Intraarterial treatment for acute ischemic stroke
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Chapter 1

General Introduction
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Acute Ischemic Stroke

Acute ischemic stroke (AIS) starts with a sudden loss of blood circulation to an area of the brain, resulting in loss of neurological function. Loss of neuronal function in specific regions of the brain causes different types of symptoms. In contrast to acute intracranial hemorrhage, where intracranial bleeding results in loss of neurological function, loss of blood circulation in AIS is most often caused by an embolus or thrombotic occlusion (see Figure 1.1). At presentation, a physician is unable to distinguish AIS from acute intracranial hemorrhage on clinical grounds alone. Neuroimaging is needed to rule out hemorrhage, in order to start adequate therapy.

Figure 1.1 Potential sites of thrombus formation causing intracranial large vessel occlusion. (reprinted with permission of Springer)

Until recently, the only proven reperfusion therapy was intravenous alteplase (IVT) administrated within 4.5 hours after symptom onset.1-3 However, well-recognized limitations of this therapy include the narrow therapeutic time window and contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage.4 In addition, IVT appears to be much less effective at opening
proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior circulation stroke. Early recanalization after IVT is seen in only about one third of patients with an occlusion, and the prognosis without revascularization is generally poor for such patients. To provide an alternative to patients that are not eligible for IVT, or do not respond favorably, intra-arterial treatment (IAT) options were explored. At the beginning of my PhD project there was no proof of effectiveness. A Cochrane review published in 2009 found 4 trials were thrombolytic agents were administered intra-arterially. Results showed a direction of benefit for intra-arterially applied thrombolytic agents, but authors emphasized that analysis should be regarded with extreme caution due to differences in design, and the absence of comparison to usual care. In the years that followed, an emerging interest grew in the use of thrombectomy devices to treat large vessel occlusions. The reported recanalization rates of these devices were excellent, but they were only tested in case-series and single arm registries. The Cochrane review was updated after the results from IMS-III and SYNTHESIS Expansion, indicating that IAT conferred no benefit over IVT, either in terms of reduced dependency or death. Authors concluded that intra-arterial thrombolysis or mechanical thrombectomy should only be used in randomized trials. Taken together, the primary aim of this thesis has been to proof the effectiveness and safety of intra-arterial treatment.

Pathophysiology

At least five fundamental mechanisms are believed to lead to loss of function and eventually, cell death: excitotoxicity and ionic imbalance, oxidative/nutritive stress, peri-infarct depolarization, inflammation, and apoptosis. This cascade begins within minutes after symptom onset (see Figure 1.2). In the absence of fast and adequate reperfusion therapy, areas with severely reduced blood flow (0-10ml/100 g brain tissue per minute) will develop irreversible damage due to excitotoxicity and necrotic cell death. This area is often called the core of the ischemic territory. Around the ischemic-core is a zone, which is called the ischemic penumbra. In this region cell death occurs relatively slow. This non-infarcted tissue is potentially salvageable. A third area can be identified within the penumbra, referred to as oligaemia, which will recover spontaneously. The alteration from penumbra to core depends on several factors, which includes collateral supply, infarct core-size at presentation and time to reperfusion. Collaterals, are preexistent vascular anastomoses, which provide varying degrees of blood flow to brain tissue when the primary supply pathways fail. Expression of collaterals varies among individuals and patients with poor or absent collaterals may gain less clinical benefit from reperfusion therapies. Another highly variable parameter is infarct-core at the time of presentation. Infarct-core estimation is often done with the aid of the Alberta Stroke Program Early CT Score (ASPECTS) on non-contrast computed tomography (NCCT). ASPECTS is a semiquantitative method of...
estimating infarct size during the acute phase. Patients with low ASPECTS (equals large infarct volume at baseline) appear to have less benefit from reperfusion therapies. We will go into further detail in Chapters 3 and 5.

