Intra-arterial treatment in acute ischemic stroke

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Introduction

Ischemic stroke

Stroke is one of the leading causes of mortality and morbidity in the world.[1] In the Netherlands more than 40.000 people suffer from a stroke each year and over 9500 people die as a consequence every year.[2]
Ischemic stroke is caused by an acute occlusion of one of the cerebral arteries. This can be due to a cardioembolism, such as in atrial fibrillation. Other causes include small artery occlusion (associated with diabetes mellitus and hypertension) and large artery occlusion due to proximal (carotid stenosis) of more distal (occlusion of the medial cerebral artery) artherosclerosis.[3,4] Acute stroke treatment aims at resolving these acute artery occlusions.

Intravenous and intra-arterial treatment

In the search for better treatments of acute ischemic stroke, intravenous thrombolysis was developed in the early nineties. The NINDS-rtPA trial studied the effect of intravenous rtPA within the first three hours of stroke onset and showed no increased mortality. Moreover, favourable outcome was increased in patients treated with rtPA.[5] However, as only a minority of patients with anterior circulation stroke presented within the first three hours of stroke onset, further trials were done to study a longer therapeutic window. In 1998 the European multicenter trial (ECASS II) showed trends towards better outcome in patients treated with intravenous alteplase within 6 hours of stroke onset, though not proven statistically.[6] In 2008, the ECASS III trial, could confirm that intravenous thrombolysis can safely be applied within the first 4.5 hours after stroke onset without further increasing the risk of symptomatic intracranial hemorrhage.[7] These results are still used nowadays in daily practice with intravenous thrombolysis being applied within 4.5 hours of stroke onset.

In addition to the search of a longer therapeutic window, other methods of delivery of the thrombolytic drug were also investigated. The PROACT I trial studied the effect of direct intra-thrombus delivery of the thrombolytic drug, in this case urokinase, in patients with acute anterior stroke within six hours of stroke onset.[8] In this trial, only patients who showed an acute, symptomatic intracranial occlusion of the middle cerebral artery were included. Recanalization was significantly more often seen in patients treated with intra-arterial urokinase. However, intracerebral hemorrhage occurred also more often in patients treated with intra-arterial urokinase and seemed to depend on the dose of heparine that was also applied during the intra-arterial procedure (in both the urokinase and placebo groups).

The Emergency Management of Stroke (EMS) Bridging trial was the first to study the combined technique of both intravenous and intra-arterial treatment of acute ischemic stroke. Intravenous thrombolysis dose was adjusted to 0.6 mg/kg (instead of the NINDS rtPA trial dosage of 0.9mg/kg).[9] Recanalization rates were higher in the combined treatment group and number of symptomatic intracerebral hemorrhage were similar in both groups. However, these results were not associated with improved clinical outcomes. In the same year the PROACT II study was published. This trial differed from the PROACT I in that higher dosages of urokinase were applied with only a low heparine dose. This resulted in higher recanalization rates and higher rates of good clinical outcome.[10]
In 2005 the MERCI study was published.[11] This was the first study to report on mechanical thrombectomy in acute ischemic stroke. The MERCI device removes the thrombus by deployement of a corkscrew shaped coil loop into the thrombus that is retracted when the device is removed. Only patients inelegible for intravenous thrombolysis who presented within 8 hours of stroke onset were included. Recanalization rates were higher than in historical controls and succesful recanalization resulted in higher rates of good clinical outcome.[11] Subsequently the multi-MERCI study was published and showed that intra-arterial thrombectomy with the MERCI device could also safely be applied after intravenous rt-PA.[12]
In the next years several studies on the use of a newer thrombectomy device, the stent-retriever, were published. A stent-retriever attains recanalisation by deploying itself into the thrombus and relocating the thrombus against the blood vessel wall. The deployed stent then incorporates the thrombus that is retrieved with the removal of the stent-retriever. These studies all showed high recanalisation rates and high rates of good clinical outcome. However, these were either small prospective cohort studies in which patients were treated with only one type of device[13,14] or studies that compared a new type of stentretriever with the MERCI device.[15,16]
Unfortunately, subsequent larger trials showed no significant difference in functional outcome with intra-arterial therapy. IMS III compared intravenous therapy followed by intra-arterial treatment versus intravenous therapy alone.[17] Due to futility this trial was terminated prematurely. The MR RESCUE trial, that also studied the addition of intra-arterial therapy to standard care, showed no superiority of intra-arterial treatment over standard treatment alone.[18] In addition, a favourable penumbral pattern on neuroimaging did not differentiate between patients who were likely to benefit from intra-arterial therapy. Possible explanations for the observed results were the longer time to reperfusion and the limited use of stent-retrievers.

In 2015 the Dutch MR CLEAN trial published its results and was the first to show superiority of intra-arterial treatment over standard care including intravenous thrombolysis.[19] In this trial patients with an anterior circulation stroke with proven proximal intracranial artery occlusion fared clearly better if treated with intra-arterial treatment compared with standard treatment. The majority of patients treated with intra-arterial treatment also received intravenous thrombolysis prior to the intra-arterial treatment and were treated with stent-retrievers. In the same year four additional tials were published that confirmed these positive results.[20,21,22,23] In 2016 pooled data from these five trials were published.[24] This pooled analyis showed that endovascular thrombectomy led to significantly reduced disability at 90 days with a number to reduce disability by at least one level on mRS of 2.6. The treatment effect was equal among subgroups including elderly patients and patients treated more than 300 minutes after symptom onset. Recently, several trials have shown a treatment effect even beyond six hours after symptom onset.[25,26] Unfortunately, only patients fullfilling strict radiological criteria were included. Whether this patient population can be broadend is currently under study.[27]

Development of acute ischemic strke treatment in the Netherlands

In 1996 the first Dutch report on the use of intravenous thrombolysis in acute ischemic stroke was published in the "Nederlands Tijdschrift voor Geneeskunde".[28] At that time, intravenous thrombolysis was considered to be used only under very strict conditions such as treatment within three hours of stroke onset, severe strokes were excluded, and no extensive ischaemia was to be visible on CT scanning. In 2000 Maastricht and Utrecht Academic Centers reported on their first experiences with intravenous thrombolysis in the Netherlands.[29,30] In that same year intravenous thrombolysis was added to the national Stroke guideline (CBO richtlijn Beroerte) as useful treatment in acute ischemic stroke.[31]
In 2002 intra-arterial treatment was applied for the first time in the Netherlands in a patient with acute ischemic stroke. Initially, only patients with posterior circulation strokes were treated. Later on this shifted to the anterior circution stroke. The first part of this thesis describes this early development of intra-arterial treatment in the Netherlands (chapters 2 and 3).

Clinical dilemma's in intra-arterial treatment

With the more common use of intra-arterial treatment in acute ischemic stroke new dilemma's arose. Before the use of intra-arterial treatment, patients on oral anticoagulants were excluded from acute stroke treatment because intravenous

thrombolysis is not to be used in patients with prolonged clotting times. With intra-arterial treatment, the use of thrombolytics became less necessary. We studied whether intra-arterial treatment could be applied safely in patients on oral anti-coagulants and if this resulted in better clinical outcomes as well (chapter 4). Another dilemma arose from the treatment of elderly patients with acute ischemic stroke. Initially, patients aged above 80 years were excluded from intravenous thrombolysis as these patients were not included in the large trials.[5,6] In addition, the first intra-arterial treatment studies also contained relatively young patients. The PROACT trials excluded all patients aged over 85 years and the mean age in the treatment groups was around 65 years.[8,10] The MERCI studies had no upper limit but mean age was 67 years.[12,13] Chapter 5 decribes the use of intra-arterial treatment in elderly patients and whether the use of intra-arterial treatment should be considered safe and usefull with increasing age.

Diagnostics in stroke and intra-arterial treatment.

With the emergence of better treatments for acute ischeamic stroke, selection of the patients who are likely to benefit from intra-arterial treatment becomes more important. Radiological scores such as the Clot Burden Score[32], ASPECTS score[33] and collateral score[34] all aim at predicting recovery after stroke and its treatments. In chapter 6 we describe whether completeness of the circle of Willis and contribution of the carotid arteries to the cerebral circulation on CT angiography improves good clinical outcome after intra-arterial treatment. In chapter 7 we outline the use of duplex sonography in diagnosing vertebral artery stenosis in patients with posterior circulation stroke or TIA.

In chapter 8 I discuss the results of the aforementioned chapters and place them into a broader prospective.

PART I

Development of intra-arterial treatment in the Netherlands

2

Intra-arterial treatment of acute ischemic stroke: better outcome with stentretrievers?

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ABSTRACT

Background: Intra-arterial treatment is increasingly used in acute ischemic stroke. Recently, new devices have become available, aiming at better recanalization rates and outcome. We present a series of patients with acute stroke of the anterior circulation treated with intra-arterial therapy using intra-arterial thrombolysis and different types of mechanical devices.

Methods: We prospectively gathered clinical and radiological data of all patients with acute anterior stroke who were treated with intra-arterial therapy in a Dutch teaching hospital between 2009 and 2011. Patients were grouped according to the intra-arterial treatment strategy and analyzed for poor outcome (modified Rankin Scale score >2 or death), complications and recanalization rate with the Poisson regression.

Results: Eighty-four patients were treated with intra-arterial therapy, 13 with intra-arterial thrombolysis only (ND group), 22 with a Merci device (MERCI group) and 49 with a stent retriever (SR group). Overall, 52 patients (62%) had poor outcome of whom 17 (20%) died. There was a trend towards poorer outcome in the ND group (adjusted RR 1.18; 95% CI 0.74-1.88) and the MERCI group (adjusted RR 1.17; 95% CI 0.79-1.74) compared with the SR group. Furthermore, failed recanalization occurred more often in the ND group (adjusted RR 2.59; 95% CI 1.50--4.49) and MERCI group (adjusted RR 2.32; 95% CI 1.33-4.05) compared with the SR group.

Conclusion: We found higher recanalization rates with SRs. However, this resulted only in a trend towards better clinical outcome.

INTRODUCTION

Recently, three randomized controlled trials have failed to show improved clinical outcome after intra-arterial treatment in acute ischemic stroke patients, compared with standard care and intravenous thrombolysis (IVT).[1-3] By contrast, previous randomized studies have suggested a beneficial effect of intra-arterial thrombolysis compared with intravenous thrombolytic therapy both in clinical outcome[4,5] and recanalization rates.[6] Furthermore, studies using thrombectomy devices ('stent retrievers') showed highly favorable clinical outcome and recanalization rates.[7-9]

The discrepancy between the results of the recent trials and the earlier, promising results of intra-arterial treatment of acute ischemic stroke may have several reasons. First, the higher recanalization rates achieved in intra-arterial treatment compared with IVT need not to be accompanied by better clinical outcome, as the relation between successful recanalization and good clinical outcome is not clear.[10-12] Second, the recently published trials have reported on patients mainly treated with locally applied intra-arterial thrombolysis. The recently developed stent retrievers (SRs), which may achieve high recanalization rates and good clinical outcome, have been used only in few cases in the trials.[1-3] Third, time to treatment may have been longer than necessary because of the trial design, which prescribed intravenous treatment as the first line of treatment.[1,3]

Given these new insights, we assessed outcome and recanalization rates in patients with an acute stroke of the anterior circulation treated intra-arterially in our center, with the focus on the transition from intra-arterial thrombolysis towards mechanical thrombectomy. Therefore, we studied a cohort that was treated with intra-arterial treatment in every day routine as this probably gives a more realistic view of the real-life clinical practice and avoids selection bias that might occur in the setting of a clinical trial.

MATERIAL AND METHODS

We included all patients with an acute ischemic stroke who underwent intra-arterial treatment in a Dutch teaching hospital in the period from January 2009 to November 2011. Clinical and radiological data were prospectively collected in a database. The local ethics committee reviewed the research protocol and considered formal approval not indicated because this follow-up study was based on routinely collected data. Intra-arterial treatment was performed only after obtaining consent from the patient or his relatives.

On admission, all patients were examined by a neurologist or a resident in neurology and all underwent nonenhanced CT scanning of the head and computed tomography angiography (CTA) of the intra- and extracranial vessels (GE Lightspeed 64 slice). Demographic and clinical data were recorded at baseline (age, sex, time of symptom onset, baseline NIHSS, history of coronary artery disease, atrial fibrillation, diabetes, hypertension, peripheral artery disease). If the patients had no clinical or laboratory contraindications, no hemorrhage on nonenhanced CT scanning, a NIHSS ≥4, isolated aphasia or failed on intravenous treatment (alteplase: 0.9 mg/kg, max. 90 mg, 10% given as bolus and 90% by continuous infusion) or were ineligible for intravenous treatment, and CTA showed an occlusion of the internal carotid, middle or anterior cerebral artery, a neurointerventionalist was consulted immediately to arrange for intra-arterial treatment.

Intra-arterial treatment consisted of local intra-arterial thrombolysis, mechanical thrombectomy or a combination of both. For intra-arterial thrombolysis, urokinase, heparin or abciximab or a combination of these was used. Mechanical thrombectomy was performed with either a Merci retriever (Concentric Medical, Mountain View, Calif., USA), a Solitaire device (EV3, Irvine, Calif., USA), a Trevo device (Concentric Medical), a Revive device (Micrus Endovascular, San Jose, Calif., USA) or a combination of these. The neurointerventionalist decided which intra-arterial treatment was chosen. As newer devices became available over time, decisions on which intra-arterial treatment was used were influenced by availability of devices. Four interventionalists performed all intra-arterial treatments. All procedures were carried out only with local groin anesthesia except for 1 patient with extreme agitation who was put under general anesthesia. For each treated patient, the ASPECT score[13] on the initial CT scan, site of occlusion or stenosis on CTA, time to intra-arterial treatment (time from the start of symptoms until the start of angiography), dosage of thrombolytics (both intravenous and intra-arterial) and devices used were recorded. All patients underwent a CT scan 24 h after treatment or after any clinical impairment. Secondary preventive treatment was initiated according to the European guidelines.[14]

The primary outcome measure was poor outcome after 90 days measured by the modified Rankin Scale (mRS).[15,16] Poor outcome was defined as an mRS score of 3 or higher. All mRS scores were assessed by one investigator (A.D.R.) and based on outpatient clinical reports by the treating neurologist, rehabilitation physician or the treating physician at the nursing home. For analysis, patients were divided into

groups according to the type of mechanical device used initially: no device (ND), Merci device (MERCI) or SR (including the Solitaire, Trevo and Revive devices).

Secondary outcome measurements included death within 90 days after treatment, any cerebral hemorrhage within 30 days after treatment, and the recanalization rate. Intracerebral hemorrhages were graded according to the ECASS grading system.[17,18] Recanalization was scored at the end of the angiography by means of the TICI score.[19] If the TICI score at the end of the angiography was below 2b, recanalization was defined as failed. Both the ECASS grading and the TICI score were assigned by two neuroradiologists (G.J.L.N. and B.F.v.d.K.).

Statistical Analysis

For analysis, time to initiation of intra-arterial treatment was trichotomized as follows: 0--3, 3--6 and 6--9 h. Furthermore, we defined vascular history as positive if a patient had coronary artery disease, atrial fibrillation, diabetes, hypertension or peripheral artery disease. Descriptive statistics were used for baseline characteristics in the three treatment groups. Frequencies of poor outcome and failed recanalization were compared between the three treatment groups with risk ratios (RRs) and 95% confidence intervals (CI). Since the SR group was the largest, we used it as reference in both analyses. Adjusted RRs were calculated with the Poisson regression. As patients could have been treated with more than one device (both Merci device and SR) in order to reach recanalization, we also calculated adjusted RRs for the different treatment groups according to the last device used.

RESULTS

In the period from January 2009 to November 2011, 84 patients with an acute stroke of the anterior circulation were treated with intra-arterial therapy at our center. Baseline characteristics of these patients are given in table 1.

Thirty-three patients (39%) were women and the median age was 64 years. Thirteen patients were treated with intra-arterial thrombolysis only (ND), 22 with the Merci device (MERCI) and 49 with SR. Eight patients primarily treated with the Merci device received additional treatment with an SR. No patients in the SR group received additional treatment with the Merci device.

Baseline NIHSS did not differ between groups. In 90% of the patients, intra-arterial treatment was started within 6 h after symptom onset. In the MERCI and SR groups, more patients had an internal carotid artery occlusion leading to prolonged treatment times. Almost all patients (n = 11, 85%) in the ND group

received intra-arterial urokinase. By contrast, in the SR group, only 57% of the patients received urokinase. Abciximab was most often administered in the MERCI group (68%).

Overall, 52 patients (62%) had poor outcome (mRS >2) of whom 17 died (20%; table 2). As shown in figure 1, poor outcome (mRS >2) occurred less frequently in the SR group. Table 3 shows the RRs for poor outcome for the three treatment modalities. After adjustment for clinical and treatment parameters, we found no significant differences in the RRs for poor outcome between the three treatment modalities. Neither did we find a change in the RR for poor outcome after adjustment for recanalization. Nevertheless, there was a trend towards poorer outcome in the ND group compared with the SR group (adjusted RR 1.18; 95% CI 0.74-1.88). A similar trend was observed in the comparison between the MERCI and SR groups (adjusted RR 1.17; 95% CI 0.79-1.74). If patients were grouped according to the last device used, these trends partially resolved (table 4).

Intracerebral hemorrhage was the most frequent complication of intra-arterial treatment. We were able to retrieve the posttreatment CT scans of 82 patients (98%). For 2 patients, no follow-up scans were made, 1 patient suffered from end-stage lung cancer and died soon after the intervention. The other patient was transferred back to the primary referring center after intra-arterial treatment, where no follow-up scans were made.

Overall, 33 patients (40%) developed an intracerebral hemorrhage. Patients primarily treated with the Merci device or SR showed more intracerebral hemorrhages (43 and 44 vs. 23% in the ND group), although these were mostly hemorrhagic infarctions without a space-occupying effect (table 2) and not leading to additional symptoms. Severe parenchymal bleedings with a space-occupying effect (PH-2) were least seen in the SR group.

