Intra-arterial treatment in acute ischemic stroke

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Evolution of Intra-arterial Therapy for Acute Ischemic Stroke in the Netherlands: MR CLEAN pre-trial experience

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ABSTRACT

Introduction

The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) trial showed efficacy of intra-arterial (IA) treatment in acute ischemic stroke (AIS). We studied the evolution of IA treatment for AIS and its effects on clinical outcome and recanalization in the Netherlands in the pre-MR CLEAN era.

Methods

Data on 517 IA treated patients with AIS were collected retrospectively from all intervention centers in The Netherlands from 2002 to start of participation in the MR CLEAN trial. Clinical outcome was measured by means of the modified Rankin score (mRS) and recanalization with the Thrombolysis In Cerebral Infarction Scale (TICI).

Results

IA therapy was first used in patients with basilar artery occlusion. Over the years there was a gradual increase in number of anterior circulation strokes treated. There was a shift in applied therapies from primary IA therapy to combined intravenous and IA therapy and from IA thrombolysis to mechanical thrombectomy. Time from symptom onset to treatment decreased. Recanalization rates gradually increased. At the same time, there was a trend towards more favorable outcomes after three months and fewer deceased patients both at discharge and after three months. However, none of these changes reached statistical significance.

Conclusion

The treatment approach used in the MR CLEAN trial was the result of an evolution of practise in the preceding years, with gradual improvement in technical and clinical outcome.

INTRODUCTION

Stroke is one of the leading causes of death and disability. The last two decades intravenous thrombolysis (IVT) has been the standard of care for acute ischemic stroke (AIS). Unfortunately, only an estimated 10-15% of patients with acute ischemic stroke are eligible for IVT due to the presence of contra-indications.[1,2] Furthermore IVT only leads to recanalization in about 40% of patients[3] and this percentage drops to 10-20% if there is an occlusion of internal carotid artery or M1 segment of the middle cerebral artery.[4] These limitations lead to a continued search for better treatments. In the PROACT I and II trials intra-arterial (IA) thrombolysis was shown to lead to improved outcomes compared with placebo with regard to recanalization rates and clinical outcome after 90 days.[5,6] In later studies, IA thrombolysis was combined with IVT ("bridging") resulting in better recanalization rates. However, there was no improvement in clinical outcome compared with intra-arterial treatment alone.[7] In the MERCI registries mechanical thrombectomy was studied, at first only in patients ineligible for IVT[8], later also in combination with both intravenous and IA thrombolysis.[9] Both studies showed that mechanical thrombectomy could be performed safely and resulted in recanalization rates comparable with those from the PROACT II trial.[8,9] Several studies that investigated the outcome after IA therapy with stentretrievers, showed high recanalization rates and high rates of favorable clinical outcome.[10,11,12,13] Nevertheless, two recent trials failed to show efficacy of IA therapy as compared with standard care (including IVT).[14,15] A possible explanation for these results is that few of the IA treated patients in these trials were treated with stent-retrievers and confirmation of occlusion with avanced imaging was not required. The recently published Dutch MR CLEAN trial, in which the vast majority of patients in the IA group were treated with stent-retrievers, was the first trial to show superiority of IA therapy over standard care including IVT.[16] These positive results were confirmed in the recently published Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on minimizing CT to Recanalization Times (ESCAPE) and Extending the Time for Thormbolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND IA) trials.[17,18]

The present study reports the evolution of IA therapy for AIS in the Netherlands prior to the MR CLEAN trial. We retrieved patient and treatment characteristics of all patients with AIS treated with IA therapy in the Netherlands before the start of the MR CLEAN trial. The aim of the study was to describe the changes over the years in the IA treatment approach in the Netherlands and the effect of these changes on clinical and radiological outcome.

METHODS

Patients

Patient data were obtained from the Dutch database on IA therapy in acute stroke patients. This database was initiated in preparation of the MR CLEAN trial, a Dutch, multicenter trial on the use of IA therapy in AIS.[16,19] All 16 centers that participated in the MR CLEAN trial had to provide their pre-trial experience with IA therapy in order to be allowed to participate in the MR CLEAN trial (see appendix 1 for participating centers). This data assembly resulted in a database that contained information on all AIS patients treated with IA therapy from October 2002 until October 2013 in the Netherlands. Inclusion in this pre-trial registry continued until a center started recruiting for the MR CLEAN trial.

Because we wanted to study the evolution in applied IA therapy, we divided our cohort into four periods: before 2009, 2009, 2010 and after 2010. The periods chosen were based on rapid innovations in IA therapy which occurred around 2009 and 2010.

Demographic and clinical data were recorded at baseline including age, sex, time of symptom onset, baseline National Institutes of Health Stroke Scale (NIHSS), blood pressure and glucose on admission.

