General introduction

STROKE AND LARGE VESSEL OCCLUSION

Cerebrovascular disease is the primary cause of disability and the second cause of mortality worldwide. Approximately 85% of strokes are caused by an occlusion of an artery causing cerebral ischemia and infarction; and the minority is an intracerebral hemorrhage [1]. The location of the intracranial occlusion is an important determinant of the severity of ischemic stroke [2]. The more proximal the occlusion, the more brain tissue will be ischemic resulting in poorer functional or even fatal outcome compared to more distal occlusions [3-8]. Approximately one third of the acute ischemic strokes is caused by an occlusion in a proximal intracranial artery, like the intracranial carotid bifurcation, the M1 and M2 segment of the medial cerebral artery and the basilar artery [8].

ENDOVASCULAR TREATMENT: HISTORY AND IMPLEMENTATION IN CLINICAL PRACTICE

Intravenous thrombolytic therapy has been proven to be effective in selected patients with acute ischemic stroke within 4.5 hours after onset. With the use of perfusion imaging, recent research showed that this time window can be extended to 9 hours [9, 10]. However, thrombolytic therapy is not without risk: almost 7% of patients develops an intracerebral hemorrhage which can be fatal or lead to severe disability [11]. Furthermore, the rates of successful recanalization after intravenous thrombolysis in patients with a large vessel occlusion (LVO) is low (4-38%) and depends on the location of the occlusion [12-17]. More proximal occlusions have a lower tendency to resolve by intravenous thrombolytic agents.

Since 2015, multiple randomized clinical trials have proven the safety and efficacy of endovascular treatment (EVT) with retrievable stents in acute ischemic stroke patients due to LVO [18-22]. The results of these trials were an important turnaround in stroke care worldwide. Patients who were treated endovascularly had a significant better functional outcome and achieved more often functional independency compared to patients who were treated with usual care including intravenous thrombolytic therapy [23]. The first trial was the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) which was a pragmatic trials due to broad inclusion criteria [18]. After translation of the results to clinical practice, it was considered to be important to assess the efficacy and safety of EVT in daily practice. Therefore, the MR CLEAN Registry was established as prospective observational study in 17 Dutch stroke centers directly after the last patient inclusion in the MR CLEAN trial [18]. The first results of the ongoing MR CLEAN Registry showed that EVT was at least as effective and safe as in the MR CLEAN trial and reperfusion rates were comparable [24]. Since the MR CLEAN Registry is an observational study collecting data from routine clinical practice, patients were older with more co-morbidities. Despite this, more patients were functionally independent after EVT compared to patients who were allocated to the intervention arm of the MR CLEAN trial. This observation can potentially be explained by shorter time-windows (stroke onset to successful reperfusion or last contrast bolus) by one hour, which was the result of improvement of in-hospital workflow since the MR CLEAN trial [25].

After the results of the MR CLEAN trial were published, a steep increase of EVT was observed in the Netherlands (Figure 1 & 2). At the end of 2018, already more than 5000 patients were registered in the MR CLEAN Registry. A recent survey among 44 European countries showed that in the Netherlands the proportion of EVT-treated patients due to ischemic stroke (4.6%) is relatively high in comparison to the average in Europe (1.9%).

