CT perfusion in acute ischemic stroke

Optimizing image-based patient selection for endovascular treatment

Hoving, J.W.

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Chapter 10

General Discussion

The primary aim of this thesis was to provide more insight into the added value of CT perfusion (CTP) in the diagnostic workup of patients with acute ischemic stroke. Secondary aims included evaluating the diagnostic accuracy of available CTP software packages by using a standardized validation; better understanding the association between CTP parameters and functional outcome and lastly, quantifying the health and cost effects of including CTP into a diagnostic imaging protocol consisting of noncontrast CT and CT angiography.

Not many fields in medicine have experienced such breakthroughs over the past three decades as the field of acute ischemic stroke. In 1996, the National Institute of Neurological Disorders and Stroke (NINDS) tissue-type plasminogen activator (tPA) trial showed a beneficial effect of intravenously administered tPA in acute ischemic stroke patients.[1] Although these results were promising and various other trials have emphasized the efficacy of thrombolysis in the 0-4.5h time window[2], it took until 2015 before the next great breakthrough in acute ischemic stroke treatment was established: endovascular treatment (EVT).[3] It is hard to imagine the revolution that the positive landmark EVT trials have brought to the field of acute ischemic stroke. Next to the progress that has been made in therapeutic options for acute ischemic stroke, major strides have been made in the diagnostic possibilities in the (hyper)acute intra-hospital management of acute ischemic stroke.[4] Whilst the first CT scan of the brain was acquired over 50 years ago and perfusion imaging has been possible for more than 40 years, renewed interest in perfusion imaging of the brain was sparked after the first positive EVT trials showed a tremendous benefit of EVT, especially in patients who were selected using perfusion imaging.[5,6] Although CTP is currently well-established and increasingly being performed in the diagnostic setting of acute ischemic stroke, there has always been a lively debate throughout the field of stroke research about its added value.[7–9] Many studies have focused on the optimal imaging selection modality and its effect on therapy outcomes in the current era of endovascular treatment and advanced imaging in stroke.[8,10–14] Two recent prospective trials investigated the added value of diagnostic stroke imaging and showed that patients with specific imaging profiles may be more likely to benefit from reperfusion therapies than patients who did not have such imaging profiles.[15,16] However, it should be noted that these studies only answered a specifically focused research question and that a diagnostic intervention – such as CTP imaging – does not alter clinical outcomes by itself.[17]

When I entered the field of stroke research, as a third-year medical student, the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial – which was the first trial to demonstrate safety and efficacy for EVT in patients with acute ischemic stroke – were published only nine months prior.[18] Together with (initially) four other randomized trials on the

safety and efficacy of EVT in acute ischemic stroke, the MR CLEAN trial formed the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaboration.[3] From 2015 onwards, publications on endovascular treatment for acute ischemic stroke followed one another rapidly and it soon appeared to me that I had entered the field of (acute ischemic) stroke research at the dawn of a golden era. Shortly after the publication of the MR CLEAN trial, the foundation for a – at that time highly innovative – cross-institutional, observational, and nationwide stroke registry was laid: the MR CLEAN Registry. In the MR CLEAN Registry, data from all stroke patients who underwent EVT in the Netherlands were collected, enabling many researchers to study the effect of EVT in routine clinical practice.[19] In this context, and within the well-organized research environment of the MR CLEAN Registry and the HERMES collaboration, I took my next steps into the field of stroke research. During my final years as a medical student, I shifted the focus of my research projects toward CTP imaging in acute ischemic stroke. It was then during the research internship for my master's thesis in Melbourne that the basis for this thesis was laid: aiming to determine the added value of CTP imaging in acute ischemic stroke.

First, we assessed the accuracy of CTP in estimating the ischemic core for two commonly used commercially available software packages (Part 1: Volumetric and spatial accuracy of CT perfusion imaging). Second, we investigated the association between CTP and clinical outcomes, using data from the MR CLEAN Registry and the MR CLEAN-NO IV trial (Part 2: Clinical applications of CT perfusion imaging). Third, we focused on the costs and health effects of including CTP in the diagnostic workflow of acute ischemic stroke (Part 3: Cost-effectiveness of CT perfusion imaging in the Netherlands).