Registration and use of the data were approved by the institutional review board from the coordinating institution (Erasmus MC Rotterdam). The decisions to treat a patient with intra-arterial therapy were decisions made for each patient individually and intra-arterial treatment was performed only after obtaining consent from the patient or his relatives.

Intra-arterial treatment

IA therapy consisted of local intra-arterial thrombolysis, mechanical thrombectomy, thrombo-aspiration or a combination of these techniques. For IA thrombolysis, alteplase or urokinase was used, often in combination with abciximab or heparin. Mechanical thrombectomy was performed with either a MERCI retriever (Concentric Medical, Mountain View, California, USA), Solitaire device (EV3, Irvine, USA), Trevo device (Cocentric Medical, Mountain View, California, USA), Revive device (Micrus endovascular, San Jose, California, USA), Catch device (Balt Extrusion, Montmorency, France), or a combination of these. Thrombo-aspiration was applied with the Vasco aspiration device (Balt Extrusion, Montmorency, France), the "distal access Catheter" (DAC, Concentric Medical, Mountain View, California, USA) and the Penumbra device (Penumbra Inc, Alameda, California, USA). The interventionalist decided which IA treatment was chosen. Secondary preventive treatment was initiated according to European guidelines.[20]

Radiological characteristics

For each treated patient, site of occlusion or stenosis on CTA, time to intra-arterial treatment (time from start of symptoms until start of angiography), dose of thrombolytics (both intravenous and intra-arterial), devices used and degree of recanalization (TICI score[21]) were recorded. TICI scores were assessed on angiography by experienced neuro-radiologists blinded for clinical outcome. Recanalization was regarded successful if the TICI score at the end of the intra-arterial procedure was 2b or 3. Most patients underwent a CT scan 24 hours after treatment or after any clinical deterioration.

Clinical outcomes

Clinical outcome was retrospectively measured with the modified Rankin Score (mRS) [22,23] at discharge and after three months (3-month data from two hospitals only (244 patients); Medical Center Haaglanden, The Hague and St. Antonius Hospital, Nieuwegein). Good outcome was defined as an mRS score of 2 or lower. In addition, we studied complications both during the intra-arterial procedure and during admission. Complications were registered by the local stroke physicians.

Statistical analysis

Descriptive statistics were used for baseline, treatment and complication characteristics. Rates of good clinical outcome were compared across all four periods with risk ratios (RR) and 95% confidence intervals (CI). Adjusted risk ratios were calculated with Poisson regression.

RESULTS

Patients

A total of 517 patients was included in the database. Of these, 137 patients were treated before 2009, 102 in 2009, 167 in 2010 and 111 after 2010, the last being included in October 2013. Most patients were men (59%), median age was 62 years and the median NIHSS was 16. There were no major differences between the four groups in baseline characteristics (Table 1). Over time, more anterior strokes were treated and time from symptom onset IVT and IA treatment both decreased.

Therapy

Overall, 334 patients (65%) received IVT preceding IA treatment, in most cases with alteplase. Of these, 16 patients (3.1%) received IVT as only treatment, for various reasons such as absence of occlusion on angiography or technical inability to reach the occlusion due to complex anatomy of the carotid arteries

or for other technical reasons. Seventy-nine patients (15%) were treated with additional IA thrombolytics, 93 patients (18%) were treated with additional mechanical thrombectomy and 146 patients (28%) received a combination of both IA thrombolysis and mechanical thrombectomy after IVT (Tables 2 and Webtable 1). Over the years, more patients who underwent IA treatment also received IVT in advance to their IA treatment (47% <2009 versus 80% >2010, Webtable 1). Of the 180 patients (35%) not treated with IVT, the majority was treated with IA thrombolysis in combination with IA thrombectomy (Table 3). There was a clear shift in type of IA treatment with initially mostly IA thrombolysis using urokinase (80% <2009 versus 26%>2010; Webtable 1) whereas later mechanical thrombectomy was used more often. Among thrombectomy options, a shift from extraction devices towards stent-retrievers was seen (Webtable 1).

Complications

Table 3 shows an overview of all complications during the intra-arterial procedure and hospital admission. Overall, 207 patients (40%) suffered from a complication during the procedure or admission. Symptomatic intracranial hemorrhage (sICH) was the most frequent complication. Eleven percent of all patients developed such a hemorrhage and this percentage remained stable over the years. During the IA procedure arterial spasms were the most frequent complication. There was an increase in arterial spams (6%<2009 versus 11% and 13% in 2009 and 2010) over time, probably due to the use of stent-retrievers (15% in patients treated with stent-retriever versus 8% in patients who were not treated with stent-retrievers; crude RR 2.01 95%CI 1.19-3.41). However, there was no clear relationship between arterial spasms and clinical deterioration (data not shown).

