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General discussion

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In 2015, endovascular treatment (EVT) proved to be an effective treatment for patients with ischemic stroke due to proximal large vessel occlusion (LVO) [1]. Before the publication of the pivotal EVT trials, intravenous thrombolysis (IVT) has been standard of care in ischemic stroke regardless the location of intracranial occlusions. After publication, EVT was implemented in international guidelines and healthcare policies [2]. Also, the research field of (interventional) neuroradiology, clinical neurology, and public health continued steadily as many questions on the effectiveness in subgroups of patients were still left unanswered.

This thesis focused on three main research topics in the field of EVT. I aimed:

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.

CAUSES OF INTRACRANIAL LARGE VESSEL OCCLUSION IN PATIENTS WITH ISCHEMIC STROKE

In the first part of this thesis, the aim was to investigate the different causes of ischemic stroke in relation to imaging characteristics of LVO. In the first chapter, I provided an overview of causes of ischemic stroke due to LVO in patients who were eligible for EVT. In addition, the role of atherosclerotic disease in patients with undetermined cause of ischemic stroke was described. In the following three chapters, I focused on carotid webs in the carotid bifurcation, their association with acute ischemic stroke and on the thromboembolic mechanism that may be responsible for this association.

Main findings

In **Chapter 2.1**, I presented an overview of causes of LVO in acute ischemic stroke patients who were included in the MR CLEAN trial. We found that large artery atherosclerosis and cardiac embolism are main causes of intracranial LVO. Furthermore, calcifications of the carotid bifurcation were commonly present in patients who had an undetermined cause of ischemic stroke.

In **Chapter 2.2**, I investigated the association between carotid webs as potential cause of (recurrent) ischemic stroke. We found that the diagnosis of a carotid web on computed tomography angiography (CTA) is consistent between trained neuroradiologists. Furthermore, we observed more carotid webs in the symptomatic (2.5%) than in

the asymptomatic carotid bifurcation (0.5%) among patients with acute ischemic stroke due to LVO, which supported the hypothesis that webs could be a cause of LVO. Most patients with a carotid web in the symptomatic carotid bifurcation were women without other notable major risk factors or causes for ischemic stroke.

In **Chapter 2.3**, I studied carotid webs in a series of patients with acute ischemic stroke. In case webs are a cause of LVO, we would expect more webs in the symptomatic carotid bifurcation compared to the asymptomatic carotid bifurcation in patients with embolic vessel occlusions resulting in infarctions. Indeed, the prevalence of carotid webs in patients with non-lacunar stroke was higher in the symptomatic carotid bifurcation (1.5% and 0.6%, respectively). This was also the case in patients with lacunar infarction although differences were smaller (1.0% and 0.5%, respectively). However, no significant differences were found which may be related to the small number of patients due to the rarity of carotid webs.

Finally, I evaluated the hypothesis that the morphology of a carotid web leads to disturbed flow patterns and therefore increases the risk of thrombus formation in **Chapter 2.4**. We evaluated simulated flow patterns of carotid webs with the use of patient-specific computational fluid dynamics (CFD) and found that carotid webs have considerable recirculation zones and regional increased flow-induced frictional forces on the vessel wall. Both flow characteristics are associated with disturbed flow which might stimulate thrombus formation and increases the risk of acute ischemic stroke [3-5].

Considerations

Causes of embolic events in patients with ischemic stroke due to LVO are similar to the causes in the general ischemic stroke populations except that the prevalence of extracranial carotid artery dissections is higher in patients with LVO. Assessment of the etiology of ischemic stroke remains a challenge in current classifications schemes as it requires a comprehensive workup to confirm or exclude possible causes which are not always relevant in clinical practice. Common causes of stroke are atrial fibrillation and atherosclerotic carotid disease. The proportion of patients with an undetermined cause of ischemic stroke is high. Several factors contribute to this high proportion. The role atherosclerotic disease of the aortic arch or supra-aortic arteries may be underestimated as it is difficult to assess [6, 7]. Also, most classification schemes use a strict cut-off point of 50% or more to classify a carotid stenosis as a possible cause of stroke. This may cause underestimation of the contribution of less severe atherosclerotic disease to the occurrence of intracranial large vessel occlusion [8]. Finally, also incomplete reporting of etiological diagnostic workup may be present as patients are transferred back to the referring primary stroke center after EVT. We frequently observed calcifications as markers of atherosclerotic disease in the category of undetermined cause. The concept of

atherosclerotic vulnerable plaque could explain why LVO can occur in plaque with a stenosis grade less than 50% [9, 10].