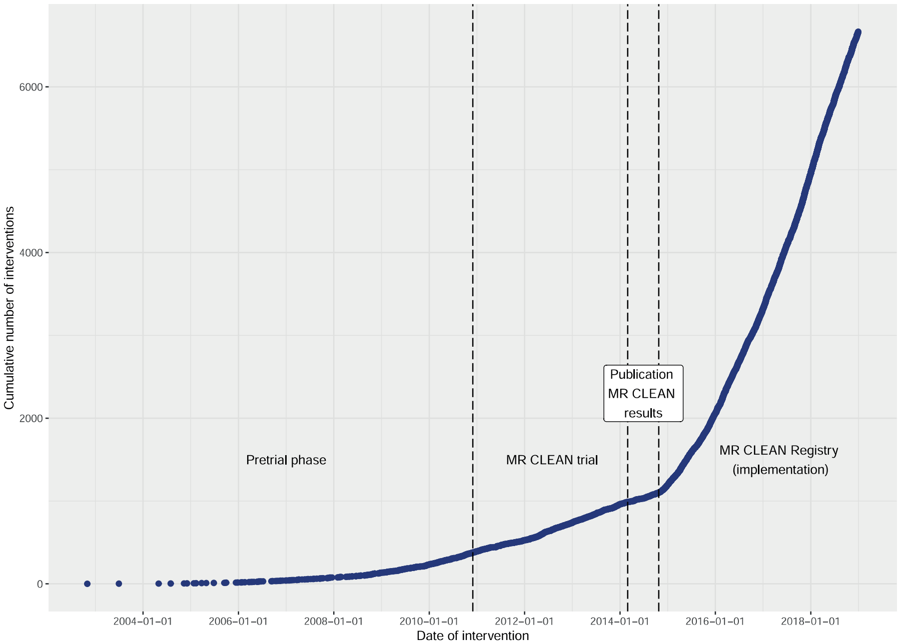

Figure 1. Cumulative plot showing the trend over time regarding the use of endovascular treatment (EVT) in the Netherlands. *Obtained from mrclean-trial.org.*

The MR CLEAN trial and Registry were designed to assess treatment effect and quality of care after implementation and efficacy in routine clinical practice. However, the detailed dataset can also be used to answer important clinical research questions concerning potential causes of ischemic stroke, treatment of important clinical subgroups of patients and to evaluate potential imaging outcomes as early surrogate marker for future trials.

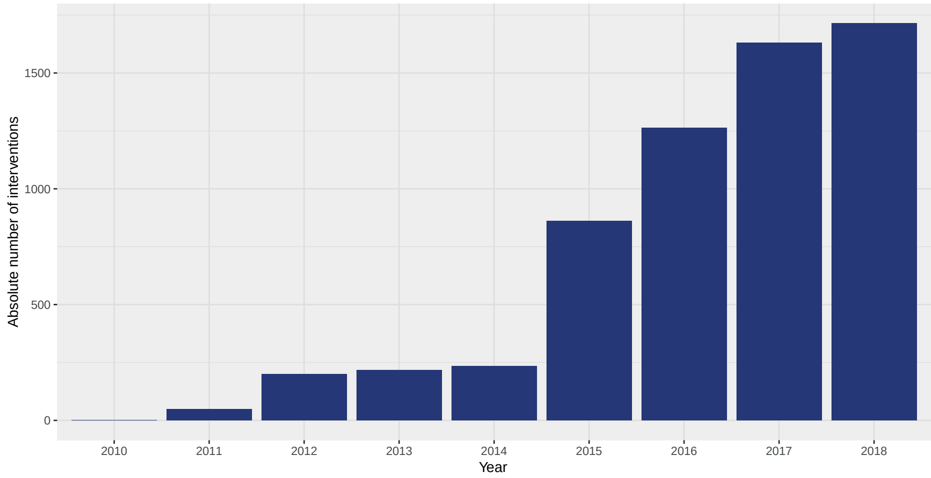

Figure 2. Absolute number of EVT-treated patients per year since the inclusion period of the MR CLEAN trial (2010, December 1) until the final registration of patients in the MR CLEAN Registry (2018, December 31).

CAUSES OF INTRACRANIAL LARGE VESSEL OCCLUSION AND CAROTID WEBS IN ISCHEMIC STROKE PATIENTS

Classification of subtypes of ischemic stroke

An occlusion of a large artery supplying the cerebral cortex will result in a non-lacunar infarction while a small vessel occlusion will result in lacunar (subcortical) infarction. The underlying causes of large vessel occlusion ischemic stroke have been extensively studied in general stroke populations and showed that major causes are cardiac embolism and large artery atherosclerosis [26]. Cardiac emboli are the result of blood stasis which can be caused by atrial fibrillation, or due to valvular disease such as mitral prolapse [27]. Large artery atherosclerosis is a systemic and chronic disease which leads to increased cardiovascular morbidity and mortality [1]. Atherosclerotic plaque development might cause stenosis or occlusion of an artery. In acute events, a vulnerable plaque can rupture leading to intraluminal thrombus formation which can eventually cause an ischemic stroke [28, 29].