Clinical outcome at discharge

Overall, good clinical outcome (mRS ≤2) at discharge was observed in 112 patients (22%; Webtable 2). Over the years, good clinical outcome tended to decrease (from 26% in the period<2009 to 19% in the period >2010; crude RR 0.74 95%CI 0.46-1.19), though differences were not statistically significant. This trend was more evident in patients suffering from an anterior circulation stroke (from 31% in the period<2009 to 21% in the period >2010; crude RR 0.72 95% CI 0.42-1.22; Webtable 3). By contrast, a decrease in deaths during admission was seen (34% vs 24% crude RR 0.70 95%CI 0.47-1.06). After adjustment for both clinical and several treatment variables the risk ratios for good clinical outcome at discharge remained essentially the same (Webtable 4).

Clinical outcome at three months

In contrast with outcome at discharge, patients with good clinical outcomes after three months were slightly more frequent in the later treatment years. The most notable difference (though not statistically significant) was seen between the treatment period before 2009 compared with 2009 (30% vs 38%, crude RR 1.25 95%CI 0.76-2.03). From 2009 on, rates of favorable clinical outcome remained essentially the same (Webtable 2, Figure 1 and 2). In addition to this trend towards more patients with good clinical outcome at three months, an evident decrease in deaths was seen (38% vs 22%, crude RR 0.57 95%CI 0.29-1.10 respectively). Additional analysis showed that this positive trend originated from better outcomes at three months in patients with a posterior circulation stroke (Webtable 3). After adjustment for both clinical and several treatment variables, the risk ratios for good clinical outcome after three months remained essentially the same (Webtable 5).

Recanalization

We were able to retrieve recanalization rates in 311 patients (62%). Of these, successful recanalization was reached in 133 patients (43%). An increase in successful recanalization rates was observed over the years with successful recanalization rates of 36% in the first period versus 52% and 47% in the later years (crude RR 1.46 95%CI 1.01-2.11 and crude RR 1.31 95%CI 0.87-1.98 respectively, Webtable 2).

DISCUSSION

In our overview of the experience with IA therapy in the Netherlands in the pre-MR CLEAN era we found that over the years more patients with anterior circulation strokes were treated and time to treatment (both intravenous and intra-arterial) shortened. In addition, there was a shift in applied therapies with more IA therapy applied in combination with IVT. Moreover, within IA treatment options, mechanical thrombectomy with stent-retrievers was applied more often in the later periods in contrast to IA thrombolysis (with urokinase) that was used more often in the earlier years. Concomitantly, we found a trend towards more patients with favorable outcome after three months and less deceased patients at both discharge and after three months and higher recanalization rates. However, none of these trends reached statistical significance.

Compared with previously published large trials on IA therapy, including MR CLEAN, we found similar rates of favorable outcome after three months.[6,9,13,16]

Although our recanalization rates improved during time, possibly due to the use of stent-retrievers, our recanalization rates are lower compared with other studies including the recently published results of the MR CLEAN that showed successful recanalization in 58.7%.[6,7,9,12,16] The fact that we did reach comparable rates of favorable clinical outcome at three months without matching recanalization rates is a remarkable finding as from previous studies recanalization is known to relate to clinical outcome.[24,25] With regards to procedural complication rates, our rates are higher compared with other studies.[9,12] However, these studies did not include arterial spasms or contrast extravasation in their definition of procedural complications. These are the two complications that were most frequent in our cohort, with the incidence of arterial spasms increasing over time. The latter is probably the result of more frequent use of thrombectomy devices in the second period.[26] Fortunately, presence of arterial spasms during the IA procedure did not lead to worse outcome. Furthermore, the incidence of symptomatic intracerebral hemorrhages, the most feared complication of IA therapy, is similar to that found in PROACT II and Multi MERCI[5,9] but higher than that observed in the MR CLEAN trial (7.7%), but both estimates have wide confidence intervals.[16]

Our study has several limitations. First, we had limited data on long term follow-up. Three-month data were only available for two of the participating hospitals. However, these hospitals collected almost half of all data. Secondly, our study was retrospective, hence not all data were complete. However, data on type of IA treatment applied, complication rates and outcome rates at discharge were available for at least 97% of all cases. The most important strength of our study is that we were able to present a relatively large series including all IA treated patients in the Netherlands from both university and large teaching hospitals, highly representative for early experience with IA therapy in the Netherlands.

