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Publication date
2023
Document Version
Final published version

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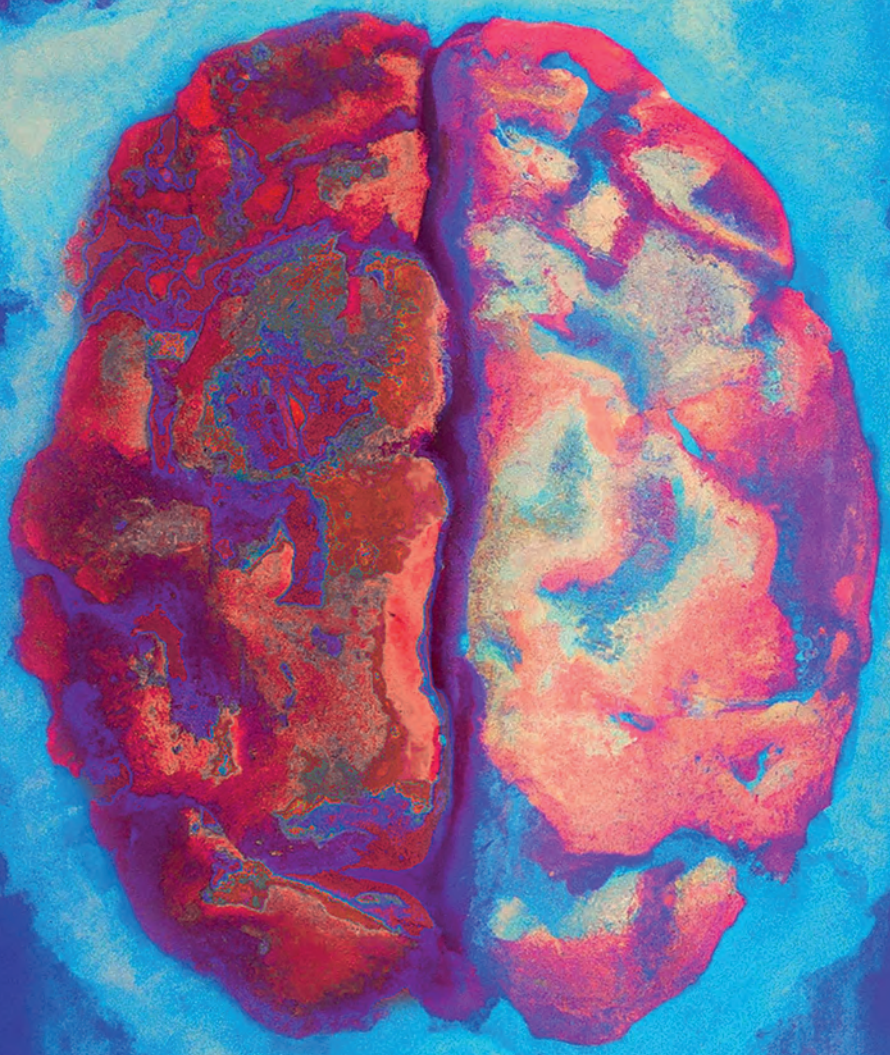

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Colophon

ISBN: 978-94-6469-346-1

Cover: Katinka R. van Kranendonk

Illustrations and lay-out: Lotte Souwer

Printed by: ProefschriftMaken

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Hemorrhagic transformation in acute ischemic stroke

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek

ten overstaan van een door het College voor Promoties
ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 2 juni 2023, te 16.00 uur
door Katinka Rebekka van Kranendonk
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General introduction

Chapter 1

Ischemic stroke

Acute ischemic stroke is one of the most common causes of morbidity and mortality worldwide.[1] Every passing minute approximately 1.9 million neurons are lost when a large vessel occlusion remains untreated.[2] Eventually, an untreated ischemic stroke results in irreversible tissue damage and consequently permanent neurological deficit or death. Therefore, an ischemic stroke is a neuro-emergency that needs to be treated as soon as possible.[2] In the last decade many advances in stroke treatment have been made. Particularly endovascular therapy (EVT) after an acute ischemic stroke due to a large vessel occlusion has immensely improved functional outcomes. EVT is a mechanical treatment using stent retriever and/or aspiration devices to retrieve the occluding thrombus and restore cerebral blood flow. For every 100 patients EVT results in 20 more patients to be functional independent and 38 patients less dependent on others compared to best medical treatment without EVT.[3] Trials have established benefit of this treatment up to 24 hours after last seen well.[4,5] As a result of the introduction of EVT in clinical practice in 2015, ischemic stroke treatment has changed dramatically.[6–12] Despite this major improvement in stroke treatment approximately half of the patients with an acute ischemic stroke has a poor functional outcome and is functional dependent, severely disabled or dead.[3] Several factors associated with poor outcome such as greater age and severe stroke at admission, have been identified previously.[13] However, one of the most feared complications after an acute ischemic stroke is hemorrhagic transformation. [14–16]

Hemorrhagic transformation

Hemorrhagic transformation after brain tissue infarction can occur as stroke progresses or as a complication of stroke treatment and attributes to a poor functional outcome.[14–16] Damage to the blood-brain barrier (BBB) is thought to be the underlying mechanism of hemorrhagic transformation.[17] The BBB is a border of endothelial cells that regulates the transmission of substances between the blood circulation and intracellular space of the central nervous system. For instance, it allows nutrients to pass and allows the exchange of several ions, molecules and cells.[18] Most importantly, the BBB protects the central nervous system from possible harmful substances in the blood.[18] Ischemia may cause structural damage to the endothelial cells and basal membrane of the arterioles involved. Damage to the endothelial cells and basal membrane could lead to increased BBB permeability and eventually hemorrhagic transformation through leakage of blood.[17] In addition to BBB damage caused by ischemia, administration of intravenous thrombolysis (IVT) (a common

treatment of acute ischemic stroke) could also damage the BBB through its cytotoxic properties to the endothelial wall.[19] Additionally, IVT was found to be neurotoxic and could further damage neurons when crossing a defective BBB due to infarction.[19]

Imaging of hemorrhagic transformation

Hemorrhagic transformation varies in severity. It is commonly classified according to the European Cooperative Acute Stroke Study (ECASS) classification. The ECASS classification divides hemorrhagic transformation in four subtypes based on its radiological appearance.[14] Hemorrhagic infarction is defined as the presence of small petechial bleedings along the margins of the infarct (type 1) or more confluent petechial bleedings (type 2). Parenchymal hematomas are frank hematomas that are further classified based on its volume compared to the volume of infarcted tissue. Parenchymal hematom type 1 involves less than 30% of the infarcted area with no or mild space occupying effect while type 2 involves more than 30% with a significant space occupying effect. Examples of all hemorrhagic transformation subtypes are presented in figure 1.

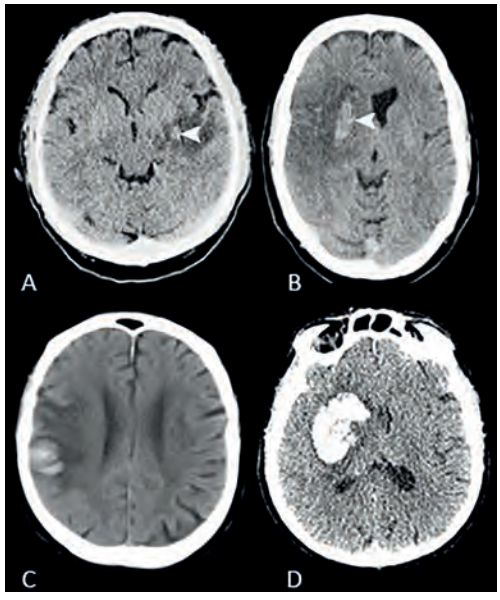

Figure 1. Non-contrast CT images of all hemorrhagic transformation subtypes. *Hyperdense areas as pointed by the arrows indicate hemorrhagic transformation. A: hemorrhagic infarction type 1, B: hemorrhagic infarction type 2, C: parenchymal hematoma type 1, D: parenchymal hematoma type 2.*

Radiological follow-up imaging is performed for a number of reasons, most commonly when a patient deteriorates neurologically after admittance for ischemic stroke. Follow-up imaging is used to determine a possible underlying cause for the deterioration such as hemorrhagic transformation. During most randomized controlled trials routine follow-up imaging at 24 hours and 5-7 days after stroke onset has been performed.[6,20] Follow-up imaging can be acquired using NCCT or magnetic resonance imaging (MRI). When follow-up NCCT or MRI during routine follow-up it is possible hemorrhagic transformation is a coincidental finding. As shown in figure 1, Hemorrhage appears hyperdense on non-contrast enhanced computed tomography (NCCT) in the acute and subacute phase (until 7 days from stroke

onset).[21] On MRI however, hemorrhage appears hypointense on most sequences.[21–25] Oxidation products of hemoglobin affect the appearance of hemorrhage on MRI. [22] For example, hemorrhage on T1 –weighted images appears isointense in the hyperacute phase due to intracellular oxyhemoglobin (<24h), iso- to hypointense in the acute phase due to deoxyhemoglobin (1-3 days) and hyperintense due to methemoglobin in the subacute phase (3-7 days).[22] On T2-weighted images, hemorrhage appears iso- to hyperintense in the hyperacute phase and hypointense in the acute and early subacute (>3 days) phases.[22] Finally, in the chronic phase (>14-28 days), hemorrhage appears hypointense in the periphery of the hemorrhage on both T1- and T2-weighted images.[21,22] Gradient echo weighted MRI (e.g. T2*- or susceptibility-weighted imaging) is most sensitive in depicting hemorrhage due to the paramagnetic effects of deoxyhemoglobin.[21–23] Figure 2 shows an example image of T2*-weighted MRI of hemorrhagic transformation. Location of the hemorrhage also affects its visibility on MR images. Subarachnoid hemorrhage for example, is more difficult to detect on T1- and T2-weighted images than parenchymal hemorrhage because the cerebrospinal fluid delays the oxidation of oxyhemoglobin in paramagnetic deoxyhemoglobin.[21] Classifying hemorrhagic transformation can be difficult as some hemorrhages seem to fit more than one classification, which may result in poor inter-observer agreement.[26,27] Usage of both NCCT and MRI based imaging as follow-up imaging after an acute ischemic stroke may complicate classifying hemorrhagic transformation even further due to their different appearance on each modality. For example, when MRI is used as follow-up imaging, more hemorrhagic infarctions type 1 are detected that might not even be detected on NCCT.[21] Additionally, the petechial nature of hemorrhagic infarction type 2 could be overestimated and interpreted as frank hematoma seen in parenchymal hematoma type 1 because of the susceptibility artefact on gradient echo sequences.[21]

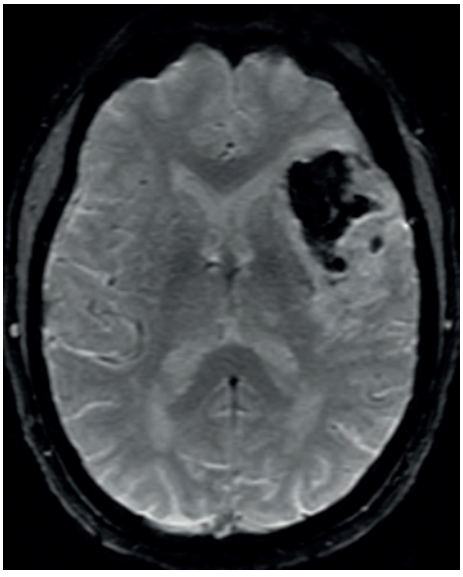

Figure 2. T2*-weighted image of hemorrhagic infarction type 2

Symptomatic and asymptomatic intracranial hemorrhage

Intracranial hemorrhage can be either symptomatic or asymptomatic. Intracranial hemorrhage is symptomatic when patients show neurological deterioration and hemorrhage is visible on follow-up imaging. Determining whether intracranial hemorrhage is symptomatic can be complicated as progression of stroke itself could also cause a neurological decline. To complicate matters further, multiple definitions exist, each with different cut-offs regarding the severity of the deterioration and size of the hemorrhage necessary to qualify as symptomatic intracranial hemorrhage .[14,28–30] Currently, the Heidelberg Bleeding classification is most commonly used. This classification combines the classification of symptomatic intracranial hemorrhage with the ECASS classification.[14,30] According to the Heidelberg Bleeding Classification, an intracranial hemorrhage is symptomatic when an intracranial hemorrhage of relevant size compresses intact brain tissue causing neurological symptoms with an increase in the National Institute of Health Stroke Scale (NIHSS) score.[30]

Large space-occupying hematomas (parenchymal hematoma type 2) are often classified as symptomatic intracranial hemorrhage. Smaller hemorrhages, such as hemorrhagic infarction type 1 and 2, are thought to be less or not clinically relevant and are often not classified as symptomatic, regardless of neurological deterioration. While these smaller hemorrhages might not cause acute deterioration, they could have an impact on longer term functional outcome. Some studies suggest that these patients with smaller asymptomatic hemorrhages are associated with better functional outcomes compared to patients without hemorrhagic transformation and that it might be a sign of early reperfusion.[31,32] However, other studies found that asymptomatic hemorrhage can have a negative impact on functional outcome. Therefore, the impact of these smaller hemorrhages remains unclear.[15,16,33] Since blood products such as thrombin, hemoglobin and free iron are neurotoxic, they could damage surrounding healthy brain tissue, which may also result in less favorable functional outcomes.[34]

Ischemic stroke treatment and hemorrhagic transformation

Two treatment options for acute ischemic stroke are currently available: IVT and EVT. In short, IVT (most commonly with alteplase, a recombinant tissue plasminogen activator)

is used in an effort to dissolve the thrombus and restore cerebral blood flow.[35] However, since the therapeutic effect of thrombolytics is a trade-off between its lytic effect and increased hemorrhage risk, patients with a pre-existing increased risk for bleeding are excluded for treatment with IVT. Additionally, patients presenting after 4.5 hours are not eligible for treatment with IVT if they do not fulfill strict imaging criteria because beyond 4.5 hours the benefit of IVT does not outweigh the risks.[36] Aside from the bleeding risks, not all patients benefit from IVT as some thrombi do not dissolve due to their size or composition.[35] In contrast to IVT, EVT is a mechanical treatment. It is unclear whether EVT increases the risk of hemorrhagic transformation. Since EVT is an endovascular treatment with a mechanical device it could damage the vessel wall, and with additional circulating IVT that could cause cause excessive bleeding.