In the recent years, carotid webs are increasingly recognized as a possible cause of ischemic stroke [11]. However, most studies describe small numbers of patients and carotid webs are uncommon. Previously, carotid webs were considered as an atypical variant of fibromuscular dysplasia (FMD), although a possible association between webs and FMD could not be demonstrated, taking into account the typical vascular lesion characteristics on imaging [12-15]. We studied the interobserver variability between neuroradiologists for diagnosing a carotid web on CTA. A fair to good agreement was found. This is in line with a recent study which described different imaging modalities for the diagnosis of a carotid web [16]. In this study, the authors also observed that CTA outperforms ultrasound examination. Little is known about the role of MRI in the diagnosis of carotid webs although an optimized MRI scan protocol has been published [17]. Although CTA scans are the first choice in diagnosing a carotid web, in a research context magnetic resonance imaging (MRI) could provide complementary data concerning vessel wall composition and patient specific hemodynamic flow patterns [16, 18].

The hypothesis that carotid webs could result in LVO was supported by our simulation study in which disturbed flow patterns distal from the carotid web were observed. In our simulation study to evaluate the flow patterns in carotid bifurcations with a carotid web, we observed a large variability in flow patterns distal to the lesion which can be explained by the complex and variable geometry of carotid webs. It can be expected that in addition to the disturbed flow patterns introduced by the morphology of a carotid web, also biochemical mechanisms may play an important role in the development of a thrombus as carotid webs are likely to be present for a long time. A hypercoagulable state is characterized by an increased predisposition to form blood clots. However, also other factors from Virchow's triad (stasis, hypercoagulability, endothelial damage) may be involved [19]. Therefore, it is not yet possible to assess which factors increases the chances of a (recurrent) ischemic stroke in patients with a carotid web.

Clinical implications and future perspectives

Carotid webs have a typical appearance on imaging and a good interobserver variability. In addition, patients with a carotid web are more frequently women without common risk factors for ischemic stroke such as atherosclerosis or atrial fibrillation. Currently, the clinical significance of carotid webs might be underappreciated. CTA scans are increasingly performed for selection of EVT-eligible patients and as a result carotid webs may be detected more often.

Regarding the treatment of carotid webs to prevent recurrent stroke, there is an ongoing debate regarding the optimal treatment strategy. Several strategies has been proposed in case reports or case series, such as endovascular treatment (e.g. carotid

angioplasty or stenting) or carotid endarterectomy [20-23]. Treatment with antithrombotic agents alone in patients with a carotid web may not be sufficient to prevent recurrent strokes [13, 20]. Furthermore, current studies on carotid webs have all been conducted in patients with ischemic stroke. Therefore, the prevalence of this fibrous lesion in a healthy population and its relative risk of embolic stroke are unknown. Further research performed in nested case-cohort studies to evaluate the risk of (recurrent) ischemic events in patients with a carotid web could be of added value.

ENDOVASCULAR TREATMENT IN SUBGROUPS OF PATIENTS WITH LVO

Shortly after publication of the MR CLEAN trial results, multiple post-hoc analyses have been performed to identify subgroups of patients that would or would not benefit from EVT [1, 24-27]. However, due to the low number of patients in these subgroups, estimations of treatment effect were less precise. Current guidelines suggest that EVT in patients with an occlusion of the M2 segment of the middle cerebral artery or in patients with an additional extracranial occlusion might be reasonable, although further evidence is needed. Therefore, we investigated the role of EVT in patients with an M2 occlusion, and its role in patients with a tandem lesion due to CAD in the observational MR CLEAN Registry. In doing so, we used a previously published definition of M2 segment where an occlusion in branches that are distal to the main bifurcation at the distal end of the horizontal M1 segment to the circular sulcus of the insula are considered as an M2 occlusion [25]. Furthermore, the treatment effect of EVT in patients with intracranial atherosclerosis vessel disease was evaluated in a post hoc analysis in the MR CLEAN trial. The clinical outcome and safety aspects of endovascular treatment in all three subgroups was investigated as secondary aim of this thesis.