Identification of the underlying cause of ischemic stroke is important in clinical practice to estimate risk of recurrent stroke and implement treatment for secondary prevention. Several classifications have been proposed to identify the most likely cause of ischemic stroke which can be used as well in clinical practice as in research. A widely used classification scheme is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification using clinical information and radiological imaging [30]. Previous studies regarding cause of ischemic stroke according TOAST were conducted in a general stroke population. After the implementation of EVT in daily practice, it is of importance to assess causes of LVO in patients suffering ischemic stroke.

Carotid webs

Carotids webs are fibrous lesions causing circumferential narrowing in the proximal internal carotid bulb (Figure 3). Although these lesions are rare and clinical data is scarce, carotid webs might be an important cause of (recurrent) ischemic stroke [31, 32]. Interestingly, previous studies stated that carotid webs occur in women without other apparent cause of stroke [32, 33]. The pathophysiological mechanism for thromboembolic strokes is unknown, but it is speculated that the impact of the web morphology on blood flow patterns might lead to thrombus formation [32]. Due to the shelf-like fibrous lesion, which differs from an atherosclerotic stenosis, flow patterns might be greatly disturbed and therefore increasing the risk of an embolic stroke.

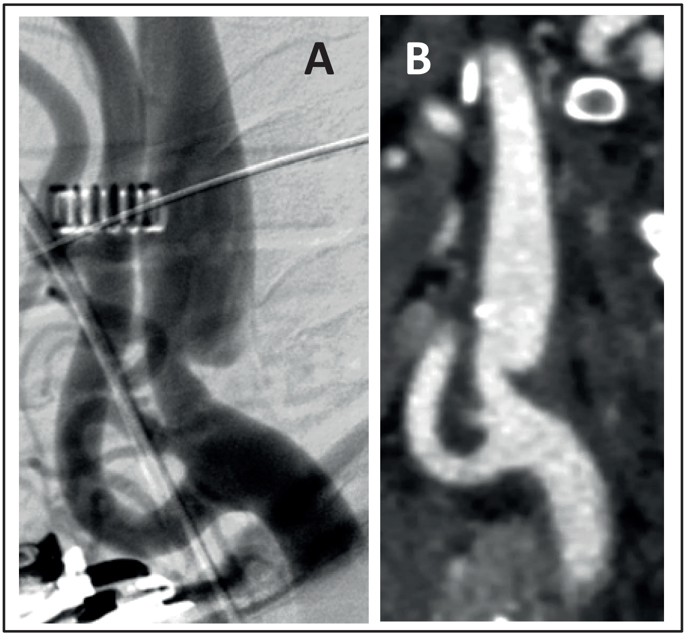

Figure 3. Digital subtraction angiography (**A**) and sagittal reconstruction of computed tomography angiography (**B**) demonstrating a carotid web in the carotid bifurcation.

More insight into the prevalence of carotid web may help to assess the role of this less-known lesion as an important cause of ischemic stroke. Furthermore, more evidence is needed to support the hypothesis that the morphology of carotid webs introduces disturbed blood flow patterns and consequently causes ischemic strokes.

ENDOVASCULAR TREATMENT IN SUBGROUPS OF PATIENTS WITH LVO

Distal occlusions

A meta-analysis of patient-level data from previous EVT trials has confirmed the beneficial effect of EVT [23]. However, in several subgroups of patients, precise estimates of treatment effect could not be made. The question whether patients suffering ischemic stroke due to a more distally located occlusion, in the M2 segment of the middle cerebral artery (distal to the main bifurcation at the distal end of the horizontal M1 segment), benefit from EVT could not be answered (Figure 4). Patients with distal occlusions often remain functionally dependent after their stroke [34, 35]. This suggests that reopening the artery and reperfusion of small ischemic brain regions can be important, as these brain regions may involve eloquent areas [34, 35]. However, considering the distal location, smaller caliber and thinner walls of the M2 segment artery, the beneficial effects of EVT can be nullified by increased risks of periprocedural complications such as intracerebral hemorrhage. Current stroke guidelines state that it may be reasonable to treat stroke patients suffering from an M2 occlusion with EVT, but further evidence is still needed [36]. The discussion is muddled by the existence of multiple definitions and terminology for distal occlusions.