Clinical factors influencing hemorrhagic transformation

Previous research identified various risk factors for the occurrence of hemorrhagic transformation. These include greater age, anticoagulant use, increased glucose levels, hypertension, severe strokes and treatment with thrombolytic agents.[37–42]

Several studies identified greater age as a risk factor for hemorrhagic transformation after an acute ischemic stroke treated with IVT.[37,43,44] However, this association was not found in another study that assessed the association of patients over 80 with hemorrhagic transformation.[45] Patients with an increased age still benefitted from IVT.[46] With increasing age different biochemical and physiological changes such as hypertension and atrial fibrillation occur, resulting in an increased risk for cerebrovascular disease.[47] As atrial fibrillation is associated with large ischemic strokes and it is treated with anticoagulants, it increases the risk for hemorrhagic transformation after ischemic stroke treated with IVT.[48]

During an acute ischemic stroke, about two thirds of the patients have an increased blood pressure to compensate brain hypoperfusion caused by the occluded vessel.[49] Patients with increased blood pressures have a better functional outcome than patients with relative hypotension (systolic blood pressure 120-140 mmHg). However, blood pressure exceeding 180 mmHg is associated with poor functional outcomes.[49] A previous study showed that poor functional outcomes in patients with hypertension not treated with IVT or EVT were due to recurrent stroke.[50] However, hypertension in combination with IVT was associated with symptomatic intracranial hemorrhage and poor functional outcomes.[49] It is

unclear whether EVT in addition to IVT in ischemic stroke patients with hypertension alters the risk for symptomatic intracranial hemorrhage.

Hyperglycemia is commonly observed in patients with an acute ischemic stroke. Hyperglycemia can occur in patients with diabetes, which is an evident risk factor for vessel disease and therefore ischemic stroke. However, hyperglycemia is also observed in patients without pre-existing diabetes.[51] It is thought that some patients might have had diabetes that remained undiagnosed until their hospital admittance for ischemic stroke or hyperglycemia was induced by stress during the stroke. [52] Another hypothesis is that hyperglycemia is caused by a defect in the regulation of the hypothalamo-hypophyseal-adrenal axis due to ischemia.[52] Hyperglycemia is pro-inflammatory and can cause oxidative stress which eventually in combination with ischemia could lead to BBB permeability and therefore increase the risk of hemorrhagic transformation.[52,53]

In case of suspicion of ischemic stroke, patients are examined to assess the severity of the stroke. For this purpose, the NIHSS is commonly used.[28] In this scale, points are attributed for each stroke symptom with higher scores indicating more severe strokes. Large vessel occlusions (e.g. occlusions of the intracranial carotid artery or middle cerebral artery) affect a large brain area and result in severe strokes. When a large brain area is affected, this increases the risk for hemorrhagic transformation as the BBB is damaged in a large brain area.[48] Therefore, high NIHSS could be indicative for hemorrhagic transformation.

It is unclear whether risk factors for hemorrhagic transformation after treatment with EVT and after IVT are similar. Additionally, most studies identified risk factors for symptomatic intracranial hemorrhage or overall hemorrhagic transformation and not for the hemorrhagic transformation subtypes.[38–42] Therefore it is unclear whether previously identified risk factors are associated with hemorrhagic infarction, parenchymal hematoma or both.

In addition to clinical factors that could identify patients at risk for hemorrhagic transformation, several imaging parameters could also aid in identifying patients with an increased risk for hemorrhagic transformation.

Imaging markers and hemorrhagic transformation

When a patient with stroke symptoms is admitted to a hospital, one of the first steps is to determine whether the patient has an ischemic or hemorrhagic stroke. Differentiation between ischemic and hemorrhagic stroke can be made using NCCT imaging to rule out a hemorrhage.[54] Several signs on NCCT imaging could be indicative for an ischemic stroke, such as loss of gray-white matter differentiation, hypodense areas and a hyperdense artery sign, indicating the presence of thrombus.[54] Hypodense areas on NCCT are indicative for edema, which is a marker of ischemic brain tissue.[55] The extent of these early ischemic changes on NCCT can be assessed with The Alberta Stroke Program Early CT score (ASPECTS).[55] Previous studies showed that ASPECTS of less than seven is associated with parenchymal hematoma in patients treated with IVT or EVT for an acute ischemic stroke.[55,56] While most patients with symptomatic intracranial hemorrhage have a parenchymal hematoma, ASPECTS was not associated with symptomatic intracranial hemorrhage.[57,58] Therefore the predictive value of ASPECTS for hemorrhagic transformation remains unclear. Additionally, it is unclear whether ASPECTS is associated with hemorrhagic infarction type 1 or 2.

It is important to determine where the occlusion causing the stroke is located since this information is necessary for treatment decision making. Whether the stroke is caused by a large vessel occlusion needs to be confirmed and its location needs to be determined by CT angiography (CTA).[54] This imaging modality visualizes vessels after intravenous contrast agent administration. CTA also provides information about the collateral circulation.[59] Collateral circulation (e.g. through the circle of Willis or pial collaterals) could provide sufficient blood to maintain viability of brain tissue affected by the occluded artery. Collateral scores are used to assess collateral capacities. For example, the Tan score is commonly used. [59] This score describes whether a patient has good collaterals (100% filling of occluded territory), moderate collaterals (>50% and <100% filling of occluded territory), poor collaterals (>0% and <50% filling of occluded territory) or absent collaterals (0% filling of occluded territory).[59] A previous study showed that a collateral score with <50% filling of occluded territory was associated with a higher chance of hemorrhagic transformation in patients treated with IVT and successful recanalization.[61] In patients without recanalization, collateral score was not associated with hemorrhagic transformation.[61] It is unclear whether this association of collateral score with hemorrhagic transformation is similar in patients treated with EVT.

Aims and outline of this thesis

The aims of this thesis were, to determine the impact of hemorrhagic transformation on functional outcome, to determine which patients are at increased risk for hemorrhagic transformation, and to determine whether reperfusion therapy increases this risk. Additional aims were to determine whether hemorrhage volume quantification could be an alternative measure for the hemorrhagic transformation classification and whether hemorrhagic transformation assessments on NCCT and MRI are similar.

In many cases, hemorrhagic transformation is a coincidental finding, and patients did not show symptoms of hemorrhagic transformation when follow-up imaging was acquired. Although hemorrhagic transformation might not be clinically apparent, it could have an impact on functional outcome after an acute ischemic stroke. With the improved outcomes due to EVT, we determined whether hemorrhagic transformation has an impact on functional outcome after EVT. Additionally, we determined whether patients with hemorrhagic transformation still had benefit from EVT **(chapter 2 and 3)**.

Discriminating hemorrhagic transformation subtypes on NCCT can be complicated and inter-observer variation is considerable. Therefore, we determined whether hemorrhage volume quantification is a valuable alternative measure for the classification of hemorrhagic transformation. To assess the added value of hemorrhage volume quantification we determined the association of hemorrhage volume with functional outcome in comparison with the association of the ECASS classification with functional outcome **(chapter 4)**.

Several risk factors for the occurrence of hemorrhagic transformation have been identified in the IVT treated population. However, it is unclear whether risk factors have are different for patients also treated with EVT. Therefore we assessed the associations of clinical and imaging markers with hemorrhagic transformation in patients with an anterior circulation acute ischemic stroke treated with EVT. Additionally, we compared whether risk factors for hemorrhagic transformation differed between EVT and medical treatment **(chapter 5)**.

Both NCCT and MRI are commonly used as follow-up imaging modalities. As such, the hemorrhagic transformation classification has been adapted to MRI. Because hemorrhage are overestimated on several MRI sequences (gradient echo and susceptibility weighed imaging) compared to NCCT it could hamper the classification of hemorrhagic

transformation. The B0 series of echo planar diffusion weighted imaging is less sensitive for hemorrhage and more accurate than general sequences (T1, T2 and FLAIR). Therefore, In **chapter 6** we assessed whether hemorrhagic transformation classification is comparable for NCCT and the B0 series of echo planar diffusion weighted imaging by determining the inter-modality agreement and differences in hemorrhage size between NCCT and the B0 series of echo planar diffusion weighted MRI.

It is unclear what the main cause is for hemorrhagic transformation in patients undergoing reperfusion therapy: both IVT and reperfusion of an occluded vessel itself have been suggested the main cause. Therefore we used data from an EVT treated population randomized for IVT to determine whether IVT or reperfusion are associated with hemorrhagic transformation. Additionally, we determined whether IVT before EVT results in an increase in hemorrhage size compared to EVT without IVT **(chapter 7)**.

In **chapter 8**, the implications of our findings and relevant literature are discussed. Furthermore, future research directions are considered.

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Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion

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Journal of Neurointerventional Surgery. May 2019, 11(5):464-468

Abstract

Background and purpose

Hemorrhagic transformation (HT) is a complication that may cause neurological deterioration in patients with acute ischemic stroke. Various radiological subtypes of HT can be distinguished. Their influence on functional outcome is currently unclear. The purpose of this study was to assess the associations between HT subtypes and functional outcome in acute ischemic stroke patients with proven large vessel occlusion.

Methods

All patients with follow-up imaging were included. HT was classified on follow-up CT scans according to the ECASS II classification. Functional outcome was assessed using the modified Rankin Scale (mRS) 90 days after stroke onset. Ordinal logistic regression analysis with adjustment for potential confounders was used to determine the association of HT subtypes with functional outcome.

Results

Of 478 patients, 222 had HT. Of these, 76 (16%) patients were classified with hemorrhagic infarction type 1, 71 (15%) with hemorrhagic infarction type 2, 36 (8%) with parenchymal hematoma type 1, and 39 (8%) with parenchymal hematoma type 2. Hemorrhagic infarction type 2 (adjusted common odds ratio [acOR] 0.54, *95% Confidence interval [CI]: 0.32-0.89*) and parenchymal hematoma type 2 (acOR:0.37,*95%CI:0.17-0.78*) were significantly associated with a worse functional outcome. Hemorrhagic infarction type 1 and parenchymal hematoma type 1 were not significantly associated, although their point estimates pointed in the direction of worse outcome.

Conclusion

This study suggests that not only parenchymal hematoma type 2 is relevant for functional outcome after an acute ischemic stroke, but that also smaller HT might influence long-term functional outcome.

Introduction

Hemorrhagic transformation (HT) manifests as natural progression of acute ischemic stroke (AIS) or complication of thrombolytic treatment[1,2] and can cause neurological deterioration.[1] With the recent introduction of endovascular treatment (EVT) as standard of care in AIS, the effect of HT on outcome became of increased interest.[3–7] Based on the radiological appearance, HT is categorized as hemorrhagic infarction (HI) or parenchymal hematoma (PH).[8] Both types have been subdivided in small and large subtypes (suffixes 1 and 2, respectively). Some hemorrhages cause acute neurological deterioration and are classified as symptomatic intracranial hemorrhage (sICH). No significant differences in incidence of sICH between patients treated with and without EVT have been observed.[3–7] The incidence of HT in these patients has not been reported. In most sICHs the underlying hemorrhages are large.[8,9] Therefore it has been suggested that the patient's wellbeing is not influenced by the small hemorrhage subtypes of HI1,2 and PH1.[10] Some studies even suggest that HI is associated with better functional outcome than patients without HI because it is a sign of early revascularization.[11,12]infarct volume, and outcome. Methods-- Thirty-two patients with acute stroke caused by proximal MCA occlusion treated with rtPA <3 hours of symptom onset were prospectively studied. Serial transcranial Doppler examinations were performed on admission and at 6, 12, 24, and 48 hours. Presence and type of HT were assessed on CT at 36 to 48 hours. Modified Rankin scale was used to assess outcome at 3 months. Results-- Early and delayed recanalization was identified in 17 patients (53.1% However, as some of the patients with HI show acute neurological deterioration, the impact of HI on functional outcome might be underestimated.[13] Even though, most patients with HI do not show acute neurological deterioration, it still could have a negative impact on long term functional outcome.[14]

The main purpose of this study was to determine the incidence of HT and assess the association between subtypes of HT and functional outcome, approximately 90 days after stroke onset.

Methods

In this *post hoc* analysis, all patients with follow-up imaging were eligible for inclusion. HT was classified according to the ECASS II (European Cooperative Acute Stroke Study II) classification.[8] Hemorrhagic infarction 1 (HI1) was defined as small petechiae along the margins of the infarct; hemorrhagic infarction 2 (HI2) as confluent petechiae within

the infarcted area but no space-occupying effect; parenchymal hematoma 1 (PH1) as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal hematoma 2 (PH2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect.[8] HT was identified by two experienced observers from the core imaging committee. Patients with any intracranial hemorrhage and neurological deterioration (increase of 4 points on the National Institute of Health Stroke Scale (NIHSS)) were classified as sICH.[3] Follow-up imaging acquired at approximately 5 days was examined first to reduce the chance of contrast staining being classified as HT. When 5-day follow-up imaging was not available, 24-hour follow-up imaging was used for the classification of HT. HI rates at 24-hour and 5-day follow-up were compared to detect a possible overestimation of HI due to contrast staining. Functional outcome was defined according to the modified Rankin Scale (mRS) assessed at 90 days (+/- 14 days) after acute ischemic stroke onset. The mRS is a score to assess functional outcome and ranges from 0 to 6, where 0 indicates “no symptoms” and 6 “death”.

Statistical analysis

HT was divided in four groups; HI1, HI2, PH1 and PH2.[8] The effect of HI1, HI2, PH1, and PH2 on functional outcome with no HT as reference level was assessed with a multivariable ordinal logistic regression analysis. Functional outcome was assessed on the full mRS at 90 days. Differences in outcome between subgroups were estimated as a common odds ratio, which summarizes the shift in the direction of a better outcome on the mRS. Common odds ratios smaller than one signify a shift in the direction of worse outcomes. Adjustment for potential confounders included diabetes mellitus, systolic blood pressure, intravenous thrombolysis (IVT), EVT, time from onset to randomization, history of ischemic stroke, age, atrial fibrillation, and follow-up lesion volume. Follow-up lesion volume was determined using a validated automated measurement including both the infarct and hemorrhage volume.[16] Additionally, we report the median follow-up lesion volume for all HT subgroups. The association of sICH with full-scale functional outcome was analyzed separately using “no sICH” as reference. Since it is highly likely that acute neurological deterioration in patients with sICH was caused by hemorrhage and these hemorrhages are mostly large we adjusted for the same potential confounders as mentioned above, excluding follow-up lesion volume.

As secondary outcome we dichotomized the mRS (mRS 0-2 vs 3-6) and assessed the association of HT with good functional outcome (mRS 0-2) using multivariable logistic regression. We adjusted for the same potential confounders as the primary analysis.

Due to death, decreased kidney function or insufficient scan quality, there were no analyzable 24-hour follow-up CTA's to evaluate recanalization rate for 96 patients. With the large amount of missing values we chose not include recanalization rate in the multivariable analysis. Recanalization rate is of high importance to functional outcome and although we adjusted for EVT and IVT which are the two major factors causing recanalization, we conducted a sensitivity analysis with the patients for which recanalization rate could be assessed.

Patient characteristics were compared using the $\chi 2$ test for trend for categorical data, one-way ANOVA for normally distributed continuous data and the Kruskal Wallis test for non-normally distributed continuous data. The statistical analysis was performed using R (R Core Team (version 3.4.2 (2017)). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Used packages: rms[17], ggplot2[18], tableone[19]).