Main findings

In **Chapter 3.1**, I found that patients with ischemic stroke due to an M2 occlusion had similar functional outcomes compared to stroke patients with an M1 occlusion. Additionally, regarding neurological recovery (delta-NIHSS) and safety aspects no significant differences were observed in both groups. These findings could be explained by the observation that in most patients the occlusion was located in the dominant division of the M2 branch.

In the MR CLEAN trial and Registry, a small proportion of endovascular treated patients had a tandem occlusion due to CAD (resp. 6% and 4%). The clinical outcomes and possible complications after EVT in these patients were evaluated in **Chapter 3.2**. Neurological improvement (delta-NIHSS) of patients with CAD was similar to improvement

in patients without an extracranial tandem occlusion. However, patients with CAD were significantly more often functionally independent at 3 months follow-up, than patients without CAD. This difference could be explained by lower age and less cardiovascular risk factors in patients with CAD.

In **Chapter 3.3**, studying the data of the MR CLEAN trial, I observed that calcifications in the symptomatic intracranial carotid artery were highly prevalent in ischemic stroke patients. We did not find evidence for modification of the effect of EVT by intracranial carotid artery calcifications (ICAC) volume. Next, we investigated the association of ICAC pattern with functional outcome. A statistically significant modification of treatment effect by ICAC pattern was observed. We noted a significant treatment effect in patients with medial calcification pattern but not in patients with an intimal calcification pattern.

Considerations

Although we described that EVT in patients with an M2 occlusion might be effective and safe in clinical practice, we have not been able to estimate the effect of EVT in our study due to the lack of a control arm as in randomized controlled trials (**Chapter 3.1**). A recent publication by the HERMES Collaboration performed a post hoc analysis on M2 occlusions among 7 EVT trials [28]. There was no significant treatment effect of EVT in patients with an M2 occlusions compared to patients with an M2 occlusion who did not receive EVT.

However, in their subgroup analysis regarding occluded dominant M2 branches, a statically significant treatment effect was observed. In the HERMES study a higher proportion of functional independency after EVT was observed than in our study (62% versus 39%) which can be explained by the increased number of older patients with more comorbidities in the MR CLEAN Registry [28]. In addition, multiple trials in HERMES were less pragmatic compared to the MR CLEAN trial making translation of the HERMES findings to clinical practice difficult. In another meta-analysis of mainly observational studies, the rate of functional independency after EVT of M2 occlusions of 59% was significantly better compared to M1 occlusions. However, no stratification regarding anatomical variation was reported. A post-hoc analysis of the randomized controlled trial IMS III, explicitly mentioned the anatomical location of the occlusion with a focus on the M1-M2 trunk and branches [24]. Overall, 41% of patients with an M2 occlusion reached functional independency. However, no attention was paid to caliber or potential dominance of M2 divisions.

We introduced a pragmatic approach in defining the dominant branch (larger diameter than the other branch or if the perfusion defect was larger than 50% of MCA territory) assuming supplying the majority of the parietal lobe and therefore causing substantial ischemic infarction. However, it is not well known how the anatomical variation of the M2 pattern is related to brain perfusion defects in ischemic stroke.

EVT in patients with an intracranial occlusion and an additional extracranial CAD has been described in several studies [29-33]. In accordance to our study, a recent observational study found a non-significant higher prevalence of functional independence in patients with CAD compared to atherosclerotic carotid artery occlusion after adjustments for baseline characteristics. As mentioned earlier in our study, lower age and less cardiovascular risk factors in patients with CAD could explain differences in results between unadjusted and adjusted statistics. Furthermore, several studies had included patients with tandem lesions but did not perform a stratification by the type of tandem lesion. Due to different mechanism of stroke, clinical characteristics and prognosis between type of tandem lesion such as carotid artery dissection and atherosclerotic carotid artery occlusion, might vary and might require stratification in future research.

Treatment strategy might be of importance in patients with CAD. In our study (**Chapter 3.2**), we did not evaluate the effect of carotid stenting or antithrombotic agents. Also, long-term follow up might be required to evaluate different treatments and its effect on recurrent strokes. At this moment, no randomized controlled trial of the effect of EVT in patient with CAD is performed although a post-hoc analysis of the MR CLEAN trial was performed [26]. However, an observational study performed in two centers described an increased functional independency at follow-up in patients treated with EVT compared to intravenous thrombolysis (71% versus 52%) [34]. More importantly, the authors also concluded that a tandem lesion due to CAD should not be a contraindication for EVT since no potential safety issues were observed.