Advances in acute ischemic stroke treatment

As mentioned earlier in this thesis, only a few fields in medicine have experienced such progress in treatment over the past two decades as the field of acute ischemic stroke. However, this breakthrough did not go without any hitch. Even though the first endovascular stroke therapy was reported as early as 1958,[20] it lasted almost six decades before endovascular treatment (EVT) was proven to be effective and was incorporated in the international acute ischemic stroke guidelines we know today.[21,22] This finally occurred after the publications of the landmark EVT trials, demonstrating the tremendous benefit of EVT over intravenously administered alteplase in patients with acute ischemic stroke.[5,23–27]

Some have proposed that potential explanations for this relatively gradual adaptation of new therapeutic interventions may lie in the natural history and development of the field of acute ischemic stroke.[28] Even though endovascular treatment for acute ischemic stroke was introduced in 1958[20] – almost two decades before the first endovascular

coronary angioplasty of patients with stable angina in 1977 – cardiologists were early adopters of randomized trials for new treatments and could introduce this new treatment to patients within five years after its first mentioning.[29] Stroke trials, on the other hand, mainly concerned uncontrolled, single-arm studies which evaluated the benefit of mechanical clot retrieval devices, including the MERCI and Penumbra trials.[30,31] Since these single-arm trials did not allow for comparing patients who were treated vs. patients who were not treated with the device, acute ischemic stroke trials from that era were restricted to comparing baseline characteristics of patients who did undergo treatment with either of the clot retrieval devices. Commonly, AIS patients were divided into binary categories of stroke severity (e.g., National Institutes of Health Stroke Scale Score [NIHSS] <6 vs. ≥6) or infarct burden (Alberta Stroke Program Early CT Score [ASPECTS] <6 vs. ≥6).

Development and current applications of CTP imaging

To quantify the amount of irreversibly damaged brain tissue and to assess whether there is potentially salvageable tissue present, and thus determine the eligibility for endovascular treatment, CTP imaging is increasingly used in the diagnostic workup of patients with acute ischemic stroke.[32]

However, in acute ischemic stroke – where 'time is brain'[33] – the added value of additional diagnostic imaging should be balanced against the additional time, radiation, and intravenous contrast agent administration which is required to acquire a CTP – in addition to the default imaging protocol consisting of NCCT and CTA. Currently, the AHA/ASA and ESO/ESMINT guidelines do not recommend the use of CTP in the (0-6h) time window for patient selection for EVT.[21,22] However, the current guidelines do recommend the use of (CT or MR) perfusion imaging for triaging patients with unknown time of onset or beyond 4.5 and 6 hours for IVT and EVT, respectively.[21,22] These recommendations for perfusion image-based selection were based on two randomized trials which showed a benefit of EVT in the 6-24h time window in patients who were selected using CTP or MR perfusion.[34,35]

CTP may also be of additional diagnostic value in the 0-6h time window, for example, to detect arterial occlusions which are challenging to identify on conventional (NCCT and CTA) imaging, such as more distal medium vessel occlusions (commonly referred to as MeVOs).[36] As the experience with EVT for acute ischemic stroke grows, it could well be that more therapeutic options come available for patients with these more distal – and harder to detect on CTA – occlusions in the near future.[37] If so, even more hospitals will likely implement perfusion imaging into their standard diagnostic stroke imaging protocol. Given that in the emergency setting, CT imaging is a fast and the most widely available imaging modality in the Netherlands, most hospitals in the Netherlands will

likely opt to primarily use CTP for the diagnostic workup of patients with acute ischemic stroke.

Volumetric and spatial accuracy of CT perfusion imaging

With the increasing implementation of CTP imaging for treatment decisions in acute ischemic stroke, it becomes highly important to understand the diagnostic accuracy and impact of CTP and be aware of the differences which exist among the wide range of commercially available CTP analysis software packages. In **Chapter 2**, we investigated the volumetric and spatial agreement of the ischemic core as estimated by RAPID CTP software (RapidAI, Menlo Park, CA, USA) with the 24h follow-up infarct lesion on diffusion-weighted imaging (DWI) in patients from the HERMES collaboration and the EXTEND-IA TNK trial (NCT02388061).[3,5] We showed that CTP-estimated ischemic core volumes – using a relative cerebral blood flow (rCBF) threshold <30% – had a moderate volumetric and spatial agreement with the follow-up DWI lesion (Dice 0.24). The median CTP-estimated ischemic core volume was substantially smaller than the median follow-up DWI lesion volume, likely due to infarct growth between baseline CTP and follow-up imaging. This is in contrast with various previous studies which suggested that CTP was likely to overestimate the final infarct volume, which led to concerns about whether using CTP would preclude potentially eligible patients from reperfusion therapy.[38–41] However, ischemic core overestimation >10 mL was relatively uncommon when using the RAPID software. If overestimation did occur, this was predominantly in white matter areas. Although previous studies had expressed concerns that faster and better reperfusion therapies might lead to the reduced predictive performance of CTP parameters and thresholds,[40,42–46] we did not find an association between overestimation and imaging-to-reperfusion time.