Results

Twenty-two patients were excluded because of missing follow-up imaging due to death. Of the remaining 478 patients, 361 (76%) patients had follow-up CT imaging at approximately 5 days. For 117 (25%) patients, 24-hour follow-up CT was assessed. Of all included patients, 222 patients had HT (46%); 16% HI1 (n=76), 15% HI2 (n=71), 7.5% PH1 (n=36), and 8.2% PH2 (n=39). Baseline characteristics were evenly distributed between all groups except for NIHSS (p=0.002), atrial fibrillation (p=0.003), systolic blood pressure (p<0.001) and follow-up lesion volume (p<0.001) (Table 1). HI did not differ between 24-hour and 5-day follow-up imaging. Thirty-six patients were classified with HI on 24-hour CT scans (31%) and 111 patients on 5-day follow-up CT scans (31%).

Table 1. Patient characteristics

	No HT n=256)	HI1 (n=76)	HI2 (n=71)	PH1 (n=36)	PH2 (n=39)	P-value
EVT (per protocol) – no. (%)	111 (43.4)	28 (36.8)	35 (49.3)	21 (58.3)	17 (43.6)	0.286
Treatment with IV alteplase – no. (%)	228 (89.1)	66 (86.8)	65 (91.5)	33 (91.7)	36 (92.3)	0.398
Age – mean (sd)	64 (14.3)	65 (12.6)	66 (12.9)	64 (14.8)	68 (14.1)	0.406
Baseline NIHSS – mean (sd)	17 (5.7)	19 (6.1)	18 (4.4)	18 (4.3)	19 (4.8)	0.002
History of ischemic stroke – no. (%)	26 (10.2)	7 (9.2)	8 (11.3)	1 (2.8)	9 (23.1)	0.233
Atrial fibrillation – no. (%)	58 (22.7)	17 (22.4)	25 (35.2)	15 (41.7)	14 (35.9)	0.003
Diabetes mellitus – no. (%)	27 (10.5)	13 (17.1)	9 (12.7)	5 (13.9)	7 (17.9)	0.192
Systolic blood pressure – mean (sd)	143 (22.4)	144 (26)	142 (27.5)	153 (23.6)	160 (31.4)	<0.001
Time from stroke onset to randomization per 10 minutes – median [IQR]	19 [15-25]	22 [15-26]	21 [16-28]	21 [17-29]	22 [18-27]	0.112
ASPECTS – median [IQR]*	9 [8-10]	9 [7-10]	8 [7-10]	9 [7-10]	9 [7-10]	0.058
Collateral score – no. (%)†						0.205
Good collaterals	84 (33.1)	11 (14.9)	17 (23.9)	6 (16.7)	9 (24.3)	
Moderate collaterals	100 (39.4)	32 (43.2)	29 (40.8)	12 (33.3)	16 (43.2)	
Poor collaterals	70 (27.6)	31 (41.9)	25 (35.2)	18 (50)	12 (32.4)	
Follow-up lesion volume – median [IQR] ‡	47 [18-118]	132 [58-207]	120 [78-243]	172 [97-274]	165 [93-323]	<0.001
Recanalization rate – no. (%)§						0.928
No recanalization	50 (23)	19 (32.8)	13 (21.3)	6 (24)	2 (9.5)	
Incomplete, no distal flow	11 (5.1)	5 (8.6)	8 (13.1)	1 (4)	1 (4.8)	
Incomplete, any distal flow	30 (13.8)	10 (17.2)	12 (19.7)	8 (32)	3 (14.3)	
Complete recanalization	126 (58.1)	24 (41.4)	28 (45.9)	10 (40)	15 (71.4)	
Symptomatic ICH – no. (%)	2 (0.8)	1 (1.3)	2 (2.8)	2 (5.6)	28 (72)	

Abbreviations: EVT, endovascular treatment; HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; mRS, modified Rankin scale; NIHSS, national institute of health stroke scale; IQR, interquartile range; ASPECTS, Alberta stroke program early CT score.

Mean and sd are used to summarize normally distributed variables, for non-normal distributed variables the median and IQR are used.

* ASPECTS was missing for 4 patients

† Collateral score was assessed on baseline CTA as poor collaterals (0% and >50% filling of occluded area), moderate collaterals (filling of 50% and >100% of the occluded area) and good collaterals (100% filling). Collateral score was not available for 6 patients.

‡ Follow-up lesion volume was not available for 13 patients due to death or insufficient scan quality.

§ 24-hour follow-up CTA to evaluate recanalization rate was not available for 96 patients due to death, decreased kidney function or insufficient scan quality.

Primary outcome

The mRS distribution for the individual HT subtypes is shown in figure 1. Twenty-three (66%) of the 35 patients with sICH died. For HI1, HI2, PH1 and PH2 these rates were 17%, 28%, 19% and 46%, respectively. In patients without HT, 18% of the patients died. None of the patients with any HT had a score of 0 on the mRS. After adjustment for potential confounders, PH2 and HI2 were significantly associated with a worse functional outcome (acOR: 0.37, 95% CI 0.17 - 0.78) (acOR: 0.54, 95% CI 0.32 - 0.89), respectively. For HI1 and PH1, the point estimates also aimed in the direction of worse outcome but were not statistically significant (Table 2). Patients with HT have larger lesion volumes than patients without HT (Figure 2) (p<0.001).

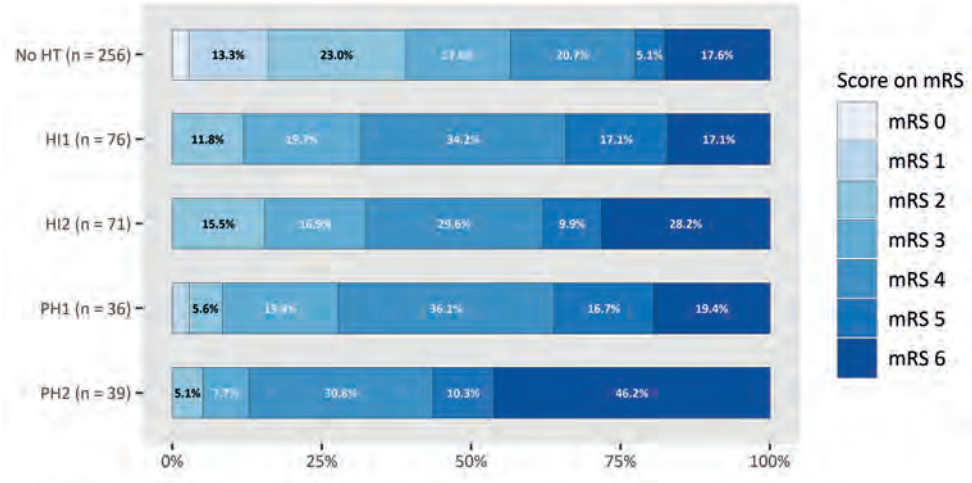

Figure 1. Functional outcome defined by the modified Rankin Scale per group.

Table 2. Adjusted and unadjusted odds ratios of the association of hemorrhage with functional outcome

	Unadjusted OR and 95% CI	Adjusted OR and 95%CI	Adjusted P-value	Adjusted OR and 95% CI (including recanalization rate	Adjusted P-value (including recanalization rate)
Primary outcome (full mRS scale)					
HI1	0.40 (0.26 - 0.62)	0.63 (0.39 -1.02)	0.058	0.67 (0.39 - 1.15)	0.146
HI2	0.35 (0.22 - 0.56)	0.54 (0.32 - 0.89)	0.017	0.37 (0.21 - 0.67)	0.001
PH1	0.36 (0.20 - 0.65)	0.77 (0.40 - 1.48)	0.42	0.57 (0.26 - 1.25)	0.162
PH2	0.16 (0.08 - 0.29)	0.37 (0.17 - 0.78)	0.009	0.21 (0.08 - 0.53)	< 0.001
Secondary outcome (dichotomous mRS scale)					
HI1	0.21 (0.09 - 0.42)	0.34 (0.13 - 0.84)	0.025	0.34 (0.12 - 0.90)	0.035
HI2	0.29 (0.14 - 0.55)	0.62 (0.26 - 1.39)	0.252	0.40 (0.14 - 1.04)	0.068
PH1	0.14 (0.03 - 0.41)	0.45 (0.09 - 1.74)	0.283	0.39 (0.05 - 1.82)	0.272
PH2	0.08 (0.01 - 0.28)	0.22 (0.03 - 0.97)	0.075	0.15 (0.02 - 0.70)	0.03

This table lists the primary outcome which was the association of hemorrhagic transformation with the full-scale mRS score with patients without hemorrhage as reference. And the secondary outcome of the association of hemorrhagic transformation with good functional outcome (mRS 0-2). An additional analysis was conducted were recanalization rate was added to the adjusted analysis.
Adjusted for age, diabetes mellitus, systolic blood pressure, IVT, EVT, time from stroke onset to randomization, previous stroke, atrial fibrillation and follow-up lesion volume.
Abbreviations: HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; FLV, follow-up lesion volume.

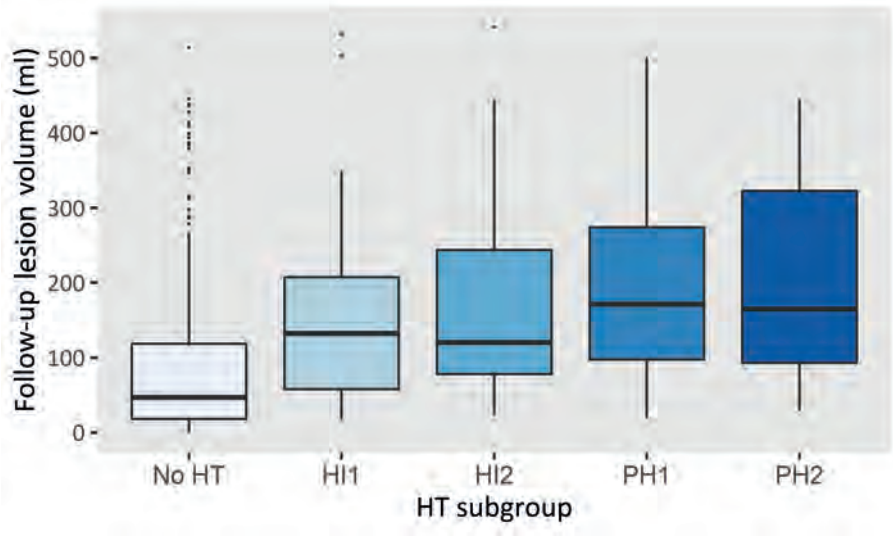

Figure 2. Follow-up lesion volume per group.

Follow-up lesion volume includes hemorrhage and infarct volume Patients with any subtype of HT have larger lesion volumes than patients without HT (p<0.001).

Of the patients with SICH, 28 had a PH2 (80%), 2 patients had a PH1 (5.7%), 2 had an HI2 (5.7%), 1 had an HI1 (2.9%) and 2 patients had a subarachnoid hemorrhage (SAH) (5.7%). Both patients with a symptomatic PH1 died, as did one of the patients with symptomatic HI2. The other patient with a symptomatic HI2 had a moderately severe disability (mRS 4) as did the patient with symptomatic HI1. Two patients with SICH due to a PH2 underwent hemicraniectomy. Of the 37 patients with a PH2, 27 were classified as SICH (73%). Patients with SICH had a strong association with a worse functional outcome (acOR: 0.17, 95% CI: 0.08 - 0.35).

Secondary outcome

In the adjusted analysis of the association of HT with functional outcome on a dichotomous scale, only HI1 (acOR: 0.35, 95% CI 0.13 – 0.85) and PH2 (acOR: 0.22, 95% CI 0.03 – 0.96) were significantly associated with a poor functional outcome (Table 2). HI2 and PH1 were not statistically significant associated with this secondary outcome measure.

Recanalization rate

In the sensitivity analysis in which recanalization rate was included to the analysis, in the analysis using the full mRS scale, HI2 (acOR: 0.37, 95% CI 0.21 – 0.67) and PH2 (acOR: 0.21, 95% CI 0.08 – 0.53) were significantly associated with a worse functional outcome. In the analysis using the mRS as dichotomous scale, HI1 and PH2 were significantly associated with a poor functional outcome (aOR: 0.34, 95% CI 0.12 – 0.90 and aOR: 0.15, 95% CI 0.02 – 0.70, respectively) (Table 2).

Discussion

In our patient group, there was a high incidence of HT. HI1, HI2 and PH2 were significantly associated with worse functional outcome compared to patients without HT. However, point estimates of all types of HT aimed in the direction of a worse functional outcome. After adjusting for revascularization rate, the results did not change largely and showed comparable point estimates as the analysis without adjustment for revascularization rate. Patients with PH2 had the largest adverse effect on functional outcome and higher mortality than patients with HI1, HI2 or PH1.

Only few studies reported an association of HI1 or 2 with functional outcome. Nogueira et al. (2005) reported a significant association of HI and PH with a worse functional outcome.[20]hemorrhagic infarction (HI Further, Dzialowski et al. (2007) reported that HI2, PH1 and PH2 were significantly associated with a worse functional outcome compared to

patients without HT.[14] Other studies did not find an association of HI or PH1 with a worse functional outcome.[9–12,21–24]a randomized, placebo-controlled, phase III trial of intravenous recombinant tissue plasminogen activator in acute ischemic stroke. Findings on 24- to 36-hour CT were classified into 5 categories: no hemorrhagic transformation, HI types 1 and 2, and PH types 1 and 2. We assessed the risk of concomitant neurological deterioration and of 3-month death and disability associated with subtypes of hemorrhagic transformation, as opposed to no bleeding. Risks were adjusted for age and extent of ischemic damage on baseline CT. Results--Compared with absence of hemorrhagic transformation, HI1, HI2, and PH1 did not modify the risk of early neurological deterioration, death, and disability, whereas, in both the placebo and the recombinant tissue plasminogen activator groups, PH2 had a devastating impact on early neurological course (odds ratio for deterioration, 32.3; 95% CI, 13.4 to 77.7 This difference might be explained by a smaller sample size in some studies,[11,12,22,24]infarct volume, and outcome. Methods-- Thirty-two patients with acute stroke caused by proximal MCA occlusion treated with rtPA <3 hours of symptom onset were prospectively studied. Serial transcranial Doppler examinations were performed on admission and at 6, 12, 24, and 48 hours. Presence and type of HT were assessed on CT at 36 to 48 hours. Modified Rankin scale was used to assess outcome at 3 months. Results-- Early and delayed recanalization was identified in 17 patients (53.1% or by the lower incidence of HT compared to our study.[9,10,23] Treatment with IVT might be the reason for this difference in incidence because IVT increases the risk of developing HT.[25,26] In our population, 90% of the patients received IVT whereas these rates were much lower in other studies.[9,10,23] Additionally, the high incidence of HT in our study might be explained by our broad inclusion criteria. Patients with early signs of infarction on CT indicating severe strokes were not excluded, in contrast to other studies with a lower incidence of HT.[9,10,23]

Since large infarct volumes are associated with a worse functional outcome and with HT, a large underlying infarct could drive an observed association of HT with functional outcome.[10] Therefore, we adjusted for final lesion volume. However, it should be noted that this necessary adjustment for lesion volume might lead to underestimation of the association of HT with functional outcome. First, because follow-up lesion volume and HT are identified on the same follow-up CT, which will make it complicated to statistically separate them. Further, lesion volume includes infarct volume and hemorrhage. However, it is complicated to separate the impact of infarct volume and HT on functional outcome since the infarct size of patients with PH2 is masked by hemorrhage and therefore its size cannot be determined.