Three patients (all in the MERCI group) developed a groin hematoma; 1 patient deteriorated because of accumulation of clot material in the intracranial vessels caused by manipulation of the catheter; 1 patient developed rectal blood loss after treatment, and 1 patient experienced an epileptic seizure during the intra-arterial procedure. In 1 patient, the Solitaire stent detached from the pusher wire and could not be retrieved resulting in a permanent occlusion of the middle cerebral artery.

Overall, recanalization failed in 46% (n = 39) of the treated patients. In the ND group, recanalization failed in 77% (n = 10), in 68% (n = 15) in the MERCI group and in 29% (n = 14) in the SR group (table 2). The RRs for failed recanalization at the end of the intra-arterial treatment showed significantly more failures in the

ND group compared with SR treatment (adjusted RR 2.59; 95% CI 1.50-4.49) and the Merci device (adjusted RR 2.32; 95% CI 1.33-4.05; table 5).

If the patients were analyzed according to the last device used, those treated without device experienced significantly more failed recanalization compared with the SR (adjusted RR 2.22; 95% CI 1.45-3.40), and there was a trend towards more failed recanalization in those treated with the Merci device versus the SR (RR 1.31; 95% CI 0.69-2.47; table 4).

DISCUSSION

In this paper, we presented a large single-center cohort of patients with an acute ischemic stroke of the anterior circulation treated with intra-arterial therapy in every day clinical practice. Our study group reflects the developments in intra-arterial treatment of acute ischemic stroke, with a shift from local intra-arterial thrombolysis towards mechanical thrombectomy. Our results confirm the findings in recent reports showing higher recanalization rates with SRs.[7,8,20] However, we did not find a significant difference in clinical outcome between the different treatment modalities. Nevertheless, there was a trend towards better clinical outcome in patients treated with SRs compared with thrombolysis alone and Merci device.

Overall, 62% of our patients had poor outcome at 3 months after treatment and 20% had died. These outcome rates are similar to those in the IMS III and SYNTHESIS trials (poor outcome in 59.2 and 58%, respectively)[1, 2] and more favorable compared with the MR RESCUE trial (poor outcome in 86% in the penumbral group and 91% in the nonpenumbral group).[3] Death rates after 3 months were comparable to those found in the SYNTHESIS and MR RESCUE trials (19.1% and 18% for the penumbral group and 20% for the nonpenumbral group, respectively).[2,3] In our population (40%), bleeding complications were similar to those seen in the Multi-MERCI study (40.2%)[21] and less frequent compared with the MR RESCUE trial (64.7% in the penumbral group and 76.7% in the nonpenumbral group).[3] From previous studies, it is known that only PH-2. hemorrhages influence outcome and death after 3 months.[22,23] We found PH-2 hemorrhages in 7% of our patients which is comparable to the IMS III study (6.0%)[1] and the TREVO 2 trial (6.7%)[7].

Successful recanalization was reached in 54% of the patients with the highest recanalization rates found (71%) in the SR group. By contrast, in the MERCI group, 32% of the patients reached successful recanalization. Previous studies have also shown higher recanalization rates in patients treated with an SR compared with

the Merci device, confirming that the SR is currently the most powerful tool to achieve recanalization.[7,8,20]

A possible limitation of our study is the selection of our patients. Intra-arterial treatment was initiated after counseling between the vascular neurologist and the neurointerventionalist, which may have led to selection bias. However, this is also a strength because it reflects real-life clinical practice. Another limitation is that this study is a single-center study, possibly limiting generalization of our findings. On the contrary, due to the single-center design, all patients were treated according to the uniform emergency and stroke unit protocols resulting in a good comparability between the treatment groups.

Our study has several strengths. First, only four interventionalists carried out all intra-arterial treatments, and all procedures were performed in the same angiography room and with the same angiography setting. Second, there was a 24/7 availability of intra-arterial therapy during the whole study period resulting in relatively short treatment times. Third, we also included patients who were treated with the SR device only. Last, we adjusted the calculated RRs for possible confounders resulting in a valid comparison between the treatment groups.

The fact that the higher recanalization rates in our study did not result in a better clinical outcome may have several causes. First, TICI 2b was scored as successful recanalization, but this does not represent a complete reopening of the vessel. Previous studies have shown that reocclusion occurs in 17-18% of intra-arterially treated patients.[24,25] Reocclusion seems to occur more often after incomplete recanalization and is associated with poor outcome.[25] Another factor may be the time to the start of the intra-arterial treatment. In 10% of our study population, intra-arterial treatment was initiated 6 h or more after the start of complaints. In these cases, recanalization may have been reached, with the ischemic damage already being irreversible. However, the ASPECTS scores were rather high in all groups indicating little ischemic damage before the start of the intra-arterial therapy.[13] Another explanation might be that the TICI score has limitations in grading whether a treatment was successful. The TICI scoring system specifically evaluates recanalization at the primary occlusion. During intra-arterial treatment, distal emboli or emboli to other parts of the cerebral circulation might occur as a result of the clot manipulation. These occlusions, other than the primary occlusion, are not included in the TICI score.

CONCLUSIONS

Up to date, intra-arterial treatment has not been proven to be superior to IVT. Nevertheless, the recent large trials addressing this issue have mainly used local intra-arterial thrombolytics instead of the probably more effective SRs. Our study suggests that, given the higher recanalization rates achievable with SRs, future trials, including SRs as main treatment strategy, may show a benefit from intra-arterial treatment.

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TABLES

TABLE 1 Baseline characteristics according to the mechanical device used

	All (n = 84)	ND (n = 13)	MERCI (n = 22)	SR (n = 49)
Median age (min–max), years	64 (23–89)	67 (44–87)	72 (23–89)	60 (26–80)
Female sex, n	33 (39%)	5 (39%)	11 (53%)	17 (35%)
History of vascular disease[a], n	50 (60%)	9 (69%)	9 (41%)	32 (65%)
Mean NIHSS (min–max)	18 (4–38)	18 (4–32)	17 (6–35)	18 (7–83)
Intravenous thrombolysis, n	66 (79%)	12 (92%)	15 (68%)	39 (80%)
Treatment interval[b], h				
0–3	33 (39%)	3 (23%)	10 (46%)	20 (41%)
3–6	43 (51%)	7 (54%)	10 (46%)	26 (53%)
6–9	8 (10%)	3 (23%)	2 (9%)	3 (6%)
ICA occlusion, n	26 (31%)	2 (15%)	6 (27%)	18 (37%)
Mean ASPECTS score[c] (min–max)	9.2 (3–10)	9.2 (5–10)	9.1 (7–10)	9.2 (3–10)
Intra-arterial urokinase, n Median IU (min–max)	56 (67%) 200,000 (0–900,000)	11 (85%) 300,000 (0–750,000)	17 (77%) 325,000 (0–900,000)	28 (57%) 100,000 (0–850,000)
Abciximab, n	22 (26%)	3 (23%)	15 (68%)	4 (8%)
Heparin, n	13 (16%)	2 (15%)	10 (46%)	1 (2%)
Treatment time (SD)[d], min	106 (44)	75 (22)	112 (43)	111 (47)

[a] Either diabetes, coronary artery disease, peripheral artery disease, hypertension or atrial fibrillation. [b] From the start of symptoms until the start of angiography. [c] Initial ASPECTS score; n = 83. [d] Duration of the intra-arterial treatment from the start of angiography until the end of the procedure.

TABLE 2 Outcomes according to the mechanical device used

	All (n = 84)	ND 0(n = 13)	MERCI (n = 22)	SR (n = 49)
Poor outcome[a]	52 (62)	09 (69)	15 (68)	28 (57)
Intracerebral hemorrhage[b]	33 (40)	03 (23)	09 (43)	21 (44)
HI 1	11 (13)	01 (8)	03 (14)	07 (15)
HI 2	15 (18)	00 (0)	04 (19)	11 (23)
PI 1	01 (1)	00 (0)	00 (0)	01 (2)
PI 2	06 (7)	02 (15)	02 (10)	02 (4)
Death	17 (20)	03 (23)	07 (32)	07 (14)
Failed recanalization[c]	39 (46)	10 (77)	15 (68)	14 (29)

Values are n (%). [a] Defined as mRS >2; [b] n = 82; [c] TICI <2b.

TABLE 3 Unadjusted and adjusted RRs for poor outcome according to the first device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 13)	SR (n = 49)	MERCI (n = 22)	SR (n = 49)	MERCI (n = 22)	ND (n = 13)
Poor outcome[a], n	9 (69%)	28 (57%)	15 (68%)	28 (57%)	15 (68%)	09 (69%)
Unadjusted RR	1.21 (0.78–1.87)		1.19 (0.82–1.74)		0.95 (0.62–1.56)	
Adjusted RR						
Age	1.14 (0.72–1.79)		1.18 (0.81–1.71)		1.04 (0.64–1.66)	
Female sex	1.22 (0.78–1.91)		1.23 (0.86–1.78)		1.01 (0.64–1.61)	
History[b]	1.20 (0.77–1.89)		1.25 (0.85–1.85)		1.04 (0.64–1.70)	
NIHSS	1.22 (0.79–1.88)		1.20 (0.82–1.75)		0.99 (0.62–1.57)	
IVT	1.25 (0.81–1.92)		1.16 (0.80–1.70)		0.93 (0.59–1.49)	
IAT	1.21 (0.77–1.88)		1.19 (0.82–1.74)		0.99 (0.62–1.57)	
Treatment interval[c]	1.19 (0.75–1.88)		1.18 (0.81–1.72)		1.00 (0.60–1.65)	
Treatment time[d]	1.31 (0.80–2.13)		1.19 (0.82–1.74)		0.91 (0.55–1.51)	
ASPECTS	1.24 (0.79–1.95)		1.22 (0.85–1.76)		0.98 (0.62–1.56)	
Failed recanalization[e]	1.17 (0.73–1.87)		1.16 (0.77–1.74)		0.99 (0.63–1.57)	
Three factors[f]	1.18 (0.74–1.88)		1.17 (0.79–1.74)		0.99 (0.61–1.62)	

IAT =Intra-arterial therapy. [a] Defined as mRS >2. [b] Either diabetes, coronary artery disease, peripheral artery disease, hypertension or atrial fibrillation. [c] From the start of symptoms until the start of angiography. [d] Duration of the intra-arterial treatment from the start of angiography until the end of the procedure. [e] TICI <2b. [f] Adjusted for age, history of vascular disease, and intravenous thrombolysis.

TABLE 4 Unadjusted and adjusted RRs for poor outcome and failed recanalization according to the last device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 12)	**SR (n = 57)**	**MERCI (n = 15)**	**SR (n = 57)**	**MERCI (n = 15)**	**ND (n = 12)**
Poor outcome[a], n	8 (67%)	33 (58%)	11 (73%)	33 (58%)	11 (73%)	08 (67%)
Unadjusted RR	1.15 (0.73–1.82)		1.27 (0.87–1.85)		1.10 (0.66–1.82)	
Adjusted RR for three factors[b]	1.10 (0.68–1.78)		1.16 (0.78–1.72)		1.05 (0.61–1.81)	
Failed recanalization[c], n	10 (83%)	21 (37%)	8 (53%)	21 (37%)	8 (53%)	10 (83%)
Unadjusted RR	2.26 (1.48–3.46)		1.45 (0.81–2.59)		0.64 (0.37–1.10)	
Adjusted RR for three factors[d]	2.22 (1.45–3.40)		1.31 (0.69–2.47)		0.59 (0.32–1.07)	

[a] Defined as mRS >2. [b] Adjusted for age, history of vascular disease, and intravenous thrombolysis.
[c] TICI <2b.

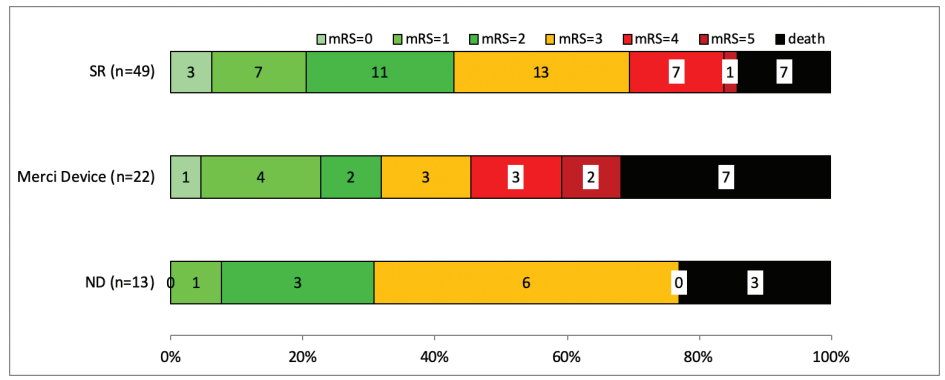
TABLE 5 Unadjusted and adjusted RRs for failed recanalization according to the first device used

	ND vs. SR		MERCI vs. SR		MERCI vs. ND	
	ND (n = 13)	**SR (n = 49)**	**MERCI (n = 22)**	**SR (n = 49)**	**MERCI (n = 22)**	**ND (n = 13)**
Failed recanalization[a], n	10 (77%)	14 (29%)	15 (68%)	14 (29%)	15 (68%)	10 (77%)
Unadjusted RR	2.69 (1.58–4.59)		2.39 (1.41–4.04)		0.89 (0.59–1.34)	
Adjustment RR for three factors[b]	2.59 (1.50–4.49)		2.32 (1.33–4.05)		0.90 (0.58–1.39)	

[a] TICI <2b. [b] Adjusted for age, history of vascular disease, and intravenous thrombolysis.

FIGURES

FIGURE 1 mRS score according to the treatment modality



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3

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

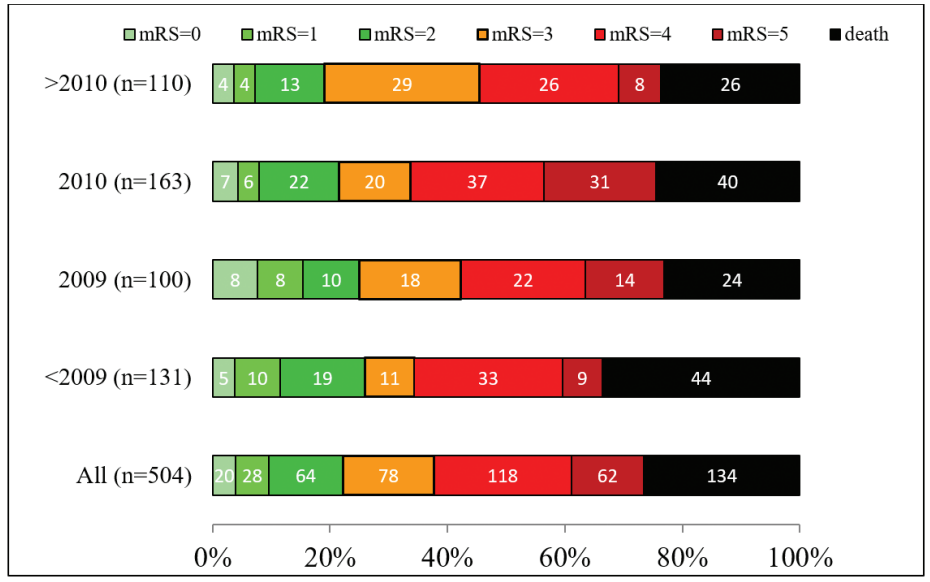
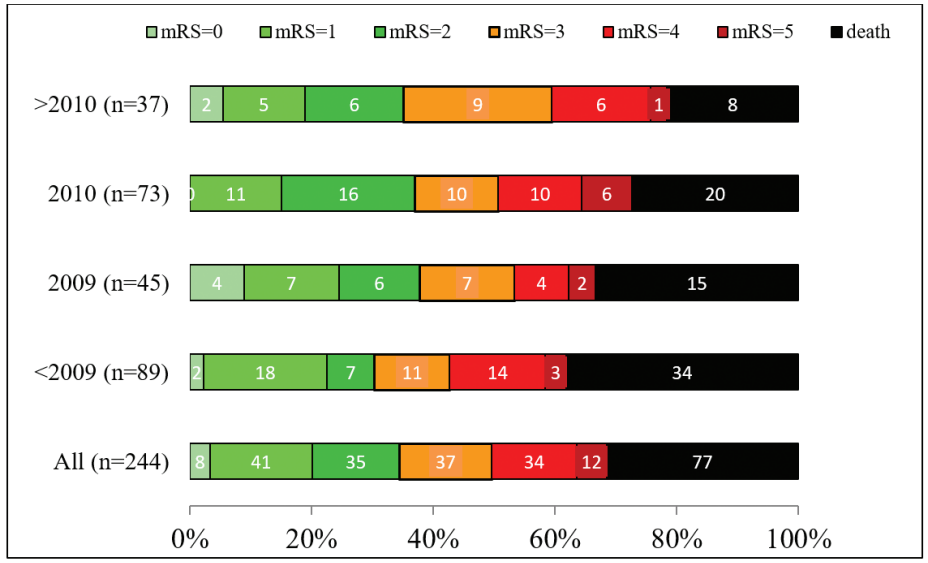


FIGURE 2 modified Rankin Scores (mRS) after 3 months. Data from two hospitals only.



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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).

PART II

Intra-arterial treatment in specific treatment groups

4

The effect of age on outcome after intra-arterial treatment in acute ischemic stroke: a MR CLEAN pretrial study

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ABSTRACT

Background

In recent randomized controlled trials (RCTs) intra-arterial treatment (IAT) has been proven effective and safe for patients with acute ischemic stroke (AIS). So far, there seemed to be no interaction between older age (>80) and main treatment effect. We studied the association of older age with outcome and adverse events after IAT in a cohort of intra arterially treated patients.