This chapter highlights a few important things to consider when evaluating the diagnostic accuracy of CTP. First, in this chapter, we compared the CTP ischemic core volume with the follow-up lesion on DWI acquired approximately 24 hours after treatment. Although 24 hours is a pragmatically chosen and commonly used endpoint for follow-up lesion assessment[47], the comparison between both lesions is suboptimal since there is a full day between the acquisition of the CTP and DWI. It is known that in the first 24 hours – and up to days after stroke onset –, the ischemic lesion still evolves despite early reperfusion.[47–51] Infarct growth could have occurred in the observed median approximately two hours between baseline CTP and the follow-up DWI acquisition, especially in patients with incomplete reperfusion after EVT.[47,51] However, follow-up lesion assessment at other time points also has its limitations.[52] For example, assessment at 5 days would likely overestimate the lesion substantially – since this is at the peak of vasogenic edema development. At later time points (e.g. at 90 days), atrophy is present which leads to an underestimation of the infarct.[52] Several prior studies used contemporaneous DWI

acquisitions to assess the accuracy of CTP ischemic core estimations.[53–56] However, in the current era of rapid endovascular treatment, it is not feasible to acquire both CTP and DWI before treatment and CTP validation studies are therefore commonly reliant on follow-up imaging data – which, in the Netherlands, is only sparsely acquired. Other studies used follow-up NCCT to determine the follow-up infarct volume.[57–59] However, measuring the final infarct volume in the subacute time window (i.e., at approximately 24 hours) may result in an overestimation of the infarct volume because of edema, especially when the final infarct volume is measured using NCCT.[47,50]

Second, we only investigated the accuracy of one specific perfusion parameter and threshold. It has been demonstrated that the rCBF<30% has the best agreement with contemporaneous DWI.[55] However, this threshold has only been validated on one software package and may therefore not apply to CTP software packages from other vendors. Third, we assessed the accuracy of one CTP software package (i.e., RAPID) and the results may not be generalizable to other software packages, as it is known that large differences between software packages exist.[57,60,61] Currently, there are over 10 software packages commercially available. In the Netherlands, the most used platforms include syngo.via (Siemens Healthineers, Forchheim, Germany), IntelliSpace Portal (Philips Healthcare, Best, the Netherlands), StrokeViewer (Nicolab, Amsterdam, the Netherlands), RAPID (RapidAI, Menlo Park, CA, USA), and Vitrea (Vital Images, Minnetonka, MN, USA).

The wide range of available CTP analysis software packages and the variety of perfusion parameters and thresholds that are used for the ischemic core and penumbra estimations make it hard to oversee which software package performs best and should therefore be used in a specific clinical setting. In addition, the acquisition protocol, contrast bolus administration, and scanner used for the acquisition may affect CTP results,[62–64] which complicates the mutual comparison of available CTP platforms even further. Several previous studies assessed the performance of various CTP software packages in terms of agreement with the RAPID CTP software[57,65–70] as this is a commonly used software package that was also used for perfusion imaging analysis in the DAWN and DEFUSE-3 trials.[34,35] However, an important caveat of this approach is that the agreement between the concerning CTP-estimated ischemic core estimates and the follow-up lesions in these studies was commonly not reported.

To allow a more accurate comparison – preferably both spatially and volumetrically – between CTP ischemic core estimates and follow-up lesions, a standardized validation set is desired. Ideally, this validation set should contain contemporaneous CTP and DWI imaging data acquired using the same acquisition protocol and similar CT and MR scanners. In reality, this approach has practical challenges since a delay in reperfusion treat-

ment is not desired. Alternatively, recalibration of ischemic core estimates by CTP could be performed using phantom data or follow-up infarct segmentations from patients with fast and complete reperfusion.[71]

To assess the performance of the most used CTP software packages in the Netherlands, we developed such a CTP-DWI validation set consisting of successfully reperfused patients with large vessel occlusion anterior circulation ischemic stroke who presented within 24 hours after symptom onset and received follow-up DWI at approximately 24 hours. In **Chapter 3**, we used this validation set to investigate to what degree the volumetric and spatial agreement between the (syngo.via) CTP-estimated ischemic core and the follow-up lesion on DWI would be affected by using different parameters and thresholds to estimate the CTP ischemic core.