Depending on outcome measure (i.e. dichotomized or full mRS, respectively) both HI1 and HI2 were significantly associated with poor functional outcome. Additionally, all point estimates point in the direction of a poor functional outcome for patients with any HT. This might indicate that, both HI1 and HI2 could have a negative influence on functional outcome compared to patients without HT. However, due to the alternating statistical significance it is complicated to determine their actual influence on functional outcome.

HI1, HI2 and PH2 were all significantly associated with poor functional outcome. In contrast, PH1 was not significantly associated with poor functional outcome. This might be explained by the small number of patients in the PH1 group, combined with less adverse outcomes compared to the similarly common PH2. The point estimate, however, does indicate an association with poor outcome.

In the newly proposed Heidelberg classification, HT is defined as HI1, HI2, and PH1. In this classification, PH2 is classified separately from HT, as the radiological entity PH2 appears to be distinctly different and because of the assumption that only PH2 is clinically relevant.27 Our study suggests otherwise. While patients with PH2 are likely to show acute neurological deterioration in contrast to patients with other subtypes of HT, not only PH2 is relevant for functional outcome. The smaller subtypes of HT, were associated with a worse functional outcome after approximately 90 days of stroke onset and should additionally be considered relevant for functional outcome.

There are a few limitations of this study. First, this was a *post-hoc* analysis of a randomized trial that was not designed to determine an association of HT with functional outcome. Therefore, the results should be interpreted with caution. Second, not all 5-day follow-up CT scans were available. In 117 cases 24-hour CT scans were used to identify HT. It is possible that some of the patients who were identified with HT on a 24-hour CT had contrast staining which cannot be distinguished from a hemorrhage on a conventional 24-hour CT scan. Although these patients with contrast staining have a blood-brain barrier disruption, they might not all develop HT. Therefore, some patients might incorrectly be identified with HT, while these patients had in fact contrast staining. This might have influenced the data in two different ways. First, the occurrence of HI might be overestimated. Second, patients with contrast staining might not develop any hemorrhage and therefore would not have an impaired functional outcome which might have resulted in a more positive functional outcome for patients with HI. However, the rates of HI were not different between 24-hour and 5 day CT scans.

In conclusion, not only PH2 is relevant for functional outcome after an acute ischemic stroke, but even smaller types of HT might influence functional outcome. Still, it is complicated to determine their true impact on functional outcome. Future studies should focus on identifying patients with high risk characteristics and a suitable treatment that may reduce HT development. Treatment with thrombolytic agents is associated with an increased risk for HT. An upcoming trial (MR CLEAN-MED) that randomizes periprocedural antithrombotic drugs and aims to improve microvascular reperfusion might further improve our knowledge regarding HT risk.[28] Additionally, other upcoming trials that randomize treatment with thrombolytic agents (MR CLEAN-NO IV, SWIFT DIRECT, DIRECT-SAFE and DIRECT MT) might clarify whether EVT alone will reduce the risk of HT and improve functional outcome after AIS.[29–32]

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The association of hemorrhagic transformation after acute ischemic stroke due to large vessel occlusion, with functional outcome and treatment benefit, a meta-analysis of seven randomized controlled trials

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Key points

Question

What is the impact of hemorrhagic transformation after ischemic stroke on functional outcome? Does hemorrhagic transformation decrease benefit of endovascular treatment?

Findings

In this post hoc analysis, all hemorrhagic transformation subtypes were significantly associated with poor functional outcome. After additional adjustment for follow-up lesion volume, this association remained significant for HI2 and PH2 only. EVT effect was apparent for all HT subtypes, only patients with HI2 had less treatment benefit than patients without HT.

Meaning

Hemorrhagic transformation is associated with poor functional outcome in patients with ischemic stroke, but these patients still had benefit from endovascular treatment. Patients who carry an increased risk of HT could still benefit and should not be excluded from endovascular therapy.

Abstract

Introduction

It is unclear whether hemorrhagic transformation (HT) of cerebral infarction contributes to the poor functional outcomes or is simply an epiphenomenon of larger volume infarction. We evaluated the association of HT and follow-up lesion volume with functional outcome at 90 days after acute ischemic stroke. Additionally, we determined whether classification of patients by HT status post-EVT identified a group of patients with diminished endovascular treatment (EVT) effect.

Methods

We used the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials) data set, including seven randomized controlled trials on EVT compared with best medical care without EVT. All patients with follow-up imaging were included. Follow-up lesion volume (including infarct and hemorrhage) was assessed on CT or MRI. Patients with HT were classified according to the Heidelberg bleeding classification. We assessed functional outcome using the modified Rankin Scale 90 days after stroke onset. Ordinal logistic regression with adjustment for potential confounders was used to determine the association between HT and follow-up lesion volume with functional outcome. An interaction term was added to determine whether patients with HT still had benefit from EVT treatment.

Results

Of all included patients (n=1764), 35% had any degree of HT (n=611). HT was associated with a shift in the direction of poor functional outcome (hemorrhagic infarction type 1: adjusted common odds ratio (acOR):0.72 ,95% confidence interval (CI):0.55–0.92, hemorrhagic infarction type 2 (HI2): acOR:0.39,95%CI:0.3-0.5, parenchymal hematoma type 1: acOR:0.36,95%CI:0.23-0.56, and parenchymal hematoma type 2: acOR:0.11,95%CI:0.06-0.21). After adjustment for follow-up lesion volume, only hemorrhagic infarction type 2 (acOR:0.59,95%CI:0.45-0.76) and parenchymal hematoma type 2 (acOR0.43,95%CI:0.2-0.9) were associated with poorer functional outcome. Post-treatment classification of patients by HT type showed that the treatment effect of EVT was beneficial in all patients, but the magnitude of benefit was smaller in patients with HI2 (EVT interaction term for HI2: P <0.01).

Conclusions

In the pooled HERMES data, post-treatment HT identifies a group of acute ischemic stroke patients who more often had poor functional outcomes compared to those without HT. However, all patient subgorups still showed a treatment benefit of EVT.

Introduction

Hemorrhagic transformation (HT) is common after acute ischemic stroke (AIS) and is widely assumed to be causative for impaired functional outcome.[1] HT after reperfusion treatment (thrombolysis or EVT) occurs early and is detected early because of the routine use of next-day brain imaging. It occurs spontaneously as part of the natural history of ischemic stroke, but has a much higher prevalence after reperfusion therapies, both intravenous thrombolysis and endovascular thrombectomy (EVT) [1,2] HT is categorized clinically as either symptomatic or asymptomatic; symptomatic intracranial hemorrhage (sICH) means that the patient is clinically worse in association with hemorrhage. Radiologically, we classify HT as hemorrhagic infarction (HI) or parenchymal hematoma (PH).[3,4] Both types are further subdivided into minor and major subtypes, using the suffixes 1 and 2. There is a strong correlation between sICH clinically and PH2 radiologically; nearly all PH2 hemorrhages are symptomatic and most but not all sICHs are PH2-type.[5] Smaller HT, like HI1, HI2 and PH1 are less likely to be associated concurrently with acute neurological deterioration as they do not have a space occupying effect.[4]

Common belief is that only PH2 is important because HI1, HI2, PH1 are not associated with poor prognosis. However, analysis cohorts of patients treated with thrombolysis have suggested a small negative effect of all but HI1 hemorrhages.[6] Previous literature has shown HI might be associated with poorer long-term functional outcome even after adjustment for follow-up infarct volume.[7] This could be due to further damage to brain parenchyma in small hemorrhages since blood products can be neurotoxic.[8] Whether HI1 and HI2 within large infarcts have a negative impact on functional outcome after EVT remains unclear. Blood-brain barrier damage occurs after ischemia.[9] Subsequent reperfusion might cause leakage of blood through increased perfusion pressure, leading to HI.[9] While common belief suggests an association between reperfusion and HT, the opposite has generally been shown: early reperfusion is associated with a reduced chance of HT, implying that the timing of reperfusion might be relevant.[10] HI and PH are more common in patients with large ischemic core, and the association of large core and poor outcome might confound the association between HI and outcome.[10]

This study aimed to evaluate the association of HT subtypes and follow-up lesion volume with functional outcome at 90 days after AIS. Additionally, we determined whether patients with HT still had benefit of EVT.

Methods

Patients

We included all patients with follow-up imaging from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration.[11] HERMES comprises pooled individual-patient data from seven randomized controlled trials that assessed the efficacy and safety of EVT in addition to best medical treatment (intervention group) compared to best medical treatment without EVT (control group) for an acute ischemic stroke due to a large vessel occlusion in the anterior circulation.[12–18] Best medical treatment included intravenous alteplase 0.9 mg/kg if patients were eligible according to the local guidelines. The seven trials (MR CLEAN trial [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands], EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial], ESCAPE [Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times], SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment], REVASCAT [Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset], PISTE [Pragmatic Ischaemic Thrombectomy Evaluation] and THRACE [Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke]) were published between 2015 and 2017.[12–18] Clinical data of all trials were pooled by the independent statistician of the HERMES collaboration (SB). Written informed consent was acquired from all included patients by the individual trials.[12–18] Execution of all trials was approved by the relevant Ethical Review Boards.[12–18]

Imaging

The imaging data of all HERMES trials were pooled and centrally reviewed by an independent core laboratory.[11] Hemorrhagic transformation was classified according to the Heidelberg Bleeding classification on follow-up CT or MRI dependent on availability.[4] Follow-up lesion volume was measured automatically with validated software.[19] As previously described, follow-up lesion volume included infarct volume, parenchymal hemorrhage, cerebral edema even when extending in the contralateral hemisphere.[20] Intraventricular hemorrhage and subarachnoid hemorrhage were not included in follow-up lesion volume.[19] Reperfusion was centrally assessed with the mTICI (modified thrombolysis in cerebral infarction) score on angiography images at the end of the endovascular

procedure; mTICI 2b and 3 was considered as successful reperfusion.

In the HERMES database follow-up imaging was acquired using CT and/or MRI which was dependent on availability. MRI is more sensitive for detecting HT and to minimize the difference between CT and MRI, HT was first classified on CT.[21] When CT was not available, HT was classified on MRI. Available MRI sequences were FLAIR, DWI and SWI or T2*.

Outcomes

The primary outcome of this study was functional outcome on an ordinal scale defined by the modified Rankin Scale (mRS) at approximately 90 days after stroke onset.

We used two secondary outcomes for which we dichotomized the mRS; (1) functional independence (mRS 0-2 vs. mRS 3-6) and (2) mortality (mRS 0-5 vs. mRS 6).

Statistical analysis

Univariate and multivariable ordinal logistic regression was used to determine the association of HT with functional outcome (ordinal mRS), resulting in an (adjusted) common odds ratio ([a]cOR) with 95% confidence interval (95%CI). A cOR<1 represents an odds with a shift towards poor outcomes. Univariable and multivariable binary logistic regression was used to determine the association of HT with functional independence and mortality, resulting in (adjusted) odds ratios ([a]OR) with 95%CI. The following adjustment variables were included as potential confounders; age, diabetes mellitus, systolic blood pressure, intravenous thrombolysis, endovascular treatment, time from stroke onset to randomization, previous stroke and atrial fibrillation. In order to assess the independence of HT effects from follow-up lesion volume, continuous lesion volume (in milliliters) was added as adjustment variable. In separate models, an interaction term between HT and treatment group (intervention vs. control) was added to determine whether EVT benefit differed for patients with HT.

Means with standard deviation (SD) were used to summarize normally distributed variables; for non-normally distributed variables, median and interquartile range (IQR) were used. Counts and percentages were used for categorical variables. All statistical analyses were performed with R (tables and summaries), {R Core Team [V.3.5]; R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria} or SAS version 9.4 (statistical modeling).

Results

Among 1764 patients who were included in the HERMES trials, 611 patients had HT (35%); 212 (12%) were classified with HI1, 282 (16%) HI2, 74 (4%) with PH1 and 43 patients (2%) were classified with PH2.

Patient characteristics are presented in Table 1. Patients with HT had higher baseline National Institutes of Health Stroke Scale (NIHSS) than patients without HT (HI1: median 17 IQR [15-21], HI2: 18 [15-21], PH1: 18 [15-20], PH2: 18 [15-20] vs no HT: 17 [13-20]). Patients with PH2 more often had hypertension (74% vs. 57%) and higher systolic blood pressure at baseline ((median, [IQR]) 149 [141-161] vs. 142 [128-160], mmHg) compared to patients without HT. Patients with PH2 had more often a collateral grade of 0 compared to patients without HT (31% vs 1%). Patients with HT had larger follow-up lesion volumes than patients without HT ((median, [IQR]) HI1: 40 [20-119], HI2: 88 [39-194], PH1: 126 [54-247], PH2: 176 [116-293] vs. no HT: 26 [8-89], ml).

Table 1. Characteristics of patients with and without hemorrhagic transformation

	No HT n=1128	HI1 n=212	HI2 n=282	PH1 n=74	PH2 n=43	Not available
EVT, % (n)	46% (517)	51% (107)	60% (168)	47% (35)	58% (25)	
intravenous thrombolysis % (n)	89% (1002)	90% (190)	88% (249)	95% (70)	93% (40)	
Age (years), Mean ± SD	65 ± 14	65 ± 15	65 ± 13	68 ± 11	69 ± 11 (43)	0.2% (3)
NIHSS at baseline, Median] (IQR)	[17] (13,20)	[17] (15,21)	[18] (15,21)	[18] (15,20)	[18] (15,20)	0.7% (12)
Female sex, % (n)	48% (543)	49% (104)	47% (131)	35% (26)	35% (15)	0.1% (2)
Prior stroke, % (n)	10% (116)	13% (27)	8% (22)	12% (9)	21% (9)	0.7% (13)
Hypertension, % (n)	57% (634)	52% (110)	52% (146)	64% (47)	74% (32)	
Atrial fibrillation, % (n)	30% (231)	37% (58)	42% (95)	31% (18)	42% (14)	24% (424)
Diabetes mellitus, % (n)	15% (173)	18% (39)	16% (44)	23% (17)	23% (10)	0.5% (8)
Systolic blood pressure (mmHg), [Median] (IQR)	[142] (128,160)	[144] (130,160)	[144] (130,159)	[152] (131,161)	[149] (141,161)	0.6% (11)
Onset to randomization time in minutes, [Median] (IQR)	[175] (134,235)	[199] (147,265)	[207] (164,278)	[185] (147,248)	[211] (164,243)	0.5% (8)
ASPECTS at baseline, [Median] (IQR)	[8] (7,9)	[8] (7,9)	[7] (6,8)	[8] (7,9)	[7] (7,9)	2% (27)
Occlusion location, % (n)						7% (114)
ICA	25% (257)	28% (58)	35% (92)	23% (16)	28% (11)	
M1	67% (695)	67% (137)	59% (157)	68% (47)	63% (25)	
M2	9% (90)	5% (10)	7% (18)	9% (6)	10% (4)	
Other	0.2% (2)	0% (0)	0% (0)	0% (0)	0% (0)	
Clot burden score, [Median] (IQR)	[4] (4,6)	[4] (3,6)	[4] (1,4)	[4] (4,6)	[4] (4,6)	6% (108)
Collateral grade, % (n)						27% (470)
0	1% (8)	1% (2)	1% (3)	2% (1)	31% (11)	
1	14% (110)	16% (26)	18% (38)	17% (10)	43% (15)	
2	43% (347)	41% (67)	45% (95)	48% (28)	26% (9)	
3	42% (336)	42% (68)	36% (75)	34% (20)	31% (11)	
mTICI 2b/3, % (n)	76% (326)	77% (72)	70% (107)	57% (17)	76% (16)	58% (1012)
Follow-up lesion volume (ml), [Median] (IQR)	[26] (8,89)	[40] (20,119)	[88] (39,194)	[126] (54,247)	[176] (116,293)	6% (99)

Abbreviations: HT, Hemorrhagic Transformation; HI1, Hemorrhagic Infarction type 1; HI2, Hemorrhagic Infarction type 2; PH1, Parenchymal Hematoma type 1; PH2, Parenchymal Hematoma type 2; EVT, Endovascular Therapy; tPA, tissue Plasminogen Activator; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Carotid Artery; M1, medial cerebral artery segment 1; M2, medial cerebral artery segment 2; mTICI, modifiedThrombolysis In Cerebral Infarction; SD, standard deviation; IQR, interquartile range.