Methods and findings

Data from all AIS patients with proven proximal anterior circulation cerebral artery occlusion who were intra arterially treated between 2002 until the start of the MR CLEAN trial were studied retrospectively. Duration of the procedure, recanalization (Thrombolysis In Cerebral Infarction score (TICI)), early neurological recovery (i.e. decrease on NIHSS of ≥8 points) after one week or at discharge, good functional outcome at discharge by modified Rankin Scale (mRS≤2) and the occurrence of neurological and non-neurological adverse events were assessed and the association with age was investigated. In total 315 patients met our inclusion criteria. Median age was 63 years (range 22-93) and 17 patients (5.4%) were over 80. Age was inversely associated with good functional outcome (adjusted Odds Ratio (aOR) 0. 80, 95% CI: 0.66-0.98) for every 10 years increase of age. Age was not associated with longer duration of the procedure, lower recanalization rate or less early neurological recovery. The risk of all adverse events (aOR 1.27; 95% CI: 1.08-1.50) and non-neurological adverse events (aOR 1.34; 95% CI: 1.11-1.61) increased, but that of peri-procedural adverse events (aOR 0.79; 95% CI: 0.66-0.94) decreased with age.

Conclusion

Higher age is inversely associated with good functional outcome after IAT in patients with AIS. However, treatment related adverse events are not related to age. These findings may help decision making when considering treatment of older patients with AIS.

BACKGROUND

Stroke is one of the leading causes of death and disability. Risk of stroke increases with age.[1] Higher age is often an exclusion criterion in randomized trials especially in those evaluating acute treatment. This applied to the first trials evaluating the effect of intravenous thrombolysis.[2]

Later studies and meta-analyses, however, demonstrated the effect of intravenous alteplase in older patients.[3-5] Recently, the safety and efficacy of intra-arterial treatment (IAT) was established in several large trials.[5-9] Although not all trials included patients aged >80 years,[6,7] in those intervention trials that included older patients treatment effect seemed similar in the young and the old, but the proportions of older patients were small, suggesting selection bias.[8,10,11] In older patients, longer procedure time and higher complication rates may be expected, due to technical difficulties such as advanced atherosclerosis and vessel tortuosity. Low quality collateral circulation and brain tissue vulnerability may lead to delayed or diminished neurological recovery.

We studied the association between age and procedure duration, rate of recanalization, occurrence of adverse events, neurological recovery and functional outcome after IAT in patients with acute ischemic stroke (AIS) due to a large vessel occlusion in the anterior circulation. We analysed data from the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) pretrial registry.

METHODS

Patients

In this cohort study, we selected patients with a clinical diagnosis of AIS similar to criteria of MR CLEAN[12] from the prospective patient registries of the participating centers. Approval for this retrospective study was obtained by the central medical ethical committee of the Erasmus University Medical Center Rotterdam and because of the retrospective nature of the study no written informed consent was obliged from each participant. Patients were treated intra-arterially in 16 large stroke hospitals in The Netherlands between October 2002 and start of participation of the hospital in the MR CLEAN trial, between 2010 and 2012. We selected all patients with a neurological deficit on the National Institutes of Health Stroke Scale (NIHSS) of at least two points. Intracranial haemorrhage was ruled out by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Intracranial arterial occlusion was confirmed by Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography

(DSA) and was located in the distal part of the internal carotid artery, the middle cerebral artery (M1 and M2 segment), or the anterior cerebral artery (A1 segment). Intra-arterial treatment had to be started within 6 h from onset of symptoms and patients had to be 18 years or older. There was no upper age limit. Patients were excluded if systolic blood pressure was > 185 mmHg or diastolic blood pressure was >110 mmHg, if blood glucose level was <2.7 or >22.2 mmol/l, if intravenous treatment with alteplase was given in a dose exceeding 0.9 mg/kg or 90 mg, or if intravenous alteplase was given despite contraindications such as major surgery, gastro-intestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at a non-compressible site within the previous 7 days. Specific exclusion criteria applied for patients treated mechanically or with intra-arterial thrombolysis. Patients treated with mechanical devices were excluded when there was laboratory evidence of coagulation abnormalities (platelet count <40*109/l, APTT>50 s or INR>3.0). Patients treated with intra-arterial thrombolysis were excluded when the platelet count was <90 * 109/l, APTT>50 s, or INR>1.7.

We obtained all clinical and radiological data of the patients who were prospectively registered in the participating centres and all patient data were anonymized prior to analysis. Missing values of NIHSS were reconstructed with the help of a validated algorithm.[13]

Intervention

Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion. At the level of the occlusion the interventionist could decide to deliver a thrombolytic agent, perform mechanical thrombectomy or both. This choice was left to the discretion of the interventionist. Pre- and post-intervention angiograms were made to assess location and grade of occlusion and final recanalization.

Outcomes

We tabulated baseline risk factors and results by tertiles of age.

Functional outcome was assessed by means of the modified Rankin Scale (mRS) at discharge. Good functional outcome was defined as a mRS score of 0, 1 or 2. Neurological status after the intervention was evaluated with the NIHSS, assessed at one week after the procedure (or at discharge in case discharge was within the first week). Early neurological recovery was defined as a decrease on the NIHSS of 8 points or more after one week or at discharge compared with baseline NIHSS. The duration of the procedure was determined by the time interval between the first and last angiographic series plus 5 min. Occlusion status was assessed with

the TICI score, at the start and at the end of the procedure. Recanalization was defined as a TICI score of 2b or 3 at the end of the procedure. Digital subtraction angiography images were assessed by one of three experienced neuroradiologists (PB, GL, SJ). They were blinded for clinical data of the patient, and did not assess angiograms from their own centre.

Adverse events

We defined symptomatic intracerebral haemorrhage (SICH) as intraparenchymal blood on cranial CT being compatible with neurological deterioration. Symptomatic haemorrhagic transformation was defined as CT detected haemorrhagic transformation of the acute infarct accompanied by neurological deterioration. Recurrent ischemic stroke, stuttering stroke, brain herniation and craniotomy accompanied with neurological deterioration were all clustered as progression of ischemic stroke.

Adverse events were categorized as neurological adverse events, neurological serious adverse events, nonneurological adverse events and peri-procedural adverse events. Neurological adverse events were any symptomatic intracerebral haemorrhage, haemorrhagic transformation, progression of ischemic stroke, intracranial haemorrhage and transient neurological dysfunction including seizures. Neurological serious adverse events were symptomatic intracranial haemorrhage, haemorrhagic transformation of the infarct and progression of ischemic stroke with an increase on the NIHSS of 4 points or more. Nonneurological adverse events, without neurological sequelae, were pneumonia, urinary tract infections, cardiac rhythm disturbances, and other complications. Other complications included pulmonary embolism, cerebral venous thrombosis, bacteraemia, use of antibiotics without a confirmed infection, oral mycosis, delirium, acute kidney failure and falls. Peri-procedural adverse events included development of distal micro-emboli, technical problems including unfolding of stent retriever, iatrogenic damage of arterial vessel wall, groin hematoma and peri-procedural seizures.

Statistical analysis

We analysed the association of age with good functional outcome (mRS 0-2) with regression models expressed as odds Ratio (OR). Multiple linear regression was used to determine the association of age with the duration of the procedure and the neurological outcome (NIHSS) after the procedure. We analyzed the association of age with recanalization and occurrence of adverse events, with logistic regression models. In all regression models, age was a continuous variable, and

effect parameters were expressed per 10 years of age. Precision of effect estimates was described by 95% confidence intervals. We always adjusted for sex, onset to treatment time, stroke severity at baseline (NIHSS), use of a retrievable stent and presence of intracranial carotid T occlusions. Values missing at random were imputed with their mean or modus. Statistical analyses were carried out with Stata statistical software (release 12.0 College Station, Texas).

RESULTS

During the study period 529 patients with ischemic stroke were treated with IAT in the participating centers. Of these, 160 had a posterior circulation stroke and were not included in this study. From the remaining 369 patients, we excluded 19 (5.1%) who underwent IAT more than 6 h after symptom onset, 15 (4.1%) because of AIS secondary to a surgical procedure, 1 patient (0.3%) in whom carotid artery dissection was the cause and 1 patient (0.3%) who had a distal anterior circulation cerebral artery occlusion (M3 segment). We also excluded 2 patients (0.5%) because of age <18 years, 4 patients (1.0%) because systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, 11 patients (3.0%) because of coagulation disturbances and 1 patient (0.3%) because of pre-treatment glucose level >22.2 mmol/l.

As a result 315 patients were included. Median age of the included patients was 63 years (range 22-93) and 17 patients (5%) were older than 80. Median NIHSS was 16 (IQR 12-18) and 245 patients (78%) were treated with intravenous alteplase prior to IAT (Table 3.1).

IAT consisted of stent thrombectomy in 132 (42%). The median duration of the procedure was 116 min (IQR 80-153). At the end of the procedure a TICI 2b or 3 was reached in 119 patients (43%) (see Table 3.2). SICH occurred in 23 patients (7.0%) and prevalence of SICH was highest in the third age tertile (10/96, 10%). Mortality was higher in older patients, 22% in the third tertile versus 9% in the first tertile.

We found a significant inverse association between age and good functional outcome (mRS 0-2) (aOR 0.80; 95% CI: 0.66-0.98) for every 10 years increase of age. Furthermore, we found a significant association between age and the occurrence of all adverse events (aOR 1.27, 95% CI: 1.08-1.50) as well as the occurrence of non-neurological adverse events (aOR 1.34, 95% CI: 1.11-1.61) (Table 3.3). Age was significantly associated with less peri-procedural adverse events (aOR 0.79, 95% CI: 0.66-0.94) (Table 3.4). We found no association between age and neurological recovery after IAT (aOR 0.88, 95% CI: 0.75-1.04). No associations were observed between age and duration of the procedure (regression coefficient -2.96 95% CI: -7.35-1.44), recanalization (aOR 0.94, 95% CI: 0.79-1.11), neurological serious adverse events (aOR 1.22, 95% CI: 0.96-1.56) and neurological adverse events (aOR 1.05, 95% CI: 0.89-1.24).

DISCUSSION

In the present study we show that the likelihood of good functional outcome after IAT was inversely associated with age, whereas we did not find an increased risk for neurological (serious) adverse events after IAT in older patients although the likelihood of developing non-neurological adverse events increased with age. Interestingly, the risk of developing peri-procedural adverse events decreased with increasing age.

Our results are in line with recent studies that also showed lower rates of good clinical outcome in elderly stroke patients treated with IAT. These retrospective nonrandomized studies do not allow conclusions about the treatment effect of IAT in older aged patients. Therefore results of randomized controlled trials are needed. Several large randomized controlled trials have investigated the effect of IAT in AIS, but only three of these had no upper age limit.[10,14,15] In two of those no effect modification by age was present,[8,10] but a more refined analysis on age has not been performed so far. Selection bias, by including only the relatively healthier older patients in the trials, cannot be excluded.

Our study has several limitations. First, although patients were prospectively registered, all patient data had to be assessed retrospectively from the hospital records. However, we are confident that all intra-arterially treated patients are included and that there are no missing data on important medical information as the occurrence of adverse events, because all centers kept prospective registries of intra-arterially treated patients and our research team had access to all data. Second, we did not systematically register comorbidity, such as previous myocardial infarction and previous ischemic stroke. However, it is well known that comorbidity increases with age and this may explain some of the excess mortality and poor outcome. Third, the relatively low percentage of recanalization might be explained by the relative low percentage of treatments with latest generation thrombectomy devices, as these devices only entered the market halfway the inclusion period.[16] These so called stent retrievers have a proven better recanalization success rate than the first generation devices.[11,17] Fourth, the small percentage of patients above 80 years old (5%) in this cohort suggests a strong selection bias. This might explain the lower peri-procedural adverse event rate in the older patients: exclusion from treatment of patients with hostile vessels

is more likely when patients are older. Fifth, the lack of a reference population to compare with and to know if there was a selection bias for the higher aged subjects who underwent IAT. However, the goal of this study was to describe a relation between age and outcome in intra-arterially treated patients to assess whether un upper age limit in randomized controlled trials is indicated. To have the best comparison between age and treatment effect in age in IAT we need the results of randomized controlled trials.

Our study has several strengths: First, we could make use of prospective registries of the participating hospitals in which all IAT treated patients were documented. As such, all patients treated in these centers are included in this study. Second, all stroke intervention centers in the Netherlands participated in this study what makes it very unlikely that more than just a few patients were not registered and included in this study. And thirdly, all participating centers were comprehensive stroke services with a central function for acute stroke treatment for regional hospitals.

CONCLUSION

In summary, we confirm that older age is inversely associated with good functional outcome after IAT in patients with AIS. Furthermore age is associated with increased non-neurological adverse events. Our results, however, do not confirm an increased risk of treatment related events nor an increase of neurological adverse events. This might explain the findings in recent RCTs that older age does not interact with treatment effect of IAT. Knowledge about the effect of age on clinical outcome, procedure related features and adverse events of IAT may enhance proper decision making in treatment of older patients with AIS.

TABLES

TABLE 1 Baseline characteristics of the included patients

	Overall 22–93 years	**Tertile 1** 22–55 years	**Tertile 2** 56–70 years	**Tertile 3** 71–93 years
Number of patients	315	106	113	96
Age, median (IQR)	63 (52–72)	48 (40–52)	64 (60–68)	77 (73–80)
Male sex, n (%)	168 (53 %)	52 (49 %)	75 (66 %)	41 (43 %)
Systolic blood pressure, mean (SD)	146 (23)	138 (21)	149 (24)	152 (20)
Diastolic blood pressure, mean (SD)	82 (16)	78 (16)	85 (15)	84 (17)
Stroke severity at admission (NIHSS) mean (SD)[a]	16 (6.0)	15 (5.0)	16 (5.0)	16 (7.0)
Prior treatment with intravenous rtPA, n (%)[b]	245 (78 %)	77 (73 %)	91 (81 %)	75 (80 %)
Time from onset symptoms to intra-arterial treatment (minutes), mean (SD)[c]	93 (58)	96 (70)	87 (67)	77 (53)
Use of stent, n (%)[d]	132 (42 %)	41 (39 %)	52 (46 %)	39 (41 %)
Carotid T top occlusion, n (%)[e]	25 (8.0 %)	11 (10 %)	11 (10 %)	3 (3.0 %)

SD standard deviation, IQR interquartile range, ER emergency room. [a]65 unknown (21%); [b]13 unknown (4.1%); [c]177 unknown (56%); [d]4 unknown (0.6%); [e]2 unknown (0.6%)

TABLE 2 Clinical and radiological outcomes in patients with IAT for acute ischemic stroke caused by proximal arterial intracranial occlusion of the anterior circulation by age

	Overall 22–93 years	**Tertile 1** 22–55 years	**Tertile 2** 56–70 year	**Tertile 3** 71–93 years	**P for trend**
N patients	315	106	113	96	
Procedural duration in minutes, median (IQR)	116 (80–153)	125 (81–160)	110 (78–143)	116 (82–158)	0.19
Recanalization (TICI 2b and TICI 3)	119 (43 %)	41 (34 %)	45 (38 %)	33 (28 %)	0.46
TICI 0, *n* (%)	38 (14 %)	12 (12 %)	12 (12 %)	14 (17 %)	
TICI 1, *n* (%)	18 (6.0 %)	10 (10 %)	5 (5.0 %)	3 (4.0 %)	
TICI 2a, *n* (%)	103 (37 %)	36 (36 %)	35 (36 %)	32 (39 %)	
TICI 2b, *n* (%)	36 (13 %)	13 (13 %)	17 (18 %)	6 (7.0 %)	
TICI 3, *n* (%)	83 (30 %)	28 (28 %)	28 (29 %)	27 (33 %)	
NIHSS after IAT, mean (SD)	13 (12)	12 (10)	13 (11)	15 (13)	0.14
Neurological recovery (decrease in NIHSS of 8 points or more), *n* (%)	133 (42 %)	47 (44 %)	49 (43 %)	37 (39 %)	
Functional outcome, mRS, *n* (%)					0.03
mRS 0–1, *n* (%)	37 (12 %)	15 (14 %)	9 (8 %)	13 (14 %)	
mRS 0–2, *n* (%)	78 (25 %)	29 (27 %)	27 (24 %)	22 (23 %)	
mRS 0–3, *n* (%)	132 (42 %)	46 (43 %)	49 (43 %)	37 (39 %)	
mRS 0–4, *n* (%)	222 (70 %)	80 (75 %)	82 (73 %)	60 (63 %)	
mRS 0–5, *n* (%)	261 (83 %)	96 (91 %)	92 (81 %)	73 (76 %)	
Death, *n* (%)	51 (16 %)	10 (9 %)	20 (18 %)	21 (22 %)	0.01
All adverse events, *n* (%)	177 (56 %)	46 (43 %)	71 (63 %)	60 (63 %)	0.004
Serious adverse events, *n* (%)	47 (15 %)	13 (12 %)	18 (16 %)	16 (17 %)	0.11

TABLE 2 Continued

Symptomatic intracranial hemorrhage, *n* (%)	23 (7.0 %)	5 (5.0 %)	8 (7.0 %)	10 (10 %)	
Hemorrhagic transformation infarct, *n* (%)	6 (2.0 %)	2 (2.0 %)	4 (4.0 %)	0 (0.0 %)	
Progression of ischemic stroke, *n* (%)	32 (10 %)	8 (8.0 %)	13 (12 %)	11 (12 %)	
Neurological adverse events, *n* (%)	119 (38 %)	38 (36 %)	48 (42 %)	33 (34 %)	0.60
Asymptomatic intracranial hemorrhage, *n* (%)	22 (7 %)	2 (2.0 %)	15 (13 %)	5 (5.0 %)	
Seizures, *n* (%)	16 (5.0 %)	4 (4.0 %)	4 (4.0 %)	8 (8.0 %)	
Non-neurological adverse events, *n* (%)	101 (32 %)	20 (19 %)	40 (35 %)	41 (43 %)	0.002
Pneumonia, *n* (%)	41 (13 %)	9 (8.0 %)	16 (14 %)	16 (17 %)	
Urinary tract infection, *n* (%)	18 (6.0 %)	5 (5.0 %)	5 (4.0 %)	8 (8.0 %)	
Cardiac arrhythmias, *n* (%)	35 (11 %)	3 (3.0 %)	17 (15 %)	15 (16 %)	
Other, *n* (%)	29 (9.0 %)	8 (8.0 %)	9 (8.0 %)	12 (13 %)	

TABLE 3 Age in association with clinical neurological and radiological outcomes. Effect parameters are expressed per 10 years of age

Association		Unadjusted	Sex adjusted	Fully adjusted
Intervention				
Duration of procedure, minutes	BC	−2.80 [−7.10 to 1.45]	−2.80 [−7.10 to 1.45]	−2.96 [−7.35 to 1.44]
Recanalization (TICI 2b-3)	OR	0.94 [0.80 to 1.11]	0.94 [0.8. to 1.11]	0.94 [0.79 to 1.11]
Clinical outcome				
Neurological recovery (decrease on NIHSS > 7 points)	OR	0.92 [0.79 to 1.08]	0.92 [0.79 to 1.08]	0.88 [0.75 to 1.04]
Functional outcome, mRS 0-2	OR	0.85 [0.71 to 1.01]	0.85 [0.71 to 1.01]	0.80 [0.66 to 0.98]
Safety outcome				
Peri-procedural adverse events	OR	0.79 [0.67 to 0.93]	0.79 [0.67 to 0.93]	0.79 [0.66 to 0.94]
All adverse events	OR	1.27 [1.08 to 1.49]	1.27 [1.08 to 1.49]	1.27 [1.08 to 1.50]
Neurological serious adverse events	OR	1.04 [0.89 to 1.22]	1.04 [0.89 to 1.22]	1.05 [0.89 to 1.24]
Neurological adverse events	OR	1.04 [0.89 to 1.22]	1.04 [0.89 to 1.22]	1.05 [0.89 to 1.24]
Non-neurological adverse events	OR	1.37 [1.14 to 1.64]	1.37 [1.14 to 1.64]	1.34 [1.11 to 1.61]

TABLE 4 Clinical and radiological outcome in patients younger than 80 years and patients 80 years or over

	<80 years	**≥80 years**
N patients	298	17
Procedural duration in minutes, median (IQR)	121(55)	108(54)
Recanalization (TICI 2b and TICI 3)	113(43%)	6(46%)
Neurological recovery (decrease in NIHSS of 8 points or more), n (%)	9(53%)	8(47%)
Good functional outcome at discharge, mRS 0–2, n (%)	75(25%)	3(18%)
Death, n (%)	47(16%)	4(26%)
All adverse events, n (%)	164(55%)	13(76%)
Non-neurological adverse events, n (%)	91(31%)*	10(59%)*
Neurological adverse events, n (%)	113(38%)	6(35%)
Neurological serious adverse events, n (%)	44(15%)	3(18%)

*$p = 0.02$

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5

Safety of intra-arterial treatment in acute ischemic stroke patients on oral anticoagulants. A cohort study and systematic review

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ABSTRACT

Background

Elevated INR of > 1.7 is a contra-indication for the use of intravenous thrombolytics in acute ischemic stroke. Local, intra-arterial therapy (IAT) is considered a safe alternative. We investigated safety and outcome of IAT in patients with acute ischemic stroke using oral anticoagulants (OAC).