![Figure 1.2](image.png)

Figure 1.2 Time is displayed on the x-axis, and y-axis displays the fundamental mechanism that play in important role during an acute ischemic stroke. (reprinted with permission of Trends in Neurosciences/Elsevier Science Ltd)

### Epidemiology

In the Netherlands (17 million inhabitants\textsuperscript{18}), each year more than 25.000 hospital admissions are result of stroke, with a mortality of 8500 patients per year.\textsuperscript{19} Mortality due to AIS alone was 5.451 in 2014.\textsuperscript{19} More than 175.000 individuals in the Netherlands are alive with consequences of previous stroke, and approximately half of these are seriously disabled.

For the United States of America (USA), around 795.000 patients experience a new or recurrent stroke per year. Approximately 610.000 of these are first attacks, and 185.000 are recurrent attacks.\textsuperscript{20} On average, every 40 seconds someone in the USA has a stroke. The estimated prevalence of stroke is 6.6 million for the year 2012, and projections show that by 2030, an additional 3.4 million people aged ≥18 years will have had a stroke.\textsuperscript{20}

In the Netherlands, the total number of inhabitants aged 75 and over will double from 1.2 million in 2011 to 2.6 million in 2040. With this expected ageing, the prevalence of stroke will increase with 85% from 186.000 to 343.000 by the year 2040.\textsuperscript{19} Based on data from the Promoting Acute Thrombolysis for Ischaemic Stroke (PRACTISE) study, 50% of the patients with AIS present within 6 hours after symptom onset at a Dutch hospital. An estimated 25-30% of patients are suitable for AIT, resulting in 2500 eligible patients annually.\textsuperscript{5,6,21}
Historical perspective

Intra-arterial locally administrated fibrolytic agents (urokinase, streptokinase) were first described in the beginning of the 1980’s.[22,24] A study conducted by Miyakawa reported two patients with a middle cerebral artery territory occlusion, treated with intra-arterial plasmin infusion within two hours after symptom onset, resulting in neurological recovery.[23,25] A larger case-series was published by Zeumer reporting 13 patients treated with local intra-arterial fibrinolysis of the anterior circulation.[24] The use of locally applied (intra-arterial) fibrolytic has some advantage over systemic (intravenous) administration. A lower total dosage can be used and a relatively higher dose is active in close proximity to the thrombus. This could potentially lead to higher chance of recanalization and to lower risk of hemorrhage, a well-known and feared complication of fibrolytic therapy.

The first randomized clinical controlled trial was the Prolyse in Acute Cerebral Thromboembolism (PROACT Trial), which was published in 1998. The aim was to test the safety and efficacy of locally applied recombinant pro-urokinase versus placebo in patients suffering from AIS with an angiographically proven middle cerebral artery occlusion.[25] This phase II trial randomized 46 patients between intra-arterial recombinant pro-urokinase or placebo. All patients received intravenous heparine. Recanalization (primary outcome parameter) was significantly associated with recombinant pro-urokinase without significant increase in hemorrhagic transformation.

The subsequent PROACT II trial was a phase III trial, conducted in 54 centers in the United States and Canada.[26] A total of 180 patients with AIS of less than 6 hours duration caused by angiographically proven occlusion of the middle cerebral artery were included. Patients were randomized between 9 mg of intra-arterially applied recombinant pro-urokinase plus heparin versus heparin only. The primary analysis showed a significant increase of 15% in patients with independent life after 90-days without increase in mortality or hemorrhage. This was the first trial to demonstrate a benefit of intra-arterial therapy in patients with AIS caused by a proximal arterial occlusion.

The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan was conducted to determine the safety and clinical efficacy of intra-arterial infusion of urokinase in patients with AIS treatable within 6 hours after symptom onset.[27] Patients were randomized between urokinase or control. After randomization of 114 patients the study was stopped because of national approval of intravenous infusion of recombinant tissue plasminogen activator in Japan. The primary endpoint, functional independent life after 90 days, was not statistically significant.