In summary, our observational pre-MR CLEAN cohort study shows a shift in applied IA therapy with more mechanical thrombectomy with stent-retrievers applied in the later periods, mostly combined with IVT. We found a trend towards more patients with favorable outcome after three months and lower mortality at both discharge and after three months and higher recanalization rates. This evolution in applied IA therapy is reflected in results of the subsequent MR CLEAN trial, in which mechanical thrombectomy with stent-retrievers was the predominantly applied IA therapy leading to more favorable clinical outcomes in patients treated with IA therapy compared with standard treatment.[16] These positive results were recently confirmed by the ESCAPE and EXTEND-IA trials.[17,18]

TABLES

TABLE 1 Patient characteristics

	N	All (n=517)	<2009 (n=137)	2009 (n=102)	2010 (n=167)	>2010 (n=111)
Men (%)	*517*	307 (59%)	85 (62%)	55 (54%)	106 (64%)	61 (55%)
Age in years, mean (SD)	*517*	60 (14.8)	60 (15.3)	60 (15.5)	60 (15.1)	62 (13.1)
NIHSS, median (range)	*509*	16 (1-42)	16 (1-39)	17 (1-39)	16 (3-42)	16 (5-39)
Stroke onset – presentation ER, (in minutes; median, range)	*327*	66 (5-590)	60 (17-345)	85 (7-590)	66 (5-450)	61 (15-450)
Time to IVT (in minutes; median, range)	*253*	102 (25-340)	120 (45-210)	120 (25-340)	95 (39-315)	93 (35-310)
Time to IA therapy (in minutes; median, range)	*344*	237 (65-1296)	239 (80-1150)	262 (65-945)	234 (90-1296)	210 (81-1080)
Blood pressure in mmHg, mean (SD)						
Systolic	*434*	148 (28)	147 (29)	149 (27)	149 (30)	147 (25)
Diastolic	*434*	83 (17)	85 (19)	85 (17)	81 (17)	85 (16)
Glucose in mmol/L, mean (SD)	*459*	7.5 (2.6)	7.4 (2.3)	7.5 (3.3)	7.5 (2.6)	7.5 (2.1)
Thrombocytes $*10^9$/L, mean (SD)	*452*	259 (94)	263 (86)	273 (108)	254 (101)	247 (73)
Anterior circulation stroke (%)	*515*	356 (69%)	71 (52%)	81 (79%)	116 (70%)	88 (80%)
CT-angiography performed (%)	*517*	485 (94%)	131 (96%)	98 (96%)	155 (93%)	101 (91%)
CT-perfusion performed (%)	*516*	98 (19%)	8 (6%)	24 (24%)	42 (25%)	24 (22%)
MR-angiography performed (%)	*517*	17 (3%)	8 (6%)	2 (2%)	4 (2%)	3 (3%)

NIHSS: National Institutes of Health Stroke Scale; IVT: intravenous thrombolysis; IAT: intra-arterial treatment.

TABLE 2 Applied therapies per category

Applied therapy	Total (n=517)	<2009 (n=137)	2009 (n=102)	2010 (n=167)	>2010 (n=111)
Intravenous thrombolysis (only)*	16 (3.1%)	2 (2%)	3 (3%)	6 (4%)	5 (5%)
+ Intra-arterial thrombolysis	79 (15%)	26 (19%)	23 (23%)	25 (15%)	5 (5%)
+ Intra-arterial thrombolysis and Mechanical treatment	146 (28%)	32 (23%)	30 (29%)	53 (32%)	31 (28%)
+ Mechanical treatment	93 (18%)	4 (3%)	11 (11%)	30 (18%)	48 (43%)
Intra-arterial thrombolysis (only)	47 (9%)	32 (23%)	11 (11%)	4 (2%)	0 (0%)
+ Mechanical treatment	87 (17%)	33 (24%)	16 (16%)	29 (17%)	9 (8%)
Mechanical treatment (only)	46 (9%)	8 (6%)	7 (7%)	19 (11%)	12 (11%)
Failed therapy∞	3 (1%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)

*Defined as initiated IAT that was not applied eventually because the clot had already resolved on angiography.
∞Defined as initiated IAT that was not applied eventually due to technical difficulties.

TABLE 3 Complications after intra-arterial treatment

Complications during procedure	All (n=517)	<2009 (n=137)	2009 (n=102)	2010 (n=167)	>2010 (n=111)
Arterial spasms	50 (10%)	8 (6%)	11 (11%)	22 (13%)	9 (8%)
Contrast extravasation	34 (7%)	8 (6%)	11 (11%)	11 (7%)	4 (4%)
Dissection	18 (3%)	6 (4%)	3 (3%)	4 (2%)	5 (5%)
Groin hematoma	11 (2%)	5 (4%)	3 (3%)	3 (2%)	0 (0%)
Complications during admission	**All (n=517)**	**<2009 (n=137)**	**2009 (n=102)**	**2010 (n=167)**	**>2010 (n=111)**
sICH	57 (11%)	17 (13%)	15 (15%)	14 (8%)	11 (10%)
aICH	28 (5%)	5 (4%)	5 (5%)	11 (7%)	7 (6%)
Hemorrhagic transformation	38 (7%)	13 (10%)	6 (6%)	13 (8%)	6 (5%)
Recurrent stroke	5 (1%)	1 (1%)	2 (2%)	2 (1%)	0 (0%)
Major extracranial hemorrhage	6 (1%)	2 (1%)	2 (2%)	2 (1%)	0 (0%)
Any complication during procedure or admission	207 (40%)	56 (41%)	47 (46%)	66 (40%)	38 (34%)

SICH, Symptomatic IntraCerebral Hemorrhage; AICH, Asymptomatic IntraCerebral Hemorrhage.