Methods

Data were obtained from a large national Dutch database on IAT in acute stroke patients. Patients were categorized according to International Normalized Ratio (INR): >1.7 and ≤1.7. Primary outcome was symptomatic Intracerebral Hemorrhage (sICH), defined as deterioration in National Institutes of Health Stroke Scale (NIHSS) score of ≥4 and ICH on brain imaging. Secondary outcomes were clinical outcome at discharge and three months. Occurrence of outcomes was compared with risk ratios and corresponding 95% confidence intervals. Further, we performed a systematic review and meta-analysis on sICH risk in acute stroke patients on OAC treated with IAT.

Results

456 patients were included. Eighteen patients had an INR > 1.7 with a median INR of 2.4 (range 1.8-4.1). One patient (6%) in the INR>1.7 group developed a sICH compared with 53 patients (12%) in the INR≤ 1.7 group (RR 0.49, 95% CI 0.07-3.13). Clinical outcomes did not differ between the two groups. Our meta-analysis showed a first week sICH risk of 8.1% (95% CI 3.9-17.1%) in stroke patients with elevated INR treated with IAT.

Conclusion

The use of OAC, leading to an INR>1.7, did not seem to increase the risk of a sICH in patients with an acute stroke treated with IAT.

INTRODUCTION

The most feared complication of intravenous thrombolysis in acute ischemic stroke is symptomatic intracerebral hemorrhage (sICH) which occurs in 7.7% according to the Cochrane review on the use of thrombolytics in acute stroke.[1] Hence, intravenous thrombolysis in patients with acute ischemic stroke on oral anticoagulants (OAC) is restricted to those with an internationalized standard ratio (INR) of ≤1.7.[2] As a result, in our experience, a considerable number of stroke patients is withheld thrombolytic therapy. With the advent of intra-arterial therapy (IAT), it has become possible to treat patients with acute ischemic stroke by applying local thrombolytic therapy only or mechanical thrombectomy – which often requires no additional thrombolytics. Conceivably, these techniques may therefore be less prone to bleeding complications.

Previous reports on IAT in patients with acute ischemic stroke on OAC suggest that there is no increased risk of intracerebral hemorrhages in these patients.[3-9] However, there are only few such studies and the number of patients studied is limited. In addition, these studies report mainly on patients treated with subtherapeutic INR levels (below 2.0),[5,6] on patients who received IAT after reversion of anticoagulants with fresh frozen plasma[7] or on patients with disturbed hemostasis not related to oral anticoagulants.[4] Therefore, risk of developing sICH and the effect on functional outcome in patients on OAC with acute ischemic stroke treated with IAT is still largely unknown.

We investigated safety and outcome of intra-arterial therapy in patients with acute ischemic stroke on OAC in a large Dutch cohort. To this study, we added a systematic review of the literature on the risk of sICH after intra-arterial therapy.

MATERIALS AND METHODS

Patients

Patient data were obtained from a national Dutch database on intra-arterial treatment in acute stroke patients. This database was initiated in preparation of the MR CLEAN trial, a Dutch, national trial on the use of intra-arterial therapy in acute ischemic stroke. All centers that were willing to participate in the MR CLEAN trial had to provide their “pre-trial experience” (see appendix 1 for participating centers). This assembly of data resulted in a database that contained information on all acute ischemic stroke patients treated with IAT from October 2002 until October 2013 in the major Dutch stroke hospitals. Inclusion in this dataset continued until a center started recruiting for MR CLEAN.

Demographic and clinical data were recorded at baseline (age, sex, time of symptom onset, baseline NIHSS, blood pressure on admission, International Normalized Ratio (INR) on admission).
Registration and use of the data was 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.

Oral anticoagulants

Patients were grouped based on INR; group1 INR >1.7 and group 2 INR ≤1.7. Oral anticoagulants were not reversed prior to the IAT. No patients on direct oral anticoagulants (DOACs, such as factor Xa and direct thrombin inhibitors) were included in the study.

Intra-arterial treatment (IAT)

Intra-arterial treatment consisted of local intra-arterial thrombolysis, mechanical thrombectomy, thrombosuction, acute carotid stenting or a combination of these techniques. For intra-arterial 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 (Concentric Medical, Mountain View, California, USA), Revive device (Micrus endovascular, San Jose, California, USA), Catch device (Balt Extrusion, Montmorency, France), "distal access Catheter" (DAC, Concentric Medical, Mountain View, California, USA), Penumbra device (Penumbra Inc, Alameda, California, USA), or a combination of these. Carotid stenting was performed with the Wallstent (Boston Scientific), or comparable dedicated carotid stents. Thombosuction was applied with the Vasco aspiration device (Balt Extrusion, Montmorency, France). The neuro-interventionalist decided which intra-arterial treatment was chosen. Secondary preventive treatment was initiated according to European guidelines.[10]

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 were recorded. Most patients underwent a CT scan 24 hours after treatment or after any clinical deterioration.

Outcomes

Primary outcome measure was symptomatic intracerebral hemorrhage (sICH). sICH was defined as deterioration in National Institutes of Health Stroke Scale Score (NIHSS) of ≥4 and an ICH on CT or MRI scan according to the ECASS II criteria.[11] Secondary outcome measures were asymptomatic intracerebral hemorrhage (aICH), clinical outcome at discharge and after three months (3 month data from two hospitals only; MC Haaglanden, The Hague and St. Antonius Hospital, Nieuwegein) and recanalization. Clinical outcome was assessed with the modified Rankin Score (mRS).[12,13] Good outcome was defined as a mRS score of 2 or lower. Death from all causes was a separate secondary outcome. Recanalization was assessed with the TICI score [14] 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.

Statistical analysis

Descriptive statistics were used for baseline characteristics in the two INR groups. Frequencies of symptomatic intracranial hemorrhage and secondary outcomes were compared between the two groups with risk ratios and 95% confidence intervals. Adjusted risk ratios were calculated with Poisson regression.

Systemic review and meta-analysis

We searched Pubmed for published papers on cohort studies on the risk of sICH in patients with acute ischemic stroke on oral anticoagulation. We combined the concepts "acute ischemic stroke" AND "intra-arterial therapy" AND "oral anticoagulation". We excluded studies containing less than 5 patients on oral anticoagulants and included only studies that were written in English language. Of all publications found, one author (AR) assessed titles for relevance. In case of doubt co-authors were consulted. Reference lists of relevant articles were checked for additional publications.
From each article, number of patients at risk and number of patients with sICH was determined and for each study the one-week risk of sICH with corresponding 95% confidence interval was calculated. For the overall risk assessment, we performed a meta-regression using Poisson regression.

RESULTS

A total of 456 patients were included in the national Dutch database (table 1). Sixty percent of all patients were men and their median age was 62 years. Of these, 18 patients had an INR>1.7 prior to treatment, 438 patients had INRs ≤ 1.7. In the group with INR>1.7, median INR was 2.4 (range 1.8-4.1). The majority of all patients an ischemic stroke in the anterior circulation (72%).

Treatment

Sixty-six percent of all patients were treated with intravenous thrombolysis before intra-arterial therapy was initiated (table 1). However, in the group of 18 patients with elevated INR, only 3 patients (17%) received intravenous thrombolysis before intra-arterial treatment. Their INRs were 1.9, 2.0 and 3.0, respectively. Overall, we were able to retrieve the dose of intravenous alteplase in 160 patients. Of these patients, we were able to retrieve their weight in 136 patients. 91 Patients (67%) received the full-weight-adapted dose and 45 patients (33%) received less of whom 13 patients (10%) received the bridging dose of 0.6mg/kg.

Almost half of all patients (48%) were treated with both intra-arterial thrombolysis and mechanical thrombectomy (Webtable 1, online only). Of these, 79 patients (36%) were treated with a combination of intra-arterial thrombolytics and mechanical thrombectomy and 140 patients (64%) were treated with a combination of intravenous thrombolysis, intra-arterial thrombolytics and mechanical thrombectomy. In 17 (4%) of all 456 patients the endovascular procedure was initiated, but no treatment was performed due to absence of a treatable thrombus or inability to access the site of occlusion (table 1).

Outcome

Intracerebral hemorrhage

Overall, 54 (12%) developed a sICH. In the 18 patients with INR>1.7 one sICHs occurred. This patient was a 49 year old male with a basilar artery thrombosis. He used oral anticoagulants because of atrial fibrillation. His INR previous to treatment was 4.1. Only a mechanical thrombectomy was applied. Two patients (11%) with INR>1.7 developed an aICH compared with 55 (13%) in the group with INR≤1.7 (differences not statistically significant, table 2).

Outcome at discharge and recanalization

In total, 112 patients (25%) died after treatment. Of these, 5 (28%) were in the group with INR >1.7 prior to treatment and 107 (25%) had INRs≤1.7. Of all patients, 99 (22%) had good functional outcome (mRS≤2) at discharge. In the INR>1.7 group

2 patients (11%) had good functional outcome at discharge and in the INR≤1.7 group 97 patients (23%) (differences not statistically significant; table 2, figure 1). Recanalization data were available for 285 patients (63%). Of these 232 (81%) had a complete occlusion (TICI 0) at the start of the intra-arterial procedure. All other patients had a partial occlusion. Recanalization was achieved in 43% of all patients. There were no major differences in recanalization rates between the two groups (table 2). All risk ratios remained essentially the same upon adjustment for age, sex, intravenous treatment, the use of intra-arterial thrombolytics or mechanical thrombectomy (data not shown).

Outcome at three months

Two hospitals (MC Haaglanden, the Hague and St. Antonius hospital, Nieuwegein) also registered functional outcome after three months. Of these 217 patients, 10 had an INR>1.7, 207 had an INR≤1.7. There were no major differences in baseline characteristics between the two groups (Webtable 2, online only).

No additional sICH occurred between discharge and three months follow-up. Functional outcome and death after three months did not differ between INR groups (table 2, figure 1), also after adjustment for covariables (data not shown).

Systematic review and meta-analysis

We identified 5 studies (including our own) that reported on sICH in patients with ischemic stroke treated with intra-arterial therapy who were on oral anticoagulation (table 3).

The number of patients at risk ranged from 7 to 21. The overall incidence of sICH was 8.1% (95% CI 3.9-17.1%) in the first week (figure 2).

DISCUSSION

Our results suggest that patients on OAC might have no increased risk of sICH when applying IAT in acute stroke. Furthermore, we did not find a significant difference in clinical outcome at discharge and after three months. Our meta-analysis review showed an incidence of sICH of 8.1% (95% CI 3.9-17.1%) in the first week after stroke.

These results support the results of previous studies that did not show an increased risk for intracerebral hemorrhage in patients with increased INR treated with intra-arterial treatment.[3-9] However, previous data are limited and heterogeneous. In one study OAC was reversed prior to IAT[7], and two other studies reported on treated patients with subtherapeutic INR levels.[5,6] We were able to present a

substantial number of patients with acute ischemic stroke treated with IAT who used OAC prior to stroke and had an INR within therapeutic range with OAC that was not reversed before treatment. The percentage of 8.1% (95% CI 3.9-17.1%) sICH found in our meta-analysis is comparable with the percentage of symptomatic (including fatal) intracerebral hemorrhage found in a large Cochrane review on thrombolytic therapy for acute ischemic stroke (7.7%).[1] However, it is important to realize that this review represents a heterogenic group of patients from various studies with different definitions of sICH. Previous studies on warfarine treated-patients with acute ischemic stroke treated with intravenous thrombolysis show conflicting results. Smaller, single center, cohort studies report on highly increased risk of sICH in patients on warfarin-treated with intravenous thrombolysis.[14,15,16] On the contrary, a large prospective multicenter by Xian et al report no increased risk of sICH in patients on warfarin.[17] However, all of these studies report on patients on warfarin with subtherapeutic INRs (INR<1.7). Therefore, an adequate comparison between these data and our data is not possible.

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. In addition, all ICHs developed in the first week after IAT during hospitalisation which makes a long-term follow-up not crucial for this study. Secondly, our study was retrospective, hence not all data were complete. However, key data on sICH were missing in less than 1% (3/483). Furthermore, our patient groups were rather young (median age 62 years). As most patients that use OAC are older, this limits the generalizability of our results. Another important limitation of our study is that we investigated retrospective collected data of every day clinical practice with no formal inclusion or exclusion criteria defined. We did not have information on how many patients with an elevated INR were not treated. This might result in a rather heterogeneous patient group prone to selection bias. However, this might also be a strength as these results reflect every day clinical practice.

Our results may seem counter-intuitive. One of the possible explanations for our results might be that the use of oral anticoagulants led to direct intra-arterial treatment with shorter waiting times before treatment because intravenous thrombolysis was withheld. Indeed, in our cohort median time to IAT was half an hour shorter in the INR>1.7 group. This shorter time to intra-arterial treatment may have led to less ischemic brain damage resulting in a lower bleeding risk. Another explanation might be that an increased risk of intracerebral hemorrhage in patients on OAC does not lead to worse outcomes because most ICHs remain asymptomatic. However, the percentage of aICH found in the two groups were

essentially the same. Furthermore, the fact that mechanical thrombectomy was the preferred treatment in patients with prolonged bleeding times might explain the low incidence of sICH in our cohort. Nevertheless, 8 patients in the INR>1.7 group were also treated with intra-arterial thrombolytics and 3 also received intravenous thrombolysis.

Our data and those from the meta-analysis do not indicate that patients on OAC are at increased risk of sICH after IAT. However, the results should be considered with caution as our data was limited and our patient groups were rather young. Nevertheless, intra-arterial treatment could be considered in patients on OAC with acute ischemic stroke that would otherwise be excluded from acute treatment.

TABLES

TABLE 1 Baseline Characteristics

	INR > 1.7 (n=18)	INR ≤ 1.7 (n=438)	Total (n=456)
Median age (range)	61.5 (27-80)	62 (12-93)	62 (12-93)
Male sex (%)	16 (89%)	255 (58%)	271 (59%)
NIHSS, median (range)	14.5 (5-38) (n=18)	16 (1-42) (n=434)	16 (1-42) (n=452)
Anterior circulation stroke (%)	12/18 (67%)	314/437 (72%)	326/455 (72%)
Carotid artery occlusion (%)	0 (0%)	10 (2%)	10 (2%)
Carotid T-top occlusion (%)	2 (11%)	26 (6%)	28 (6%)
MCA occlusion (%)	10 (56%)	278 (64%)	288 (63%)
Posterior circulation stroke (%)	6/18 (33%)	123/437 (28%)	129/455 (28%)
Vertebral artery occlusion (%)	1 (6%)	16 (4%)	17 (4%)
Basilar artery occlusion (%)	5 (28%)	104 (24%)	109 (24%)
PCA occlusion (%)	0 (0%)	3 (1%)	3 (1%)
Stroke onset – presentation ER, median in min (range)[a]	52.5 (10-70) n=12	65 (5-590) n=292	65 (5-590) n=304
Time to IVT, median in min (range)[b]	92.5 (65-120) n=2	100 (25-340) n=229	100 (25-340) n=231
Time to IAT, median in min (range)[c]	206 (90-1150) (n=15)	235 (65-1296) (n=304)	235 (65-1296) (n=319)
Intravenous thrombolysis (%)	3 (17%)	299 (68%)	302 (66%)
Intra-arterial thrombolysis (%)	8 (44%)	312 (71%)	320 (70%)
Mechanical (%)	15 (83%)	325 (74%)	340 (75%)
Failed procedure[d]	1 (6%)	16 (4%)	17 (4%)

INR Internationalized standard Ratio, *NIHSS* National Institutes of Health Stroke Scale, *MCA* Middle Cerebral Artery, *IAT* Intra-arterial Treatment. [a] Defined as time from onset of complaints to presentation on the emergency room. [b]Defined as time from onset of complaints to the start of IVT. [c]Defined as time from onset of complaints to start of IAT. [d]Defined as initiated IAT that eventually was not applied.