These studies and result from two smaller randomized controlled trials[28,29] were included in a subsequent meta-analysis that showed benefit for treatment with pro-urokinase or urokinase. However, their results were not directly applicable to current decision making about treatment because the control groups did not include
intravenous alteplase, and mechanical approaches have largely replaced locally applied thrombolytic agents as first-line therapy.\textsuperscript{30}

Two years before the publication of the recent randomized controlled trials, three clinical trials published in the same edition of the New England Journal of Medicine, showed neutral results.\textsuperscript{31-33} The largest study was Interventional Management of Stroke (IMS-III), which investigated the safety and effectiveness of additional endovascular therapy in patients receiving intravenous tissue plasminogen activator.\textsuperscript{31} Patients with moderate-to-severe AIS and presentation within 3 hours after symptom onset without contra-indications for intravenous tissue plasminogen activator were eligible for inclusion. Patients were randomly assigned to endovascular therapy and intravenous tissue plasminogen activator or tissue plasminogen activator alone. The trial was stopped early because of futility after 656 of the planned 900 patients were randomized. The study showed similar results on functional independence and safety outcomes after 90-days.

The Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial conducted a head-to-head comparison of endovascular therapy versus intravenous tissue plasminogen activator.\textsuperscript{32} The results of this trial with 362 patients showed no difference between standard treatments with intravenous tissue plasminogen activator compared to endovascular treatment.

In Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) 118 eligible patients were randomized bases on penumbral pattern on neuroimaging.\textsuperscript{33} The trial found no favorable penumbral pattern that would identify patients that would benefit more from endovascular therapy, nor was it able to show difference between endovascular therapy or standard of care.

**Intra-arterial therapy**

Some types of intra-arterial therapy have previously been described. In this paragraph, we will discuss these types in more detail. AIT starts with arterial catheterization, with the femoral artery as most preferred access site. Other access sites included the radial artery and direct puncture of the cervical carotid artery. After introduction of the sheath, a guide wire is used to deliver a microcatheter in close proximity to the occluded vessel. The whole procedure is conducted under digital subtraction angiography, in which radiation and iodinated contrast agents are used to create images to guide treatment and to assess vessel patency. After access to the occlusion site is secured the interventionalist can choose between locally applied thrombolytic agents and/or mechanical treatment. The anesthetic management during the procedure is roughly divided in two approaches. In the first approach, patients are treated without general anesthesia, but with applying local anesthesia in the groin, with or without subsequent use of conscious sedation. In the second approach patients are treated under general anesthesia, and an anesthetic agents are used to to induce a coma with the loss of protective reflexes.
Intra-arterial thrombolysis

As previously mentioned, local application of thrombolytic agents may lead to dose reduction, and theoretically to less intracranial hemorrhage. An important disadvantage is that infusion of thrombolytic agents and the subsequent thrombus dissolution is time consuming. In contrast to mechanical thrombectomy, where revascularization occurs immediately after thrombus removal. In addition, mechanical thrombectomy can target different types of clot compositions. Some clots are very resistant to inhibitory pathways compared to other. Another advantage of mechanical thrombectomy is the option to bypass of thrombolytic agents, which may cause a decrease in incidence of intracranial hemorrhage.

MERCI retriever

The Mechanical Embolus Removal for Cerebral Ischemia (MERCI) device was invented in 1995. When unsheathed from the microcatheter, the corkscrew-shaped device was designed to engage with clot surface (see Figure 1.3). The device was tested in the MERCI and Multi MERCI trials, which were prospective, single-arm, multi-center studies.\(^{34,35}\) The results showed high recanalization rates and similar risk of symptomatic intracranial hemorrhage compared to historical controls from the PROACT-II. The United States Food and Drug Administration (FDA) approved the MERCI retriever in 2004. Despite promising results, the MERCI device was never compared to standard of care in a randomized clinical controlled trial.