SUPPLEMENTARY FILES

WEBTABLE 1 Applied therapies

	N	All (n=517)	<2009 (n=137)	2009 (n=102)	2010 (n=167)	>2010 (n=111)
Intravenous thrombolysis	517	334 (65%)	64 (47%)	67 (66%)	114 (68%)	89 (80%)
Alteplase	504	326 (65%)	58 (44%)	67 (67%)	113 (69%)	88 (81%)
Abciximab	517	5 (1%)	1 (1%)	0 (0%)	4 (2%)	0 (0%)
Heparin	511	16 (3%)	7 (5%)	2 (2%)	3 (2%)	4 (4%)
Intra-arterial thrombolysis	517	364 (70%)	123 (90%)	80 (78%)	115 (69%)	46 (41%)
Alteplase	512	83 (16%)	14 (10%)	26 (26%)	37 (22%)	6 (6%)
Abciximab	517	41 (8%)	10 (7%)	21 (21%)	7 (4%)	3 (3%)
Heparin	513	90 (17%)	27 (20%)	25 (25%)	21 (13%)	17 (16%)
Urokinase	512	256 (50%)	108 (80%)	49 (48%)	71 (43%)	28 (26%)
Mechanical treatment	517	372 (72%)	77 (56%)	64 (63%)	131 (78%)	100 (90%)
Retraction	514	184 (36%)	63 (47%)	52 (51%)	51 (31%)	18 (16%)
Aspiration	513	33 (6%)	4 (3%)	7 (7%)	13 (8%)	9 (8%)
Stent placement	513	218 (42%)	23 (17%)	21 (21%)	90 (54%)	84 (76%)
Stent-retriever	517	137 (27%)	0 (0%)	4 (4%)	57 (34%)	76 (69%)
Other	517	142 (28%)	36 (26%)	44 (43%)	45 (27%)	17 (15%)
Failed procedure∞	516	23 (5%)	2 (2%)	4 (4%)	9 (5%)	8 (7%)

* data missing ∞Defined as initiated IAT that was not applied eventually.

WEBTABLE 2 Clinical outcomes at discharge and after three months and recanalization

Clinical outcome at discharge	**All (n=504)**	**<2009 (n=131)**	**2009 (n=100)**	**2010 (n=163)**	**>2010 (n=110)**
mRS=0	20 (4%)	5 (4%)	4 (4%)	7 (4%)	4 (4%)
mRS=1	28 (6%)	10 (8%)	8 (8%)	6 (4%)	4 (4%)
mRS=2	64 (13%)	19 (15%)	10 (10%)	22 (14%)	13 (12%)
mRS=3	78 (16%)	11 (8%)	18 (18%)	20 (12%)	29 (26%)
mRS=4	118 (23%)	33 (25%)	22 (22%)	37 (23%)	26 (24%)
mRS=5	62 (12%)	9 (7%)	14 (14%)	31 (19%)	8 (7%)
Death (mRS=6)	134 (27%)	44 (34%)	24 (24%)	40 (25%)	26 (24%)
Good outcome (mRS<2)	112 (22%)	34 (26%)	22 (22%)	35 (22%)	21 (19%)
Clinical outcome at 3 months*	**All (n=244)**	**<2009 (n=89)**	**2009 (n=45)**	**2010 (n=73)**	**>2010 (n=37)**
mRS=0	8 (3%)	2 (2%)	4 (9%)	0 (0%)	2 (5%)
mRS=1	41 (17%)	18 (20%)	7 (16%)	11 (15%)	5 (14%)
mRS=2	35 (14%)	7 (8%)	6 (13%)	16 (22%)	6 (16%)
mRS=3	37 (15%)	11 (12%)	7 (16%)	10 (14%)	9 (24%)
mRS=4	34 (14%)	14 (16%)	4 (9%)	10 (14%)	6 (16%)
mRS=5	12 (5%)	3 (3%)	2 (4%)	6 (8%)	1 (3%)
Death (mRS=6)	77 (32%)	34 (38%)	15 (33%)	20 (27%)	8 (22%)
Good outcome (mRS<2)	84 (34%)	27 (30%)	17 (38%)	27 (37%)	13 (35%)
Recanalization	**All (n=311)**	**<2009 (n=67)**	**2009 (n=71)**	**2010 (n=109)**	**>2010 (n=64)**
TICI≥2b #	133 (43%)	24 (36%)	22 (31%)	57 (52%)	30 (47%)

mRS: modified Rankin Score; TICI: Thrombolysis in Cerebral Infarction. * Data from two hospitals only. # Data missing, n=311.