TABLE 2 Risk ratios for primary and secondary outcomes.

	INR > 1.7		INR ≤ 1.7[a]		
Outcome	**n/N[b]**	**(%)**	**n/N[b]**	**(%)**	**RR (95% CI)**
sICH	1/18	(6%)	53/437	(12%)	0.49 (0.07-3.13)
aICH	2/18	(11%)	55/437	(13%)	0.88 (0.23-3.38)
mRS≤2 at discharge	2/18	(11%)	97/430	(23%)	0.49 (0.13-1.84)
mRS≤2 at 3 months[c]	4/10	(40%)	72/207	(35%)	1.15 (0.53-2.51)
Death at discharge	5/18	(28%)	107/430	(25%)	1.12 (0.52-2.39)
Death at 3 months[c]	4/10	(40%)	64/207	(31%)	1.29 (0.59-2.84)
Recanalization[d]	4/10	(40%)	118/275	(43%)	0.93 (0.43-2.02)

INR Internationalized Standard Ratio, *RR* risk ratio, *CI* confidence interval, *sICH* symptomatic ICH, *aICH* asymptomatic ICH. [a] reference; [b]denominators sometimes smaller because of missing data; [c]data from two hospitals only; [d]successful when TICI ≥2B.

TABLE 3 Characteristics of the studies included in the meta-analysis.

	Study Design	N	INR	sICH (N)	IVT (N)	IAT (N)	Mechanical (N)
Brekenfeld[3]	Cohort study	7	[a]	1	0	7	*
De Marchis[5]	Cohort study	20	1.8 (1.4-2.3)[b]	1	0	10	16
Nogueira[4]	Cohort study (MERCI)	20	2.4 (1.8-4.9)[c]	2	0	8	20
Rizos[9]	Prospective observation study	21	1.8 (1.4-2.4)[d]	2	12	9[e]	6[e]
Rozeman	Cohort study	18	2.4 (1.8-4.1)[d]	1	3	8	15

INR International Standardized Ratio, *sICH* symptomatic IntraCerebral Hemorrhage, *IVT* IntraVenous Thrombolysis, *IAT* IntraArterial Treatment. [a] data not supplied in article; [b] median (IQR), [c] mean (min-max); [d] median (min-max); [e]Type of intra-arterial treatment not specified.

SUPPLEMENTARY FILES

WEBTABLE 1: Applied therapies

	N[a]	INR>1.7 (N=18)	Median dosage (range)	INR≤1.7 (N=438)	Median dosage (range)
Intravenous thrombolysis	*456*	3 (17%)		299 (68%)	
Alteplase	*446*	2 (11%)	77mg (77-77mg)	294 (69%)	70mg (8-90mg)
Abciximab	*456*	0 (0%)	-	5 (1%)	300mg (300-300mg)
Heparine	*453*	1 (6%)	5000IU	12 (3%)	2750IU (1000-5000IU)
Intra-arterial thrombolysis	*456*	8 (44%)		312 (71%)	
Alteplase	*453*	4 (22%)	17.5mg (15-23mg)	72 (17%)	19.5mg (2-80mg)
Abciximab	*456*	0 (0%)	-	39 (9%)	8mg (2-10mg)
Heparine	*453*	1 (6%)	5000IU	84 (19%)	5000IU (500-50,000IU)
Urokinase	*453*	3 (17%)	500,000 IU (250,000-1,000,000 IU)	219 (50%)	500,000IU (50,000-1,500,000)
Mechanical treatment	*456*	15 (83%)		325 (74%)	
Retraction	*454*	12 (67%)		158 (36%)	
Aspiration	*453*	1 (6%)		31 (7%)	
Stent placement	*453*	4 (22%)		194 (45%)	
Stent-retriever	*456*	3 (17%)		119 (27%)	
Other	*456*	10 (56%)		123 (28%)	

[a] data missing

WEBTABLE 2: Baseline characteristics of the patients with 3-month outcome data (data from two hospitals only)

	INR > 1.7 (n=10)	INR≤1.7 (n=207)	Total (n=217)
Median age (range)	58.5 (46-80)	63 (23-91)	62 (23-91)
Male sex (%)	9 (90%)	149 (64%)	158 (65%)
NIHSS (median)	12.5 (5-38) (n=10)	16 (1-42) (n=206)	15.5 (1-42) (n=216)
Anterior circulation stroke (%)	6 (60%)	142 (69%)	148 (68%)
Carotid artery occlusion (%)	0 (0%)	2 (1%)	2 (1%)
Carotid T-top occlusion (%)	1 (10%)	13 (6%)	14 (7%)
MCA occlusion (%)	5 (50%)	126 (61%)	131 (60%)
Posterior circulation stroke (%)	4 (40%)	65 (31%)	69 (32%)
Vertebral artery occlusion (%)	1 (10%)	15 (7%)	16 (7%)
Basilar artery occlusion (%)	3 (30%)	48 (23%)	51 (24%)
PCA occlusion (%)	0 (0%)	2 (1%)	2 (1%)
Stroke onset – presentation ER, median in min (range)[a]	81 (45-170) (n=5)	61.5 (5-149) (n=120)	62 (5-419) (n=125)
Time to IVT, median in min (range)[b]	120 (n=1)	103 (27-315) (n=97)	104 (27-315) (n=98)
Time to IAT, median in min. (min-max)[c]	205.5 (90-458) (n=8)	210 (65-1111) (n=121)	210 (65-1111) (n=129)
Intravenous thrombolysis (%)	2 (20%)	131 (63%)	133 (61%)
Intra-arterial thrombolysis (%)	3 (30%)	159 (77%)	162 (75%)
Mechanical	8 (80%)	170 (82%)	178 (82%)
Failed procedure[d]	1 (10%)	2 (1%)	3 (1%)

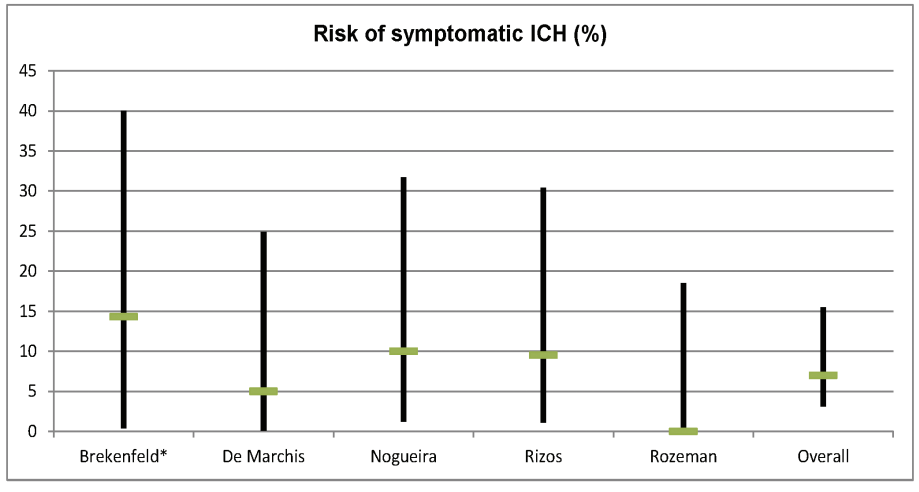
INR Internationalized standard Ratio, *NIHSS* National Institutes of Health Stroke Scale, *IAT* Intra-arterial Treatment. [a] Defined as time from onset of complaints to presentation on the emergency room. [b]Defined as time from onset of complaints to the start of IVT. [c]Defined as time from onset of complaints to start of IAT. [d]Defined as initiated IAT that eventually was not applied.

FIGURES

FIGURE 1 Clinical Outcomes at discharge (A) and after 3 months (B)

FIGURE 2 Meta-analysis: first-week sICH risk after IAT in patients on OAC

* upper limit confidence interval truncated at 40%.



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APPENDICES

Appendix 1 Participating centers

AMC Amsterdam, Rijnstate hospital Arnhem, UMC Groningen, MC Haaglanden The Hague, HAGA The Hague, LUMC Leiden, MUMC Maastricht, St. Antonius hospital Nieuwegein, UMC Nijmegen, Erasmus MC Rotterdam, St. Elisabeth hospital Tilburg, UMC Utrecht, Isala hospitals Zwolle, Atrium MC Heerlen, Medical Spectrum Twente Enschede, Reinier de Graaf hospital Delft.

PART III

Diagnostics in stroke and intra-arterial treatment

6

Duplex ultrasonography for detection of vertebral artery stenosis. A comparison with CT angiography

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ABSTRACT

Objectives

Vertebrobasilar stenosis is frequent in patients with posterior circulation stroke and it increases risk of recurrence. We investigated feasibility of duplex ultrasonography (DUS) for screening for extracranial vertebral artery stenosis and compared it with CT angiography (CTA).

Materials & Methods

We gathered data on 337 consecutive patients who had DUS because of posterior circulation stroke or TIA. Matching CTA studies were retrieved and used as reference. Stenosis on CTA was considered "significant" if >50%, at DUS if Peak Systolic Velocity (PSV) >140 cm/s for the V1 segment and PSV>125cm/s for the V2 segment. We determined the area under the ROC curve (AUROC). In addition, we calculated which PSV cut-off value resulted in highest sensitivity with acceptable specificity.

Results

DUS was able to make an adequate measurement in 378 of 674 V1 segments and 673 of 674 V2 segments. DUS detected a significant stenosis in 52 of 378 V1 segments; 12 were confirmed by CTA (AUROC 0.73, 95% Confidence Interval 0.63-0.83). The optimal DUS PSV cut-off value for this segment was 90cm/s. For the V2 segment there were too few stenoses to allow reliable assessment of diagnostic characteristics of DUS.

Conclusions

Although DUS has a fair AUROC for detecting significant stenosis, adequate assessment of the V1 segment is often not possible due to anatomic difficulties. Assessment of the V2 segment is feasible but yielded few stenoses. Hence, we consider usefulness of DUS for screening of extracranial vertebral artery stenosis limited.

INTRODUCTION

About 25% of all strokes are posterior circulation strokes.[1,2] Vertebrobasilar stenosis is an important cause of posterior circulation stroke and is found in 26.2% patients with such stroke.[3] In addition, the presence of vertebrobasilar stenosis is known to double or triple the risk of a recurrent posterior circulation stroke.[3,4] Digital subtraction angiography (DSA) is the gold standard for the diagnosis of vertebrobasilar stenosis. However, it is expensive and patients undergoing DSA have a 1-2% risk of neurological complications.[5,6] Contrast-Enhanced Magnetic Resonance Angiography (CE-MRA), Computed Tomography Angiography (CTA) and Duplex UltraSonography (DUS) offer less invasive alternatives for imaging the vertebrobasilar system. Both CE-MRA and CTA have high sensitivity and specificity for detecting vertebral artery stenosis.[7,8] However, they require the use of radiation and intravenous contrast material that have their own disadvantages. DUS is a cheap and non-invasive imaging technique that has proven to be reliable for diagnosing carotid stenosis.[9] For vertebrobasilar stenosis, however, its diagnostic value is less clear.[7,8,10-12] We investigated the feasibility of DUS as a screening tool for the detection of extracranial vertebral artery stenosis in patients with posterior circulation TIA or stroke and assessed its diagnostic characteristics in comparison with CTA.

MATERIALS & METHODS

Patients

We retrospectively retrieved data on all patients who underwent a DUS of the extracranial large arteries in the period 2008-2012 in the Department of Clinical Neurophysiology of a large teaching hospital. Of these patients, matching CTA studies were retrieved. Only patients who were diagnosed with a TIA or ischemic stroke of the posterior circulation were included. In total 342 patients fulfilled the inclusion criteria. If patients had more than one examination, only the first one was included. Formal approval from the local ethics committee was not indicated because this study was based on routinely collected data.

Duplex ultrasonography (DUS)

DUS was performed by a qualified technician in clinical neurophysiology with a color-coded duplex machine (iU22, Philips, Eindhoven, the Netherlands) equipped with a compound imaging 9-3 MHz linear-array transducer. A vascular pre-set was used. Patients were investigated in a supine position with the neck slightly extended. The vertebral artery was localized in a longitudinal plane at the sixth

cervical vertebra where the vertebral artery usually enters the transverse foramina. The diameter of the artery was measured. With doppler, direction of flow was established. For analysis, we divided the course of the vertebral artery into two segments: V1 (from the origin of the vertebral artery until the point where it enters the fifth or sixth cervical vertebra) and V2 (the part of the vertebral artery that courses cranially to the transverse foramina until it emerges besides the lateral mass of the atlas).[13] Segments were studied in B mode and color mode. Doppler samples were taken and Peak Systolic Velocity (PSV) was recorded. Criteria used for grading ≥50% stenosis were focal elevated blood flow velocity with a PSV cut-off point at the V1 segment of the vertebral artery of 140 cm/s and 125 cm/s at the V2 segment.[10,12,14,15]

CT angiography (CTA)

CTA studies were performed on a 64 slice CT scanner (Lightspeed VCT; General Electric Medical Systems, Little Chalfont, Buckinghamshire, United Kingdom) with the gantry angled to the orbitomeatal line, 64 1-second rotations of 1.25-mm collimation, a table speed of 1.5 mm/second, a 512 x 512 matrix, a 16-cm field of view, a tube voltage of 120 kV with a maximum tube current of 600 mA and a small focus. 50 cc Visipaque contrast material [320 mg iodine/ml] was injected intravenously at a rate of 6 cc/second with an automated power injector. A timing bolus was used to calculate the injection delay after contrast passage through the aortic arch for automated triggering of image acquisition, followed by a 'chaser' bolus of 20 cc saline. The CTA source image data were post-processed creating coronal, axial and sagittal source image reconstructions with a dedicated image processing computer workstation, after which luminal measurements were done with an automated vessel tracking software module (Advantage Workstation 4.4 & AVA Express; Global Electronics Medical Systems). Measurement of the degree of stenosis was done according to the NASCET criteria.[16] A vertebral artery stenosis of ≥50% was considered significant. Measurements were done by an experienced neuroradiologist (GL) and resident in neuroradiology (HH).

Analysis

For all included patients DUS and CTA studies were re-evaluated. DUS re-evaluation was done without knowledge of the CTA results and vice versa. CTA was used as "gold standard". The results of the DUS were compared with the results from CTA. The results of the CTA were dichotomized in "no significant stenosis" and "significant stenosis". For each segment (V1 and V2 segment) ROC curves were drawn and the area under the ROC curve (AUROC) was determined. Sensitivity and

specificity of DUS were calculated, at first at the above mentioned established cut-off values. As we aimed at studying whether DUS could be used as a screening tool for possible vertebral stenosis and hence as a selection tool for patients needing to undergo more invasive imaging with CTA, we calculated which DUS PSV cut-off value resulted in highest sensitivity with acceptable specificity. In addition, we calculated positive predictive values (PPV) and negative predictive values (NPV) for DUS at the predefined cut-off values.

RESULTS

A total of 425 patients who were diagnosed with a TIA or ischemic stroke of the posterior circulation had a DUS of the extracranial arteries; in 83 of them no CTA was made. From the remaining 342 patients, with 684 segments, 10 segments were occluded and hence excluded.

Therefore, 337 patients were included. Of these 198 patients were men (59%) and the median age was 67 years (range from 26 to 93). Table 1 shows an overview of all measured vertebral artery segments in our cohort.

DUS detected significant stenosis in 62 segments (5%), mostly at the V1 segment of the vertebral artery (52 segments, 84%). CTA detected 64 significant stenoses (5%) also mostly located at the first segment of the vertebral artery (60 segments, 94%). Of the 62 stenoses found with DUS, 14 (23%) were confirmed with CTA.

Of the 674 V1 segments, 608 segments (90%) could be adequately measured with CTA and 378 segments (56%) with DUS. DUS detected significant stenosis in 52 segments (14%) of which 12 were confirmed with CTA. The ROC curve showed that the PSV as measured by DUS was fairly capable of discriminating whether there was a vertebral artery stenosis at the V1 segment of this vertebral artery on CTA (AUROC 0.73, 95% CI 0.63-0.83, Figure 1).

Of the 674 V2 segments, 669 segments (99%) could be measured adequately with CTA and 673 segments (100%) with DUS. DUS detected 10 stenoses (2%) at the V2 segment of which 2 were confirmed with CTA. Due to this low number of stenoses, reliable assessment of the diagnostic characteristics of DUS compared with CTA was considered not possible at the V2 segment.

Though we did not measure distal vertebral artery segments with DUS, we did search for distal vertebral artery stenosis and occlusions, PICA ending vertebral arteries and basilar artery stenosis and occlusion with CTA. We found 40 distal vertebral artery stenoses, 24 distal vertebral artery occlusions, 31 PICA ending vertebral arteries, 6 basilar artery stenoses and 4 basilar artery occlusions. In these arteries, 4 proximal vertebral artery segments (V1 and V2 segments) were

found to have an occlusion according to DUS. None of these were confirmed with CTA.

Table 2 shows the sensitivities and specificities for the various cut-off values of the PSVs at the V1 segment of the vertebral artery. If calculated according the predefined cut-off of 140 cm/s, the sensitivity of DUS was 39% and the specificity was 88% with a corresponding positive predictive value (PPV) of 23% and the negative predictive value (NPV) of 94%. A cut-off at PSV of 90 cm/s at the V1 segment resulted in best sensitivity with acceptable specificity. Prior chance of stenosis of 8.2% (31/378) reduces to a chance of 3.0% (5/169) if DUS shows a PSV < 90cm/s. Also NPV improved from 94% at a cut-off of 140 cm/s to 97% at a PSV cut-off of 90 cm/s. For the V2 segment such an analysis was not feasible because of the limited number of stenoses.

