total amount of treatment provided. Treatment could be delivered at the local treatment facility or at home, whatever was most convenient for patients.

The control group received no language treatment during the first four weeks after randomization. Minimal counseling was allowed, aimed at preventing communication problems and included elaborate information about aphasia and providing communication advice. Concise diagnostics for therapy goal setting was allowed also.

The trial coordinator had at least two-weekly contact with the SL-therapists to ensure no treatment was provided in the control group and to monitor compliance in the intervention group. After four weeks, further SLT was left to the discretion of the local SL-therapist in both groups.

Assessments

An extensive linguistic test protocol was conducted at three time points; four weeks, three months and six months after randomization, with the following tests for language and communication: Amsterdam-Nijmegen Everyday Language Test (ANELT) for everyday functional verbal communication,[25] a semi-standardized interview from the Aachen Aphasia Test (AAT) rated with the reliable and valid ordered categorical six-point ASRS; the ScreeLing, the Token Test, and the Boston Naming Test. The battery also included tests for semantic processing: Semantic Association Test (SAT), verbal version; Comprehensive Aphasia Test (CAT), word comprehension; and Category Fluency; and for phonological processing: Nonword repetition and Auditory Lexical Decision from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) and Letter Fluency. In addition, we assessed general functional outcome with the EQ-5D-3L for quality of life, and the modified Rankin Scale (mRS) and Barthel Index for level of independency.

Outcomes

Primary outcome was the ANELT-A score 'understandability' (score range: 10 to 50, higher scores equal better performance), measuring the adequacy of verbal communication, four

weeks after randomization. This valid and reliable test was chosen to verify whether the impairment-based CLT generalizes to everyday communication.[25] All ANELTs were audio-recorded and rated by five experienced and additionally trained independent assessors, blinded to intervention and time point. Each ANELT was scored by two assessors. If scores of the two assessors differed more than six points, they were asked to rate the test again without providing them details about the direction of the differences. The mean of these two scores was used for analyses. In case of persistent differences between assessors, the scores were averaged with the score of a third independent assessor, who was unaware of other scores. Secondary outcomes were scores on the linguistic tests, EQ-5D-3L and mRS at four weeks, and scores on the ANELT-A, the linguistic tests, EQ-5D-3L, and mRS at three and six months after randomization.

Sample size

We considered a four-point difference between both groups on the ANELT-A a clinically worthwhile treatment effect. This is 50% of the critical difference for individual improvement and half a standard deviation of average ANELT-A scores in previous RATS trials.[25-27] We estimated that a sample of 150 participants would provide 84% power to find a statistically significant treatment effect at a 5% two-sided significance level.

Blinding and data safety

To ensure data safety and blinding, the primary outcome for each patient was scored by two of the five independent assessors, who were blinded to treatment allocation and time point. Furthermore, data were collected in four separate anonymized databases, which were merged after patient inclusion and data collection were completed. Hence, during data collection the trial coordinator could only access individual patient data. Scores on the primary outcome measure remained masked for the entire RATS-3 investigator team until data collection was completed.

An independent assessor verified a random sample of 10% of all participants' files, by comparing all data points in the databases with the original source files. Apart from minor inaccuracies, no critical errors endangering data quality were found. Yet, all data points were checked against source data again by the study coordinator, further minimizing errors.

The trial was not overseen by a data monitoring committee, as this concerned a non-medical intervention study without anticipated adverse events.

Statistical analyses

Primary analyses were performed on intention-to-treat basis. In addition, on-treatment analyses were performed, with on-treatment being defined for the intervention group as having accomplished at least the intended intensity of 28 hours in four weeks and for the control group as having received no language treatment during four weeks after randomization. We used linear regression to analyze the treatment effect as a mean difference in ANELT-A scores between the intervention and control group four weeks after randomization, adjusted for age (years), sex, education (high or low), baseline aphasia severity (ASRS score), type of stroke (ischemic or hemorrhagic), location of stroke (right or left hemisphere) and baseline Barthel Index score. Linear regression was also used to analyze the effect of treatment on the specific linguistic measures and measures of general functional outcome at four weeks, three months and six months after randomization, with

the same adjustments as in the primary analysis. For the ordered categorical variable mRS we used multivariable ordinal logistic regression.

Handling of missing data

Standard simple imputation techniques were used to impute missing baseline variables; study mean for continuous variables and study mode for binary and categorical data. Patients who died during the intervention period were assigned the worst score on all outcome measures and this score was carried forward during follow-up. Subjects with missing values at a certain time point were excluded from analyses at that time point. Statistical analyses were performed using IBM SPSS software version 23.0.

Post-hoc subgroup analyses

Post-hoc subgroup analyses were conducted with the ANELT-A four weeks after randomization per covariate used for baseline adjustment in the regression analyses. We also compared treatment effects in patients treated with intravenous alteplase and those who were not, and in patients with and without a cardiac source of emboli.

Synthesis of evidence

In order to put our findings into perspective we have performed a concise meta-analysis of the available evidence on the topic of early initiated SLT. In December of 2015, we searched PubMed and the Cochrane Library for studies published between 1990 and 2015 with the search terms: aphasia, stroke, treatment, therapy, rehabilitation, acute, early and timing. We selected randomized controlled trials on early initiated SLT for aphasia due to stroke, i.e. the largest part of the treatment was provided within four weeks of stroke onset. Only RCTs comparing early treatment to no treatment, or early intensive treatment to no treatment or usual care were selected. We have used results from the primary outcomes reported in the selected studies and our primary outcome for the meta-analysis by standardizing the mean differences between study arms.

RESULTS

From 1 January 2012 until 2 December 2014 we included 153 participants with first-ever aphasia due to stroke, of whom 80 were allocated to the intervention group (Figure 1). One participant in the control group was excluded after randomization, because more detailed assessment revealed that a brain tumor had been misdiagnosed as hemorrhagic infarct. The baseline distribution of clinical characteristics was similar for both groups (Table 2).

In the intervention group, two patients died in the intervention period, and in the control group one patient died in the intervention period and one just afterwards, before testing could be performed (Figure 1). During follow-up, in each group two patients died. Five participants from the intervention group did not receive the allocated treatment; one was very ill and four refused intensive treatment. In the control group, ten participants refused deferred treatment and received regular SLT. The trial coordinator did not interfere with treatment, and details on the content of SLT provided to these patients were not recorded.

