# 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.