DISCUSSION

In this study we found that DUS was a fairly adequate test for detecting vertebral artery stenosis at the V1 segment (AUROC 0.73, 95%CI 0.63-0.83). However, in almost half of all measured V1 segments no adequate PSV could be obtained due to technical difficulties such as the often deep and posterior origin of the vertebral arteries, calcified lesions, a tortuous course or short neck stature. At the V2 segment few stenoses were found and therefore we could not perform reliable analysis for this segment. Hence, we think that the usefulness of DUS in diagnosing extracranial vertebral stenosis is limited.

Compared with previous studies in patients with posterior stroke, we found approximately the same prevalence of significant vertebral artery stenosis with CTA.[3,17] However, we were not able to detect most of these stenoses with DUS. This resulted in lower sensitivity of DUS compared with earlier studies.[11,12] In addition, we found that our proportion of adequate visualization of the V1 segment was rather low. Most studies report that the V1 segment is less accessible for DUS but nevertheless report higher frequencies of adequate visualization (72-87%) than we achieved.[10,18,19]

Based on our results we found a PSV of 90 cm/s to be the optimal cut-off value for detection of a stenosis at segment 1 in the vertebral artery. Previous studies mostly recommended higher cut-off values.[12,16,20] However, our aim was to study at what cut-off value sensitivity was highest with acceptable specificity (to prevent false negatives) instead of finding an optimal cut-off value with the highest combination of both acceptable sensitivity and specificity. With this cut-off value the prior

chance of vertebral artery stenosis at the V1 segment is reduced from 8.2% to 3.0%.

This study has several limitations. First, we collected all data retrospectively which might reduce the generalizability of our results. However, in our clinic, all stroke and TIA patients are treated according to a uniform stroke protocol that includes a DUS of the extracranial large arteries. Hence, we think that out cohort represents a quite complete cohort of all patients that suffered from a posterior circulation stroke or TIA in the predefined period. Second, we used CTA as "gold standard" for detecting vertebral artery stenosis instead of DSA. This was done for pragmatic reasons, most stroke patients do not routinely undergo DSA (i.a. because of complication risks). In addition, previous studies show that CTA is adequately capable of detecting vertebral artery stenosis.[8,21] Third, the cause of posterior circulation stroke or TIA might be thrombo-embolic instead of hemodynamic. For this, evaluation of plaque morphology would be necessary which is rather difficult with ultrasound in the vertebral arteries. In addition, our study focus was on the usefulness of DUS in establishing significant vertebral artery stenosis instead of plaque morphology in case of vertebral artery stenosis.

Our results are rather disappointing with regards to the accuracy of DUS in detecting vertebral artery stenosis. Almost half of all vertebral artery segments could not be assessed with DUS. As the quality of DUS does very much depend on the experience of the ultrasound technician one could argue that our results could be due to lack of experience of our ultrasound technicians. However, our ultrasound technicians are highly qualified in clinical neurophysiology and perform several DUS studies every day.

Another explanation for our results might be that at median age of 67 years many patients may have degenerative changes of the cervical vertebrae which might hinder adequate assessment of the vertebral arteries. However, if adequate assessment of the vertebral artery was possible, DUS was not able to detect stenosis in most cases. A possible explanation might be that the PSV may erroneously seem normal as, for instance, the stenosis is localized more distally (Figure 2). One could argue that the end-diastolic velocity, the B-mode image and certain spectral changes should also be studied in addition to PSV resulting in a more reliable assessment of the vertebral artery with DUS. However, previous studies suggest that PSV is the most accurate predictor of stenosis in the extracranial vertebral artery.[12,16]

CONCLUSIONS

Our data show that assessment of the vertebral artery is difficult, especially at the V1 segment. This is, however, the segment most prone to atherosclerotic changes. In addition, if assessment of the vertebral artery with DUS was possible, there was an adequate detection of stenosis in only the minority of patients. Hence, the usefulness of the DUS as a screening tool for extracranial vertebral artery stenosis seems to be limited.

TABLES

TABLE 1 Vertebral artery stenosis as measured by DUS and CTA

		CT angiography			
		Stenosis	No stenosis	No measurement	Total
Duplex Ultrasonography	V1 segment				
	Stenosis (PSV>140cm/s)	12	40	0	52
	No stenosis	19	307	0	326
	No measurement	29	201	66	296
	Total	60	548	66	674
	V2 segment				
	Stenosis (PSA>125 cm/s)	2	8	0	10
	No stenosis	2	656	5	663
	No measurement	0	1	0	1
	Total	4	665	5	674

TABLE 2 Sensitivity and specificity for cut-off values of peak systolic velocity on duplex ultrasonography for significant vertebral artery stenosis as measured by CT angiography.

	V1 Segment		
CT-angiography	PSV Cut-off value (cm/s)	Sensitivity (%)	Specificity (%)
Stenosis ≥ 50%	140	39	88
	130	48	85
	120	61	78
	110	68	69
	100	71	57
	90	84	47
	80	84	37
	70	87	25

FIGURES

FIGURE 1 Receiver operating characteristic curve. Detection of significant vertebral artery stenosis (≥50%) on CTA by DUS based on peak systolic velocities (PSV) for the V1 segment of the vertebral artery.

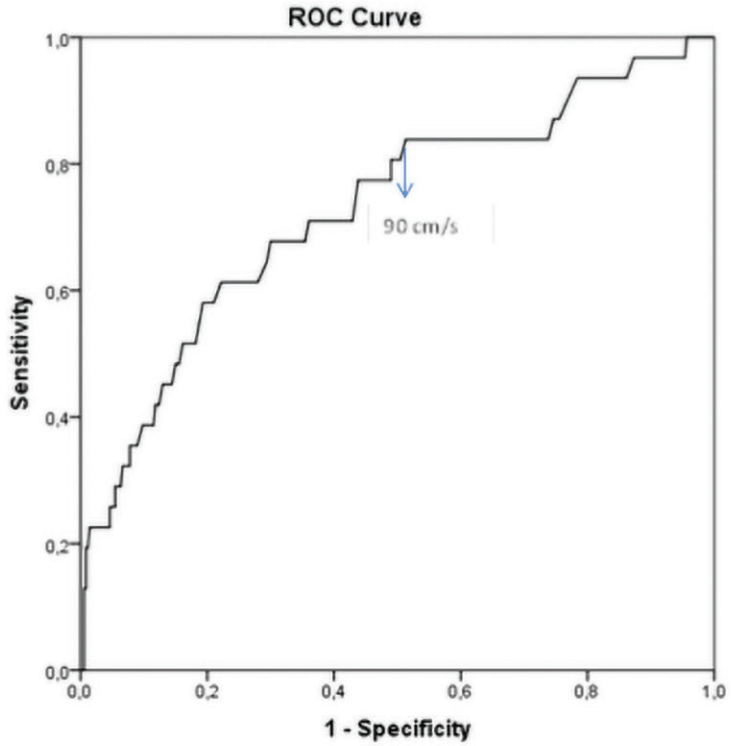
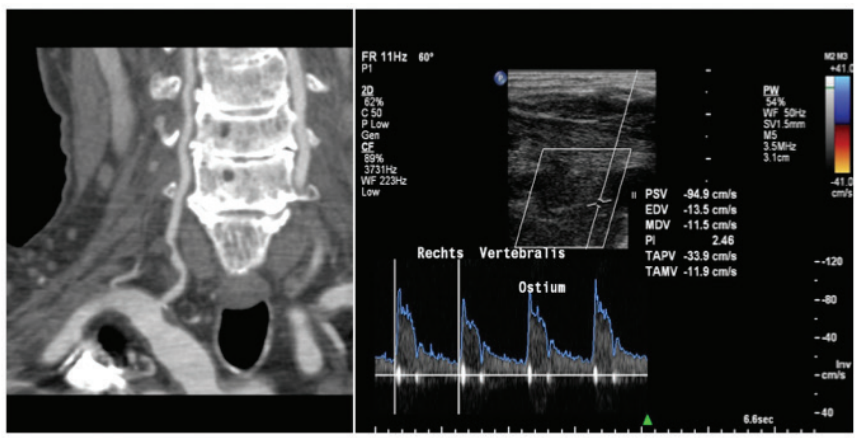


FIGURE 2 The CT angiography (right) shows a stenosis at the V1 segment. With DUS (left) a normal PSV is found.



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7

Variations in the circle of Willis and clinical outcome after intra-arterial stroke treatment

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ABSTRACT

Introduction

Intra-arterial treatment (IAT) improves outcomes in acute ischemic stroke. Presence of collaterals increases likelihood of good outcome. We investigated whether variations in the circle of Willis (CoW) and contributing carotid arteries influence outcome in stroke patients treated with IAT.

Methods

CTA-data on acute stroke patients treated with IAT were retrospectively collected. CoW was regarded complete if the contralateral A1 segment, Anterior Communicating Artery, ipsilateral Posterior Communicating Artery were fully developed and the P1 segment was visible. Carotid artery contribution was studied with a self-developed Carotid artery score ranging from 0-2 depending on the number of arteries supplying the occluded side of the CoW. Good clinical outcome was defined as modified Rankin Score ≤ 2 and measured at discharge and three months. We calculated risk ratios (RR) for the relation between completeness of the CoW, Carotid score and good outcome and performed a trend analysis for good outcome according to the Carotid score.

Results

126 patients were included for analysis. Patients with a complete and incomplete CoW had a comparable risk for good outcome at discharge (RR0.82; 95% CI 0.38-1.78) and 3 months (RR 1.01; 95% CI 0.61-1.67). A higher Carotid score was associated with a higher likelihood of good clinical outcome (p_{trend} for trend 0.24 at discharge and 0.05 at 3 months).

Conclusion

In patients with acute ischemic stroke treated with IAT, chances of good clinical outcome tended to improve with number of carotid arteries supplying the cerebral circulation. Completeness of the CoW was not related to clinical outcome.

INTRODUCTION

Stroke is one of the leading causes of death and disability. Several trials showed that intra-arterial treatment (IAT) in acute ischemic stroke treatment leads to better outcomes.[1-6] Angiographic success rate is much higher than clinical recovery rate. One of the factors involved in this discrepancy is the presence of collaterals.[9,10] The presence of adequate collaterals hinders penumbral tissue loss in acute ischemic stroke[11] and hence influence outcome after stroke.

The cerebral collateral circulation may be divided into primary collateral circulation through the circle of Willis and secondary collateral circulation through the leptomeningeal and ophthalmic arteries. Previous studies on patients with carotid artery occlusion or severe carotid stenosis, suggest that an incomplete circle of Willis increases risk of ischemic stroke.[12,13,14] In addition, extent of collateralization influences outcome in stroke patients treated with IAT.[3,15,16,17] However, most of these studies measure collateralization by visibility of leptomeningeal collaterals in the affected hemisphere as seen on CT-angiography (CTA).[3,15,16,18] In this study we investigated whether variations in collaterals, by means of the circle of Willis and number of carotid arteries supplying the cerebral circulation, are associated with clinical outcome in patients with acute ischemic stroke treated with IAT.

METHODS

Patients

All patients with acute anterior ischemic stroke, due to carotid T-top or middle cerebral artery (M1) occlusion, who were treated with IAT in the period of October 2002 to October 2013 (start of MR CLEAN trial) in Haaglanden Medical Center The Hague and Antonius Hospital Nieuwegein were included in the study. Demographic and clinical data were recorded at baseline including age, sex, time of symptom onset, NIHSS, blood pressure and serum-glucose on admission. For all patients type of intra-arterial therapy (intra-arterial thrombolysis or mechanical thrombectomy including type of device used) was registered. Patients with atherosclerotic carotid bifurcation occlusions or carotid dissections were not included in the study. The decision to treat a patient with IAT was made for each patient individually and IAT was performed only after obtaining consent from the patient or his relatives. Secondary preventive treatment was initiated according to European guidelines.[19]

Radiological characteristics

For each treated patient, site of intracranial occlusion or stenosis on CTA, presence of extracranial internal carotid artery occlusion or stenosis, Clot Burden score (CBS)[20], Alberta Stroke Programme Early CT score (ASPECTS)[21], leptomeningeal collateral flow (Collateral Flow Grading, CFG)[22], degree of recanalization after IAT (TICI score[22]) and anatomy of the circle of Willis were assessed. The circle of Willis was regarded complete if there was a fully developed and open Anterior (A)1 segment contralateral to the acute occlusion, Anterior Communicating Artery (ACoA), ipsilateral Posterior Communicating Artery (PCoA) and visible Posterior (P)1 segment.

To investigate the contribution of the carotid arteries we developed a score to determine the effect of circle of Willis variation on cerebral perfusion (Figure 1):

Carotid score 0: no contribution of either carotid artery to the collateral pathway. An example is a carotid T-top occlusion with a hypoplastic A1 segment contralaterally precluding perfusion of the circle through the contralateral anterior circulation.

Carotid score 1: the circle of Willis is perfused from one carotid artery only. This happens with:

- An M1 occlusion with a normal ipsilateral A1 segment and a hypoplastic contralateral A1 segment.
- An M1 occlusion with bilateral symmetrical A1 segments but without a visible ACoA precluding perfusion from the contralateral carotid artery.
- A carotid T-top occlusion and a dominant contralateral A1 segment, thus feeding both anterior cerebral arteries through the contralateral ICA.

Carotid score 2: perfusion from two carotid arteries:

- An M1 occlusion with normal bilateral A1 segments and a visible ACoA.

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. All radiological scores were assessed by an experienced neuro-radiologist (GLaN) blinded for clinical outcome.

Clinical outcomes

Clinical outcome was retrospectively assessed with the modified Rankin Score (mRS) [23,24] at discharge and after three months. Good outcome was defined as an

mRS score of £ 2. In addition, we recorded complications both during the intra-arterial procedure and during admission.

Statistical analysis

Descriptive statistics were used for baseline, radiological and treatment characteristics. We calculated risk ratios (RR) and 95% confidence intervals (CI) for the relation between the completeness of the circle of Willis (complete versus incomplete), the Carotid score and good clinical outcome with Poisson regression.[25] Moreover, we performed a trend analysis for good clinical outcome according to the three classes of the Carotid score by taking this characteristic as a continuous variable. In addition, we adjusted for the predefined clinical (NIHSS, age and time to IAT) and radiological characteristics (ASPECTS, CFG, and CBS). Adjusted risk ratios were calculated in bivariable analyses.

RESULTS

In the period of October 2002 to October 2013 163 patients were treated with IAT in both centers. We were able to retrieve CTA's in 129 patients. Clinical outcome was missing in one patient and in two other patients the CTA was of low quality and could therefore not be rated appropriately. Hence, 126 patients were included for analysis. Baseline characteristics were essentially the same for both the complete group of 163 patients treated with IAT and the 126 patients who were subsequently included in our analysis (Table 1). Fifty-five percent (n=69) of all patients were men and median age was 62 years; median NIHSS was 14.

Treatment

Overall 89 patients (71%) were treated with intravenous thrombolysis (IVT) and 122 patients (97%) were treated with IAT. In 4 patients (2%) the intra-arterial procedure failed. Most patients treated with IAT had mechanical thrombectomy (Table 1).

Radiological parameters

The majority of patients (84%) had an ASPECT score of 7 or more. Successful recanalization was achieved in 59 patients (49%). The median collateral flow grading was 3 (range 0-3) and the median clot burden score was 3 (range 1-8).

Clinical outcome and completeness of the circle of Willis

34 patients (27%) had a good clinical outcome at discharge and 53 patients (42%) had good clinical outcome at three months (Table 2).

Patients with a complete circle of Willis and patients with incomplete circle of Willis had a comparable risk for good clinical outcome at discharge (RR 0.82; 95% CI 0.38-1.78) and at 3 months (RR 1.01; 95% CI 0.61-1.67, Table 2).

Clinical outcome and the Carotid score

The majority of patients (n=78, 62%) had cerebral perfusion from both carotid arteries (Carotid score 2). Of the patients with a complete circle of Willis (n=26, 21%), 22 patients had Carotid score 2. Patients with only one carotid artery (Carotid score 1) supplying the intracranial circulation, tended to have better outcomes compared with patients with Carotid score 0 (RR at discharge 1.29; 95% CI 0.20-8.43 and RR 2.00; 95% CI 0.32-12.59 at 3 months). Further, patients with a Carotid score of 2 tended to have more often a good clinical outcome at discharge (RR 1.85; 95% CI 0.30-11.39) and at 3 months (RR 2.92; 95% CI 0.48-17.75) compared with those with Carotid score 0. In addition, compared with Carotid score 1, patients with Carotid score 2 also tended to have higher chances of good clinical outcome (RR at discharge 1.44; 95% CI 0.80-2.49 and RR at 3 months 1.46; 95% CI 0.90-2.37). A higher Carotid score was associated with a higher chance of good clinical outcome at three months (p_{trend} = 0.05), but not at discharge (p_{trend} = 0.24)

After adjustment for age, NIHSS at presentation, time to start of intra-arterial treatment, ASPECTS score, collateral flow grading and clot burden score the risk ratios remained essentially the same (Web table).

DISCUSSION

The number of carotid arteries supplying the cerebral circulation (Carotid score) in the setting of IAT for large (M1 or T-top) artery occlusion seems to be an independent predictor of good clinical outcome after three months. However, we observed no relation between completeness of the circle of Willis and clinical outcome after IAT.

Incompleteness of the circle of Willis may result in worse cerebral perfusion and hence more damage in case of acute cerebral ischemia.[12,13,14] Previous studies have shown that completeness of the circle of Willis, particularly the posterior circle of Willis, is a hallmark of deteriorated cerebral perfusion.[26,27] We could not confirm

such a detrimental effect in stroke patients with an incomplete circle of Willis treated with IAT.

Contralateral carotid occlusion is well known to increase risk of stroke or death in patients treated with Carotid Endarterectomy (CEA) because of symptomatic carotid stenosis.[28] In addition, contralateral carotid artery stenosis has been shown to be an independent predictor of poor clinical outcome in stroke patients with acute tandem occlusion treated with IAT.[29] These studies are in line with our results, showing that that loss of carotid arteries supplying the cerebral circulation reduces the likelihood of good clinical outcome. Conversely, another study showed that there was no strong effect of a coexisting ICA stenosis in acute MCA stroke on tissue status or perfusion parameters on MRI.[30] Moreover, Cerebral Blood Volume (CBV) was found to be elevated in stroke patients with coexisting ICA stenosis, possibly reflecting improved peripheral collateral circulation. However, patients with carotid occlusions were excluded in this study, only ipsilateral carotid stenosis was studied.