Figure 1. Flow-chart Rotterdam Aphasia Therapy Study – 3

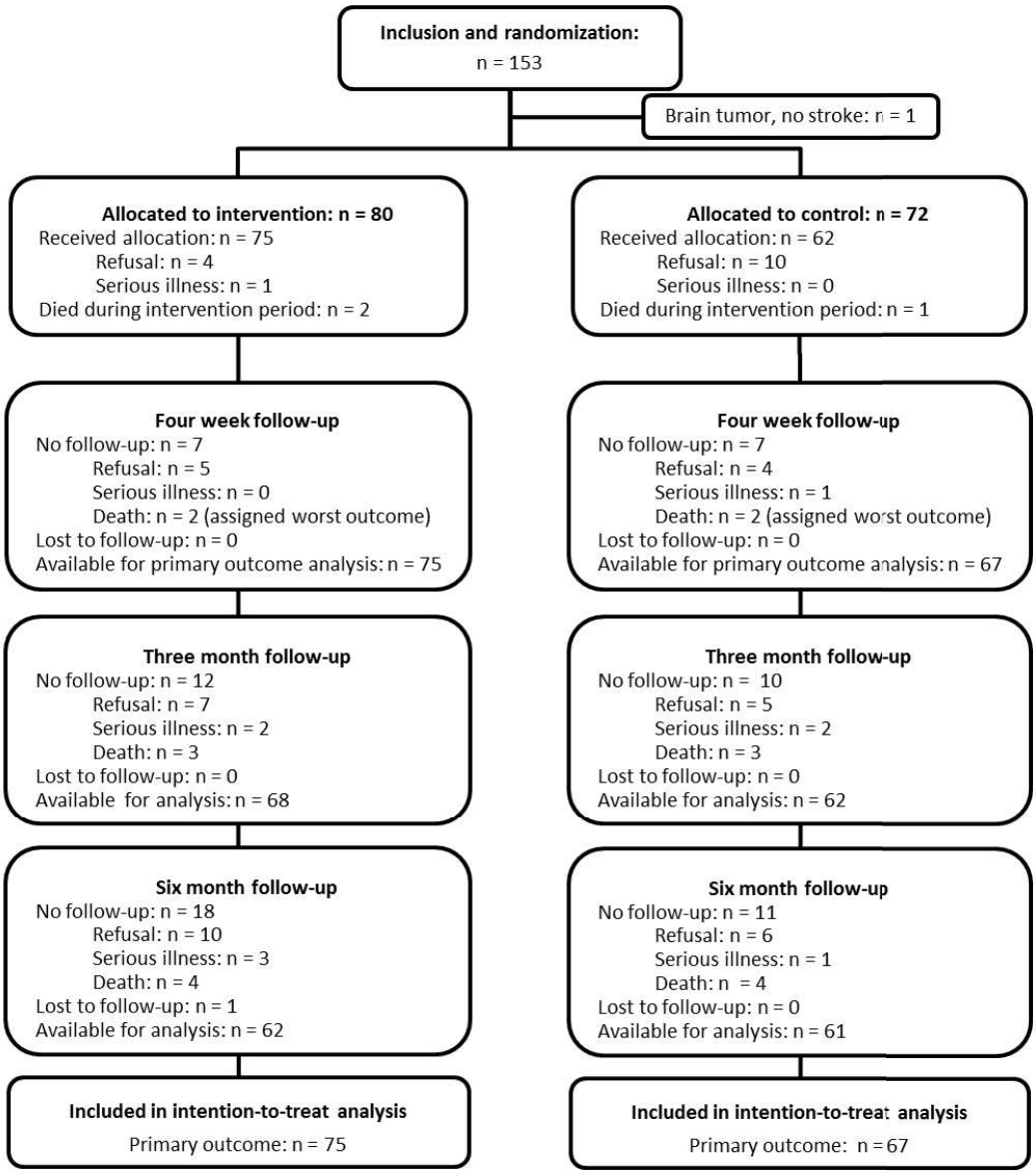


Table 2. Baseline characteristics of participants in RATS-3

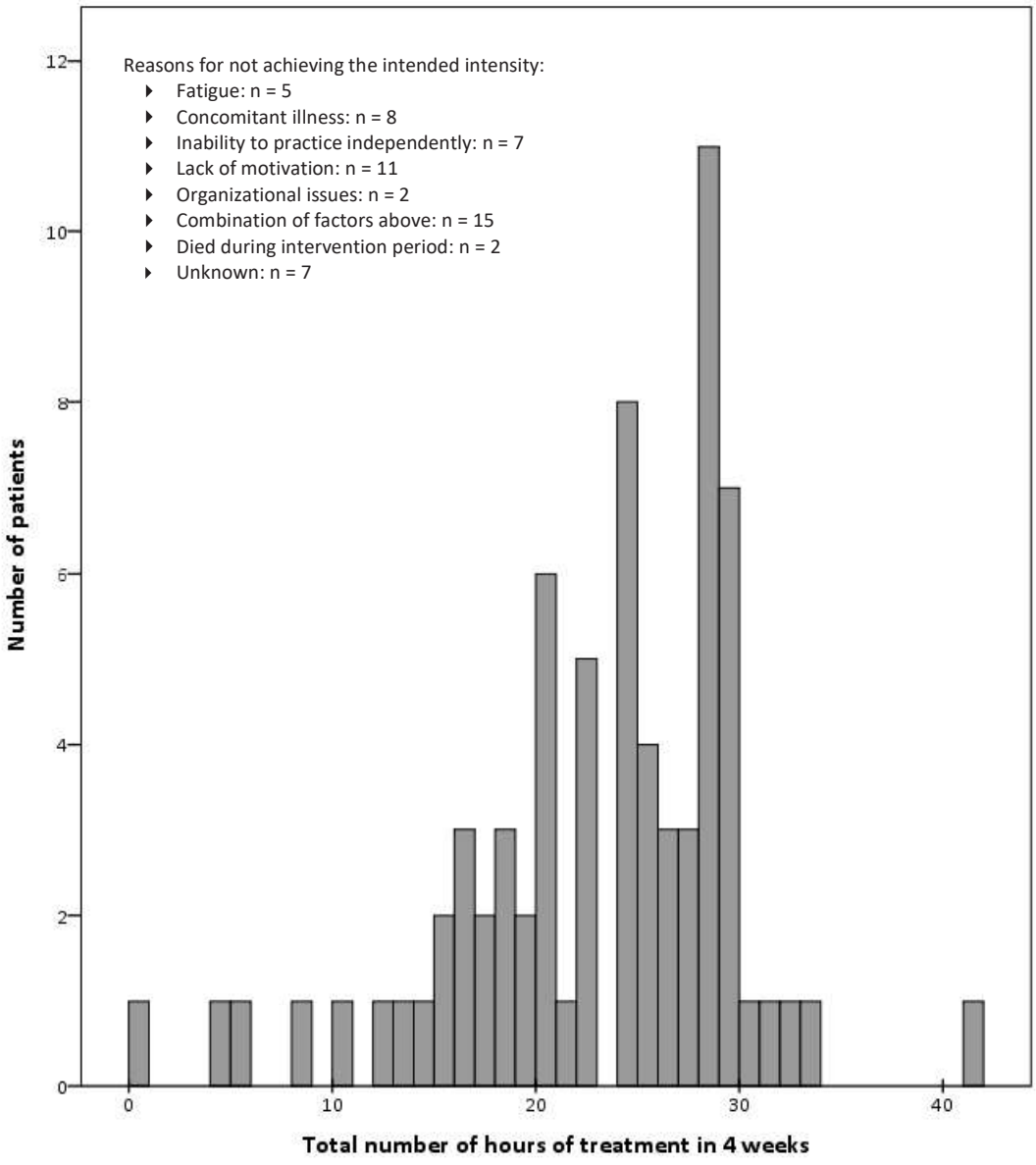
	Intervention group (n = 80)	**Control group (n = 72)**
Age in years, mean (SD)	66 (12)	66 (12)
Male sex, n (%)	48 (60%)	37 (51%)
Handedness, n (%)		
Right	63 (79%)	61 (85%)
Left	6 (8%)	7 (10%)
Ambidextrous	5 (6%)	1 (1%)
Unknown	6 (8%)	3 (4%)
Level of education, n (%)		
No/unfinished elementary school	3(4%)	0
Elementary school	13 (16%)	11 (15%)
Unfinished junior secondary vocational education	4 (5%)	8 (11%)
Junior secondary vocational education	27 (34%)	13 (18%)
Total low education	47 (59%)	32 (44%)
Senior vocational education	17 (21%)	16 (22%)
Higher education	13 (16%)	18 (25%)
University	2 (3%)	3 (4%)
Total high education	32 (40%)	37 (51%)
Unknown	1 (1%)	3 (4%)
Type of stroke, n (%)		
Ischemic	60 (75%)	61 (85%)
Hemorrhagic	20 (25%)	11 (15%)
Location of lesion, n (%)		
Left hemisphere	77 (96%)	69 (96%)
Right hemisphere	3 (4%)	3 (4%)
Treatment with intravenous alteplase, n (%)		
Yes	28 (35%)	16 (22%)
No	50 (63%)	55 (76%)
Unknown	2 (3%)	1 (1%)
Time between stroke and randomization in days, mean (range)	8 (1-18)	8 (2-15)
Time between stroke and start treatment in days, mean (range)	12 (5-22)	n.a.
Barthel Index score, median (IQR)	15 (6-20)	17 (7.5-20)
Aphasia severity, n (%)		
Severe (ASRS score = 0 to 2)	44 (55%)	30 (42%)
Mild-moderate (ASRS score = 3 to 4)	36 (45%)	42 (58%)
Fluency, n (%)		
Fluent aphasia	26 (33%)	30 (42%)
Non-fluent aphasia	52 (65%)	42 (58%)
Missing	2 (3%)	0