We found that CTP-estimated ischemic core volume had a moderate volumetric agreement with the follow-up lesion for all four investigated estimation approaches in patients with successful reperfusion after endovascular thrombectomy (defined as expanded treatment in cerebral ischemia [eTICI] 2b-3). In patients with complete reperfusion, the volumetric agreement was excellent, suggesting that infarct growth in patients with successful – yet not complete – reperfusion (i.e., eTICI 2b-2c) does indeed affect the volumetric agreement. Therefore, the results of studies assessing the volumetric accuracy of CTP should always be interpreted in the context of the reperfusion rates of the dataset used. For all estimation approaches, the spatial agreement between the CTP ischemic core volume and follow-up lesion was low (median Dice range 0.16-0.21). Several explanations for this low spatial agreement are possible. First, coregistration errors might have contributed to this finding. In addition, we found lower accuracy in patients with substantial edema formation or hemorrhagic transformation, suggesting that both edema and hemorrhagic transformation likely affected our results. Of note, patients with eTICI 2b showed substantially lower spatial agreement compared with patients with complete reperfusion for all approaches (median Dice range 0.05-0.16 vs. 0.19-0.26).

In addition, we showed in this chapter that using different estimation approaches may result in statistically significantly different ischemic core volumes. The approach using cerebral blood volume (CBV) thresholded at <1.2 mL/100mL with a default smoothing filter applied, showed similar ischemic core volume estimates as the approach using a relative cerebral blood flow (rCBF) parameter thresholded at <20% using the same smoothing filter for the core and penumbra segmentations. The approach using rCBF <30% with a smoothing filter resulted in the highest degree of severe volumetric overestimation >50mL by CTP (in 24% of patients), compared to 3% and 7% for CBV<1.2mL/100mL and rCBF<20%, respectively. This is in line with a previous study by

Koopman et al. which showed that the ischemic core volume was systematically larger than the RAPID CTP ischemic core volume when a rCBF<30% was applied in syngo.via.[57] To avoid potentially EVT-eligible patients being excluded from endovascular treatment, it is crucial that CTP analysis software provides an accurate estimation of the follow-up lesion volume and that severe overestimation of the ischemic core volume is rare. At the same time, (consistent) underestimation of the ischemic core is not desirable either. Potentially, perfusion maps with probabilistic information on the confidence of the perfusion status of the brain could further help to improve the interpretation of CTP results in the future.[72]

Although both CBV and rCBF describe different perfusion-related features (i.e., the volume of blood in a given amount of brain tissue vs. the volume of blood passing through a given amount of brain tissue), our findings suggest that, using syngo.via, both estimation approaches using CBV<1.2 mL/100 mL and rCBF<20% showed similar volumetric and spatial agreement between the CTP-estimated ischemic core and the follow-up lesion at 24 hours. However, it should be noted that for individual cases, we still found volume differences up to 40 mL between the CBV<1.2 mL/100mL and rCBF<20% approach.

When determining which parameter and threshold to use to estimate the ischemic core in clinical practice, there are a few things to consider: First, is high spatial overlap desired even when this is at the expense of more volumetric overestimation? As discussed in this thesis, one should be cautious with interpreting metrics such as Dice to determine which CTP software package provides the optimal ischemic core estimation. Namely, the Dice score can be very easily affected by 'false negative voxels', especially in relatively small segmentations such as infarct segmentations.[73] This is also reflected by the fact that we found the highest spatial agreement for the approach based on rCBF<30% with a smoothing filter, whilst this approach also resulted in the highest frequency of severe overestimation >50 mL. Thus, this approach could potentially be harmful by falsely excluding patients from EVT. Second, the volumetric agreement (defined by the intraclass correlation coefficient [ICC]) should be interpreted in the context of the (validation) dataset that is used. For example, in our validation set, a substantial number of patients had suboptimal reperfusion (i.e., eTICI 2b-2c) and approximately 80 minutes between imaging and reperfusion, which both affect the volumetric and spatial agreement.

Clinical applications of CT perfusion imaging

Next to the diagnostic information that can be obtained from CTP, CTP may also provide additional prognostic information – for example regarding functional outcome at 90 days.[74–77] A pooled meta-analysis of the HERMES collaboration showed that CTP isch-

emic core volume was independently associated with functional outcomes at 90 days. However, the CTP ischemic core did not alter the treatment effect of EVT.[75] Since most 0-6h time window trials did not use CTP for patients, the use of CTP for selection for EVT within six hours after symptom onset is not recommended by the current guidelines.[21,22] However, in the Netherlands, most comprehensive stroke centers (~80%) currently perform CTP imaging – in addition to NCCT and CTA imaging – for all suspected stroke patients regardless of the time of symptom onset, according to an unpublished survey which was performed by the CLEOPATRA study group[78] among 16 Dutch comprehensive stroke centers (personal communication).