Our study has several limitations. First, our study focused on the collateral circulation by the circle of Willis and carotid arteries. Previous studies have shown that the leptomeningeal collaterals play a key role in chances of successful recovery after intra-arterial treatment. [3,15,16,17,31,32] We, therefore, included a score for leptomeningeal collaterals (CFG)[21] and corrected the risk ratio for good clinical outcome for this score (see webtable). After this adjustment, however, the risk ratios remained essentially the same. Second, we did not measure the flow in the ophthalmic artery. When flow is reversed in the ophthalmic artery, it also functions as collateral for the cerebral circulation. Nevertheless, this reversed flow is merely considered an indicator of diminished cerebral perfusion[26] and as such not a rescue pathway for cerebral circulation in case of an acute cerebral arterial occlusion. Third, extracranial carotid disease and basilar artery disease was not included in the study. One could hypothesize that any atherosclerotic disease on these locations also influence the cerebral collateral circulation. In addition, we did not register the presence of fetal type posterior cerebral artery. However, given the rather low number of patients included in our study we assume that these effects are limited. Fourth, patients included in our cohort were treated with IAT in the era before IAT was standard of care. As a result, one might consider our results less generalisable. However, as our study aimed at finding causal relation between completeness of the circle of Willis and clinical outcome after IAT and hence studied cause of disease, this seems less relevant.

A possible explanation for the lack of a positive relation between completeness of the circle of Willis and clinical outcome might be that we studied the primary

circulation in the *acute* setting. Previous studies showed that collateralization may take months to develop and animal models show that restoration of blood flow through collateral vessels after middle cerebral artery occlusion takes a month.[33,34] Most of these studies focused on the role of the collateral circulation by the circle of Willis in patients with atherosclerotic carotid artery disease. We did not select our cohort based on the presence of carotid artery disease. However, we did study the effect of number of carotid arteries supplying cerebral circulation and found a relation between this Carotid score and clinical outcome.

Conclusion

In patients with acute ischemic stroke treated with IAT, chances of good clinical outcome improve with the number of carotid arteries supplying the cerebral circulation. Completeness of the circle of Willis does not seem to relate to clinical outcome after IAT. Further studies are needed to confirm our findings in a larger cohort.

TABLES

TABLE 1 Demographics

	Total (n=163)	With CTA (n=126)
Median age (in years, range)	63 (23-91)	62 (23-89)
Men (%)	98 (60%)	69 (55%)
Median NIHSS (range)	14 (3-38)	14 (3-38)
Site of occlusion (%)		
Carotid	3 (2%)	3 (2%)
Carotid T-top	15 (9%)	11 (9%)
Middle Cerebral Artery	145 (89%)	112 (89%)
Time onset to ER (median in minutes, range)	62 (5-359)	68 (5-359)
Time onset to IVT (median in minutes, range)	105 (27-274)	110 (27-274)
Time onset to IAT (median in minutes, range)	207 (65-1111)	207 (65-1111)
IVT (%)	113 (69%)	89 (71%)
IAT (%)	159 (98%)	122 (97%)
Use of thrombolytics (%)	120 (74%)	97 (77%)
Mechanical (%)	133 (82%)	101 (82%)
Failed procedure (%)	4 (3%)	4 (3%)
Radiological parameters		
ASPECTS > 7 (%)	126 (75%)	106 (84%)
Median Collateral Flow Grading (CFG, range)		3 (0-3)
Median Clot Burden Score (CBS, range)		3 (1-8)
Successful Recanalization (%)	68 (44%)	59 (49%)
Complete Circle of Willis (%)		26 (21%)
Carotid score		
0		6 (5%)
1		42 (33%)
2		78 (62%)

NIHSS: National Institutes of Health Stroke Scale; ER: Emergency Room; IVT: IntraVenous Thrombolysis; IAT: Intra-Arterial Treatment; ASPECTS: Alberta Stroke Program Early CT score[21]; CGF: Collateral Flow Grading[22]; CBS: Clot Burden Score[20].

TABLE 2 Clinical outcome at discharge and at 3 months

		Circle of Willis		Carotid score*			
	All	**Complete**	**Incomplete**	**0**	**1**	**2**	**P for trend**
		N=26	**N=100**	**N=6**	**N=42**	**N=78**	
Good clinical outcome at discharge (%)	34 (27%)	6 (23%)	28 (28%)	1 (17%)	9 (21%)	24 (31%)	
Risk Ratio (95% CI)		0.82 (0.38-1.78)	Ref	Ref	1.29 (0.20-8.43)	1.85 (0.30-11.39)	0.24
Good clinical outcome at 3 months (%)	53 (42%)	11 (42%)	42 (42%)	1 (17%)	14 (33%)	38 (49%)	
Risk Ratio (95% CI)		1.01 (0.61-1.67)	Ref	Ref	2.00 (0.32-12.59)	2.92 (0.48-17.75)	0.05

* Carotid Score 0 - no carotid artery supplying cerebral circulation; Carotid Score 1 - 1 carotid artery supplying cerebral circulation; Carotid Score 2 - 2 carotid arteries supplying cerebral circulation

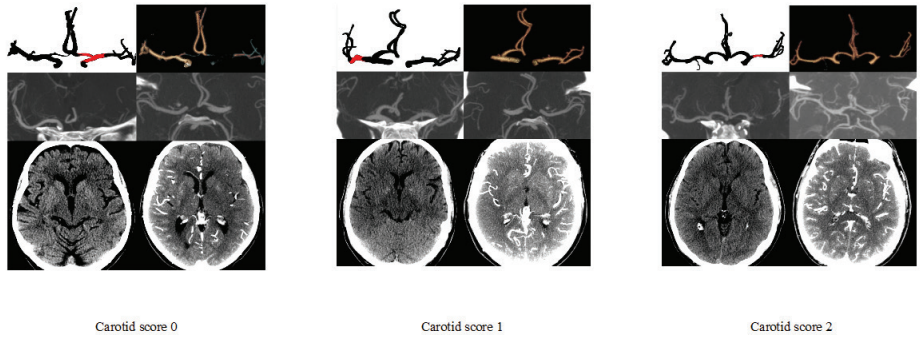
WEB TABLE Adjusted Risk ratios for good clinical outcome at discharge and 3 months

		Complete vs incomplete Circle of Willis	Carotid score		
			1 vs 0	2 vs 0	1 vs 2
At discharge	Risk ratio (RR, 95% CI)	0.82 (0.38 - 1.78)	1.29 (0.20 - 8.43)	1.85 (0.30 - 11.39)	1.44 (0.74- 2.80)
	Adjusted RR Age	0.79 (0.38 - 1.67)	1.13 (0.18 - 7.10)	1.48 (0.24 - 9.11)	1.32 (0.68 - 2.60)
	Adjusted RR NIHSS[1]	0.84 (0.42 - 1.65)	1.22 (0.20 - 7.46)	1.48 (0.25 - 8.58)	1.22 (0.63 - 2.33)
	Adjusted RR time to IAT	0.86 (0.33 - 2.23)	1.05 (0.16 - 6.90)	1.49 (0.25 - 8.91)	1.41 (0.61 - 3.25)
	Adjusted RR ASPECTS[2]	0.90 (0.44 - 1.85)	1.76 (0.28 - 11.11)	2.41 (0.40 - 14.41)	1.37 (0.72 - 2.62)
	Adjusted RR CFG[3]	0.96 (0.46 - 2.01)	1.00 (0.19 - 5.12)	1.26 (0.26 - 6.12)	1.28 (0.67 - 2.44)
	Adjusted RR CBS[4]	0.82 (0.38 - 1.75)	1.30 (0.20 - 8.66)	1.83 (0.29 - 11.34)	1.39 (0.71 - 2.72)
At 3 months	Risk ratio (RR, 95 CI)	1.01 (0.61 - 1.67)	2.00 (0.32 - 12.59)	2.92 (0.48 - 17.75)	1.46 (0.90 - 2.37)
	Adjusted RR Age	0.98 (0.61 - 1.57)	1.83 (0.29 - 11.56)	2.53 (0.41 - 15.52)	1.38 (0.84 - 2.24)
	Adjusted RR NIHSS[1]	1.02 (0.62 - 1.67)	1.90 (0.32 - 11.41)	2.68 (0.46 - 15.72)	1.42 (0.87 - 2.31)
	Adjusted RR time to IAT	1.10 (0.61 - 2.00)	1.82 (0.34 - 9.62)	2.68 (0.54 - 13.30)	1.47 (0.82 - 2.63)
	Adjusted RR ASPECTS[2]	1.08 (0.66 - 1.76)	2.30 (0.37 - 14.21)	3.30 (0.56 - 19.58)	1.43 (0.89 - 2.32)
	Adjusted RR CFG[3]	1.05 (0.62 - 1.76)	1.56 (0.29 - 8.37)	2.25 (0.43 - 11.66)	1.45 (0.88 - 2.39)
	Adjusted RR CBS[4]	1.00 (0.60 - 1.65)	1.99 (0.32 - 12.53)	2.98 (0.48 - 18.32)	1.51 (0.92 - 2.48)

[1] NIHSS: National Institutes Health Stroke Scale. [2]ASPECTS: Alberta Stroke Program Early CT score[21]. [3] CGF: Collateral Flow Grading[22]. [4] CBS: Clot Burden Score[20].

FIGURES

FIGURE 1



Carotid scores on NECT, CT angiograhy and MIP recontructions. Carotid score 0: no contribution of either carotid artery to the collateral pathway. Carotid score 1: the circle of Willis is perfused form one carotid artery only. Carotid score 2: perfusion form two carotid arteries.

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8

General Discussion

This thesis describes the evolution of intra-arterial stroke treatment in the Netherlands. It captures the period before publication of the large randomized controlled trials that would eventually lead to implementation of intra-arterial treatment as standard treatment for patients with acute ischemic stroke caused by large cerebral artery occlusion.

Evolution of intra-arterial treatment

In the Netherlands intra-arterial treatment was first applied at the beginning of this century. Initially, intra-arterial treatment consisted of administration of thrombolytics at the site of the occlusion. Later this evolved to the use of clot-retrieval devices. While the first intra-arterial treatments were done in patients suffering from posterior circulation stroke, nowadays intra-arterial treatment merely focusses on treatment of anterior circulation stroke. In chapter 1 we describe the early developments in a large Dutch teaching hospital and in chapter 2 we broaden this to a nationwide database of intra-arterial treated patients treated in the period before start of the MR CLEAN trial.[1] We studied the shift from intra-arterial therapy with local application of thrombolytics to the clot towards the use of mechanical clot retrieval devices. First, thrombectomy was performed with the Merci device, later with stent-retrievers. During the observation period, time to treatment was reduced and intra-arterial treatment was more often combined with intravenous therapy. This led to higher rates of successful recanalisation and favourable outcome.

The usefulness of stent-retrievers in reaching recanalization and hence higher rates of favourable outcome is also reflected in several large trials. At first, trials such as IMS III and MR RESCUE in which stent-retrievers were infrequently used, did not show a favourable effect of intra-arterial treatment.[2,3] In IMS III only a small minority of patients was treated with a stent-retriever and MR RESCUE merely used first generation embolectomy devices, not including stent-retrievers.[2,3] Second, three out of the five subsequent large clinical trials that evidently showed more favourable outcomes in patients treated with intra-arterial therapy, used stent-retrievers exclusively in their intervention arm (EXTEND IA, SWIFT PRIME and REVASCAT).[4,5,6] In addition, in the other two, the MR CLEAN and ESCAPE trials, stent-retrievers were used in over 80% in the intervention arm.[1,7]

A recent development in intra-arterial treatment is the so called ADAPT technique. ADAPT stands for A Direct Aspiration first Pass Technique and involves placement of the catheter in the proximal part of the clot followed by forceful suction. As the catheter does not have to travel through the whole clot, as is the case with the use of a stent-retriever, recanalisation may be accomplished faster. In addition,

because the clot is invaded only proximally, there may be less clot disruption and lower risk of distal emboli during the procedure. Several cohort studies report high recanalisation rates and shorter times to recanalisation with the ADAPT technique compared with the use of the stent-retrievers.[8,9] One would expect that these shorter times to recanalisation and high recanalisation rates result in higher rates of favourable clinical outcome. However, ASTER, until now the only randomized trial that compared the ADAPT technique with the use of stent-retrievers, failed to show a significant difference between the two techniques. Successful recanalisation was achieved in 85.4% in the aspiration group versus 83.1% in the stent-retriever group. Also, functional outcome did not differ between these two groups.[10] In addition, analysis of treatment techniques used in the MR CLEAN Registry also showed no difference in functional outcome nor recanalisation in patients treated with direct aspiration versus patients treated by a stent-retriever.[11]

In the aforementioned studies[8,9], the stent-retriever technique was often applied as escape therapy if ADAPT fails. It would be interesting to investigate whether primarily applying a combined stent-aspiration technique results in higher recanalisation rates, less distal emboli and hence higher rates of favourable clinical outcome. So far, only small cohort studies have reported on the use of this combination technique.[12,13,14]

The combination of thrombectomy techniques can be broadened even further. The PROTECT (PRoximal balloon Occlusion TogEther with direCt Thrombus aspiration during stent retriever thrombectomy) technique encompasses the use of a balloon guided catheter in addition to the aspiration and stent-retriever technique. The balloon guided catheter is used as an aid in achieving proximal flow arrest and hence results in less fragmentation and distal emboli during thrombectomy.[15] Moreover, a recent paper reported on the use of the combination of the PROTECT technique with the SAVE (stent-retriever-assisted vacuum-locked extraction) technique; the so called PROTECT^{PLUS}. PROTECT^{PLUS} resulted in higher rates of first pass complete recanalisation and a trend towards better clinical results and lower rate of embolization to new, previously unaffected vascular territories compared with PROTECT.[16] In the coming years, it may be expected that other techniques will appear to further improve intra-arterial treatment.

Factors influencing outcome after intra-arterial treatment

Though the use of stent-retrievers increased over time and recanalisation rates improved with the use of these devices, recanalisation does not automatically lead to better clinical outcome. The percentages of good clinical outcome (mRS

£ 2) found in the two cohorts described in chapters 2 and 3 were similar to that observed in the MR CLEAN trial[1], though recanalisation rates were lower. It is likely that other characteristics, apart from recanalisation, influence outcome. In chapter 7, we describe the influence of circle of Willis anatomy and carotid artery contribution on good clinical outcome after intra-arterial treatment. We hypothesized that good collateral circulation through the circle of Willis results in a higher chance of favourable clinical outcome. Contrary to our expectation, circle of Willis anatomy as such did not influence outcome. The contribution of carotid arteries to the cerebral circulation, however, did influence outcome. Completeness of the circle of Willis contributed to the influence of the carotids: only with two fully developed A1 segments and anterior communicating artery, contralateral carotid contribution can compensate for the burden of acute ipsilateral carotid or M1 occlusion.

As stated above, recanalisation and contribution of the carotid arteries to the cerebral circulation are not the only characteristics that influence outcome after intra-arterial treatment. Thrombectomy devices fragment clots and hence may create distal emboli. In the MR CLEAN trial embolization of clot fragments into new territories was seen in 8.6%.[1] Due to these distal emboli, collateral circulation becomes disrupted, influencing outcome negatively.[17] In addition, complete recanalisation does not always lead to complete (microvascular) reperfusion.[18] Incomplete microvascular reperfusion might explain for these patients with fast and complete recanalisation that they do no reach functional independence.[19] MR CLEAN MED, a trial in which heparine or acetylsalicylic acid is administered during intra-arterial treatment, aims at better reperfusion of the microcirculation.[20]

The combination of all the aforementioned characteristics in interaction with for instance, presence of leptomeningeal collaterals, clot length and time elapsed from onset of complaints probably reflect the extent of infarct core and penumbra and as a result determine good clinical outcome after intra-arterial treatment. With CT perfusion and MRI DWI/FLAIR it is possible to calculate the size of infarct core and penumbra.[21,22,23] Patients suffering from acute ischemic stroke can undergo CT-perfusion or MRI to establish if they have a favourable penumbra/infarct core ratio. In such patients, acute stroke treatment has proven to result in better clinical outcomes compared with standard treatment even after > 4.5 hours (wake-up strokes treated with intravenous thrombolysis)[21] or after >6 hours of "last seen well" (intra-arterial treatment).[22,23]

In addition to selection of suitable patients for late intra-arterial interventions, one could also hypothesize that certain patient groups with unfavourable scan profiles should be excluded from intra-arterial treatment. This results in a shift in patient

selection from a "time based" principle to a "tissue based" principle. Previous studies showed that patients with unfavourable scan profiles with large infarct cores and small penumbra, treated with intravenous thrombolysis, have a lower chance of good clinical outcome and higher chance of developing intracerebral hemorrhage.[24,25] However, the large individual patient data meta-analysis of the HERMES collaboration pooled patient data showed that ischemic core volume did not influence treatment benefit of intra-arterial treatment applied within 6 hours of stroke onset. [26,27] In other words: even in patients with large infarct cores a positive treatment effect of intra-arterial therapy is seen if treatment starts within 6 hours. Using imaging solely as predictor of good clinical outcome thus seems unwise. Future studies should combine both clinical and imaging characteristics in order to define favourable and unfavourable patient profiles resulting in better selection of patients for treatment with intra-arterial treatment.

Observational research

In addition to differences in patient characteristics that might lead to different outcomes, study design might also influence the study results. Observational studies are considered to be prone to bias due to incomparability of treatment groups and misjudgement of the treatment effect.[28] In chapter 4 we describe the effect of age on functional outcome after intra-arterial treatment in an observational cohort study. Age was found to be inversely associated with good functional outcome after intra-arterial treatment. Pooled patient analysis from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND-IA also showed lower percentages of favourable clinical outcome after 3 months in older patients treated with intra-arterial treatment versus younger patients treated with intra-arterial treatment. However, if intervention was compared with no intervention (control), a trend favouring intervention over control was seen for patients over 80 years of age compared with younger patients.[29]

Our study did not include a control group and hence the fact that elderly suffer from higher rates of mortality and morbidity after stroke was not accounted for.

