Endovascular treatment for acute ischemic stroke patients

Summary

Acute ischemic stroke is caused by obstruction of a supplying artery which leads to a decrease in blood flow to the vascular territory of that particular blood vessel with subsequently hypoxia of the involved brain tissue. As a result, an ischemic core starts to develop which consists of brain tissue that is irreversibly damaged. Residual blood flow through alternative pathways (*collaterals*) contributes to the preservation of the viable tissue surrounding the ischemic core, the so called *penumbra*. However, if reperfusion of the vessel is not achieved, the penumbra will eventually transform into ischemic core. Saving the penumbra from becoming irreversibly damaged is the aim of reperfusion therapy and should be performed as soon as possible.

Both the ischemic core and penumbra are responsible for sudden occurrence of neurologic deficit in stroke patients. Severe neurologic deficit is often caused by a large vessel occlusion (LVO) for which two reperfusion therapeutic approaches are available. First, administration of intravenous thrombolysis (IVT) aims to dissolve the intracranial obstruction. However, in patients with intracranial large vessel occlusion the rate of reperfusion by IVT is fairly low (10-32%). Fortunately an alternative treatment has been developed in which reperfusion is achieved by mechanical removal of the occluding thrombus through endovascular approach. In 2015 the MR CLEAN trial was the first to demonstrate that this endovascular treatment (EVT) is safe and effective for anterior circulation large vessel occlusion stroke. Since then, EVT has been implemented as a standard treatment in the Dutch health care system, which has led to an exponential growth of EVT procedures. Nevertheless, the effect of EVT still remains uncertain for specific patient subgroups that may present with a large vessel occlusion at the emergency department. To monitor the effect of EVT in routine clinical practice, all acute ischemic stroke patients treated with EVT have been registered in the MR CLEAN Registry database. By the use of MR CLEAN trial and registry data, we focused on several areas of uncertainty: the effect of predisposing factors on clinical outcome after EVT; the effect of repeated EVT; the effect of EVT beyond the 6-hour time window ('late window' stroke patients); and the effect of EVT in PCS patients.

The main objective is to reflect on the best clinical approach in patients with a LVO for whom efficacy of EVT has not been determined by providing physicians insights in the relation between specific characteristics and functional outcome of stroke patients treated with EVT in current routine practice.

Chapter 1 describes the relation between body mass index (BMI) and outcome after EVT in a large randomized controlled trial: the MR CLEAN trial. This post-hoc analysis shows a positive effect of increased BMI on functional outcome and mortality in acute ischemic stroke patients with LVO, confirming the *obesity paradox*. Safety analysis also

showed a lower risk of stroke progression in patients with higher BMI. Since there was no interaction between BMI and EVT effect, all BMI classes may expect the same benefit from endovascular treatment.

Chapter 2 describes the relation between peripheral artery disease (PAD) and outcome after EVT in a large observational database: the MR CLEAN Registry. Previous research suggests a paradoxical association based on a neuroprotective phenomenon called 'remote ischemic preconditioning (RIPC)'. Preclinical studies have also related RIPC to improved cerebral perfusion during stroke, possibly through increased collateral blood flow. However, our analysis shows no association between PAD and outcome after EVT nor an independent association between PAD and collateral blood flow. As such, it questions whether RIPC does occur in PAD patients with acute ischemic stroke due to LVO.

Chapter 3 reports on the frequency and outcome of recurrent stroke in formerly EVT treated patients, who now underwent repeat EVT (rEVT). We used a combined cohort of three databases: MR CLEAN pre-trial, MR CLEAN trial and MR CLEAN Registry. In this large cohort, covering the period between 2002 and 2017, performance of rEVT was rare (0.7%). Stroke etiology of the recurrent LVO was mainly cardio-embolic and often the therapeutic levels of anticoagulants as part of secondary prevention too low. Most recurrent LVO's in which rEVT was performed occurred ipsilateral. The outcome of repeated EVT was comparable with single EVT, underlining its safety and effectiveness in this selected patient population.

Chapter 4 describes the characteristics and outcomes of stroke patients treated with EVT in the late time window (>6.5h from stroke onset) in routine clinical practice. In 2018 two clinical trials showed that EVT is safe and effective in a subgroup of patients treated in the extended time window up to 16 or 24 hours after symptom onset or time last known well. However, the results apply to a highly selected patient population based on perfusion imaging which, until then, was not regularly used in the acute stroke setting.
In this post-hoc analysis of the MR CLEAN Registry similar outcomes are observed in selected patients treated beyond 6.5 hours compared to patients treated within the 6.5-hour time window. Moreover, the late window patients appeared to be younger with better collaterals on baseline CTA than patients treated in the early window. These results suggest that clinical and radiological characteristics other than perfusion variables may also predict good outcome for late-window EVT.

In **Chapter 5** the MR CLEAN LATE trial protocol is described in detail. This randomized clinical study will provide insight into whether EVT is safe and effective for stroke

patients treated between 6 and 24 hours from symptom onset or time last known well after selection based on presence of collateral flow on CTA.

Chapter 6 reports on the characteristics and outcome of posterior circulation stroke patients treated with EVT in routine clinical practice. We used the MR CLEAN Registry database, which covers a period in which a randomized controlled trial (RCT) was introduced to investigate the effect of EVT for basilar artery occlusion in posterior circulation stroke patients. Patients who were randomized for the RCT were not included in the MR CLEAN Registry. Our study shows that high rates of successful reperfusion and favorable clinical outcome can be achieved with EVT for posterior large vessel occlusion stroke, despite high mortality. Characteristics and outcomes of patients who were not randomized and treated in trial centers versus non-trial centers were similar, indicating that our cohort is representative of clinical practice, although a moderate effect of the simultaneously running trial cannot be completely excluded.

Chapter 7 reports on the distribution of stroke etiology and the association with functional outcome in patients with posterior circulation stroke treated with endovascular thrombectomy. Out of 264 patients treated for posterior circulation stroke included in the MR CLEAN Registry, most frequent determined etiology was large artery atherosclerosis (LAA) followed by cardioembolism (CE), arterial dissection and embolic stroke of undetermined source (ESUS). Patients with a dissection were younger, had a lower NIHSS at baseline, and had a lower chance of successful reperfusion compared with other etiologic subtypes. After adjustment for potential prognostic factors primary analysis showed better functional outcome for CE and ESUS compared to LAA.