In **Chapter 4**, we studied the association of CTP-, CTA-, and NCCT-based imaging biomarkers with poor functional outcomes in the MR CLEAN Registry, between July 2016 and November 2017. For this study, poor functional outcome was defined as a modified Rankin Scale (mRS) 5-6. The rationale behind this was that if a specific CT-based imaging biomarker could identify patients with a high risk of mortality or severe disability, this could potentially inform treatment decisions.

We found that CTP ischemic core volume was associated with poor functional outcome, a lower likelihood of improved functional outcome, and a lower chance of functional independence at 90 days. In addition, we found that the absence of a target mismatch (TMM) profile was associated with poor outcome. In contrast to CTP ischemic core volume, neither Alberta Stroke Program Early CT Score (ASPECTS) nor CTA collateral score (CTA-CS) was functional outcome at 90 days.

It should be noted that only a minority of patients (19%) in the MR CLEAN Registry up to November 2017 had CTP imaging as the results of the DAWN and DEFUSE-3 trials (which used CTP to select patients beyond 6h after stroke onset) were not published yet.[34,35] This might have affected our findings, which is also suggested by the fact that other post-hoc analyses in larger (sub)groups of the MR CLEAN Registry and HERMES collaboration did show different results regarding the association of ASPECTS and CTA-CS with functional outcome.[79–81] Yet, in line with our conclusions, both other studies did not demonstrate a significant modification of the EVT effect by either ASPECTS or CTA-CS.[79,80]

Even though there is no clear consensus yet regarding the additional value of (CT-based) imaging biomarkers, CTP- (or MRI-) based core volume, ASPECTS, and CTA-CS are commonly used to include patients in EVT trials.[3,4,34,35,82,83] For example, in the early window EVT trials, patients with low ASPECTS (i.e., ASPECTS 0-5) were mostly excluded.[3] In the 6-24 h time window trials, patients had to meet specific perfusion-related criteria,

but also in these trials, patients with extensive infarct at baseline – defined as ASPECTS 0-6 – were excluded.[34,35]

When evaluating whether CT-based imaging biomarkers should be included in the diagnostic workup of acute ischemic stroke patients, one should consider that all imaging biomarkers have their limitations, which has been pointed out earlier in this thesis. It is known that CTP, for example, is susceptible to patient motion, requires accurate contrast agent administration, and that the results of CTP imaging vary from vendor to vendor.[41,57,84] At the same time, ASPECTS and CTA-CS are limited by the fact that results may vary widely between observers.[85,86]

Apart from the CT imaging biomarkers which are commonly used in acute ischemic stroke (e.g. ASPECTS, CTA-CS, ischemic core volume, penumbral volume, and mismatch ratio), other brain imaging biometrics such as the degree of brain atrophy are associated with functional outcome after EVT.[87–92] We hypothesized that a similar ischemic core volume would have a more profound impact on the functional outcome of patients with more extensive cerebral atrophy (and thus a smaller total brain volume [TBV]) compared to patients with less cerebral atrophy. We aimed to assess whether the association between the ischemic core volume and the functional outcome would be strengthened if the ischemic core volume is adjusted for the TBV in **Chapter 5.** We found that the association between the ischemic core volume and functional outcome was not improved when the proportion of ICV or TBV that was affected by the CTP-estimated ischemic core was considered. However, in line with previous studies, we did find that the ischemic core volume, ICV, and TBV alone were associated with functional outcomes after EVT.[90,93,94] This underlines the complexity of potential relationships with brain imaging biometrics and functional outcomes.