An advantage of observational research is that it is possible to study treatment effects in patients who would otherwise not be included in a randomized controlled trial. In chapter 5 we describe the use of intra-arterial treatment, including intra-arterial thrombolysis, in patients on oral anticoagulants. These patients were historically excluded or only allowed to participate in a trial if they had subtherapeutic INR levels, or if the oral anticoagulant was reversed.[30,31,32] We found that intra-arterial treatment could be safely applied in patients with prolonged INR yielding similar clinical outcomes as those with normal INRs. In the MR

CLEAN, ESCAPE and REVASCAT trials, patients with prolonged INR were no longer excluded from intra-arterial treatment.[1,6,7] The MR CLEAN and REVASCAT trials allowed inclusion of patients with an INR up to 3 and in the ESCAPE trial no upper limit of INR was defined for inclusion.[1,6,7] In addition, in the most recent national protocol on stroke treatment in Netherlands, the use of oral anticoagulants and higher age are no longer mentioned as a contra-indication for the use of intra-arterial treatment.[33]

Diagnostics

CT angiography (CTA) is used as diagnostic technique for detection of arterial occlusion or stenosis in ischemic stroke in most stroke centers over the world. For the acute setting, CTA is the preferred diagnostic technique as it can rapidly establish an acute intracranial large artery occlusion. However, for the diagnosis of high grade carotid artery stenosis, as a cause of stroke, duplex sonography is often used. Vertebral artery stenosis is related to posterior circulation stroke in the same way as carotid artery stenosis is to anterior circulation stroke. In chapter 6 we describe the use of duplex sonography for the detection of extracranial vertebral artery stenosis. We found that although duplex sonography is very capable of detecting a significant stenosis (> 50% stenosis), adequate assessment of the vertebral artery segments is often not possible due to anatomical difficulties. Most stroke patients are elderly and hence are likely to have degenerative changes of the cervical vertebrae which might hinder adequate assessment of the vertebral arteries.

The treatment of high grade, symptomatic, carotid artery stenosis is proven to result in lower risk of recurrent stroke.[34,35] For vertebral artery stenosis this is less clear. Only two trials have been performed, and both trials stopped enrolment prematurely. The first, the Vertebral Artery Stenting Trial (VAST), showed high (5%) periprocedural risk and no reduction in recurrent stroke risk in patients treated with stenting.[36] The second, the Vertebral Artery Ischaemia Stenting Trial (VIST), did report a reduction in risk of recurrent strokes in patients treated with stenting, but without reaching statistical significance.[37] Both trials included mostly proximal, extracranial vertebral artery stenoses. However, intracranial vertebral artery stenosis is considered to have a much higher recurrent stroke risk compared with extracranial vertebral artery stenosis.[38]

In summary, duplex sonography is technically capable of detecting extracranial vertebral artery stenosis, but adequate assessment is often not possible due to anatomical difficulties. In addition, if such stenosis is found, there is no evidence-based treatment, such as stenting, in addition to best medical treatment. Moreover, the extracranial artery stenosis has a lower recurrent stroke risk compared with

intracranial stenosis. Hence, it does not seem reasonable to routinely determine the presence of extracranial vertebral artery stenosis with duplex sonography in patients with vertebrobasilar stroke or TIA.

Final conclusions

In the last decade, there has been a large change in acute treatment of ischemic stroke. In the Netherlands, the first patients were treated with intra-arterial treatment at the beginning of this century and nowadays it is part of standard treatment. During this period, there has been a shift from intra-arterial thrombolysis to mechanical thrombectomy. With the use of stent-retriever devices, recanalisation rates and favourable outcomes have increased.

Selection of the appropriate patient for intra-arterial treatment remains essential. Patients on oral anticoagulants and elderly people should not be withheld such treatment. In addition, identification of predictors of favourable clinical outcome such as contribution of the carotid arteries to the circle of Willis, may help in deciding which patients should be selected for intra-arterial treatment.

Future perspective

Currently, patients are selected to undergo intra-arterial treatment within 6 hours after stroke onset if CT angiography shows a symptomatic, intracranial large vessel occlusion. Recently, for certain patient groups with a favourable penumbra/infarct core ratio, indication for intra-arterial treatment was broadened beyond 6 hours. Though different scan techniques can assist in deciding which patient would benefit from intra-arterial treatment, this should not be the only selection criterion. Future studies should focus on combining hands-on clinical and radiological characteristics that enable the clinician to make adequate treatment decisions quickly.

Besides broadening of indication for intra-arterial treatment, technical and procedural improvements will continue. Nowadays, intra-arterial treatment is mostly performed with a stent-retriever. However, aspiration techniques also seem adequate at reaching successful recanalisation with less periprocedural complications. Currently, the use of heparin during intra-arterial treatment with the aim to reduce distal emboli and restore microcirculation is studied in the MR CLEAN MED.[21] In addition, MR CLEAN No IV studies whether intra-arterial treatment without preceding intravenous thrombolysis might reduce the prevalence of hemorrhage after acute stroke treatment.[39] The results of these and other trials may result in higher recanalisation rates, shorter time to recanalisation, and less peri-procedural complications. In turn, this should result in higher rates of favourable outcomes in stroke patients.

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9

English summary

Stroke is one of the leading causes of mortality and morbidity in the world. Stroke can be divided in ischemic stroke and hemorrhagic stroke. Ischemic stroke is most often caused by an acute occlusion of one of the cerebral arteries. Acute stroke treatment aims at resolving these acute artery occlusions. This can be done with intravenous thrombolysis or with locally applied therapy, i.e. intra-arterial, with thrombolytics or mechanical thrombectomy.

This thesis focuses on the evolution of intra-arterial stroke treatment in the Netherlands. It captures the period before publication of the large randomized controlled trials that would eventually lead to implementation of intra-arterial treatment as standard treatment for patients with acute ischemic stroke caused by large cerebral artery occlusion. The first part of this thesis contains two studies on patients treated with intra-arterial treatment in the period before the start of the Dutch nationwide MR CLEAN trial (2010-2014). In chapter 2 we studied a cohort treated with intra-arterial therapy in the period 2009-2011. During this period newer devices became available, the so-called stent-retrievers. A stent-retriever achieves recanalisation by deploying itself into the thrombus and relocating the thrombus against the blood vessel wall. The deployed stent then incorporates the thrombus that is retrieved with the removal of the stent-retriever. We were able to show that recanalisation rates were higher with the use of stent-retrievers, with a trend towards higher rates of favourable outcome after three months. In chapter 3 we describe a national cohort containing all patients treated with intra-arterial treatment from 2002 to the start of the MR CLEAN trial in 2010. We showed that, over the years, door to groin times reduced, intra-arterial treatment was more often combined with intravenous treatment and mechanical thrombectomy was more often used instead of intra-arterial thrombolysis. In addition, a shift in type of device used for mechanical thrombectomy was seen with more stent-retrievers being used in the later period. Together, this resulted in a trend towards higher rates of favourable outcome at discharge and after three months. In addition, recanalisation rates tended to improve.

In the second part of this thesis, we focus on specific treatment groups. In chapter 4 we studied the effect of age on outcome after intra-arterial treatment. We found that higher age was inversely related to favourable clinical outcome. In addition, risk of non-neurological adverse events was higher with increasing age. However, there was no increased risk of treatment related adverse events nor an increase of neurological adverse events. Hence, we concluded that increasing age lessens chances of favourable outcome after stroke but does not seem to interact with

treatment effect of intra-arterial treatment. In chapter 5 we describe a cohort with prolonged bleeding times (INR>1.7) treated with intra-arterial treatment. Patients with prolonged bleeding times are considered prone to bleeding complications. We compared these patients with patients with normal bleeding times treated with intra-arterial treatment and found no increased risk of intracerebral hemorrhage (RR 0.49, 95% confidence interval 0.07-3.13). Our meta-analysis on risk of symptomatic intracerebral hemorrhage in patients on oral anticoagulants suffering from acute ischemic stroke treated with intra-arterial treatment showed a first week bleeding risk of 8.1%. This bleeding risk is comparable with the percentage of symptomatic intracerebral hemorrhage found in a large Cochrane review on thrombolytic therapy for acute ischemic stroke. We therefore concluded that there was no increased risk of symptomatic intracerebral hemorrhage in patients with prolonged bleeding times treated with intra-arterial treatment. In the most recent Dutch national guideline on acute stroke treatment, the use of oral anticoagulants is no longer mentioned as contra-indication for the use of intra-arterial treatment.

In the third part of this thesis we focus on diagnostics in ischemic stroke and intra-arterial treatment. We studied the feasibility of duplex ultrasonography for screening of extracranial vertebral artery stenosis (chapter 6). To this end, we compared duplex sonography with CT angiography in patients with posterior circulation stroke or TIA. We found that duplex sonography was able to detect significant stenosis quite adequately (AUC-ROC 0.73, 95% confidence interval 0.63-0.83). However, due to anatomic difficulties, adequate assessment of the most proximal segment of the vertebral artery was often not possible rendering duplex sonography less useful in daily practice.
Furthermore, we studied variations in Circle of Willis anatomy on CT angiography and its relation to outcome in acute stroke patients given intra-arterial treatment (chapter 7). We hypothesized that a complete Circle of Willis would result in better (primary) collateral circulation and hence better outcome. In addition, we studied the number of carotid arteries supplying the Circle of Willis and its influence on clinical outcome. Circle of Willis was regarded complete if the A1 segment contralateral to the occluded side, the posterior communicating artery ipsilateral to the occluded side and the anterior communicating artery were fully developed. Contrary to our expectation, completeness of Circle of Willis was not related to clinical outcome. However, chances of good clinical outcome tended to improve with the number of carotid arteries supplying the cerebral circulation.
In the last part of this thesis the results of the aforementioned studies are discussed (chapter 8).

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Een beroerte is een van de belangrijkste oorzaken van sterfte en handicap wereldwijd. Beroertes kunnen worden onderverdeeld in herseninfarcten en hersenbloedingen. Een herseninfarct wordt meestal veroorzaakt door een afsluiting van een van de hersenslagaderen. Acute behandelingen van het herseninfarct zijn erop gericht om een dergelijke afsluiting op te heffen. Dit kan met behulp van intraveneuze trombolyse, met lokaal, in de hersenslagader, (intra-arterieel) toegediende trombolyse en met mechanische verwijdering van het stolsel, trombectomie.

Dit proefschrift beschrijft de ontwikkeling van intra-arteriële therapie als behandeling van het acute herseninfarct in Nederland. Het beslaat de periode vóór publicatie van de grote gerandomiseerde studies die hebben geleid tot invoering van intra-arteriële therapie als standaardbehandeling van het acute herseninfarct veroorzaakt door afsluiting van een van de grotere hersenslagaders. In **hoofdstuk 2** beschrijven we een cohort van patiënten met een herseninfarct die behandeld werden met intra-arteriële therapie in de periode 2009-2011. Gedurende deze periode werden de stent-retrievers geïntroduceerd. Bij het gebruik van een stent-retriever wordt er een stent in het afsluitende stolsel gebracht en ontplooid waarna de stent en het stolsel verwijderd worden. We toonden aan dat het percentage geslaagde rekanalisaties toenam met het gebruik van stent-retrievers. Daarnaast was er een trend waarbij meer patiënten een gunstige klinische uitkomst hadden na 3 maanden wanneer er gebruik was gemaakt van een stent-retriever. In **hoofdstuk 3** wordt een landelijk cohort beschreven van alle patiënten behandeld met intra-arteriële therapie vanaf 2002 tot de start van de MR CLEAN trial in 2010. Na verloop van tijd werden patiënten sneller behandeld (kortere deur-tot-lies tijd), werd intra-arteriële therapie vaker gecombineerd met intraveneuze trombolyse, en werd intra-arteriële trombectomie met stent-retrievers steeds vaker toegepast. Dit alles resulteerde in een trend naar frequenter geslaagde rekanalisatie en meer patiënten met een gunstige klinische uitkomst na 3 maanden.

Het tweede deel van het proefschrift beschrijft specifieke behandelgroepen. In **hoofdstuk 4** bestudeerden we het effect van leeftijd op de uitkomst na intra-arteriële therapie. Leeftijd was omgekeerd gerelateerd aan een gunstige uitkomst. Daarnaast was het risico op niet-neurologische complicaties hoger met het toenemen van de leeftijd van de patiënt. Er was echter geen verhoogd risico op complicaties gerelateerd aan de intra-arteriële therapie of op neurologische complicaties. Op basis hiervan veronderstelden we dat een hogere leeftijd weliswaar de kans op een gunstige uitkomst vermindert, maar dat er geen

interactie is met het effect van de intra-arteriële therapie. In **hoofdstuk 5** wordt ingegaan op het behandelen van patiënten met intra-arteriële therapie die een verlengde bloedingstijd (INR > 1.7) hebben. Van patiënten met een verlengde bloedingstijd werd verondersteld dat zij een hogere kans op een bloedingscomplicatie zouden hebben. We vergeleken patiënten met verlengde bloedingstijden met patiënten met normale bloedingstijden. We vonden geen verhoogd bloedingsrisico (relatief risico 0.49, 95% betrouwbaarheidsinterval 0.07-3.13). Daarnaast verrichtten we een meta-analyse over dit onderwerp. Het risico op een intracerebrale bloeding bleek 8.1% (95% betrouwbaarheidsinterval 3.9%-17.1%) te zijn. Dit percentage is vergelijkbaar met het percentage risico op intracerebrale bloedingen van het Cochrane review over trombolytische therapie voor het herseninfarct. We concludeerden dat er vermoedelijk geen verhoogd risico is op intracerebrale bloedingen bij patiënten met een herseninfarct en verlengde bloedingstijden. In de laatste versie van de richtlijn "Herseninfarct en hersenbloeding" van de Nederlandse Vereniging voor Neurologie wordt het gebruik van orale anticoagulantia niet meer genoemd als contra-indicatie voor het toepassen van intra-arteriële therapie.

In het derde deel van dit proefschrift gaan we in op diagnostiek bij het herseninfarct en intra-arteriële therapie. We bestudeerden het gebruik van echo-duplex ten behoeve van screening op extracraniële vernauwing van de arteria vertebralis (**hoofdstuk 6**). Hiervoor vergeleken we de echo-duplex en CT-angiografie van patiënten met een herseninfarct of TIA van de achterste circulatie. Met echo-duplex was een stenose goed vast te stellen (AUR-ROC 0.73, 95% betrouwbaarheidsinterval 0.63-0.83). Echter, het proximale deel van de arteria vertebralis is vaak moeilijk in beeld te krijgen met echo-duplex. Dit wordt veroorzaakt door omliggende anatomische structuren (wervels) en degeneratieve veranderingen ter plaatse bij de meestal wat oudere patiënt. Dit maakt de echo-duplex minder geschikt voor gebruik in de dagelijkse praktijk.

In **hoofdstuk 7** wordt de variatie van de Cirkel van Willis op CT-angiografie onderzocht in relatie tot klinische uitkomst bij patiënten met een herseninfarct behandeld met intra-arteriële therapie. We veronderstelden dat een complete Cirkel van Willis zou resulteren in een hogere kans op een gunstige klinische uitkomst omdat een complete cirkel zorgt voor betere collaterale circulatie. Daarnaast bestudeerden we de invloed van de bloedvoorziening naar de Cirkel van Willis via de arteria carotis interna. De Cirkel van Willis werd beschouwd als volledig indien het A1 segment contralateraal aan de afgesloten arterie, de

arteria communicans posterior ipsilateraal aan de afgesloten arterie en de arteria communicans anterior volledige aangelegd en open waren. In tegenstelling tot onze verwachting bleek het compleet zijn van de Cirkel van Willis niet gerelateerd te zijn aan een gunstige klinische uitkomst. Wel nam de kans op een gunstige klinische uitkomst toe met het aantal carotiden die de Cirkel van Willis van bloed voorzien.

In het laatste deel van het proefschrift worden de hiervoor genoemde resultaten bediscussieerd (**hoofdstuk 8**).

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CURRICULUM VITAE

Anouk Desirée Rozeman werd op 10 april 1981 geboren in Utrecht. Zij groeide achtereenvolgens op in Utrecht, Voorburg en Amstenrade. In Amstenrade bracht zij het grootste deel van haar jeugd door. In 1999 behaalde zij haar VWO diploma aan het St. Janscollege te Hoensbroek. In datzelfde jaar begon zij met de studie Technische Bedrijfskunde in Enschede. In 2000 werd zij ingeloot voor de studie geneeskunde en startte zij hiermee in Leiden. Met het volgen van een semi-arts stage en 2e wetenschapsstage Neurologie in het Haaglanden MC was de keuze voor de neurologie definitief. In 2007 behaalde zij haar artsexamen. Initieel werkte zij als ANIOS Neurologie in het Groene Hart Ziekenhuis te Gouda. In januari 2009 begon zij haar opleiding tot neuroloog in het Haaglanden MC met als opleiders dr. Vecht en later prof. Taphoorn.

Gedurende haar geneeskunde opleiding deed Anouk een tweetal wetenschappelijke stages waaronder één bij de Klinische Neurofysiologie en Slaapcentrum in het Haaglanden MC. Dit resulteerde in een publicatie in Journal of Clinical Sleep Medicine (2014;10:893-6). In 2011 werd de interesse in wetenschap verder uitgebouwd door gezamenlijk met Jelis Boiten en Geert Lycklama à Nijholt te werken aan een artikel over de intra-arteriële behandeling van het acute herseninfarct. Hieruit kwam, na toevoeging van Ale Algra en Marieke Wermer als begeleiders, de start van een promotietraject voort.

In maart 2015 ronde zij haar opleiding tot neuroloog af en startte zij als chef de clinique Neurologie in 't Lange Land ziekenhuis te Zoetermeer. In november van dat jaar stapte zij over naar het Albert Schweitzer Ziekenhuis waar zij in juni 2016 een vaste aanstelling kreeg als vasculair neuroloog. Zij woont samen met Alexander Kuhlmann en heeft een dochter: Valérie.

LIJST VAN PUBLICATIES

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