Primary outcome

Functional outcomes of patients with HT are presented in Figure 1. Sixty-five percent of patients with PH2 died within 90 days of incident stroke. All HT subtype were significantly associated with a graded decline in functional outcome by severity of HT, in both the unadjusted and adjusted analysis (Table 2.). After additional adjustment for follow-up lesion volume, only HI2 and PH2 remained statistically significantly associated with poor functional outcome (HI2: acOR 0.59, 95%CI 0.45-0.76; PH2: acOR 0.43, 95%CI 0.20-0.90).

Figure 2 shows functional outcomes of patients with HT per treatment group. There was statistically significant treatment interaction for HI2 ($p<0.01$), indicating that patients with HI2 had less benefit from EVT (association of HI2 with functional outcome in intervention group: acOR 0.27, 95%CI: 0.20-0.38 and control group: acOR 0.59, 95%CI 0.41-0.85).

Secondary outcomes

All HT subtypes were significantly associated with a smaller chance of functional independence in both the unadjusted and adjusted analyses. After additional adjustment for follow-up lesion volume, HI2 was the only subtype significantly associated with a lower chance of functional independence (aOR 0.53, 95% CI 0.36-0.78).

HI2 and PH2 were both significantly associated with mortality in the adjusted analyses (HI2: aOR 1.94, 95%CI 1.34-2.81, PH2: aOR 14.04, 95%CI 6.65-29.64). However, after additional adjustment for follow-up lesion volume, PH2 was the only HT subtype that remained significantly associated with mortality (aOR 5.72, 95%CI 2.28-14.37).

Table 2. Adjusted and unadjusted odds ratios of the association of all HT subtypes (in comparison to patients without HT) with functional outcome.

	Unadjusted OR and 95% CI	Adjusted OR and 95%CI*	Adjusted* OR and 95%CI including follow-up lesion volume	P value of interaction term (EVT)
Primary outcome (full mRS scale)				
HI1	0.73 (0.57, 0.94)	0.72 (0.55, 0.92)	0.84 (0.64, 1.10)	0.25
HI2	0.44 (0.34, 0.55)	0.39 (0.30, 0.50)	0.59 (0.45, 0.76)	<0.01
PH1	0.35 (0.22, 0.54)	0.36 (0.23, 0.56)	0.88 (0.54, 1.44)	0.17
PH2	0.11 (0.06, 0.22)	0.11 (0.06, 0.21)	0.43 (0.20, 0.90)	0.78
Secondary outcome (functional independence [mRS 0-2])				
HI1	0.67 (0.49, 0.91)	0.62 (0.44, 0.86)	0.77 (0.53, 1.12)	0.22
HI2	0.36 (0.26, 0.49)	0.29 (0.21, 0.41)	0.53 (0.36, 0.78)	0.29
PH1	0.33 (0.19, 0.59)	0.31 (0.17, 0.58)	0.94 (0.46, 1.95)	0.04
PH2	0.08 (0.03, 0.27)	0.07 (0.02, 0.24)	0.43 (0.11, 1.61)	0.98
Secondary outcome (mortality [mRS 6])				
HI1	0.95 (0.60, 1.51)	0.92 (0.57, 1.50)	0.72 (0.41, 1.26)	0.69
HI2	1.83 (1.30, 2.59)	2.06 (1.41, 3.01)	1.30 (0.84, 2.00)	0.05
PH1	2.03 (1.14, 3.62)	1.77 (0.95, 3.31)	0.58 (0.27, 1.25)	0.13
PH2	13.95 (7.11, 27.35)	15.28 (7.17, 32.56)	5.72 (2.28, 14.37)	0.87

*Adjusted for potential confounders: age, diabetes mellitus, systolic blood pressure, intravenous thrombolysis, endovascular treatment, time from stroke onset to randomization, previous stroke, atrial fibrillation. Subjects without verifiable follow-up imaging were excluded from this analysis.

Abbreviations: EVT, endovascular treatment; HI1, Hemorrhagic Infarction type 1; HI2, Hemorrhagic Infarction type 2; PH1, Parenchymal Hematoma type 1; PH2, Parenchymal Hematoma type 2; mRS, modified Rankin Scale;

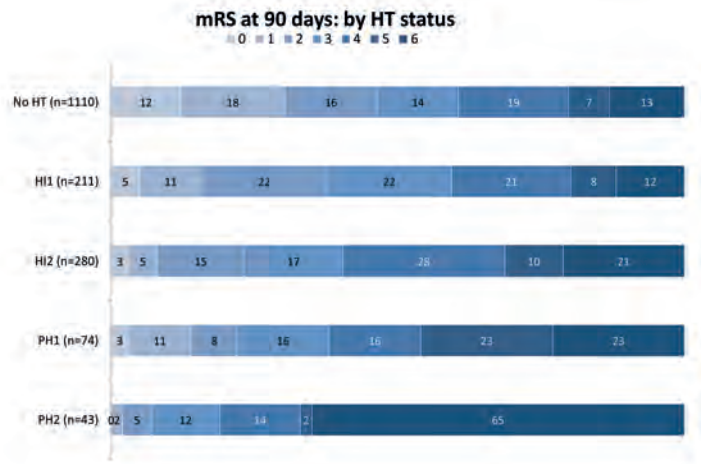

Figure 1. Functional outcomes at 90 days of patients with HT.

Abbreviations: HI1/2; hemorrhagic infarction type 1/2; HT, hemorrhagic transformation; mRS, modified Rankin Scale score; PH1/2, parenchymal hematoma type 1/2.

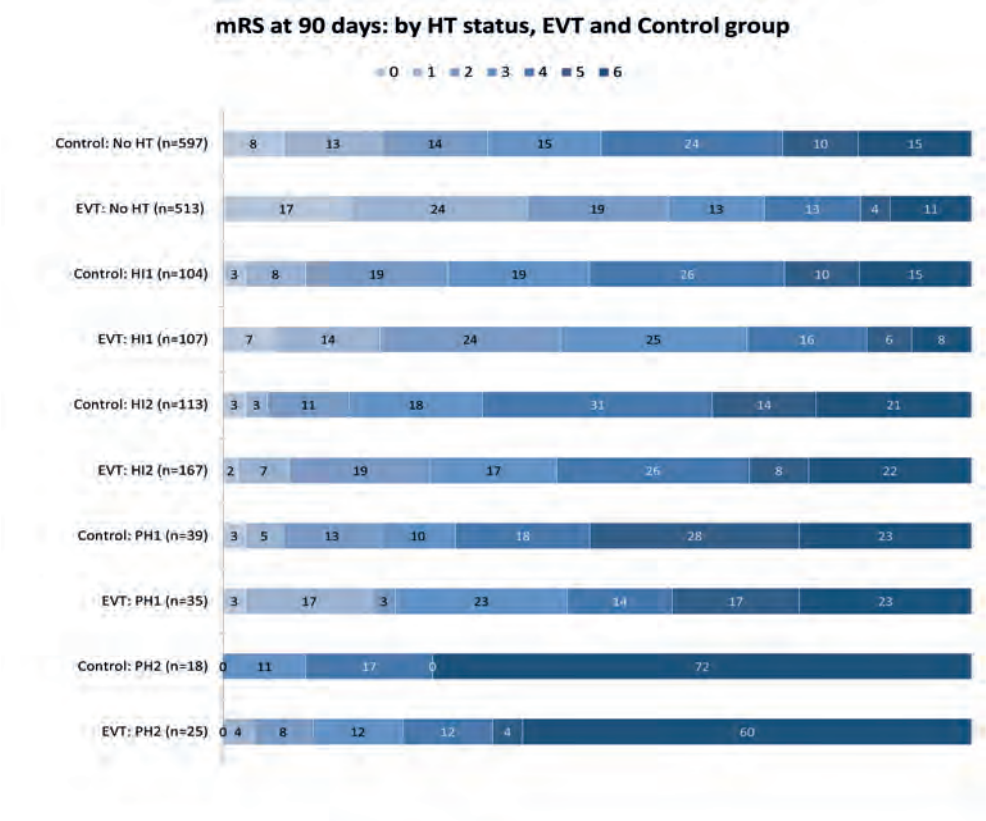

Figure 2. Functional outcomes at 90 days of patients with HT, by received treatment.

Treatment consisted of EVT in addition to best medical treatment (intervention group) or best medical treatment only (control group). Best medical treatment included intravenous alteplase for eligible patients. Abbreviations: EVT, endovascular treatment; HI1/2; hemorrhagic infarction type 1/2; HT, hemorrhagic transformation; mRS, modified Rankin Scale score; PH1/2, parenchymal hematoma type 1/2.

Discussion

All HT subtypes (HI1, HI2, PH1, PH2) were associated with worse functional outcomes compared to patients without HT. However, HI2 and PH2 were the only HT subtypes that remained associated with functional outcome after additional adjustment for follow-up lesion volume. EVT was beneficial regardless of subsequent HT, however the benefit was smaller for patients who developed HI2. Only PH2 was associated with mortality after adjustment for follow-up lesion volume.

Previous studies have also shown that HT is associated with poor functional outcome.[22–26] While frank hematoma development was associated with poor outcomes in most studies, reported results regarding petechial hemorrhages vary widely. A previous study showed that PH1 and PH2 but not HI1 and HI2 were associated with functional outcome.[25] This contrasts with our findings; in the HERMES data, only HI2 and PH2 were significantly associated with a poor functional outcome. Functional outcomes of patients with either HI2 or PH1 were similar in our study, although PH1 was not statistically significantly associated with poor outcomes after adjustment for follow-up lesion volume. This could be partially explained by a relatively small group of patients with PH1 in this study and large group of patients with HI2.[25] Additionally, patients with PH1 had larger lesion volumes than patients with HI2 most likely due to the hematoma, and therefore we might have over adjusted when adjusting for lesion volume that included both hemorrhage and infarct. Despite possible over adjusting with follow-up lesion volume, PH2 was associated with functional outcome which might be explained by the mass effect a PH2 has on (healthy) brain tissue which is not taken into account with follow-up lesion volume. Another study reported that all HT subtypes were associated with poor functional outcomes, but importantly in contrast with our study, they did not adjust for lesion volume, potentially explaining the difference between these studies as larger infarcts are more likely to contain hemorrhagic transformation.[26]

Follow-up lesion volume attenuated the association of HI1 and PH1 with functional outcome. In case of HI1, it is likely that the association with poor outcome is not entirely caused by hemorrhage but is probably for the most part due to a large infarct. Therefore, HI1 is likely to be asymptomatic and an epiphenomenon or simply part of the natural history of stroke. In the case of PH1 the mass effect is, by definition, not substantial and in this analysis we adjusted for total follow-up lesion volume (including hemorrhage volume) which may have over-adjusted and disproportionately impacted the association of PH1 with outcome. Although HI2 has been regarded as less harmful than PH1, we found that it was associated with poorer functional outcome independent of lesion volume.[4] This may indicate HI2 is more harmful than expected or HI2 is a marker of other variables associated with functional outcome for which we did not account for. For example, compared to all other patients, patients with HI2 had more ICA occlusions which are associated with less favorable outcomes than the usually more common M1 occlusions.[27] Altogether, adjusting for follow-up lesion volume would be justified in case of HI1 and HI2 but not when a space occupying hematoma (PH1 and PH2) is present, since the hematoma is included in the lesion volume it will result in over-adjustment.

A previous HERMES sub-study showed that follow-up lesion volumes of patients treated with EVT were significantly smaller than patients in the control group.[28] With smaller lesion volumes in the EVT group, it would be sensible that less HT would occur in the EVT group. However, not only did overall HT occur evenly between the groups, more HI2 occurred in the EVT group compared to the control group. It is not likely that this surprising result is caused by some sort of impact of EVT on HT because the beneficial effect of EVT was apparent in all HT subgroups. However, the occurrence of HT in the EVT group might be explained by several reasons. First, HT and contrast staining can be difficult to distinguish and therefore contrast staining might have been classified as HT which is more likely in the EVT group.[29] Second, some HT might have occurred as a result of a procedural complication during EVT. Last, the overall follow-up lesion volumes in patients with any HT were larger than patients without HT.

Although all HT subtypes were negatively associated with functional independence, this study clearly shows the devastating effect a PH2 has on both survival and functional outcome, as it was the only type of HT that was associated with increased mortality. The consistent strong association of HI2 with functional outcome, regardless of follow-up lesion volume, compared to the other subtypes is of interest. Moreover, only patients with HI2 had (slightly) less treatment benefit from EVT. Even though functional outcomes are negatively influenced by HT and despite the devastating effect of PH2, patients with any form of HT still had benefit from treatment with EVT. Therefore, patients that might carry an increased risk of HT should not be excluded from treatment with EVT if they are eligible.

An important strength of this study is that we used pooled data from seven randomized trials, affording the unique possibility to study EVT benefit without confounding by indication, and assess potential treatment interactions more reliably. More-over, all imaging data were centrally assessed by an independent blinded core-lab, and follow-up imaging was available regardless of symptomatology or clinical suspicion of hemorrhagic transformation. Further, the reliable estimation of follow-up lesion volume allowed us to adjust for this potential confounder. Several limitations exist. Most importantly, the post-hoc nature of this study predisposes to a higher likelihood of false positive findings. These results should therefore be interpreted with caution. Second, since our follow-up lesion volume measure includes hemorrhage, adjustment for this variable might result in false negative findings due to co-linearity. Third, although for most patients CT imaging was available to classify HT, when it was not available MR imaging was used. This could

have resulted in an increased number of patients with HI1 and an overestimation of some HT since MRI is more sensitive than CT and hemorrhage can appear larger due to the susceptibility artifact.

In conclusion, in the pooled HERMES data, patients with HT after acute ischemic stroke had worse functional outcomes compared to those without HT. This association was independent of lesion volume for HI2 and PH2.