As mentioned earlier in this thesis, CTP imaging enables quantification of the blood flow through the brain to estimate tissue viability and estimate the ischemic core and penumbral volumes.[75,95] Using the estimated ischemic core volume at baseline and the follow-up infarct volume (FIV) at follow-up imaging, subacute infarct evolution assessment in patients with acute ischemic stroke is possible. This might be clinically relevant as it is known that infarct growth is associated with functional outcome after EVT and varies widely among patients with acute ischemic stroke.[6,48,96–102] Notably, a previous study of the HERMES collaboration showed that the FIV alone only partially explained the benefit of EVT and that FIV is therefore not a valid proxy for estimating the treatment effect of EVT.[99]

It is generally considered that patients with extensive hypoperfusion at baseline may be more suitable candidates for EVT alone – given that larger infarcts have a higher risk of

hemorrhagic transformation when IVT is given.[104–107] Therefore, we aimed to investigate whether CTP-based perfusion characteristics could be used to identify patients who are likely to benefit from IVT before EVT in **Chapter 6**. Studied perfusion parameters were ischemic core volume, penumbral volume, mismatch ratio, and presence of a target mismatch (TMM) profile (defined as ischemic core volume <70 mL, mismatch ratio >1.8, and penumbral volume >15 mL).

In our analysis, CTP-based imaging biomarkers did not alter the treatment effect of intravenous alteplase before EVT in directly admitted patients who presented within 4.5h after symptom onset. This suggests that CTP is not able to identify patients who might benefit or benefit less from intravenous alteplase before EVT. Interestingly, in the MR CLEAN-NO IV population with CTP imaging, we did not observe a statistically significant association between ischemic core volume and improved functional outcome at 90 days. This is in contrast with previous conclusions from the observational study in the MR CLEAN Registry (**Chapter 4**). Most likely, these conflicting conclusions can be explained by the limited sample sizes in both retrospective analyses. Also, the fact that the accuracy of CTP ischemic core estimations may be different for patients with varying onset-to-imaging times might have contributed to this observation.[108] Potentially, future CTP analysis tools using multiple parameters and input variables (using artificial intelligence) would be better capable to identify patients who are more likely to benefit from reperfusion therapy compared to a dichotomized parameter approach that we are using today.

Our findings in this post-hoc analysis of the MR CLEAN-NO IV are in line with a previous analysis from the DIRECT-MT trial, which showed that the baseline infarct size – assessed using ASPECTS – did not modify the treatment effect of intravenous alteplase before EVT. Unfortunately, due to the low number of patients with a large CTP-estimated ischemic core (11% of patients with CTP ischemic core volume $\geq$70 mL), we could not investigate whether the effect of IVT was different for patients with extensive perfusion deficits on baseline CTP. Likely, not only the ischemic core volume, but also other factors such as the location of the ischemic core, the severity of hypoperfusion (which could be assessed using CTP), and the time to reperfusion should be taken into consideration when treatment decisions are made. In this chapter, we did not take the ischemic core location or the severity or the severity of the hypoperfusion into account, but it could be possible that for patients with a very short time to reperfusion, mild hypoperfusion, and an ischemic core that does not involve any eloquent brain areas, intravenous alteplase has limited added value.

In **Chapter 7**, we compared the infarct evolution between baseline and follow-up imaging for patients who received IVT and EVT vs. EVT alone in the MR CLEAN-NO IV trial.[103]

In addition, we aimed to identify which clinical and procedural characteristics are associated with infarct evolution. We found that the infarct evolution did not statistically significantly differ between directly admitted patients who received IVT and EVT vs. EVT alone within 4.5h after stroke onset. The collateral status, as assessed by the CTA-CS at baseline, the occlusion location, the number of attempts to retrieve the thrombus during EVT, and the occurrence of any hemorrhage after EVT were associated with infarct growth >10 mL. Furthermore, follow-up CTA and MR angiography data revealed that reocclusion of the targeted occlusion was not uncommon. Yet, reocclusion rates were comparable between both study arms in the MR CLEAN-NO IV trial and reocclusion was not associated with infarct growth >10 mL. However, it should be considered that only patients with available CTP imaging and follow-up imaging were included in this analysis, resulting in a relatively small sample size of 228 patients. Also, follow-up imaging was assessed on both 24h and 1-week follow-up NCCT and MR imaging, which could have affected the accuracy of our follow-up lesion assessments. Namely, edema formation is a dynamic process in the first days after stroke, and assessing FIVs at different time points will therefore likely result in different FIVs, also depending on which image modality was used.[52]

In the Netherlands, follow-up imaging is generally only acquired for research purposes and therefore only sparsely performed. To confirm our findings, infarct evolution between baseline and follow-up imaging should be analyzed in a larger cohort, for example by the Improving Reperfusion strategies in Ischemic Stroke (IRIS) collaboration, which aims to pool the data from all six randomized trials comparing EVT alone with IVT before EVT.