Thrombosuction

The Penumbra system was approved by the FDA in 2008 (see Figure 1.3). This device was actually a catheter that was attached to a suction machine to create a vacuum in order to aspirate the clot. The first-generation used a wire (called separator) to fragment the thrombus into smaller pieces in order to facilitate the suction. With the development of new large bore distal access catheter it is possible to directly aspirate the clot. During the procedure, the large bore catheter is moved close to the proximal surface of the clot and suction is applied to slowly pull the clot into the guiding catheter. In the first-generation device, the bore of the catheter was too small to grab the clot itself, and fragmentation was necessary, thereby creating potential distal emboli. The Penumbra Pivotal Stroke Trial was a single-arm, prospective, multi-center study, which was published in 2009.\(^{36}\) In total, 125 patients were included and reported post-procedural revascularization rates were higher, but only 25% of patients were independent at 90-days. As with the MERCI device, the first-generation Penumbra suction device was never compared to control population.
Retrievable stents

The Solitaire AB Neurovascular Remodeling Device received Conformité Européenne (CE) Mark for treatment in neurovascular disease in 2007 (see Figure 1.3). After the MERCI retriever and Penumbra system, fully retrievable stents are often referred to as third-generation mechanical thrombectomy devices. The Solitaire AB was initially presented for stent-assisted coiling in intracerebral aneurysm treatment. C. Castaño first described the possibility to use the Solitaire for clot removal.37 This important discovery was rapidly adopted by other interventionists for treatment of patients with AIS, and competing device companies in the field of neuro-interventional radiology started developing their own type of retrievable stents. First a balloon-guide catheter is placed in the internal carotid artery. With the use of a microguidewire, a microcatheter is inserted beyond the distal end of the clot. The retrievable stent is advanced through the microcatheter, and deployed within the clot by withdrawing the microcatheter. The self-expanding nitinol stent traps the thrombus between the vessel wall and the stent-struts (see Figure 1.3 and 1.4). The stent is left in place for about five minutes in order
to let the thrombus engage with the stent-struts. During this waiting period, flow restoration is most often already obtained. Afterwards, the stent including clot are retrieved into the guiding catheter under aspiration.

After promising results from multiple case-series,18-40 two kinds of retrievable stents were tested against the MERCI retriever.41,42 The SWIFT was a randomized clinical controlled, non-inferiority trial, comparing the Solitaire device against the MERCI retriever.42 A prespecified efficacy-stopping rule trigged an early halt to the trial after randomization of 113 patients. The primary outcome was revascularization rate, which was in favor of Solitaire (61% vs. 24%). After 90-days, 25% more patients in the Solitaire group were functionally independent. The TREVO-2 trial was a randomized clinical controlled trial that compared the TREVO retrievable stent against the MERCI device.41 The rate of successful revascularization was higher (86%) in the TREVO group, compared to the MERCI device group (60%). Both trials lacked a control arm, and no conclusions could be drawn about the effect compared to standard of care.

The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)

After publication of the neutral results, numerous concerns have been raised regarding the design and conduct of these trials, including a relatively long interval before AIT, the absence of pretreatment vascular imaging to confirm a proximal intracranial occlusion, and the limited use of third-generation mechanical thrombectomy devices such as retrievable stents. The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was designed and started randomization before the publication of the results of these neutral trials. MR CLEAN assessed whether AIT plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intra-arterially within 6 hours after symptom onset. MR CLEAN was a multicenter clinical trial with randomized treatment allocation, open-label treatment and blinded endpoint evaluation (PROBE design). MR CLEAN was a pragmatic study, in which the type of AIT and type of anesthesia were left to discretion of the treating interventionalist. IAT consisted of intra-arterial thrombolysis with alteplase or urokinase, mechanical treatment or both, as previously discussed. Patients with clinical diagnosis of stroke, aged 18 years or over were eligible for randomization. Only patients with an occlusion of distal intracranial carotid artery (ICA/ICA-T) or middle (M1/M2) or anterior cerebral artery (A1/A2) demonstrated with CT angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). The primary outcome was the score on the modified Rankin Score (mRS) scale, and the treatment effect was estimated with multivariable ordinal logistic regression.
Outcome measures in MR CLEAN