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3

Added prognostic value of hemorrhagic transformation quantification in patients with acute ischemic stroke

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Frontiers in Neurology. November 2020, 10;11:582767

Abstract

Introduction and aim

Hemorrhagic transformation (HT) occurs frequently after acute ischemic stroke and negatively influences functional outcome. Usually, HT is classified by its radiological appearance. Discriminating between the subtypes can be complicated and inter-observer variation is considerable. Therefore, we aim to quantify rather than classify hemorrhage volumes and determine the association of hemorrhage volume with functional outcome in comparison to the ECASS II classification.

Patients and methods

We included patients from the MR CLEAN trial with follow-up imaging. Hemorrhage volume was estimated by manual delineation of the lesion and HT was classified according to the ECASS II classification (petechial hemorrhagic infarction type 1 (HI1) and 2 (HI2), parenchymal hematoma type 1 (PH1) and 2 (PH2)) on follow-up CT 24 hours to 2 weeks after treatment. We assessed functional outcome using the modified Rankin Scale (mRS) 90 days after stroke onset. Ordinal logistic regression with and without adjustment for potential confounders was used to describe the association of hemorrhage volume with functional outcome. We created regression models including and excluding total lesion volume as a confounder.

Results

We included 478 patients. Of these patients, 222 had HT. Median hemorrhage volume was 3.37 ml [0.80-12.6] and per HT subgroup; HI1: 0.2[0.0-1.7], HI2: 3.2[1.7-6.1], PH1: 6.3[4.2-13] and PH2: 47[19-101]. Hemorrhage volume was associated with functional outcome (acOR 0.83,95CI:0.73-0.95) but not anymore after adjustment for total lesion volume (acOR:0.99,95%CI:0.86-1.15, per 10 ml). Hemorrhage volume in patients with PH2 was significantly associated with functional outcome after adjustment for total lesion volume (acOR:0.70,95%CI:0.50-0.98).

Conclusion

Hemorrhagic transformation volume is associated with functional outcome in patients with acute ischemic stroke but not indepdent of total lesion volume. The extent of a PH2 was associated with outcome, suggesting that measuring hemorrhage volume only provides additional benefit in prediction of outcome when a PH2 is present.

Introduction

Hemorrhagic transformation (HT) commonly occurs as natural progression or as complication of reperfusion therapy for acute ischemic stroke (AIS).[1,2] Large, but also small HT subtypes were found to be associated with poor functional outcome.[3] Incidence varies and differences in definition of HT between studies complicate comparisons between studies. Usually, HT is classified according to the ECASS II (European Cooperative acute Stroke Study II) classification based on radiological appearance.[4] This classification divides HT in four groups; hemorrhagic infarction type 1 (HI1), which is defined as small petechiae along the margins of the infarct; hemorrhagic infarction type 2 (HI2) defined as confluent petechiae within the infarcted area but no space-occupying effect; parenchymal hematoma type 1 (PH1) as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal hematoma type 2 (PH2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect.[4]

The ECASS classification only takes hemorrhage volume relative to the infarct volume in account when a PH is present and therefore small hemorrhages could be classified as PH2 when the infarct is small. The opposite is true when large hematomas develop within massive infarcts. These hematomas are not classified as PH2 when their relative size is less than 30% of the infarct while their objective size could be more than 40 ml. These hemorrhages might lead to symptomatic ICH (sICH). However, according to the Heidelberg Bleeding classification ICH other than PH2 might be symptomatic but it is advised not to classify those hemorrhages as sICH.[5]

Furhter, agreement between observers for HT is only fair, as discriminating between HT subtypes can be challenging.[6,7] This limited agreement might contribute to a variation in reported incidence of HT between studies.

As an alternative to the current rather crude classification of HT, we aim to quantify the hemorrhage volume of patients with HT and to assess its prognostic value by determining the association of hemorrhage volume with functional outcome in comparison to the ECASS II classification. Additionally, we determine whether hemorrhage volumes smaller than 30% of lesion volume might have been symptomatic.

Methods

We included all patients with follow-up imaging from the MR CLEAN trial.[8] The MR CLEAN trial was a multicenter randomized controlled trial that assessed the safety and efficacy of endovascular therapy (EVT) compared with usual care after acute ischemic stroke due to a large vessel occlusion. The MR CLEAN study protocol has been described previously.[9]

We assessed potential HT on follow-up CT scans that were acquired approximately 5 days after inclusion. When these scans were not available, 24-hour follow-up CT scans were examined. Hemorrhage volume was measured by a trained observer (KRK) by manually delineating the hemorrhages using ITK-SNAP (version 3.4.0). Hemorrhage volume consists of all hemorrhage present on the CT-scan including concomitant intraventricular hemorrhage and subarachnoid hemorrhage. HT was classified according to the ECASS II classification.[4] In the MR CLEAN trial sICH was classified as neurologic deterioration with an increase of more than 4 points on the national institute of health stroke scale (NIHSS) and hemorrhage visible on imaging.[8]

Functional outcome was assessed at approximately 90 days after stroke onset and attributed with a score according to the modified Rankin Scale (mRS). The mRS ranges from 0 to 6, where 0 indicates no symptoms and 6 indicates death.

Statistical analysis

Mean and SD are used to summarize normally distributed variables, for non-normal distributed variables the median and IQR are used. We compared hemorrhage volumes between all HT subtypes using a Kruskal Wallis test. The association of hemorrhage volume with functional outcome was assessed using ordinal logistic regression analysis using the full mRS scale as outcome measure. The association of hemorrhage volume with functional outcome was estimated as a common odds ratio (cOR) per 10 ml increase expressing the relative risk of a shift in the direction of good outcomes for every 10 ml of hemorrhage. A cOR <1 indicates a shift towards worse outcomes on the mRS. Three models were made; in the first model we assessed the association of hemorrhage volume with functional outcome. In the second model, we assessed the association of hemorrhage volume and all HT subgroups with functional outcome, and the third model described the association of hemorrhage volume and sICH with functional outcome. We adjusted every model for potential confounders; diabetes mellitus, systolic blood pressure (measured on admission), intravenous thrombolysis (IVT), EVT, time from onset to randomization, history

of ischemic stroke, age, atrial fibrillation, and baseline NIHSS (National Institutes of Health Stroke Scale). We conducted an additional subgroup analysis to assess the association of hemorrhage volume with functional outcome per HT subgroup.

Follow-up lesion volume includes both infarct and hemorrhage volume and was estimated using a validated automated measurement.[10] In some patients with a large PH, the lesion volume is equal to the hemorrhage volume and the actual infarct is masked by hemorrhage. Adjusting for follow-up lesion volume might result in an underestimation of the impact of hemorrhage volume. However, HT is more likely occur within large infarcts and not adjusting for lesion volume could overestimate the impact of HT. Therefore, we conducted analyses with additional adjustment for follow-up lesion volume. We conducted the statistical analysis using R (R Core Team (V.4.0.0 (2020); R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; used packages rms,[11] ggplot2,[12] and tableone[13]).

Results

Of all the patients with follow-up imaging (n=478), 222 had HT. Of these 222 patients with HT, we measured hemorrhage volumes of 219 patients (Figure 1). Hemorrhage volumes of three patients could not be measured due to insufficient image quality.

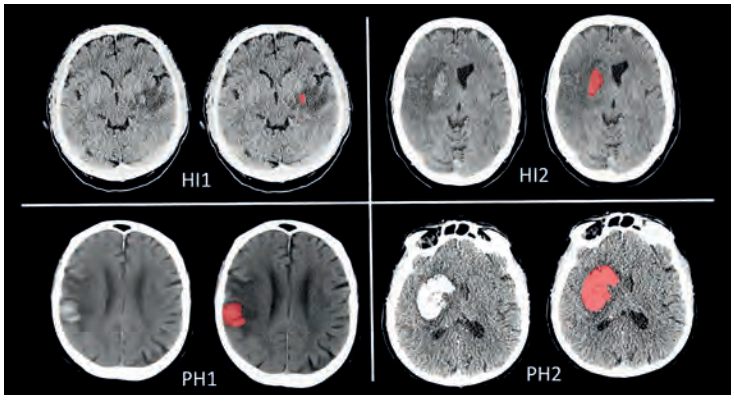

Figure 1: Quantification of Hemorrhagic Transformation per subtype.

Hemorrhage volumes differed between HT subgroups ($p<0.001$). Patients with PH2 had the largest hemorrhage volumes (46.8 [IQR: 19-101] ml) (table 1).

Table 1. Patient characteristics

	No HT (n=256)	HI1 (n=76)	HI2 (n=71)	PH1 (n=36)	PH2 (n=39)
Hemorrhage volume, ml – median [IQR]	0 [0-0]	0.17 [0-1.7]	3.2 [1.7-6.1]	6.3 [4.2-12.9]	46.8 [18.7-100.7]
EVT – no. (%)	111 (43.4)	28 (36.8)	35 (49.3)	21 (58.3)	17 (43.6)
Treatment with IV alteplase – no. (%)	228 (89.1)	66 (86.8)	65 (91.5)	33 (91.7)	36 (92.3)
Age – mean (SD)	64 (14.3)	65 (12.6)	66 (12.9)	64 (14.8)	68 (14.1)
Baseline NIHSS – mean (SD)	17 (5.7)	19 (6.1)	18 (4.4)	18 (4.3)	19 (4.8)
History of ischemic stroke – no. (%)	26 (10.2)	7 (9.2)	8 (11.3)	1 (2.8)	9 (23.1)
Atrial fibrillation – no. (%)	58 (22.7)	17 (22.4)	25 (35.2)	15 (41.7)	14 (35.9)
Diabetes mellitus – no. (%)	27 (10.5)	13 (17.1)	9 (12.7)	5 (13.9)	7 (17.9)
Systolic blood pressure – mean (SD)	143 (22.4)	144 (26)	142 (27.5)	153 (23.6)	160 (31.4)
Time from stroke onset to randomization per minute – median [IQR]	193 [147-254]	217 [148-258]	207 [158-281]	213 [165-278]	223 [181-265]
Follow-up lesion volume – median [IQR]	47 [18-118]	132 [58-207]	120 [78-243]	172 [97-274]	165 [93-323]

Abbreviations: EVT, endovascular treatment; HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; NIHSS, national institute of health stroke scale; IQR, interquartile range

Hemorrhage volume was significantly associated with worse functional outcomes in the unadjusted and adjusted analysis (common odds ratio (cOR) 0.75, 95% confidence interval (CI) 0.67 to 0.83) and (acOR 0.77, 95%CI: 0.69 to 0.87 per 10 ml) (Figure 2). After additional adjustment for follow-up lesion volume the association was weaker (acOR) 0.90 95% CI 0.80 to 1.02)(table 2, Model 1).

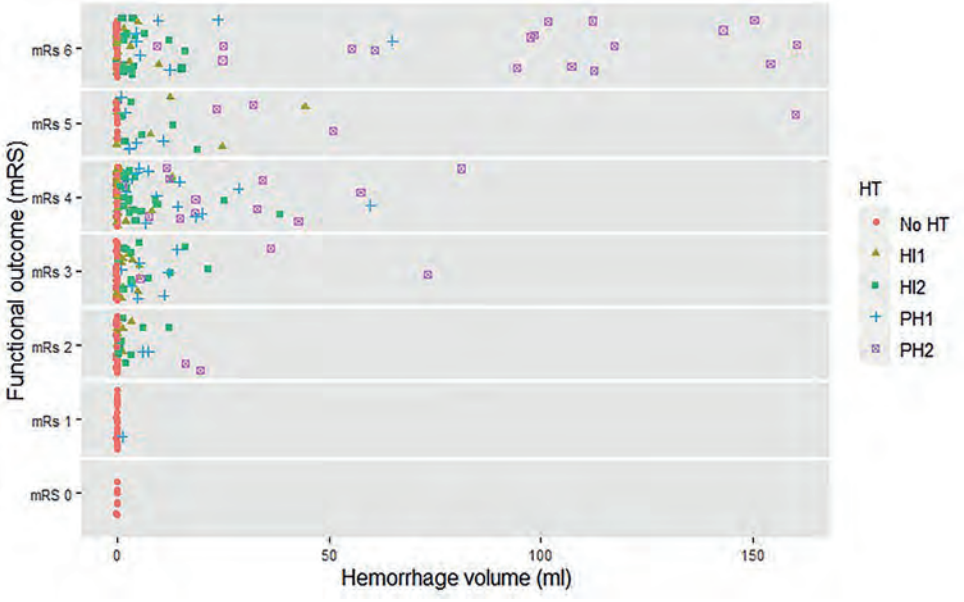

Figure 2. Hemorrhage volume and functional outcome per HT subgroup.

Table 2. Adjusted and unadjusted OR's of the association of hemorrhage volume in ml with functional outcome

Model		Unadjusted OR and 95%CI	Adjusted OR and 95%CI	Adjusted OR and 95%CI (with FLV)
1	Hemorrhage volume, per 10 ml	0.75 (0.67 to 0.83)	0.77 (0.69 to 0.87)	0.90 (0.80 to 1.02)
2	Hemorrhage volume, per 10 ml	0.79 (0.69 to 0.90)	0.83 (0.73 to 0.95)	0.99 (0.86 to 1.15)
	HI1	0.42 (0.27 to 0.65)	0.56 (0.36 to 0.89)	0.68 (0.42 to 1.06)
	HI2	0.40 (0.24 to 0.64)	0.44 (0.27 to 0.71)	0.58 (0.34 to 0.96)
	PH1	0.46 (0.25 to 0.85)	0.41 (0.22 to 0.78)	0.72 (0.37 to 1.41)
	PH2	0.55 (0.23 to 1.31)	0.50 (0.20 to 1.24)	0.37 (0.14 to 0.98)
3	Hemorrhage volume, per 10 ml	0.83 (0.73 to 0.95)	0.83 (0.73 to 0.95)	0.94 (0.80 to 1.09)
	sICH	0.31 (0.12 to 0.78)	0.45 (0.17 to 1.17)	0.69 (0.23 to 2.07)

The association of hemorrhage volume in ml with the full scale mRS score.

This table lists the association of hemorrhage volume with the full scale mRS score.

Adjusted for HT classification, atrial fibrillation, baseline NIHSS, intravenous thrombolysis, diabetes mellitus, time from stroke onset to randomization, age, endovascular therapy, previous stroke, systolic blood pressure (measured on admission). An additional analysis was conducted with follow-up lesion volume included in the adjusted analysis.

In model 2 and 3, no HT and no sICH was used as reference level when asessing the association of HT subgroups and sICH with functional outcome.

Abbreviations: FLV, Follow-up lesion volume; HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale.

In model 2, the analysis that included hemorrhage volume and all HT subgroups, hemorrhage volume and all HT subgroups except PH2 with no HT as reference level were significantly and independently associated with functional outcome in the adjusted and unadjusted analysis. After additional adjustment for follow-up lesion volume only HI2 and PH2 were associated with functional outcome (acOR 0.57, 95%CI 0.34 to 0.95 and acOR 0.36, 95%CI 0.14 to 0.97, respectively).