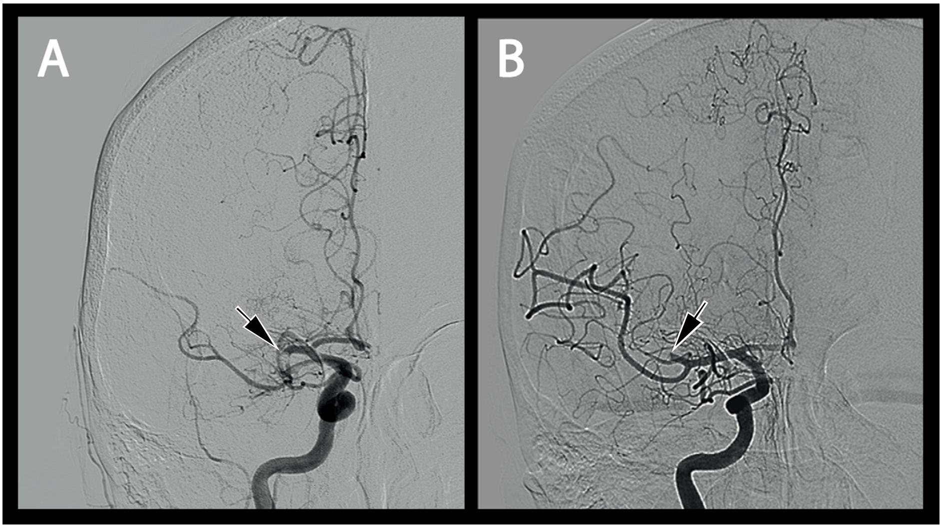

Figure 4. Digital subtraction angiography with a M1- (**A**) and M2 (**B**) occlusion (anteroposterior view).

Carotid artery dissection

There is no consensus regarding the benefit of EVT in ischemic stroke patients with intracranial occlusion and additional extracranial lesions due to carotid dissection (Figure

5). One might argue that is more challenging for the neurointerventionalist to reach the intracranial occlusion, and that the risk for thromboembolic complications is increased. Both factors can adversely influence clinical outcome. On the other hand, patients with carotid dissection are generally younger and have less cardiovascular risk factors. In a post-hoc analysis of the MR CLEAN trial, EVT was at least as effective and safe in patients with extracranial tandem lesion [37]. Stratified for the type of tandem lesion, no significant modification of treatment effect was observed by carotid dissection. However, the number of patients with a carotid dissection was low in this study and inclusion was left to

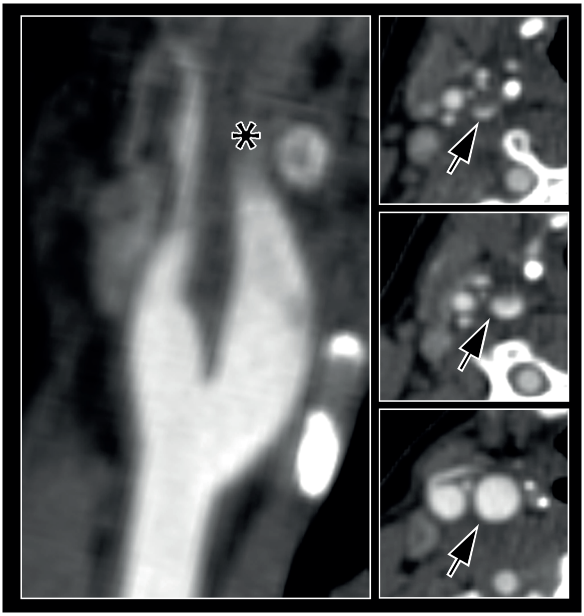

Figure 5. Computed tomography angiography of carotid artery dissection. Sagittal (asterisk) and axial (arrows) reconstructions show an eccentric narrowing of the true lumen (string sign) without involvement of the carotid bulb.

discretion of the treating physician.

Intracranial atherosclerosis

The presence of intracranial atherosclerotic disease might lead to plaque disruption and microemboli during stent retrieval. Therefore a large amount of intracranial carotid artery calcification (ICAC) may be a predictor of poor functional outcome in acute ischemic stroke patient treated by EVT [38-40]. Besides volume of ICAC, calcification pattern may relate to functional outcome in these patients. Two different patterns can be distinguished, namely calcification in the tunica intima (intimal calcification pattern) and calcification present in the tunica media (medial calcification pattern) (Figure 6) [41, 42]. These patterns have different associations with cardiovascular risk factors. For example, medical calcification pattern is associated with increased age of the patients, diabetes mellitus and high pulse pressure while intimal calcification pattern is related to smoking and hypertension [43]. Investigating pattern of calcification could provide further insights into the effect of EVT in patients with intracranial atherosclerotic disease.