Cost-effectiveness of CTP in acute ischemic stroke

The CLEOPATRA healthcare evaluation

The Cost-effectiveness of CT perfusion for Patients With Acute Ischemic Stroke (CLEOPATRA) healthcare evaluation study was designed to estimate the costs and health effects of including CTP in the diagnostic workup of patients with acute ischemic stroke in the 0-6h and 6-24h time windows in the Netherlands. CLEOPATRA is a nationwide, observational healthcare evaluation with a cost-effectiveness analysis based on a health state transition model using a retrospective, multicenter, observational data from within the Dutch healthcare system. Patients enrolled in one of the trials from the Consortium for New Treatments of Acute Stroke (CONTRAST) consortium[109] (i.e., the MR CLEAN-NO IV[103], the MR CLEAN-MED[110], and the MR CLEAN-LATE[82]) and patients included in the MR CLEAN Registry[19] were included if CTP was performed between January 2018 and March 2022. In addition, a local cohort of patients with acute ischemic stroke from our comprehen-

sive stroke center (Amsterdam UMC location University of Amsterdam, the Netherlands) was included. Details of the study design and model-based cost-effectiveness analysis are provided in **Chapter 8**. In short, patients were included if they were aged 18 years or older, had an acute ischemic stroke caused by a proximal occlusion of the anterior circulation, had a minimum National Institutes of Health Stroke Scale score of 2 or higher, and had CTP imaging with at least 8 cm coverage of the brain. All CTP data were centrally post-processed using one software package (syngo.via, version VB40). Further details on the used CTP processing software and CTP acquisition requirements are provided in the Supplement of the study protocol. The conventional diagnostic workup (consisting of noncontrast CT and CT angiography) was compared with CTP-based patient selection for EVT. We used observed clinical, imaging, and literature parameters to simulate 5-year follow-up using a Markov model. Odds ratios for EVT treatment effect available in the current literature were used to simulate patients that would not undergo EVT. We included patients from 17 comprehensive stroke centers in the Netherlands. The primary outcome was the incremental cost-effectiveness ratio (ICER). Secondary outcome measures were net monetary benefit (NMB) at a willingness-to-pay of €80,000 per quality-adjusted life year, and differences in costs and quality-adjusted life years between the simulated study arms over a follow-up horizon of 5 years.

Chapter 9 shows the results of the cost-effectiveness analysis of CTP-guided selection for EVT for patients who present within six hours after symptom onset. We included 703 EVT-treated patients with available CTP imaging within six hours after symptom onset. We found that using a CTP-estimated ischemic core volume threshold ≥70 mL or the core-penumbra mismatch ratio (MMR) threshold ≥1.8 to withhold patients from EVT resulted in a loss of health with negligible cost-savings over a 5-year follow-up period, even when unrealistically favorable conditions were simulated.

In a pre-specified subgroup analysis for patients over 80 years of age, we found a less profound loss of health when patients were excluded from EVT based on ICV or MMR. However, even in this subgroup in which a lower EVT effect was assumed, selection for EVT based on CTP was not cost-effective.

Results from this analysis and the presented scenarios should be interpreted carefully. It should be considered that the treatment effect estimates used in our model were relatively conservative since these were derived from a meta-analysis of the HERMES collaboration.[75] The HERMES collaboration pooled data from trials conducted up to December 2014 and with the improvement of endovascular techniques and workflows over the past years, it can be expected that EVT has become even more effective.[111,112] However, a lower treatment effect of EVT may still apply to countries with a less-developed stroke healthcare system or in populations with more distal occlusions.

Nonetheless, we showed that there was no benefit in costs or health effects for CTP in a hypothetical scenario with an unrealistically low EVT effect.

In addition, it should be mentioned that the quality of CTP acquisition has improved over the past two decades and therefore EVT effect modification estimates from the HERMES collaboration might not be generalizable to current clinical practice. Whilst at the time of the MR CLEAN trial, many stroke centers in the Netherlands could only acquire CTP data with a coverage of less than 5cm, currently, most scanners in the Netherlands cover at least 8 cm, resulting in more accurate estimates of the ischemic core and penumbral volume.

It should be noted that the results from this model-based health economic evaluation are based on prospectively collected data which did not provide randomized data on the treatment effect of EVT or effect modification by CTP. However, since it would be unethical to randomize patients for a treatment that is proven to be – highly – effective, it is not possible to collect randomized data from patients with acute ischemic stroke who present within six hours after onset. In addition, given that the available evidence in the literature on the long-term (i.e., 5- or 10-year) follow-up costs and health effects is limited, assumptions remain unavoidable in current health economic evaluations.[113–115] Nevertheless, model-based health economic analyses can be used to estimate long-term costs and health effects and inform policymakers.