In **Chapter 3.3**, we presented ICAC pattern as a potential modifier of EVT effect on functional outcome. Although the underlying mechanism is not known, one might hypothesize that intimal calcifications can cause local plaque disruption during stent retrieval and therefore causing micro-emboli resulting in lack of clinical effect of EVT. Patients with intimal ICAC pattern experienced also a decreased effect of reperfusion on functional outcome. We could not evaluate whether local arterial changes were present before and after retrieval of the initial thrombus [35]. We expect that vessel wall imaging might give us further insights into the underlying mechanism that related calcification morphology to outcome.

Clinical implications and future perspectives

Our results in patients with an M2 occlusion and in patients with a tandem lesion due to CAD suggest that these patients should not be routinely excluded from EVT. We showed that patients with acute ischemic stroke due to an M2 occlusion have similar neurological and functional outcomes compared to patients with M1 occlusion in clinical practice. Furthermore, the safety profile of the treatment was comparable despite the common thought that smaller arteries are more prone to injuries during stent retrieval than larger ones. Also, regarding tandem lesions due to CAD, we observed that these patients have

a similar neurological improvement as patients with intracranial occlusion only. it is concluded that acute imaging in patients with distal occlusions and additional tandem lesions plays an important role for determining treatment strategy, but should not be used to generate a 'black-and-white' rule to exclude patients for EVT. Current international guidelines state that it is reasonable to treat patients with M2 occlusions although evidence is weak [2]. However, in these same guidelines a definition of M2 segment and its branches is not provided. In our study as well as in the HERMES collaboration subgroup analysis, anatomical location regarding the occlusion of the dominant M2 branch might influence treatment effect and outcome. Together with our findings, it is evident that an unambiguous definition of the different branches of the middle cerebral artery is important and requires attention in further studies. Smaller-diameter stents for distal occlusions are being developed and the first results of observational studies have been published [36-38]. A recent observational study compared different subgroups of carotid stenting and antithrombotic agents in patients with tandem lesions in general [30]. The study showed that acute stenting combined with antithrombotic therapy resulted in improved recanalization rates but was not associated with better functional outcomes, than after treatment of the intracranial occlusion without antithrombotic agents in the acute phase. Performing randomized controlled trials regarding the treatment strategy of tandem lesions will be a challenge due to slow inclusion rate due to the low prevalence and necessary stratification based on type of tandem lesion as different treatment effects can be expected [39, 40]. Although EVT in patients with an additional CAD seems to be safe, a lot of clinical benefit can still be achieved. Merging observational data from multiple registries might be a solution to improve the current knowledge and evidence at short term. Finally, there is also still a discussion going on whether the intracranial- or extracranial occlusion in patients with a tandem lesion should be treated first, although a meta-analysis reported no differences in outcome and chosen technique is probably dependent on the clinical setting [41].

The presence and amount of ICAC might influence the success of recanalization and clinical outcome as previous studies suggested [42, 43]. In our study on ICAC in the MR CLEAN trial, we observed a smaller treatment effect in patient with intimal calcification pattern of the intracranial carotid artery. Distinguishing between intimal and medial calcification patterns in order to estimate prognosis and selecting treatment strategies for patients with acute ischemic stroke has currently no role in clinical decision making as an important gap of knowledge remains. In other words, our results were mainly hypothesis-generating regarding the pathophysiological process of intracranial atherosclerosis and its influence on the effect of EVT. Following this, ICAC patterns are distinct in terms of pathology, but also in terms of etiology as different risk factors play a role in the development of these patterns [44]. However, further studies are necessary to confirm and explore the difference in EVT effect between both ICAC patterns. Whether

different treatment approaches should be considered for both ICAC patterns requires further research including the pathophysiological mechanisms underlying the different treatment effects between both patterns.

Intracranial atherosclerotic vessel disease is related to small vessel disease. The influence of small vessel disease on EVT effect should be further studied. Imaging characteristics as white matter lesions (WML) can be regarded as a neuropathological marker, have been related to a higher risk of stroke, but might also be related to a poor functional outcome in stroke patients treated with EVT [45-54]. Numerous studies on WML in stroke patients have been performed but given the retrospective design and lack of a real control group in these studies, possible modification of the effect of EVT could not be assessed yet. Additionally, further studies on possible plaque disruption of the intracranial arteries during stent retrieval by vessel wall imaging or pathological examination on thrombi might provide further insights [35, 55, 56].