Abbreviations: n = number; SD = standard deviation; IQR = Interquartile Range; ASRS = Aphasia Severity Rating Scale; n.a. = not applicable.

Compliance

A treatment intensity of 28 hours in four weeks in the intervention group was achieved by 23 of 80 patients (29%). The median treatment intensity was 24.5 hours in four weeks (IQR: 19 to 29) (Figure 2).

Figure 2. Distribution of treatment intensity in the intervention group



Intention-to-treat analysis

The mean score on the primary outcome, the ANELT-A at four weeks, was 33.2 in the intervention group and 36.2 in the control group, with a difference of -3.01; 95% CI: -7.15 to 1.14. Baseline aphasia severity and baseline Barthel Index were strong prognostic factors in the regression model (Table 3). The adjusted mean difference in scores on the ANELT-A was 0.39; 95% CI: -2.70 to 3.47, p = 0.81 (Figure 3). There were also no statistically significant differences on the ANELT-A between groups at three months (adjusted difference = 0.54, 95% CI: -3.04 to 4.12, p = 0.77) and six months after randomization (adjusted difference = -0.41, 95% CI: -3.70 to 2.89, p = 0.81) (Figure 3).

Table 3. Prognostic factors in the linear regression model with ANELT-A at four weeks as outcome

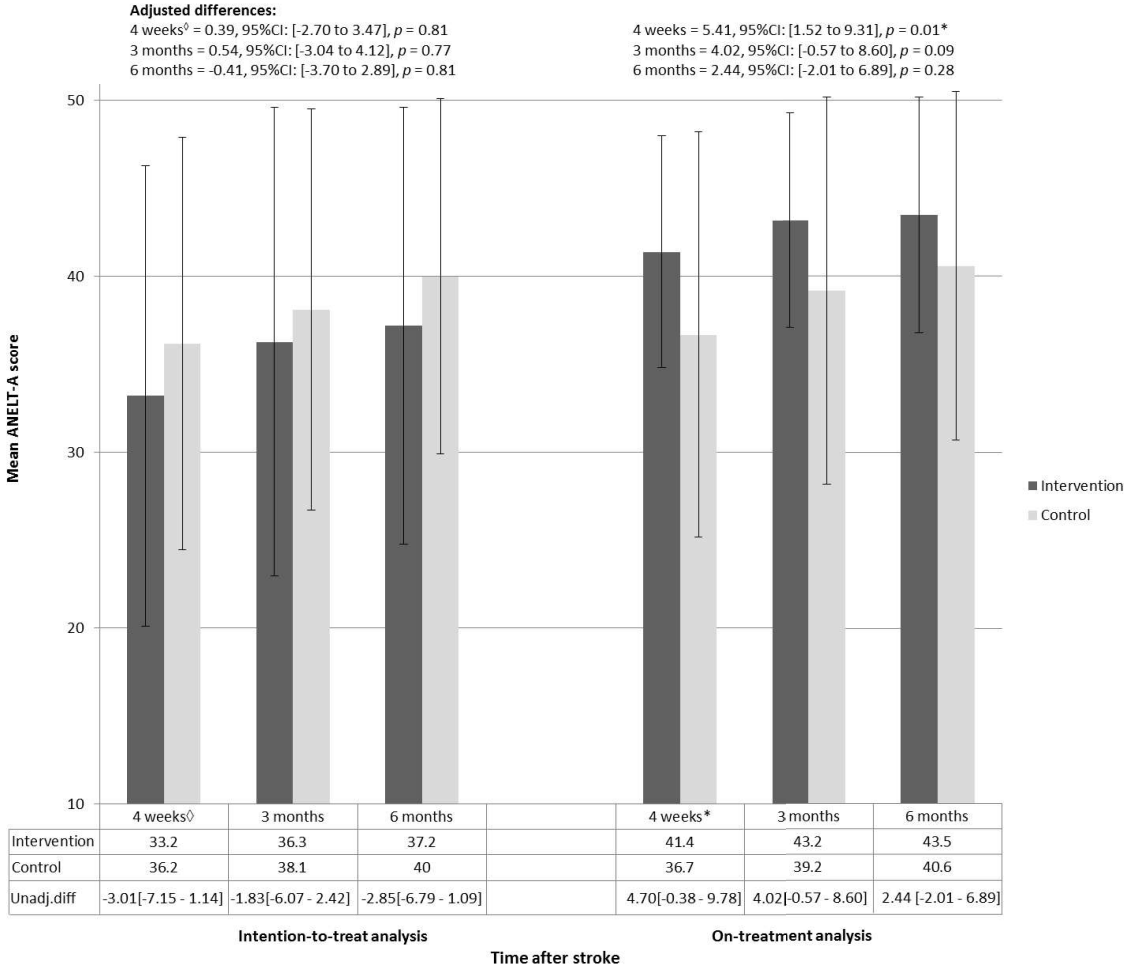
	β	95% CI	*p*-value
Sex (female or male)	-2.08	[-5.17 – 1.02]	0.19
Age	0.02	[-0.10 – 0.15]	0.74
Type of stroke (hemorrhagic or ischemic)	1.46	[-2.39 – 5.31]	0.45
Location stroke (right or left hemisphere)	0.35	[-7.16 – 7.85]	0.93
Education (high or low)	2.64	[-0.47 – 5.75]	0.10
Barthel Index score (0-20)	0.37	[0.11 – 0.62]	0.01*
Aphasia Severity Rating Scale score (0-5)	5.90	[4.58 – 7.23]	<0.01*

Abbreviations: *β* = unstandardized difference; 95% CI = 95% confidence interval.