Subgroup analysis

Hemorrhage volume in patients with PH2 was significantly associated with functional outcome in the adjusted analysis including follow-up lesion volume (acOR 0.70, 95%CI 0.50 to 0.98). This association was not observed in the other HT subtypes (figure 3).

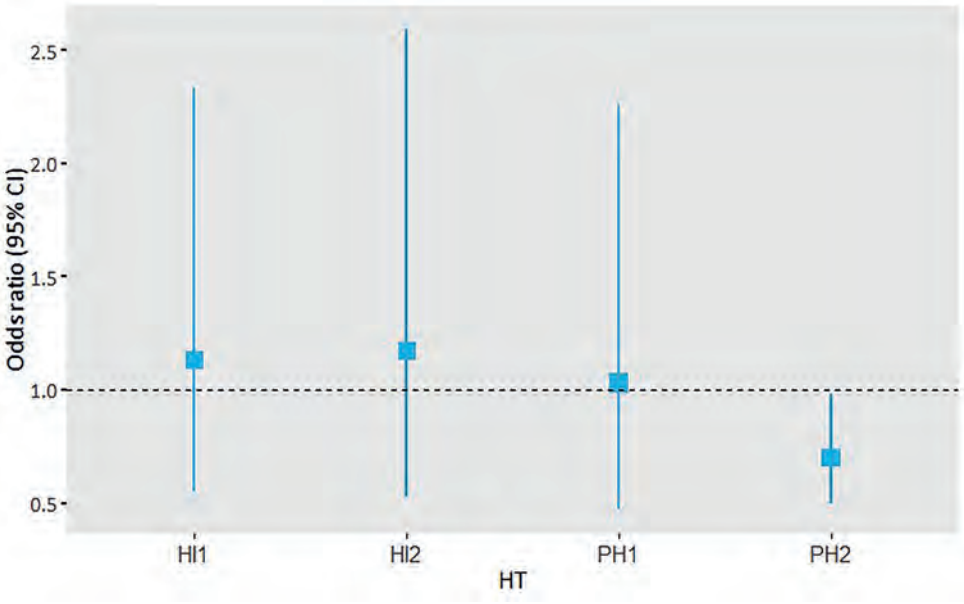

Figure 3. Adjusted OR and 95%CI of the subgroup analysis of hemorrhage volume and its association with functional outcome per HT subgroup.

sICH

35 patients with HT were classified as sICH (example in figure 4) . Median hemorrhage volume of patients with sICH was 53 [24-106] ml. Of those patients with sICH, 14 had hemorrhages < 30% of lesion volume. Some of these hemorrhages likely caused symptoms, while in some sICH not only hemorrhage would have caused symptoms but

infarct growth probably contributed to the neurological deterioration.
In model 3, hemorrhage volume and sICH were both significantly associated with functional outcome (cOR 0.83, 95%CI 0.73 to 0.95) and (cOR 0.31, 95%CI 0.12 to 0.78), respectively in the unadjusted analysis. In the adjusted analyses, sICH was not significantly associated with functional outcome. (acOR 0.45, 95%CI 0.17 to 1.17)(Table 2). After additional adjustment for follow-up lesion volume the association of hemorrhagic volume with functional outcome was attenuated.

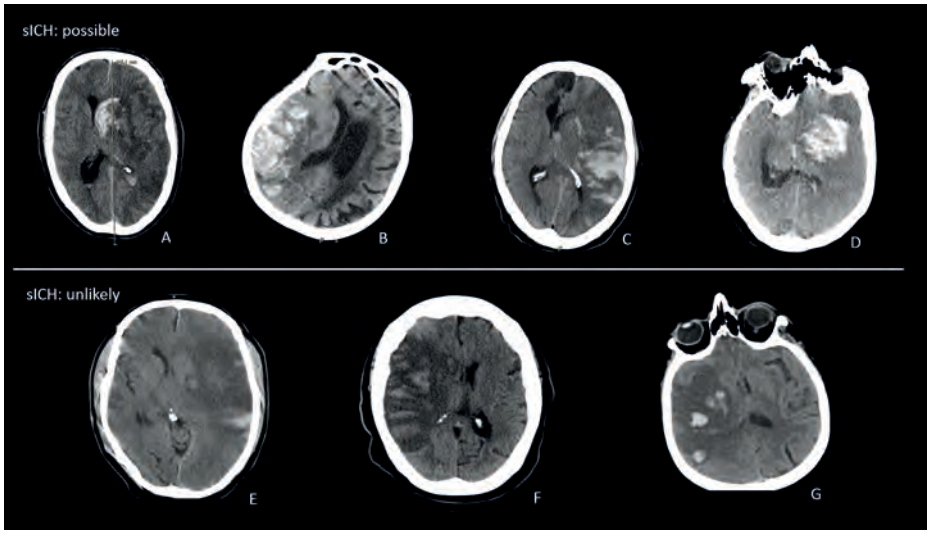

Figure 4. Examples of possible and unlikely sICH with hemorrhage volume < 30% of lesion volume.

A: hemorrhage volume: 65 ml, lesion volume: 279 ml, hemorrhage (%): 24%

B: hemorrhage volume: 61 ml, lesion volume: 275 ml, hemorrhage (%): 22%

C: hemorrhage volume: 102 ml, lesion volume: 423 ml, hemorrhage (%): 24%

D: hemorrhage volume: 51 ml, lesion volume: 347 ml, hemorrhage (%): 15%

E: hemorrhage volume: 5 ml, lesion volume: 411 ml, hemorrhage (%): 1%

F: hemorrhage volume: 13 ml, lesion volume: 215 ml, hemorrhage (%): 6%

G: hemorrhage volume: 12 ml, lesion volume: 191 ml, hemorrhage (%): 6%

Discussion

We have shown that hemorrhage volume as well as the ECASS classification are associated with functional outcome independently of each other. In the adjusted analysis, hemorrhage volume was associated with functional outcome and PH2 was not associated with functional outcome. This was also seen in the analysis with sICH. However, in the

adjusted analysis that included follow-up lesion volume hemorrhage volume was not associated with functional outcome. In the subgroup analysis, only hemorrhage volume of PH2 was associated with functional outcome.

Previous studies suggested that hemorrhage volume could be more appropriate than a radiological classification as it gives a more objective description when assessing hemorrhagic transformation.[14,15] These studies had a relatively small sample size compared with the sample size of our study. Moreover, they only included patients with PH. In our study, we have shown that patients with large PH2 are more likely to have poor functional outcomes. This effect was not seen in the smaller HT subtypes (HI1, HI2 and PH1). This suggests that hemorrhage volume has only prognostic value in patients with a PH2.

Assessing the "true" effect of hemorrhage on outcome warrants adjustment for final infarct size due to their association. However, the definition of follow-up lesion volume as used in major studies (a combination final infarct volume, swelling, edema and hemorrhage) causes some difficulty.[16] In patients with HI, adjustment for follow-up lesion volume will likely result in an accurate estimate of outcome. Quantifying these hemorrhages can be complicated as the delineation of the hemorrhage is not clear. The brain tissue can be swollen and have petechial bleedings. Delineating the petechial bleedings results in small hemorrhage volumes and the impact of the swollen brain tissue is not taken into account in this assessment. The lack of including a measure for swelling can result in a stronger observed association of the HI1, HI2 and PH1 classifications with functional outcome than hemorrhage volume alone. However, large lesion volumes (incorporating both infarct and parenchymal swelling) are associated with HT and with a poor functional outcome, prompting us to include follow-up lesion volume in the analysis.[17] As this measure includes hemorrhage, infarcted tissue and oedema while the proportion of hemorrhage is small, it will be correct to adjust for lesion volume. Conversely, for patients with a PH, hemorrhages can be large and tend to mask the infarct volume completely. In these cases, the value of the lesion volume is similar to the hemorrhage volume. Adding both values to the analysis will result in an underestimation of the association of large hemorrhage volumes with functional outcome.

Not all patients with sICH have a PH2 with a hematoma that consists of more than 30% of the infarct volume. When the infarct is very large, even a hemorrhage of 100 ml is less than 30% of the infarct volume but it might cause symptoms and neurologic deterioration. However, some of the patients that were classified with sICH were unlikely to have

symptoms due to hemorrhage. In almost all examples of sICH we showed, a midline shift was present. In four cases the hemorrhage might have contributed to the midline shift leading to poor functional outcome. In the other three cases the midline shift was probably caused by infarct growth and not due to hemorrhage. For the classification of sICH it is important to determine if it is likely that the hemorrhage is causing the symptoms as has been proposed in the Heidelberg Bleeding Classification.[5]

An advantage of quantifying hemorrhage volume is that it might be less sensitive to inter-observer variability than classifying hemorrhagic transformation. Quantifying hemorrhage volume can be time consuming. However, it may be possible to automatically quantify hemorrhage volume as this is accomplished with subarachnoid hemorrhage and hemorrhagic stroke.[18,19] In some HT cases it is difficult to distinguish petechial hemorrhage from remaining intact cortex throughout the infarct, also introducing a subjective element when performing manual assessment. Making it more accessible and less sensitive to inter-observer variability when classifying hemorrhagic transformation, it could be classified as HT or no HT and measure hemorrhage volume only when a PH is present.

This study had several limitations; some patients had diffuse brain swelling with hemorrhage, which is complicated to delineate and could have resulted in smaller hemorrhage volumes for those patients. Hemorrhage volumes were quantified by one observer and therefore the inter-observer variability could not be assessed. However, measuring hemorrhage volume by one observer leads to less variation to assess its association with functional outcome and eventually hemorrhage volume might be assessed by an automated measurement.

In conclusion, hemorrhage volume is associated with functional outcome, but not independent of total lesion volume. However, hemorrhage volume could be useful for classifying HT particularly to measure the extent of a PH.

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Clinical and imaging markers associated with hemorrhagic transformation in patients with acute ischemic stroke

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Stroke. July 2019, 50:2037–2043

Abstract

Background and Purpose

Hemorrhagic transformation (HT) after acute ischemic stroke may cause severe neurologic deterioration and affects functional outcome. Identifying patients most likely to suffer from this complication could potentially be used for future treatment selection. Reperfusion after endovascular therapy could be associated with different risk factors for HT than intravenous thrombolytics as these treatments largely differ. In this study we aimed to identify clinical and imaging markers that are associated with HT subtypes in the MR CLEAN population.

Methods

In this post-hoc analysis, all patients with follow-up imaging were included. HT was classified according to ECASS II. Variables with an association of $p<0.1$ were included in the multivariable logistic regression to identify clinical and radiological variables associated with petechial hemorrhagic infarction (HI), parenchymal hematoma (PH) and symptomatic intracranial hemorrhage (sICH).

Results

Of the 478/500 included patients in this subanalysis, 46% suffered from HT (n=222). Of these, 66% had HI (n=147) and 34% PH (n=75). sICH was observed in 7.3% (n=35) of all patients. Baseline NIHSS (OR:1.05,95%CI:1.01-1.09 per point) and absent/poor collaterals (OR: 1.90,95%CI:1.05-3.42) were significantly associated with HI. Increased systolic blood pressure (OR:1.17,95%CI:1.05-1.31 per 10 mmHg) and atrial fibrillation (OR:1.94,95%CI:1.08-3.48) were associated with PH. Increased systolic blood pressure (OR:1.28,95%CI:1.12-1.48) and antiplatelet use (OR:2.6,95%CI:1.08-6.3) were associated with sICH

Conclusions

Clinical and imaging stroke severity parameters were associated with HT, both in HI and PH, whereas baseline patients characteristics like systolic blood pressure, atrial fibrillation and antiplatelet use were only associated with PH or sICH.

Introduction

Hemorrhagic transformation (HT) can occur as natural progression of acute ischemic stroke (AIS) or as a complication of stroke treatment and may result in impaired functional outcome.[1,2] HT ranges from smaller petechial hemorrhagic infarction (HI) to more confluent parenchymal hematoma (PH). Symptomatic intracranial hemorrhage (sICH) is a HT that results in acute neurological deterioration. sICH results in high mortality and is usually a consequence of PH.[3] A small HI is less likely to lead to acute neurological deterioration than PH, although it may still have a negative impact on long-term functional outcome.[4,5] Various risk factors associated with the occurrence of HT have been identified. These include: treatment with thrombolytic agents, age, hyperglycemia, hypertension, use of antiplatelet agents, large infarct size, early ischemic changes on CT, and cholesterol level.[6–9] Most studies have examined risk factors for HT after treatment with intravenous thrombolysis (IVT).[6] Recently, endovascular therapy (EVT) has become part of usual care for patients with acute ischemic stroke due to intracranial large vessel occlusions. It is not clear whether risk factors for HT differ after treatment with EVT.[10–14] By determining factors that contribute to the development of HT, we may be able to identify patients at risk for developing HT and alter treatment to decrease this risk.

In this study, we aimed to identify clinical and imaging markers that are associated with the occurrence of HI, PH and sICH in the MR CLEAN study.[10] In addition, we explored whether the association of these characteristics would differ per treatment group.

Methods

Anonymized trial data and analytic methods that support our study findings are available from the principal investigator (Email:mrclean@erasmusmc.nl) on reasonable request

Study Design

Data was obtained from MR CLEAN, a prospective multicenter randomized trial assessing the safety and effect of additional EVT compared to usual care only. Acute ischemic stroke patients with a proximal intracranial occlusion who could be treated with EVT within six hours of stroke onset were included for randomization. Patients who endured a previous stroke within six weeks before stroke onset were excluded, as were patients with a blood pressure exceeding 185/110 mmHg before start of treatment. Additionally, patients with a history of intracranial hemorrhage were specifically excluded for intra-arterial treatment

with alteplase but not for EVT. More specific inclusion and exclusion criteria can be found in the MR CLEAN study protocol.[15]

A central medical ethics committee and the research boards of all participating centers accepted the MR CLEAN trial. From all patients or legal representatives, written informed consent was acquired.

To identify HT on radiological images, follow-up CT scans, acquired at approximately 5 days after inclusion, were assessed. When follow-up scans at 5 days were not available, 24-hour follow-up CT scans were examined. HT was identified and classified according to the ECASS II (European Cooperative Acute Stroke Study) classification[16]: HI1 was defined as small petechiae along the margins of the infarct; HI2, as confluent petechiae within the infarcted area but no space- occupying effect; PH1, as blood clots in 30% of the infarcted area with slight space-occupying effect; and PH2, as blood clots in 30% of the infarcted area with a substantial space-occupying effect. Any intracranial hemorrhage visible on CT with concurrent neurological deterioration (increase in ≥ 4 points on the National Institute of Health Stroke Scale (NIHSS)) was defined as sICH.[16] Collateral score was assessed on baseline CTA.[17] Collateral score was graded as absent collaterals, poor collaterals (≤50% filling of territory corresponding to the occluded artery), moderate collaterals (>50% filling but less than 100%) and good collaterals (100%).[17] To account for small numbers of patients with absent collaterals, we pooled the absent and poor collaterals together.