WEBTABLE 3 Clinical outcomes at discharge and after three months categorized by circulation

ANTERIOR CIRCULATION					
Clinical outcome at discharge	**All (n=352)**	**<2009 (n=70)**	**2009 (n=80)**	**2010 (n=114)**	**>2010 (n=88)**
Good outcome (mRS<2)	85 (24%)	22 (31%)	18 (23%)	27 (24%)	18 (21%)
Death (mRS=6)	60 (17%)	11 (16%)	15 (19%)	20 (18%)	14 (16%)
Clinical outcome at 3 months*	**All (n=162)**	**<2009 (n=44)**	**2009 (n=36)**	**2010 (n=51)**	**>2010 (n=31)**
Good outcome (mRS<2)	64 (40%)	19 (43%)	14 (39%)	19 (37%)	12 (38%)
Death (mRS=6)	33 (20%)	7 (16%)	11 (31%)	10 (20%)	5 (16%)
POSTERIOR CIRCULATION					
Clinical outcome at discharge	**All (n=150)**	**<2009 (n=61)**	**2009 (n=20)**	**2010 (n=48)**	**>2010 (n=21)**
Good outcome (mRS<2)	26 (17%)	12 (20%)	4 (20%)	7 (15%)	3 (14%)
Death (mRS=6)	74 (49%)	33 (54%)	9 (45%)	20 (42%)	12 (57%)
Clinical outcome at 3 months*	**All (n=82)**	**<2009 (n=45)**	**2009 (n=9)**	**2010 (n=22)**	**>2010 (n=6)**
Good outcome (mRS<2)	20 (24%)	8 (18%)	3 (33%)	8 (36%)	1 (17%)
Death (mRS=6)	44 (54%)	27 (60%)	4 (44%)	10 (46%)	3 (50%)

mRS: modified Rankin Score. * Data from two hospitals only.

WEBTABLE 4 Risk ratios for good clinical outcome at discharge

	Treated in 2009 vs treated <2009		**Treated in 2010 vs treated <2009**		**Treated >2010 vs treated <2009**	
	2009 (n=102)	<2009 (n=137)	2010 (n=167)	<2009 (n=137)	>2010 (n=111)	<2009 (n=137)
Good clinical outcome	22 %	26%	22%	26%	19%	26%
Crude risk ratio	0.85 (0.53-1.36)		0.83 (0.55-1.25)		0.74 (0.46-1.19)	
Adjusted risk ratio for:						
Age	0.85 (0.53-1.35)		0.83 (0.55-1.24)		0.76 (0.47-1.22)	
Male sex	0.85 (0.53-1.35)		0.83 (0.55-1.25)		0.74 (0.45-1.19)	
NIHSS	0.85 (0.56-1.29)		0.82 (0.55-1.21)		0.81 (0.50-1.29)	
Systolic blood pressure	0.76 (0.46-1.25)		0.81 (0.53-1.25)		0.70 (0.42-1.17)	
Diastolic blood pressure	0.75 (0.46-1.23)		0.80 (0.52-1.24)		0.70 (0.43-1.17)	
Glucose	0.74 (0.46-1.19)		0.82 (0.54-1.25)		0.66 (0.40-1.09)	
Thrombocytes	0.74 (0.45-1.21)		0.81 (0.53-1.25)		0.73 (0.44-1.20)	
Time to ER	0.74 (0.42-1.29)		0.75 (0.49-1.24)		0.58 (0.32-1.04)	
Time to IAT	0.72 (0.41-1.28)		0.71 (0.42-1.19)		0.73 (0.40-1.31)	
Intravenous thrombolysis	0.81 (0.51-1.30)		0.79 (0.52-1.20)		0.68 (0.42-1.12)	
Alteplase	0.82 (0.51-1.32)		0.77 (0.50-1.18)		0.65 (0.39-1.07)	
Abciximab	0.84 (0.53-1.34)		0.84 (0.56-1.27)		0.73 (0.45-1.18)	
Heparine	0.83 (0.52-1.77)		0.81 (0.54-1.21)		0.66 (0.40-1.10)	
Intra-arterial thrombolysis	0.86 (0.54-1.37)		0.85 (0.56-1.28)		0.78 (0.47-1.30)	
Alteplase	0.80 (0.50-1.28)		0.78 (0.51-1.19)		0.78 (0.48-1.26)	
Abciximab	0.84 (0.53-1.34)		0.83 (0.55-1.25)		0.74 (0.46-1.20)	
Heparine	0.84 (0.53-1.34)		0.84 (0.56-1.27)		0.70 (0.42-1.15)	
Urokinase	0.83 (0.51-1.35)		0.79 (0.51-1.22)		0.72 (0.43-1.20)	
Mechanical treatment	0.86 (0.54-1.37)		0.88 (0.59-1.33)		0.81 (0.50-1.33)	
Retraction	0.84 (0.53-1.34)		0.78 (0.51-1.18)		0.67 (0.41-1.10)	
Aspiration	0.85 (0.53-1.35)		0.82 (0.54-1.24)		0.73 (0.45-1.19)	
Stent placement	0.86 (0.54-1.38)		0.92 (0.61-1.40)		0.88 (0.52-1.48)	
Stent-retriever	0.84 (0.52-1.34)		0.74 (0.47-1.17)		0.60 (0.33-1.10)	
4 Factors#	0.82 (0.53-1.25)		0.82 (0.55-1.23)		0.82 (0.49-1.39)	