* Statistically significant at a 95% confidence level.

No statistically significant treatment effects were observed on the linguistic tests and on the measures for general functional outcome, at any time point (Table 4).

Figure 3. Differences in outcome and treatment effect between intervention and control on the ANELT-A



	4 weeks◊	3 months	6 months		4 weeks*	3 months	6 months
Intervention	33.2	36.3	37.2		41.4	43.2	43.5
Control	36.2	38.1	40		36.7	39.2	40.6
Unadj.diff	-3.01[-7.15 - 1.14]	-1.83[-6.07 - 2.42]	-2.85[-6.79 - 1.09]		4.70[-0.38 - 9.78]	4.02[-0.57 - 8.60]	2.44 [-2.01 - 6.89]

Abbreviations: 95% CI = 95% Confidence Interval; ANELT = Amsterdam-Nijmegen Everyday Language Test; unadj. diff = unadjusted differences.
* Statistically significant at a 95% confidence level.
◊ Primary outcome.

Table 4. Differences in outcome and treatment effect between intervention and control on secondary outcomes: intention-to-treat analyses

		Intervention mean (SD)	Control mean (SD)	Unadjusted difference [95% CI]	Adjusted difference [95% CI]	*p*-value
SAT verbal (0-30)	4 weeks	21.2 (7.9)	22.1 (7.8)	-0.86 [-3.50 – 1.78]	1.09 [-1.27 – 3.45]	0.36
	3 months	22.7 (7.6)	24.1 (6.2)	-1.41 [-3.81 – 0.99]	-0.34 [-2.58 – 1.91]	0.77
	6 months	23.0 (7.3)	24.2 (6.6)	-1.25 [-3.70 – 1.20]	-0.12 [-2.41 – 2.18]	0.92
Category Fluency (no. words/ minute)	4 weeks	12.6 (11.0)	15.9 (11.9)	-3.32 [-7.13 – 0.50]	-0.06 [-3.09 – 2.96]	0.97
	3 months	16.2 (11.0)	20.3 (12.8)	-4.13 [-8.26 – 0.00]	-1.50 [-4.86 – 1.86]	0.38
	6 months	16.5 (11.7)	21.1 (13.3)	-4.56 [-8.98 – -0.13]	-1.77 [-5.47 – 1.93]	0.35
CAT (0-30)	4 weeks	25.0 (6.9)	24.9 (7.4)	0.12 [-2.26 – 2.50]	1.40 [-0.93 – 3.72]	0.24
	3 months	25.5 (6.6)	26.4 (6.0)	-0.96 [-3.11 – 1.20]	-0.10 [-2.20 – 2.01]	0.93
	6 months	25.8 (7.0)	27.0 (5.4)	-1.18 [-3.40 – 1.05]	-0.45 [-2.66 – 1.76]	0.69
PALPA Nonword repetition (0-24)	4 weeks	16.6 (7.6)	18.3 (6.3)	-1.76 [-4.10 – 0.58]	-0.39 [-2.46 – 1.67]	0.71
	3 months	16.9 (7.6)	19.1 (6.0)	-2.15 [-4.52 – 0.22]	-1.02 [-3.04 – 0.99]	0.32
	6 months	16.7 (7.5)	18.6 (5.7)	-1.90 [-4.26 – 0.46]	-0.79 [-2.91 – 1.34]	0.47
Letter Fluency (no. words / minute)	4 weeks	11.4 (9.6)	14.0 (10.9)	-2.62 [-6.04 – 0.80]	-0.29 [-3.25 – 2.67]	0.85
	3 months	12.8 (9.7)	17.1 (12.6)	-4.33 [-8.19 – -0.47]	-2.19 [-5.65 – 1.28]	0.21
	6 months	15.0 (10.4)	17.3 (12.5)	-2.35 [-6.39 – 1.69]	0.04 [-3.56 – 3.64]	0.98
PALPA Auditory Lexical Decision (0-80)	4 weeks	67.2 (18.4)	70.8 (14.6)	-3.61 [-9.18 – 1.97]	-1.46 [-6.91 – 3.99]	0.60
	3 months	68.1 (17.6)	72.3 (14.2)	-4.23 [-9.78 – 1.32]	-2.18 [-7.57 – 3.22]	0.43
	6 months	68.7 (18.4)	72.3 (14.3)	-3.64 [-9.50 – 2.22]	-1.79 [-7.63 – 4.05]	0.55

BNT (0-60)	4 weeks	28.6 (17.9)	31.4 (20.4)	-3.08 [-9.44 – 3.29]	1.40 [-3.99 – 6.78]	0.23
	3 months	33.0 (17.7)	37.5 (18.3)	-4.42 [-10.61 – 1.76]	-1.46 [-6.85 – 3.94]	0.59
	6 months	34.9 (18.0)	39.5 (17.9)	-4.56 [-10.86 – 1.74]	-1.29 [-6.85 – 4.28]	0.65
Token Test (0-36)	4 weeks	20.9 (10.4)	23.7 (10.3)	-2.84 [-6.30 – 0.62]	-0.10 [-2.98 – 2.78]	0.94
	3 months	23.3 (10.6)	26.0 (9.3)	-2.75 [-6.17 – 0.67]	-0.86 [-3.68 – 1.95]	0.55
	6 months	23.7 (10.9)	26.7 (9.1)	-3.00 [-6.57 – 0.57]	-0.83 [-3.92 – 2.25]	0.59
EQ-5D-3L (0-1)	4 weeks	0.79 (0.11)	0.81 (0.11)	-0.02 [-0.06 – 0.02]	-0.01 [-0.05 – 0.02]	0.48
	3 months	0.82 (0.12)	0.81 (0.13)	0.01 [-0.03 – 0.05]	0.02 [-0.02 – 0.06]	0.32
	6 months	0.82 (0.13)	0.82 (0.13)	-0.01 [-0.05 – 0.04]	-0.01 [-0.05 – 0.04]	0.78
mRS◊ (5-0)	4 weeks	3	3	-0.22 [-0.80 – 0.36]	-0.01 [-0.62 – 0.62]	0.99
	3 months	2	2	-0.23 [-0.82 – 0.36]	0.06 [-0.57 – 0.70]	0.85
	6 months	2	2	-0.23 [-0.83 – 0.38]	-0.07 [-0.70 – 0.57]	0.84

Abbreviations: SD = standard deviation; 95% CI = 95% confidence interval; SAT = Semantic Association Test; CAT = Comprehensive Aphasia Test; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; BNT = Boston Naming Test; mRS = modified Rankin Scale.
◊ Mode is reported for this categorical variable.