Clinical outcome measures

Commonly used outcome scales for assessing functional outcome in stroke trials are the modified Rankin Scale (mRS), Barthel Index and National Institute of Health Scale Score (NIHSS). The mRS is a seven point scale, with ordinal hierarchy, ranging from 0 (no symptoms) until 6 (death). This score is most often used as the primary outcome in stroke trials. Earlier stroke trials used cutoffs at mRS 0-1 or 0-2 thereby dichotomizing the scale in order to create a binary outcome. This approach has several disadvantages. First, dichotomization may limit statistical power, and power calculations most often increase study size. Furthermore, stroke treatments, especially AIT, are developed to limit neurological decline and complete curative outcomes are rare. Collapsing scales to binary outcomes of favorable and unfavorable outcome does not resemble clinical practices. The primary effect variable in MR CLEAN was therefore the adjusted common odds ratio for a shift in better outcome on the mRS, this ratio was estimated with multivariable ordinal logistic regression. Secondary outcomes included the NIHSS at 24 hours and at 5-to-7 days or discharge, Barthel Index at 90-days. The EuroQol was used to assess quality of life and future planned cost-effectiveness analyses.

Radiological outcome measures

Recanalization was assessed on CTA or MRA after 24 hours in both trial arms, and was classified as complete or incomplete. This was further evaluated with the modified Arterial Occlusive Lesion (AOL) score (see the Supplemental Material of Chapter 2). To assess the final infarct volume, an automated, validated algorithm was used to analyse all follow-up NCCT scans that were obtained at day 5-to-7 (range 3-9). All calculated volumes were checked by human eye. All neuroimaging studies were evaluated for signs of intracranial hemorrhage by two neuroradiologist who were unaware of the treatment-group assignment. An independent core laboratory assessed angiographic outcomes on DSA imaging, using the modified Thrombolysis in Cerebral Infarction (mTICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion) (see the Supplemental Material of Chapter 2).
Aims and outline of the thesis

In 2010 the benefit of IAT in patients with AIS due to intracranial large vessel occlusion was still unproven. This thesis focussed on providing proof of efficacy and safety of intra-arterial treatment in patients presenting with acute ischemic stroke caused by a large vessel occlusion of the anterior circulation. A secondary aim was to evaluate the treatment effect within different subgroups in order to pave the way for a future of personalized medicine.

This thesis is divided into three parts. In the first part we describe the effect and safety of AIT. Chapter 2 describes the results of MR CLEAN (the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). We assessed whether AIT plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated within 6 hours after symptom onset. In order to improve selection of patients with AIS for IAT we explored if we could identify baseline neuroimaging characteristics that modified treatment effect.

In the second part of this thesis we therefore assessed whether baseline NCCT ASPECTS (Chapter 3), co-existing extracranial carotid disease (Chapter 4), and baseline CTA collateral status (Chapter 5) modified treatment effect in MR CLEAN.

In the third part of this thesis we described the influence of two clinical characteristics. Previous studies have shown that the effect of IVT diminishes with increasing time from symptom onset to start infusion. In Chapter 6 we assessed whether this also holds for the effect of AIT. A recently reported survey showed that controversy exists about the optimal anesthetic management during AIT. In MR CLEAN no recommendations were given about type of anesthetic management and left this decision to the discretion of the centers. Chapter 7 reports the results of a post-hoc analysis of the type of anesthetic management used during intra-arterial therapy.

A general discussion of this thesis, implications and future directions are presented in Chapter 8. It is followed by a summary in English and Dutch.
References