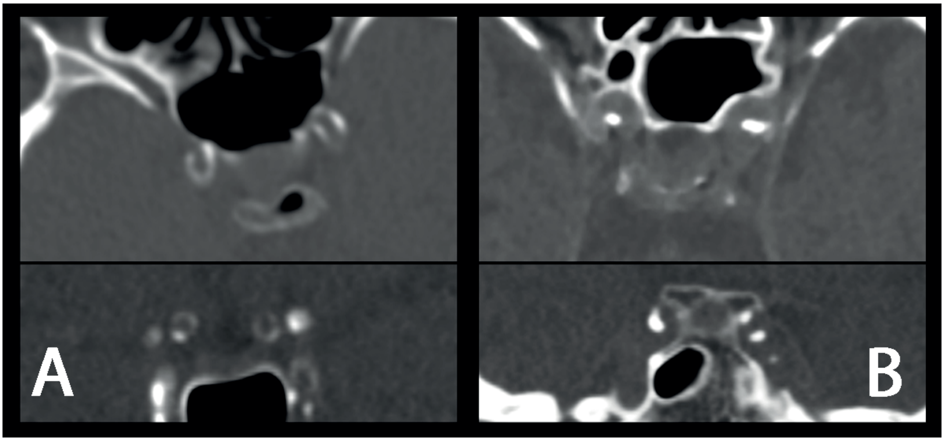

Figure 6. Non-contrast CT scans. Calcification patterns on non-contrast computed tomography. Medial calcification pattern is identified as a thin, continuous and almost circular calcification patterns in axial viewing plane (**A; upper panel**) and coronal viewing plane (**A; lower panel**). Intimal calcification pattern is identified as a thick, irregular and non-circular calcification patterns in axial viewing plane (**B; upper panel**) and coronal viewing plane (**B; lower panel**).

INFARCT VOLUME AS EARLY SURROGATE IMAGING MARKER IN FUTURE TRIALS

In all EVT trials, the modified Rankin scale (mRS) score was used as primary outcome. It is a measure of the degree of handicap and disability in everyday life of the patient. It measures functional independency or dependency on a 6-point scale. However, this qualitative measurement is sensitive to interobserver variability and requires prolonged follow-up, usually 3 months [44, 45]. Therefore, it is of interest to search for a quantitative, more reliable and surrogate endpoint that can be assessed in the first days after treatment. Recent research showed that imaging markers could play an important role as surrogate marker. Post-hoc analyses of different EVT trials showed that follow-up infarct volume on imaging is a significant and independent predictor for 3 months functional outcome. As a result, it is argued that infarct volume can be used as an early surrogate imaging biomarker in future clinical trials [46-48].

However, to investigate whether imaging could serve as an early surrogate marker for clinical outcome, the extent to which the treatment effect is explained by follow-up infarct volume needs to be investigated. In statistical terms, follow-up infarct volume on imaging could be a mediator of the effect of intervention on functional outcome in acute ischemic stroke patients (Figure 7). If clinical outcome is mediated by infarct volume, this imaging biomarker will not only be a significant predictor of the clinical outcome but the effect of intervention as independent variable will also be strongly reduced in regression models. These pathways and proportion of explained treatment effect mediated by follow-up infarct volume have not yet been investigated.