RR, Risk Ratio; CI, Confidence Interval; NIHSS, National institutes of Health Stroke Scale; ER, Emergency Room; IAT, Intra-arterial Treatment. #adjusted risk ratio for NIHSS, intravenous thrombolysis, intra-arterial thrombolysis and mechanical treatment.

WEBTABLE 5 Risk ratios for good clinical outcome after three months

	Treated in 2009 vs treated <2009		Treated in 2010 vs treated <2009		Treated >2010 vs treated <2009	
	2009 (n=45)	<2009 (n=89)	2010 (n=73)	<2009 (n=89)	>2010 (n=37)	<2009 (n=89)
Good clinical outcome	38%	30%	37%	30%	35%	30%
Crude risk ratio	1.25 (0.76-2.03)		1.22 (0.79-1.88)		1.16 (0.68-1.99)	
Adjusted risk ratio for:						
Age	1.24 (0.76-2.02)		1.15 (0.75-1.75)		1.17 (0.68-1.99)	
Male sex	1.23 (0.75-2.02)		1.22 (0.79-1.89)		1.15 (0.67-1.98)	
NIHSS	1.28 (0.81-2.04)		1.32 (0.87-2.01)		1.18 (0.69-2.01)	
Systolic blood pressure	1.04 (0.59-1.81)		1.20 (0.75-1.90)		0.92 (0.49-1.71)	
Diastolic blood pressure	1.01 (0.58-1.78)		1.16 (0.71-1.87)		0.91 (0.49-1.70)	
Glucose	1.02 (0.61-1.69)		1.17 (0.75-1.82)		0.92 (0.53-1.60)	
Thrombocytes	1.08 (0.64-1.82)		0.98 (0.60-1.60)		1.08 (0.61-1.92)	
Time to ER	1.27 (0.67-2.44)		1.20 (0.66-2.21)		0.99 (0.47-2.12)	
Time to IAT	0.87 (0.46-1.65)		0.84 (0.48-1.47)		1.06 (0.56-2.03)	
Intravenous thrombolysis	1.16 (0.71-1.90)		1.14 (0.73-1.79)		1.06 (0.61-1.82)	
Alteplase	1.16 (0.70-1.90)		1.09 (0.69-1.71)		1.03 (0.60-1.79)	
Abciximab	1.25 (0.76-2.03)		1.24 (0.80-1.91)		1.16 (0.68-1.99)	
Heparine	1.25 (0.76-2.04)		1.22 (0.79-1.90)		1.16 (0.68-2.00)	
Intra-arterial thrombolysis	1.23 (0.75-2.03)		1.21 (0.77-1.87)		1.12 (0.62-2.01)	
Alteplase	1.27 (0.78-2.08)		1.23 (0.80-1.91)		1.18 (0.69-2.03)	
Abciximab	1.27 (0.77-2.10)		1.22 (0.79-1.88)		1.15 (0.67-1.98)	
Heparine	1.24 (0.75-2.04)		1.21 (0.78-1.89)		1.14 (0.64-2.04)	
Urokinase	1.24 (0.76-2.03)		1.23 (0.80-1.91)		1.17 (0.68-2.02)	
Mechanical treatment	1.25 (0.76-2.05)		1.23 (0.79-1.91)		1.17 (0.67-2.03)	
Retraction	1.27 (0.77-2.09)		1.21 (0.78-1.88)		1.13 (0.66-1.95)	
Aspiration	1.32 (0.80-2.16)		1.24 (0.80-1.93)		1.24 (0.72-2.12)	
Stent placement	1.32 (0.80-2.17)		1.41 (0.89-2.23)		1.43 (0.79-2.58)	
Stent-retriever	1.24 (0.76-2.02)		1.81 (0.73-1.90)		1.09 (0.58-2.03)	
3 Factors#	0.86 (0.47-1.60)		0.86 (0.50-1.48)		0.96 (0.50-1.82)	

RR, Risk Ratio; CI, Confidence Interval; NIHSS, National institutes of Health Stroke Scale; ER, Emergency Room; IAT, Intra-arterial Treatment. #adjusted risk ratio for NIHSS, intravenous thrombolysis, intra-arterial thrombolysis and time to intra-arterial treatment.