On-treatment analysis

In the on-treatment analysis we included all patients of the intervention group who received at least the prespecified intensity of 28 hours in four weeks (n = 23, 29%) and all subjects in the control group who did not receive any treatment (n = 62, 86%). Baseline characteristics of the intervention and control group included in the on-treatment analyses were similar (Table 5).

When on-treatment criteria were applied, the intervention group reached significantly higher scores than the control group after four weeks on the primary outcome ANELT-A (adjusted difference = 5.41, 95% CI: 1.52 to 9.31, $p = 0.01$); SAT verbal (adjusted difference = 3.57, 95% CI: 0.36 to 6.78, $p = 0.03$) and CAT word comprehension (adjusted difference = 3.64, 95% CI: 0.58 to 6.69, $p = 0.02$) (Figure 3, Table 6). On all other outcome measures and time points results did not differ from those of the intention-to-treat analyses.

Table 5. Baseline characteristics of participants in the on-treatment analyses

	Intervention (n = 23)	**Control (n = 62)**
Age in years, mean (SD)	64 (11)	66 (12)
Male sex, n (%)	17 (74%)	31 (50%)
Handedness, n (%)		
Right	20 (87%)	53 (86%)
Left	2 (9%)	7 (11%)
Ambidextrous	1 (4%)	1 (2%)
Unknown	0	1 (2%)
Level of education, n (%)		
No/unfinished elementary school	1 (4%)	0
Elementary school	3 (13%)	9 (15%)
Unfinished junior secondary vocational education	1 (4%)	7 (11%)
Junior secondary vocational education	7 (30%)	10 (16%)
Total low education	12 (52%)	28 (45%)
Senior vocational education	4 (17%)	15 (24%)
Higher education	6 (26%)	16 (26%)
University	1 (4%)	3 (5%)
Total high education	11 (48%)	34 (55%)
Unknown	0	2 (3%)
Type of stroke, n (%)		
Ischemic	18 (78%)	53 (86%)
Hemorrhagic	5 (22%)	9 (15%)
Location of lesion, n (%)		
Left hemisphere	22 (96%)	59 (95%)
Right hemisphere	1 (4%)	3 (5%)
Treatment with intravenous alteplase, n (%)		
Yes	9 (39%)	16 (26%)
No	14 (61%)	45 (73%)
Unknown	0	1 (2%)
Time between stroke and randomization in days, mean (range)	7 (2-14)	8 (2-15)
Time between stroke and start treatment in days, mean (range)	11 (6-19)	n.a.
Barthel Index Score, median (IQR)	20 (7.5-20)	17 (6-20)
Aphasia severity, n (%)		
Severe (ASRS score = 0 to 2)	12 (52%)	25 (40%)
Mild-moderate (ASRS score = 3 to 4)	11 (48%)	37 (60%)

Abbreviations: n = number; SD = standard deviation; IQR = Interquartile Range; ASRS = Aphasia Severity Rating Scale; n.a. = not applicable.

Table 6. Differences in outcome and treatment effect between intervention and control on secondary outcomes: on-treatment analyses

		Intervention mean (SD)	Control mean (SD)	Unadjusted difference [95% CI]	Adjusted difference [95% CI]	*p*-value
SAT verbal (0-30)	4 weeks	24.8 (4.1)	22.1 (8.0)	2.67 [-0.81 – 6.14]	3.57 [0.36 – 6.78]	0.03*
	3 months	26.1 (2.5)	24.1 (6.3)	1.93 [-0.92 – 4.77]	1.92 [-0.88 – 4.73]	0.18
	6 months	26.3 (2.5)	24.2 (6.8)	2.04 [-1.23 – 5.30]	2.17 [-0.99 – 5.33]	0.18
Category Fluency (no. words/ minute)	4 weeks	17.6 (11.4)	16.4 (12.0)	1.25 [-4.48 – 6.99]	1.61 [-3.12 – 6.33]	0.50
	3 months	22.5 (10.0)	21.1 (13.0)	1.41 [-4.85 – 7.66]	1.03 [-4.49 – 6.55]	0.37
	6 months	24.1 (12.4)	21.6 (13.6)	2.46 [-4.72 – 9.63]	1.74 [-4.77 – 8.26]	0.60
CAT (0-30)	4 weeks	28.0 (2.5)	25.0 (7.3)	3.01 [-0.08 – 6.10]	3.64 [0.58 – 6.69]	0.02*
	3 months	28.1 (1.8)	26.3 (6.1)	1.80 [-0.92 – 4.52]	1.99 [-0.72 – 4.70]	0.15
	6 months	28.4 (1.9)	27.0 (5.6)	1.44 [-1.26 – 4.14]	1.50 [-1.27 – 4.27]	0.28
PALPA Nonword repetition (0-24)	4 weeks	20.0 (3.3)	18.3 (6.5)	1.73 [-1.11 – 4.56]	1.79 [-0.86 – 4.43]	0.18
	3 months	20.6 (2.6)	19.4 (5.9)	1.27 [-1.37 – 3.91]	0.85 [-1.52 – 3.21]	0.48
	6 months	20.6 (2.4)	18.6 (5.8)	2.05 [-0.76 – 4.86]	1.35 [-1.34 – 4.04]	0.32
Letter Fluency (no. words / minute)	4 weeks	15.0 (10.7)	14.3 (11.2)	0.67 [-4.70 – 6.03]	0.93 [-3.85 – 5.72]	0.70
	3 months	17.0 (10.4)	17.4 (13.0)	-0.49 [-6.77 – 5.80]	-1.12 [-6.99 – 4.75]	0.71
	6 months	21.0 (11.1)	17.5 (12.8)	3.51 [-3.19 – 10.21]	2.70 [-3.46 – 8.87]	0.39
PALPA Auditory Lexical Decision (0-80)	4 weeks	73.7 (5.9)	70.6 (15.2)	3.07 [-3.43 – 9.56]	3.31 [-3.24 – 9.86]	0.32
	3 months	75.3 (3.9)	71.9 (14.9)	3.46 [-3.12 – 10.04]	3.39 [-3.31 – 10.09]	0.32
	6 months	75.5 (3.6)	72.0 (14.9)	3.48 [-3.62 – 10.58]	3.06 [-4.21 – 10.34]	0.40