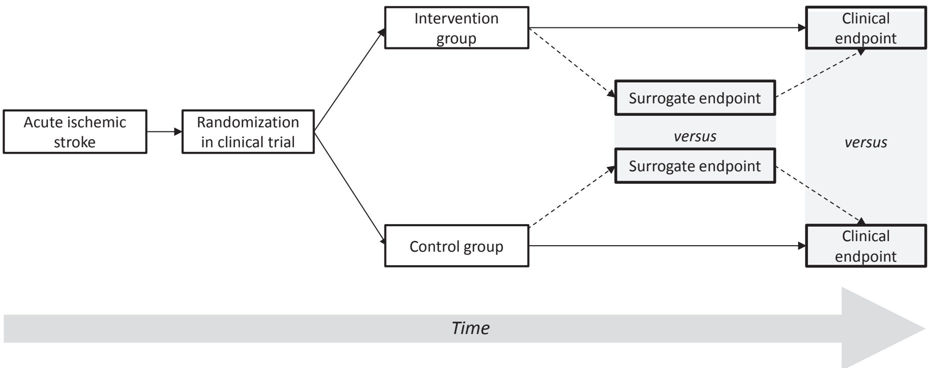

Figure 7. Causal diagram showing the pathways of patients with acute ischemic stroke in a clinical trial.

COHORTS USED IN THE PERFORMED STUDIES

MR CLEAN trial

The Multicenter Randomized Clinical trial of Endovascular treatment of Acute ischemic stroke in the Netherlands (MR CLEAN) was the first trial (n=500) that demonstrated the beneficial effect of EVT in patients with acute ischemic stroke due to a large vessel occlusion in the anterior circulation. In this pragmatic trial, patients were randomized between EVT (intervention) or no EVT (control) along with usual medical care.

MR CLEAN Registry

Directly after the last patient was randomized in the MR CLEAN trial, EVT treated stroke patients were registered in the MR CLEAN Registry to evaluate the efficacy and safety in of EVT in clinical practice. The first part of the ongoing MR CLEAN Registry, which registered patients till one and half year after publication of the trial, showed that EVT is at least as effective and safe in routine clinical practice [24]. The MR CLEAN Registry stopped registering patients on 31th December 2018, and included more than 5600 patients [49].

DUST

The Dutch acute Stroke study (DUST) was a prospective multicenter cohort study in The Netherlands which investigated the prediction of clinical and prognostic value of imaging parameters obtained from computed tomography angiography (CTA) and –perfusion (CTP). In this study, patients with clinical ischemic stroke (>18 years) between May 2009 and August 2013 with stroke symptom duration of 9 hours or less, National Institutes of Health Stroke Scale ≥2, or ≥ 1 if intravenous thrombolysis was indicated were included [50].

AIMS AND OUTLINE

The specific aims of this thesis are:

1. To investigate the underlying causes of ischemic stroke in patients with LVO.
2. To assess outcome and safety of endovascular treatment subgroup of patients: with distally located thrombi, with extracranial carotid artery dissection, and with intracranial atherosclerotic vessel disease;
3. To assess whether follow-up infarct volume on non-contrast-CT can be used as an early surrogate imaging biomarker marker for clinical outcome in future trials.

Chapter 2 of this thesis will focus on causes and imaging characteristics of acute large vessel ischemic stroke in patients. Different causes of acute large vessel ischemic stroke and corresponding imaging characteristics will be addressed in **Chapter 2.1**. In **Chapter 2.2**, we will focus on the prevalence of carotid webs and its association with acute ischemic stroke due to LVO. Carotid webs and their association with non-lacunar infarctions in a general stroke population will be described in **Chapter 2.3**. To obtain more insight in the pathophysiological mechanism of carotid webs and ischemic stroke, blood flow patterns will be evaluated with the use of computational fluid dynamics to estimate the risk of (recurrent) ischemic strokes in these patients in **Chapter 2.4**.

In Chapter 3, our aim was to investigate whether EVT is beneficial and safe in patients with acute ischemic stroke in specific subgroups of patients. Firstly, EVT of distal located occlusions in the M2 segment of the middle cerebral artery will be evaluated in **Chapter 3.1**. Secondly, in **Chapter 3.2**, we will focus on EVT in acute ischemic stroke patients due to an intracranial occlusion with an additional extracranial tandem lesion due to carotid artery dissection. Finally, the influence of intracranial carotid artery calcification volume, and pattern of calcification (tunica media or tunica intima) on the effect of EVT in ischemic stroke patients will be evaluated in **Chapter 3.3.**

In **Chapter 4**, follow-up infarct volume on imaging will be evaluated as an early surrogate imaging marker of endovascular treatment effect on functional outcome in ischemic stroke patients.

Chapter 5 and **6** provide a general discussion and summary of this thesis.

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