FIGURES

FIGURE 1 modified Rankin Scores (mRS) at discharge

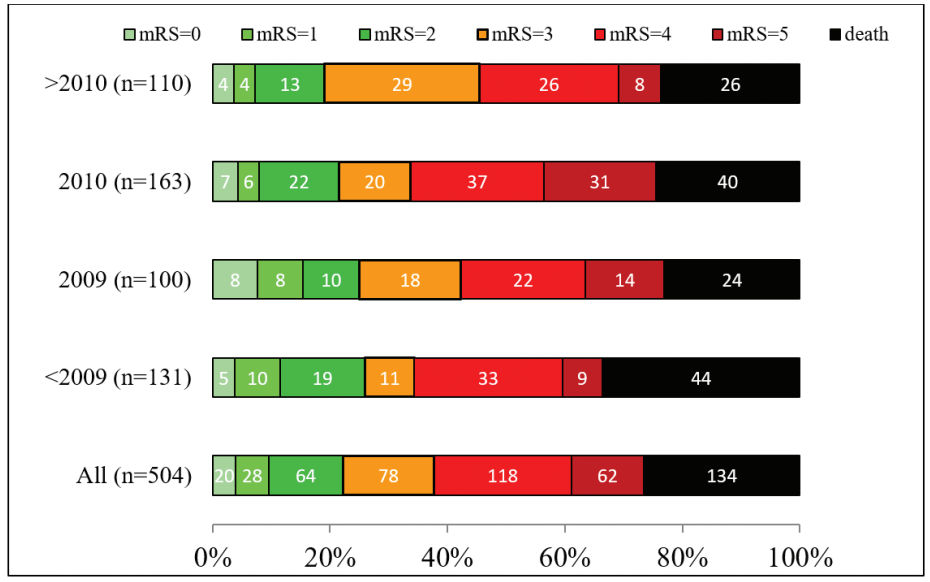
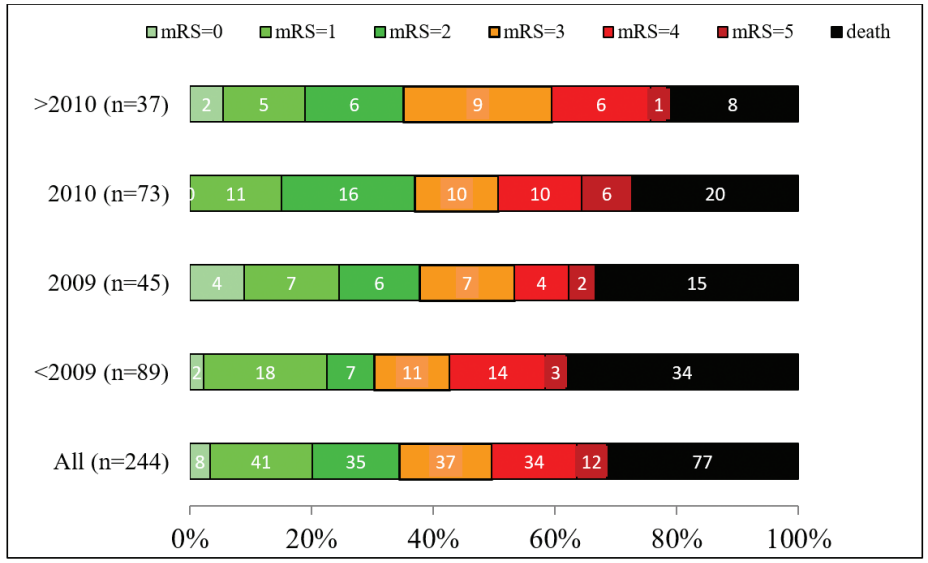


FIGURE 2 modified Rankin Scores (mRS) after 3 months. Data from two hospitals only.



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APPENDICES

APPENDIX 1 Participating centers (number of included patients)
St. Antonius hospital, Nieuwegein (n=136); Medical Center Haaglanden The Hague (n=111); HAGA hospital, The Hague (n=44); Erasmus Medical Center, Rotterdam (n=34); Maastricht University Medical Center, Maastricht (n=34); University Medical Center Utrecht, Utrecht (n=30); Academic Medical Center, Amsterdam (n=26), St. Elisabeth hospital, Tilburg (n=24); Rijnstate hospital, Arnhem (n=23); University Medical Center Nijmegen, Nijmegen (n=15); Atrium Medical Center, Heerlen (n=13), Reiner de Graaf hospital, Delft (n=8), Isala hospitals, Zwolle (n=6), Medical Spectrum Twente, Enschede (n=2), Leiden University Medical Center, Leiden (n=1).