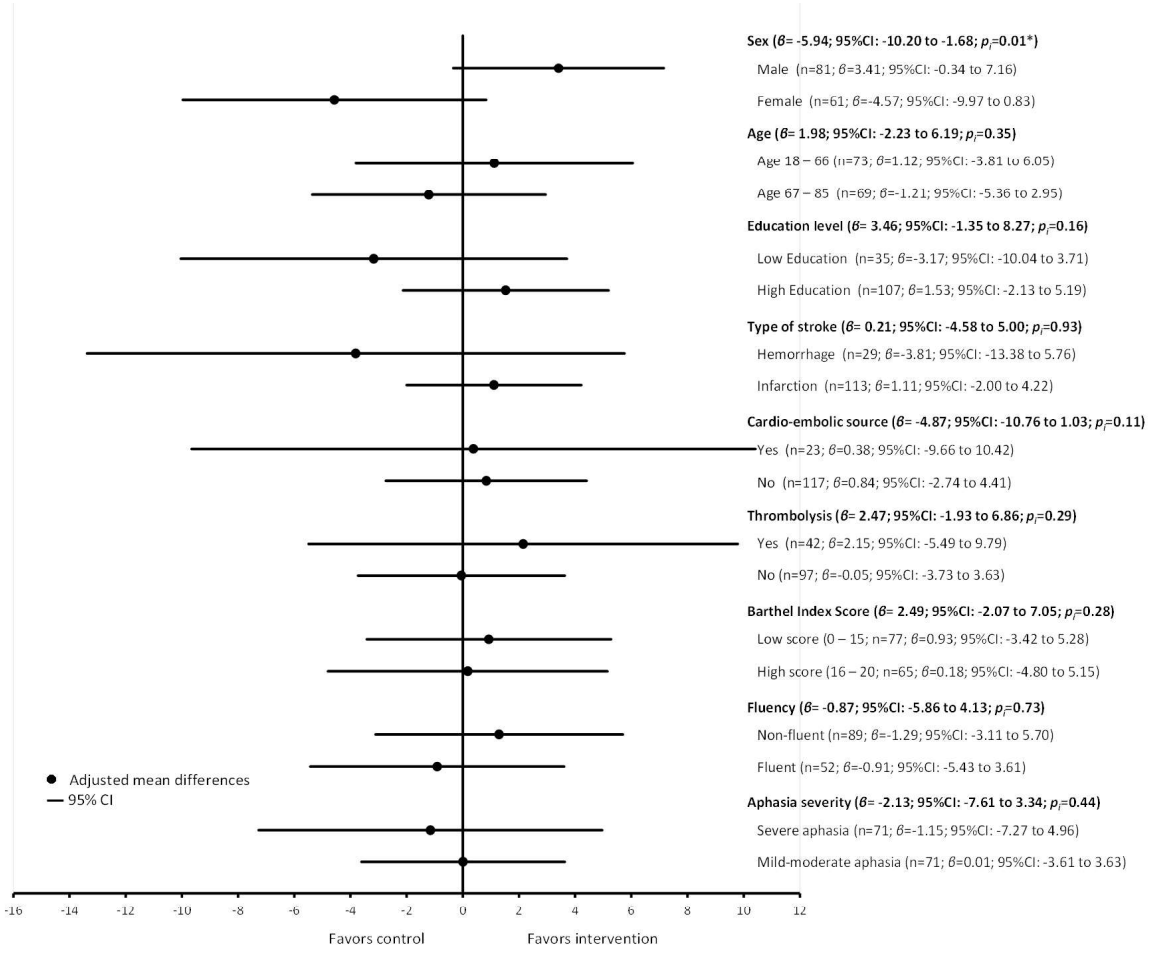
BNT (0-60)	4 weeks	37.3 (14.6)	31.7 (20.0)	5.52 [-3.57 – 14.61]	6.27 [-1.38 – 13.93]	0.11
	3 months	41.9 (13.7)	38.0 (17.9)	3.82 [-4.74 – 12.38]	4.65 [-3.39 – 12.69]	0.25
	6 months	42.7 (14.7)	40.0 (17.5)	2.69 [-6.39 – 11.76]	3.19 [-4.96 – 11.34]	0.44
Token Test (0-36)	4 weeks	24.4 (8.0)	24.1 (10.2)	0.35 [-4.35 – 5.04]	1.12 [-2.83 – 5.08]	0.57
	3 months	27.8 (7.4)	26.5 (9.2)	1.30 [-3.14 – 5.75]	1.33 [-2.57 – 5.24]	0.50
	6 months	29.4 (6.7)	26.9 (9.1)	2.59 [-2.06 – 7.25]	2.29 [-1.79 – 6.36]	0.27
EQ-5D-3L (0-1)	4 weeks	0.83 (0.12)	0.81 (0.11)	0.02 [-0.04 – 0.08]	0.01 [-0.04 – 0.06]	0.72
	3 months	0.86 (0.11)	0.81 (0.12)	0.05 [-0.02 – 0.11]	0.03 [-0.03 – 0.09]	0.29
	6 months	0.87 (0.11)	0.83 (0.13)	0.04 [-0.03 – 0.11]	0.02 [-0.05 – 0.09]	0.53
mRS◊ (5-0)	4 weeks	3	2	0.45 [-0.43 – 1.33]	0.64 [-0.31 – 1.59]	0.19
	3 months	2	2	0.35 [-0.55 – 1.24]	0.41 [-0.54 – 1.37]	0.39
	6 months	2	2	0.50 [-0.39 – 1.39]	0.62 [-0.32 – 1.57]	0.20

Abbreviations: SD = standard deviation; 95% CI = 95% confidence interval; SAT = Semantic Association Test; CAT = Comprehensive Aphasia Test; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; BNT = Boston Naming Test; mRS = modified Rankin Scale.
* Statistically significant at a 95% confidence level.
◊ Mode is reported for this categorical variable.

Post-hoc subgroup analyses

We also compared treatment effects per covariate used for baseline adjustment and we compared patients treated with intravenous alteplase and those who were not, and patients with and without a cardiac source of emboli. There was a statistically significant interaction between sex and intervention (adjusted β = -5.94; 95% CI: -10.20 to -1.68, p = 0.01), but not for other subgroups (Figure 4).

Figure 4. Subgroup comparisons for the ANELT-A at four weeks after randomization

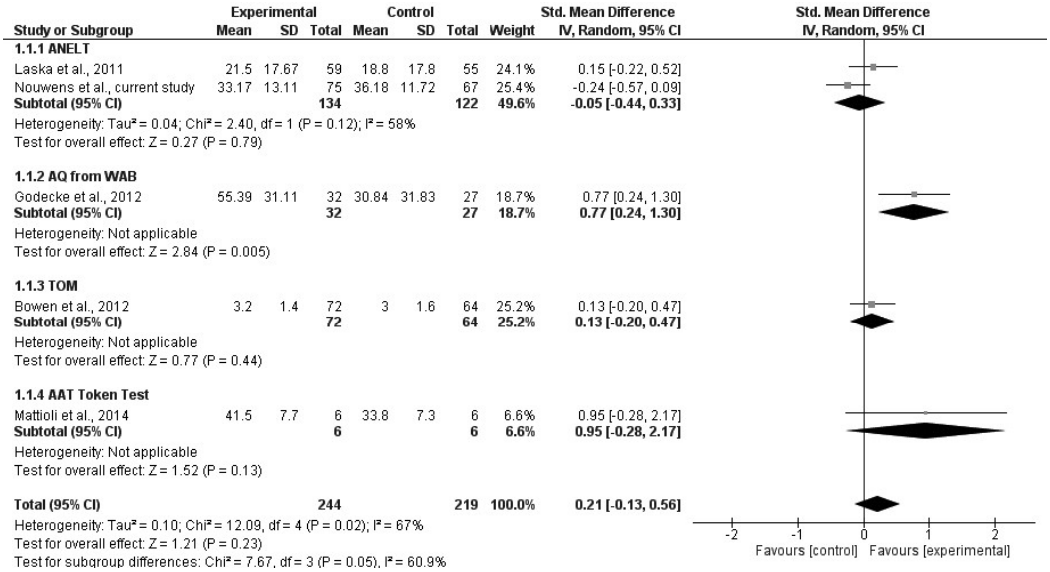


* Statistically significant interaction.