INFARCT VOLUME AS EARLY SURROGATE IMAGING MARKER IN FUTURE TRIALS

Surrogate imaging biomarkers in future clinical trials might not only be less time consuming and therefore more feasible but will also limit loss of follow up. Previous studies have suggested that follow-up infarct volume (FIV) could be used as a surrogate imaging marker to evaluate therapeutic effect and thus to assess clinical outcome [57-59].

The third objective of this thesis was to assess whether FIV on non-contrast CT (NCCT) can be used as an early surrogate imaging biomarker marker for clinical outcome in future trials.

Main findings

With the use of mediation analysis, I found that FIV on NCCT at 5-7 days was affected by treatment regime and was related to functional outcome, but only explained a modest part (14%) of the effect of intervention on functional outcome at 90 days measured by the modified Rankin scale (mRS) score (**Chapter 4**). Therefore, I conclude that FIV on NCCT should not be used as a surrogate marker for future early phase trials and could lead to conflicting results in in further phases of clinical research regarding the evaluation of the effect of intervention.

Considerations

A recently published study performed the same analytic approach in the HERMES data which represents individual patient data from 7 randomized EVT trials and observed a comparable proportion of explained effect of intervention on functional outcome that

was mediated by FIV on NCCT [60]. Furthermore, in a sensitivity analysis FIV on MRI was tested as surrogate marker, but no improvement on the proportion of explained effect was observed [60]. In our study (**Chapter 4**), we estimated the explained proportion by determining the relative difference between regression coefficients [61, 62]. The statistical methods and corresponding software packages were designed for dichotomous- rather than ordinal outcomes and requires further development [63, 64].

Clinical implications and future perspectives

Previous studies showed that infarct volume is a significantly associated with functional outcome in clinical practice. Also, in our adjusted models, FIV on NCCT was still a strong and significant predictor for functional outcome. However, this does not necessarily imply that FIV can explain treatment effect. FIV still remains an important predictor of patient outcome. For future research, taking infarct location into account could increase the relationship between FIV and clinical outcome as different locations are associated with different strengths of eloquence [65-67]. In addition, given the diversity of affected brain regions and their volumes, the use of a seven-point scale as mRS score might also be insufficient and other assessments of stroke outcome should be taken into account such as NIHSS. Finally, although MRI has also been assessed as surrogate marker by the HERMES collaboration, it might be still of interest to evaluate more advanced MRI techniques such as diffusion tensor imaging (DTI) to estimate more accurately the extent of ischemic damage, although these techniques are currently not implemented in routine clinical stroke workup. [68-70].

CONCLUSION

The purpose of this thesis was to expand the knowledge on causes and treatment of specific subgroups of patients with acute ischemic stroke due to LVO in the era of EVT, and to assess whether follow up imaging can be used as surrogate imaging marker for clinical outcome in future trials.

Causes of LVO and their prevalence in acute stroke patients who are eligible for EVT correspond to the prevalence in general ischemic stroke populations: large artery atherosclerosis and cardiac embolism are the main causes of LVO. However, the etiological significance of carotid webs might be underappreciated in acute ischemic stroke. It is important that carotid webs are recognized and acknowledged by physicians as a likely cause of ischemic stroke, and that webs deserves further attention in both drug and/or surgical treatment approaches.

EVT in clinical subgroups as patients with an occlusion of the M2 segment, patients with ischemic stroke and an additional tandem lesion due to CAD, or patients with

intracranial atherosclerotic vessel disease is safe in ischemic stroke patients, although the treatment effect can be smaller. Although FIV on follow-up NCCT is an important predictor of clinical outcome, it remains a challenge to use clinical imaging as a surrogate marker of treatment effect in future trials.

In the last decade, the field of acute ischemic stroke treatment has changed dramatically by improved imaging of early ischemic changes and the underlying visualization of the causes of cerebral ischemia, and secondly by image guided interventional treatment of LVO. It is expected that future research will broadening the treatment criteria and interventional approaches by increasing the role of imaging in clinical decision making in patients with acute ischemic stroke.

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