Based on the results from this health economic evaluation, one could argue that CTP should not be included in the diagnostic workup of patients with acute ischemic stroke who present within six hours after symptom onset. However, apart from estimating the ischemic core and the penumbral volume – which may be used to guide treatment decisions –, CTP also provides valuable additional information about the location of intracranial occlusions and improves occlusion detection in acute ischemic stroke.[116–120] Therefore, we also investigated the costs and health effects of including CTP in a diagnostic stroke imaging protocol consisting of NCCT+CTA. For this second analysis, we also used data from the CLEOPATRA database together with literature estimates. We found that for the detection of EVT-eligible occlusions, adding CTP to an imaging protocol consisting of NCCT and CTA does result in cost savings and health gain over a 10-year follow-up period. Whether CTP is cost-effective for patient selection or EVT-eligible LVO detection in patients who present beyond 6 hours after stroke onset or with an unknown time of onset should be investigated in a future analysis from the CLEOPATRA study, which will also include data from the MR CLEAN-LATE (ISRCTN19922220) trial.

Future directions and opportunities

Over the past decades, acute stroke care has experienced several breakthroughs regarding acute reperfusion therapies.[1,3] With an aging population and an expected increase in the global stroke burden,[121] further development of acute diagnostic and treatment strategies remains crucial.[122] Due to a large number of finished, current, and future stroke trials and the ongoing digitalization in healthcare, there has also been a tremendous increase in available data. In addition, in many fields, artificial intelligence (AI) has dramatically advanced, both in and outside medical research. AI is commonly defined as the ability of a computer to perform tasks that we associate with human thinking, such as learning, problem-solving, and decision-making.[123] AI can be further divided into further subfields including machine learning (ML) and deep learning (DL). ML focuses the on the learning aspect of AI and is commonly defined as the capability of a machine to learn and adapt without explicit external instructions.[124] In the field of acute ischemic stroke, various ML-based applications have already been studied and are currently used in clinical practice. ML-based algorithms can, for example, aid in detecting arterial occlusion on CTA, quantify the collateral status, and detect intracranial hemorrhages.[125–128] DL is a subset of ML which can independently learn abstract, high-order features from data without feature selection.[129] For the field of acute ischemic stroke, DL could for example be used to automatically segment thrombi or provide individualized follow-up infarct volume prediction based on native CTP images. Regarding CTP specifically, there is still room and need for further improvement.[130,131] To continue making progress on the accuracy and clinical utility of CTP, researchers, physicians, and industry partners should use their best endeavors to keep the field moving forward. The future utility of CTP outside the emergency department setting (e.g., in mobile stroke units or directly in the angio suite[132,133]) could be investigated. Furthermore, the added value and cost-effectiveness of other imaging strategies which may be able to quantify cerebral perfusion, such as multiphase CTA, should be further investigated. This might be particularly relevant for stroke healthcare systems in developing countries, which may not have immediate access to CTP. With all current developments and opportunities, it seems like we have a very promising road toward optimized and individualized stroke imaging and treatment ahead.

Conclusion

CT perfusion provides valuable prognostic information and has the potential to further aid the diagnostic workup of patients with acute ischemic stroke. However, CTP results should be interpreted carefully and always in the context of clinical findings and NCCT and CTA imaging. This thesis focused on various technical, clinical, and health-economic

aspects of CT perfusion. We observed that CTP-based estimates of the core and penumbra varied substantially across vendors and estimation approaches used and that spatial agreement with follow-up imaging on 24h DWI is limited. Second, we found that CTP-estimated ischemic core volume is associated with poor functional outcomes in current clinical practice and that this association is not altered by the intracranial or brain volume. Third, we found that infarct evolution was comparable between patients who received intravenous alteplase vs. patients who underwent EVT alone and that CTP-based imaging biomarkers do not alter the treatment effect of intravenous alteplase before EVT in directly admitted patients who presented within 4.5h after onset. Furthermore, we investigated the costs and health effects of including CTP in the selection of patients for EVT within six hours after symptom onset. We conclude that physicians should currently not base treatment decisions on CTP results alone in the first six hours after symptom onset. Yet, CTP does improve the detection of treatable occlusions and is therefore still a highly useful diagnostic imaging tool in acute ischemic stroke. Future work should focus on determining the association between collateral score and CTP results, and aim to determine the potential benefit of artificial intelligence for improved CTP acquisition techniques, thereby leading the way toward optimized CTP imaging in acute ischemic stroke.

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