Synthesis of evidence

We found two RCTs comparing early intensive SLT to no treatment, one comparing early SLT to no SLT, and one comparing early intensive SLT to usual care.[6-9] We conducted a meta-analysis with the primary outcomes reported in these trials and our findings (Figure 5). The effect of early initiated SLT over deferred regular SLT or no treatment was small and not statistically significant (standardized mean difference = 0.21, 95% CI: -0.13 to 0.56).

Figure 5. Forest plot comparing standardized mean differences between early initiated intensive SLT and no treatment or usual care



Abbreviations: ANELT = Amsterdam-Nijmegen Everyday Language Test; AQ = Aphasia Quotient; WAB = Western Aphasia Battery; TOM = Therapy Outcome Measure, functional communicative ability; AAT = Aachen Aphasia Test.

Data derived from the Cochrane Systematic Review[10] and original manuscripts.

The figure was made using Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

DISCUSSION

Principal findings

In this multicenter RCT in 152 patients with aphasia due to stroke, we found that four weeks of early intensive CLT did not result in better everyday verbal communication than no early language treatment. The 95% CIs for the adjusted differences between groups did not include the prespecified clinically relevant difference of four points on the ANELT-A, which allows us to conclude that early intensive CLT is not effective.

This contradicts the findings from two smaller RCTs in which a benefit of early intensive treatment was reported. In 59 patients, 30 to 80 minutes of impairment-based SLT per workday for four weeks initiated three days after stroke, improved communication more

than usual care (<80 minutes per week).[7] Although nearly 20% of patients in the intervention group did not achieve the minimum treatment intensity of 150 minutes per week, the authors conclude that daily treatment is feasible early after stroke and, if tolerated, is effective for recovery of aphasia. In another study, 12 patients were randomly allocated to two weeks of either one-hour sessions of impairment-based SLT on workdays starting on average 2.2 days after stroke or no SLT.[8] In addition to statistically significant better scores in the early treatment group on the AAT subparts Naming and Written language processing, the authors report significant differences between groups in post treatment recruitment of brain areas on functional MRI-scans. However, this is a very small trial with only six participants per treatment arm.

Our findings are in line with those from two larger RCTs on early initiated SLT. In a trial among 123 patients, Laska et al. found no effect of three weeks of early intensive impairment-based SLT on ANELT-A scores three weeks and six months after stroke onset.[6] Bowen et al. randomly allocated 170 stroke patients with communication deficits to either agreed best practice SLT or social support provided by trained volunteers for 16 weeks starting on average two weeks after stroke onset.[9] They found no differences regarding functional communication at follow-up and conclude that SLT is not more effective than social support. This trial differs from ours, as stroke patients with either aphasia, dysarthria or both were included, which makes the results difficult to interpret. Furthermore, treatment intensity was tailored to the individuals' needs and possibilities. Consequently, treatment intensity was on average only 1.5 hours per week, which may not have been sufficient to reach a sizeable treatment effect.[3, 18, 19]

While the concept of early language rehabilitation after stroke is attractive, the summary of evidence in our meta-analysis shows that SLT, whether or not intensive, when started within four weeks after stroke onset, is not more effective in improving verbal communication or language functioning, than regular, less intensive or deferred treatment.

Strengths and weaknesses

Strengths of RATS-3 are its large size, multicenter design, a clearly defined clinically relevant intervention contrast, and representative cohort of patients with aphasia due to stroke. The treatment programs used in the intervention group are frequently applied in daily practice in the Netherlands and have good potential to generate an effect on language recovery, as exercises are directed at facilitating word finding, an essential problem in aphasia. Consequently, results of our trial are highly generalizable to daily practice. We could have opted for a more distinct intervention contrast by actively limiting all language related activities in the control group e.g. reading, writing and computer use, but that would not reflect daily reality. In fact, our aim was to study whether intensive CLT, added to language related activities people with aphasia engage in naturally, is effective for the recovery of aphasia.

Many efficacy studies on impairment-based treatment have used impairment-based language tests as outcome measures, e.g. naming or word comprehension, as these are closely related to the intervention being studied.[28] However, scores on linguistic tests are rather artificial and do not necessarily reflect adequate functional communication in daily life, which should be the ultimate goal of aphasia treatment.[3] Therefore, a relevant and reliable measure of communication, most closely reflecting the patients' sense of recovery and return to normal functioning, is preferable.[10] Hence, in line with our previous trials, both

in which we found that improvement on the ANELT-A was correlated with improvement at the impairment level, we used the ANELT-A as primary outcome measure.[16, 26, 27]

Our study has limitations. Although we accomplished a high median treatment intensity of 24.5 hours in four weeks, achieving the intended intensity of 28 hours appeared a major challenge. Even with a strictly protocolled treatment regimen and highly motivated SL-therapists who were frequently contacted by the trial coordinator, less than 30% of the intervention group achieved the requested intensity. Patients were often too tired or ill to practice one hour per day, even if treatment was spread over the day. Although poor adherence to the protocol was mainly caused by patient related issues, organizational problems such as limited availability of therapists, or priority given to motor rehabilitation also played a role, albeit minor. While this trial was no feasibility study, the results demonstrate that even if intensive treatment had been found more effective for selected patients, feasibility is improbable for all stroke patients with aphasia early after onset. This is in line with findings from the most recent Cochrane review.[3]

Patient selection seems essential to generate a potential beneficial effect of early intensive CLT on recovery of aphasia, as the on-treatment analyses did show a limited effect. However, this finding should be interpreted with great caution, as on-treatment analyses could only be performed in patients in the intervention group who could tolerate intensive treatment, whereas the control group comprised both patients who may and may not tolerate this intensive regimen.

Completeness of follow-up for the primary outcome was 93%, which is in line with other studies in this field.[3] At six months after stroke 19% of participants had refused follow-up testing. This may have reduced the validity of our findings, but the measurements at three and six month follow-up are secondary outcomes and are in line with the primary outcome.

Implications

Despite the lack of unequivocal proof for a beneficial effect of early SLT, deferring treatment in aphasia due to stroke has long been considered unethical.[29] However, early after stroke, patients may suffer from concomitant illness or fatigue and may not tolerate intensive impairment-based treatment. Our findings demonstrate that it is not detrimental to delay CLT in the first weeks after stroke onset in these vulnerable patients, which also occasionally happens unintentionally due to waiting lists or lengthy diagnostic pathways.

However, our findings do not justify the conclusion that the work of SL-therapists is redundant in the first weeks after stroke, as patients with aphasia and their proxies definitely need guidance and help in coping with their deficits early after stroke. In times of radical changes in health care policy and budget cutbacks, SL-therapists are urged to utilize their limited resources effectively for patients with acute stroke. Instead of focusing on impairment-based treatment, they might better put more emphasis on counseling and providing communication support, which are essential for coping with communication problems and prevention of social isolation. CLT may be more effective later in the course of this disabling condition.

Future research

Future studies should aim to find the optimal timing of commonly used treatment types, either impairment-based or functional approaches. New studies may be focused on patient selection also, as results from our on-treatment analyses indicate that some patients might

benefit from early intensive treatment. International cooperation is one way to conduct large aphasia trials that allow for more reliable prespecified subgroup analyses, which is of great importance to identify factors contributing to treatment success and may enable individualization of SLT.

CONCLUSION

Our study shows that four weeks of intensive CLT aimed at semantic and phonological processing started within two weeks after stroke onset does not improve the recovery of aphasia, either in the short or long-term.

Acknowledgements

RATS-3 was funded by a fellowship granted to LL by the Brain Foundation Netherlands (project number: 2011(1)-20) and grants from Zabawas Fund, Coolsingel fund, Dura fund, Blokland fund, and the Erasmus MC Care Research Fund.

We thank Marjolein de Jong-Hagelstein and Carolina Mendez Orellana for contributing to the conception and outset of RATS-3. We acknowledge all participating centers in the Netherlands for recruiting patients and treating them according to the trial protocol. We are thankful to Irma Adbegovic, Liset Bergevoets, Yvonne Hendrick, Nienke Wolthuis and Marjolein Zomerdijk for their work as blinded ANELT assessors.

REFERENCES

1. Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke*. 2006;37:1379-1384
2. Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M. Aphasia in acute stroke and relation to outcome. *J Intern Med*. 2001;249:413-422
3. Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. *The Cochrane Database of Systematic Reviews*. 2016
4. Nouwens F, Visch-Brink EG, Van de Sandt-Koenderman MM, Dippel DW, Koudstaal PJ, de Lau LM. Optimal timing of speech and language therapy for aphasia after stroke: more evidence needed. *Expert Rev Neurother*. 2015;15:885-893
5. Robey RR. A meta-analysis of clinical outcomes in the treatment of aphasia. *J Speech Lang Hear Res*. 1998;41:172-187
6. Laska AC, Kahan T, Hellblom A, Murray V, von Arbin M. A randomized controlled trial on very early speech and language therapy in acute stroke patients with aphasia. *Cerebrovasc Dis Extra*. 2011;1:66-74
7. Godecke E, Hird K, Lalor EE, Rai T, Phillips MR. Very early poststroke aphasia therapy: a pilot randomized controlled efficacy trial. *Int J Stroke*. 2012;7:635-644
8. Mattioli F, Ambrosi C, Mascaro L, Scarpazza C, Pasquali P, Frugoni M, et al. Early aphasia rehabilitation is associated with functional reactivation of the left inferior frontal gyrus: a pilot study. *Stroke*. 2014;45:545-552
9. Bowen A, Hesketh A, Patchick E, Young A, Davies L, Vail A, et al. Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: a randomised controlled trial. *BMJ*. 2012;345:e4407
10. Brady MC, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev*. 2012;5:CD000425

11. van Hees S, McMahon K, Angwin A, de Zubicaray G, Read S, Copland DA. A functional MRI study of the relationship between naming treatment outcomes and resting state functional connectivity in post-stroke aphasia. *Hum Brain Mapp*. 2014;35:3919-3931
12. Thompson CK, den Ouden DB. Neuroimaging and recovery of language in aphasia. *Curr Neurol Neurosci Rep*. 2008;8:475-483
13. Code C. Multifactorial processes in recovery from aphasia: developing the foundations for a multileveled framework. *Brain Lang*. 2001;77:25-44
14. Kreisel SH, Bazner H, Hennerici MG. Pathophysiology of stroke rehabilitation: temporal aspects of neuro-functional recovery. *Cerebrovasc Dis*. 2006;21:6-17
15. El Hachioui H, Lingsma HF, van de Sandt-Koenderman ME, Dippel DW, Koudstaal PJ, Visch-Brink EG. Recovery of aphasia after stroke: a 1-year follow-up study. *J Neurol*. 2013;260:166-171
16. Nouwens F, de Jong-Hagelstein M, de Lau LML, Dippel DWJ, Koudstaal PJ, van de Sandt-Koenderman WME, et al. Severity of aphasia and recovery after treatment in patients with stroke. *Aphasiology*. 2014;28:1168-1177
17. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Arch Phys Med Rehabil*. 2011;92:519-530
18. Godecke E, Rai T, Ciccone N, Armstrong E, Granger A, Hankey GJ. Amount of therapy matters in very early aphasia rehabilitation after stroke: a clinical prognostic model. *Semin Speech Lang*. 2013;34:129-141
19. Bhogal SK, Teasell R, Speechley M. Intensity of aphasia therapy, impact on recovery. *Stroke*. 2003;34:987-993
20. Nouwens F, Dippel DW, de Jong-Hagelstein M, Visch-Brink EG, Koudstaal PJ, de Lau LM, et al. Rotterdam Aphasia Therapy Study (RATS)-3: "The efficacy of intensive cognitive-linguistic therapy in the acute stage of aphasia"; design of a randomised controlled trial. *Trials*. 2013;14: 24:1-8
21. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press*. 1992;1:113-119
22. Denier C, Flamand-Roze C, Dib F, Yeung J, Solignac M, Bayon de la Tour L, et al. Aphasia in stroke patients: early outcome following thrombolysis. *Aphasiology*. 2015;29:442-456
23. Visch-brink EG, Bajema IM, Sandt-Koenderman MEVD. Lexical semantic therapy: Box. *Aphasiology*. 1997;11:1057-1078
24. Van Rijn M, Booy L, Visch-Brink EG. *FIKS, een fonologisch therapieprogramma*. Lisse: Swets & Zeitlinger; 2000.
25. Blomert L, Kean ML, Koster C, Schokker J. Amsterdam-Nijmegen Everyday Language Test - Construction, Reliability and Validity. *Aphasiology*. 1994;8:381-407
26. Doesborgh SJ, van de Sandt-Koenderman MW, Dippel DW, van Harskamp F, Koudstaal PJ, Visch-Brink EG. Effects of semantic treatment on verbal communication and linguistic processing in aphasia after stroke: a randomized controlled trial. *Stroke*. 2004;35:141-146
27. de Jong-Hagelstein M, van de Sandt-Koenderman WM, Prins ND, Dippel DW, Koudstaal PJ, Visch-Brink EG. Efficacy of early cognitive-linguistic treatment and communicative treatment in aphasia after stroke: a randomised controlled trial (RATS-2). *J Neurol Neurosurg Psychiatry*. 2011;82:399-404
28. Wallace SJ, Worrall L, Rose T, Le Dorze G. Measuring outcomes in aphasia research: A review of current practice and an agenda for standardisation. *Aphasiology*. 2014;28:1364-1384
29. Thompson CK. Single subject controlled experiments in aphasia: The science and the state of the science. *Journal of communication disorders*. 2006;39:266-291