Statistical Analysis

For the statistical analysis, two analyses were performed: a) patients with HI (HI1 and HI2) and patients with PH (PH1 and PH2) were both compared with patients without HT; b) patients with any sICH were compared to patients without sICH. We assessed the relation of clinical and radiological characteristics with the occurrence of HI and PH using multinomial logistic regression analysis and sICH using binary logistic regression analysis. Univariable tests were used to identify variables associated with HI, PH and sICH. Variables with an association with $p<0.10$ were included in the multivariable regression analysis. The following variables collected at baseline were explored for their association with HI, PH and sICH: Alberta Stroke Program Early CT Score (ASPECTS); admission collateral score; EVT; administration of IV thrombolytics; age; sex; systolic blood pressure (measured on admission); National Institute of Health Stroke Scale (NIHSS); known hypercholesterolemia and statin use; antiplatelet use; atrial fibrillation; time from onset to randomization; diabetes mellitus, and previous stroke. Criteria for diagnosing diabetes mellitus in the

Netherlands are diabetes symptoms (polyuria and polydipsia) and a venous plasma glucose concentration ≥ 11.1 mmol/l or a fasting plasma glucose concentration ≥ 7.0 mmol/l. Hypercholesterolemia is defined as a total cholesterol of ≥ 6.5 mmol/l.

An additional analysis was conducted to explore possible differences in associations with HI, PH and sICH between patients treated with EVT or not treated with EVT. Therefore, the groups HI, PH and sICH were all divided per treatment, patients treated with EVT and control group respectively. The control group consisted of all patients that did not receive EVT. Revascularization rate assessed with mTICI scores was available for patients treated with EVT, therefore we added this variable to the analysis of patients with sICH after EVT. As discriminating HI from contrast staining may be difficult on a 24-hour CT scan, HI rates on scans acquired at 24-hour or 5-7 days were compared.

Baseline characteristics were analyzed with the Mann-Whitney U test for non-normally distributed continuous data, student t-test for normally distributed continuous data, and the $\chi 2$ test for categorical data. The statistical analyses were performed using R (R Core Team (version 3.5.1 (2016)). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Used packages: MASS[18], rms[19], Tableone[20]).

Results

Of the 500 patients included in the MR CLEAN trial, 478 patients were included in this study. In 22 patients follow-up imaging was missing. Of these 478 patients, 361 CT-scans were performed at approximately 5 days (3-9 days) and 117 CT-scans at 24-hours after inclusion.

Of all 478 patients, 46% had an HT (n=222). Of the patients with HT, 66% had HI (n=147) and 34% had PH (n=75). sICH was observed in 35 patients (7.3%). In the sICH group two patients had a subarachnoid hemorrhage (SAH). Both patients with a SAH had undergone EVT. HI was found in 36 of 117 (31%) patients on 24-hour imaging and in 111 of 361 (31%) patients on 5-day follow-up imaging.

Characteristics at baseline for patients with HI, PH and sICH compared with patients without HT are presented in table 1. Occurrence of any HT or sICH was evenly distributed among all four possible treatments; EVT + IV alteplase, IV alteplase, EVT only and patients

without treatment. Compared to patients without any HT, patients with HI had a higher median NIHSS score (19 vs. 17, p<0.01) and lower median ASPECTS score (9 [7-10] vs. 9 [8-10], p<0.01). In the multivariable regression analysis presented in table 2, HI was significantly associated with baseline NIHSS score (OR 1.05, 95% CI 1.01 – 1.09 (per point)) and with absent/poor collaterals (OR 1.88, 95% CI 1.04 – 3.39).

Patients with PH had a higher NIHSS score (19 vs. 17, p<0.01), were more commonly known with atrial fibrillation (39% vs. 23%, p<0.01), had a higher systolic blood pressure (155 vs. 142, p<0.01), used more often antiplatelet agents (44% vs. 26%, p<0.01) than patients without HT. In addition, more patients with PH had a history of hypercholesterolemia and statin use than patients without PH (32% vs. 20%, p=0.03). In the multivariable regression analysis presented in table 2, PH was only significantly associated with atrial fibrillation (OR 1.93, 95% CI 1.07 – 3.45) and systolic blood pressure (OR 1.17, 95% CI 1.05 – 1.31 (per 10 mmHg)).

Of the 35 patients diagnosed with sICH, 30 patients had a PH, 3 patients had HI and 2 patients had a SAH. Patients with sICH were older (75 vs. 65 years, p<0.001), had a higher NIHSS score (19 vs 17, p<0.01), had more often diabetes mellitus (31% vs. 11%, p<0.01) and had an higher systolic blood pressure (158 vs. 140, p<0.01) than patients without sICH. Pre-treatment antiplatelet use was more common among patients with sICH (60% vs. 26%, p<0.01) as was hypercholesterolemia and statin use (49% vs. 20%, p<0.01). In the multivariable regression analysis presented in table 3, sICH was significantly associated with systolic blood pressure (OR 1.28, 95% CI 1.11 – 1.47 (per 10 mmHg)) and antiplatelet use (OR 2.6, 95% CI 1.08 – 6.3).

Differences per treatment

Clinical and imaging characteristics at baseline of patients with HI and PH differed per treatment group and are presented in Supplementary Table I. In the control group, that consisted of all patients that did not receive EVT, patients with HI had higher baseline NIHSS score than patients without HT (20 vs. 17, p<0.01). In contrast, patients with HI in the EVT group did not have a significant higher baseline NIHSS score than patients without HI. PH was in the control group associated with an increased systolic blood pressure compared with patients without HT (159 vs. 143, p<0.01). In the EVT group, the association with systolic blood pressure and PH was not apparent. The univariable analyses of HI and PH per treatment group are presented in Supplementary Table II. In the univariable analysis, systolic blood pressure was associated with PH in both groups, EVT (OR 1.19, 95% CI 1.04 – 1.36 (per 10 mmHg)) and control group (OR 1.24, 95% CI 1.07 – 1.44 (per mmHg))

respectively.

Characteristics at baseline for patients with sICH per treatment group are presented in Supplementary Table III. Most associations in the sICH group did not differ per treatment group. However, in the EVT group, patients with sICH had more often diabetes mellitus (53% vs. 10%, p<0.01) than patients without sICH. The number of patients with diabetes mellitus was evenly distributed between sICH or no sICH in the control group. Diabetes mellitus was significantly associated with sICH in the EVT group (OR 4.3, 95%CI: 1.22 – 14.94) but not in the control group and systolic blood pressure was significantly associated with sICH in the control group (OR 1.25, 95%CI: 1.02 – 1.53) but not in the EVT group (Supplementary Table IV). Revascularization rate (mTICI scores) was not significantly associated with sICH in the EVT group.

Discussion

In our study, baseline characteristics that were associated with HT differ between HT subtypes. HI was statistically significant associated with an absent/poor collateral score and increased NIHSS score whereas PH and sICH were significantly associated with increased systolic blood pressure, atrial fibrillation and antiplatelet use.

Recent studies exploring associations with HT after EVT reported various results.[7–9,21,22] Altogether, possible risk factors for HT after treatment with EVT that have been reported are; an increased NIHSS score, hyperglycemia, antiplatelet use, atrial fibrillation, decreased ASPECTS, increased time from stroke onset to recanalization, diabetes mellitus and age.[7–9,21,22] Although it used to be considered as major risk for HT[23,24], treatment with IVT has not been reported as a risk factor for HT or sICH.[8,21,25]

When considering all effect estimates, including non-significant associations, our study seems to confirm presumed different underlying mechanisms for different hemorrhage types.[26] Hemorrhage development per se (HI and PH) is more likely in patients with risk factors for large infarcts (i.e. worse collateral scores and higher NIHSS score). The paradoxical effect estimate for ASPECTS can probably be explained by inclusion of both ASPECTS and collateral score in the same model, two variables very much related.[27] Larger hemorrhages that are more likely to be symptomatic (PH and sICH) might more likely develop if an additional risk factor is present; an increased hydrostatic pressure (blood pressure), impaired hemostasis (anti platelet medication) or a combination (patients

with atrial fibrillation).[7,28] With this potential mechanism in mind, elevated systolic blood pressures after revascularization might be especially harmful. A previous study suggests an association of high systolic blood pressure after revascularization with unfavorable functional outcome.[29] However, in the analysis of sICH per treatment, mTICI scores were not significantly associated with sICH which is probably due to a loss of power as only 15 patients with sICH had mTICI scores.

While exploring associations with HT in the EVT and control group, all variables differed between treatment group in their association with HT. Systolic blood pressure was significantly associated with sICH in the control group and diabetes mellitus was significantly associated with sICH after treatment with EVT. However, previous studies did not indicate an interaction between increased serum glucose and EVT on sICH as outcome measure. [30,31] Differences in associations with HT between treatment with EVT and the control group might indicate that risk factors for HT are not necessarily the same after EVT and IVT. However, the associations between EVT and control group only slightly differed and most patients that had EVT also had treatment with IVT. Therefore, differences in risk factors between patients treated with EVT only and IVT should be assessed and then, exclusion criteria for EVT may be re-examined. It is possible that more patients could be included for EVT.

In agreement with previous studies,[8,21,25] neither IVT or EVT were significantly associated with HT in our study. As pre-treatment with IVT is standard of care in eligible patients[32], all patients without IVT had contra-indications for IVT. Therefore, no reliable estimate of the true effect of tPA on hemorrhage rates can be made. Ongoing trials that randomize between IVT followed by EVT and EVT alone (MR CLEAN-NO IV, SWIFT DIRECT, DIRECT-SAFE and DIRECT MT) will give us valuable information about the actual impact of IVT on HT.[33–36]
Our study had several limitations. First, our purpose of this study was to identify variables associated with HT and therefore we did not adjust for potential confounders. Consequently, the associated variables in this study should not be interpreted as causal factors for HT. Second, not all follow-up CT scans at 5 days could be retrieved due to death (n=52) or other reasons, which resulted in the use of follow-up CT scans at two different moments.[10] This might have influenced the categorization of HI, since it is complicated to distinguish HI from contrast staining resulting in an overestimation of HI at the first scan moment (24-hour CT scan). However, HI rates were not different between the two scan moments. If some HI's were misinterpreted contrast staining, the actual HI-rate could be higher on the 5 day follow-up CT scans. Dual-energy CT can differentiate between contrast

staining and HI but dual energy CT was not part of our imaging protocol. Third, we used baseline systolic blood pressure measured on admission, which only represents a snapshot in time. Multiple measurements of blood pressure were not available. However, in previous studies as well as in this analysis, baseline systolic blood pressure had a stronger relation with outcome and HT than diastolic blood pressure, or known hypertension.[37] Further, this was a post-hoc study and therefore results should be interpreted carefully. Last, although we selected variables with care, it should be considered that some associations might have occurred by chance due to the large number of variables that were included in the analysis.[38]

In conclusion, scores indicating severe strokes such as poor collaterals and high NIHSS score are associated with HI while additional clinical characteristics such as high systolic blood pressure, atrial fibrillation and antiplatelet use are associated with PH or sICH. This information could be used to target patients with high risk characteristics for HT to offer more intense monitoring and even blood pressure control as it might reduce HT risk.[39]

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Table 1. Clinical and Radiological Characteristics at Baseline

	No HT	HT				Symptomatic ICH		
	(n=256)	HI (n=147)	P value	PH (n=75)	P value	No (n=443)	Yes (n=35)	P value
Treatment - no. (%)			0.9		0.78			0.91
EVT + IV alteplase	105 (41)	58 (40)		35 (47)		182 (41)	16 (46)	
IV alteplase only	123 (48)	73 (50)		34 (45)		215 (49)	15 (43)	
EVT only	17 (6.6)	8 (5.4)		4 (5.3)		27 (6.1)	2 (5.7)	
No treatment	11 (4.3)	8 (5.4)		2. (2.7)		19 (4.3)	2 (5.7)	
Age - median [IQR]	64 [53 - 75]	66 [57 - 76]	0.16	66 [59 - 78]	0.19	65 [54 - 75]	75 [62 - 80]	<0.01
Baseline NIHSS - median [IQR]	17 [13 - 21]	19 [15 -22]	<0.01	19 [16 - 22]	<0.01	17 [14 - 22]	19 [17 - 23]	<0.01
History of ischemic stroke - no. (%)	26 (10)	15 (10)	0.99	10 (13)	0.44	44 (9.9)	7 (20)	0.06
Atrial fibrillation - no. (%)	58 (23)	42 (29)	0.19	29 (39)	<0.01	118 (27)	11 (31)	0.54
Diabetes Mellitus - no. (%)	27 (11)	22 (15)	0.191	12 (16)	0.2	50 (11)	11 (31)	<0.01
Systolic blood pressure - median [IQR]	142 [130 - 160]	140 [125 - 155]	0.83	155 [137 - 169]	<0.01	140 [127 - 160]	158 [143 - 186]	<0.01
Time from stroke onset to randomization - median [IQR]	193 [147 - 254]	216 [150 - 267]	0.17	218 [176 - 275]	0.01	200 [149 - 259]	218 [177 - 265]	0.11
ASPECTS - median [IQR]*	9 [8 - 10]	9 [7 - 10]	<0.01	9 [7 - 10]	0.1	9 [8 – 10]	9 [7 - 10]	0.55
Collateral score - no. (%)†			<0.01		0.04			0.11
Absent/poor collaterals	70 (28)	56 (39)		30 (41)		140 (32)	16 (49)	
Moderate collaterals	100 (39)	61 (42)		28 (38)		177 (40)	12 (36)	
Good collaterals	84 (33)	28 (19)		15 (21)		122 (28)	5 (15)	
Sex (male) - no. (%)	153 (60)	83 (57)	0.52	48 (64)	0.51	262 (59)	22 (63)	0.67
Antiplatelet use - no. (%)	66 (26)	37 (25)	0.892	33 (44)	<0.01	115 (26)	21 (60)	<0.01
Hypercholesterolemia and statin use - no. (%)	50 (20)	33 (22)	0.49	24 (32)	0.03	90 (20)	17 (49)	<0.01

Abbreviations: HT, hemorrhagic transformation; sICH, symptomatic intracranial hemorrhage; HI, hemorrhagic infarction; PH, parenchymal hematoma; EVT, endovascular therapy; IV, intravenous; IQR, interquartile range; NIHSS (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta Stroke Program Early CT Score) indicates early ischemic changes;

* ASPECTS was missing for 4 patients.

† Collateral score was assessed on baseline CTA as absent/poor collaterals (0% and >50% filling of occluded are), moderate collaterals (filling of 50% and <100% of occluded area) and good collaterals (100% filling). Collateral score was not available for 6 patients.

Table 2. Univariable and multivariable associations with HT (Multinomial logistic regression

	HI				PH			
	Univariable		Multivariable		Univariable		Multivariable	
	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value
EVT	0.98 (0.65 - 1.48)	0.92	-	-	1.34 (0.8 - 2.25)	0.26	-	-
Control group*	1.01 (0.52 - 1.93)	0.99	-	-	1.41 (0.56 - 3.55)	0.46	-	-
Age	1.01 (1 - 1.03)	0.18	-	-	1.01 (0.99 - 1.03)	0.17	-	-
Baseline NIHSS	1.07 (1.03 - 1.11)	<0.01	1.05 (1.01 - 1.09)	**0.02**	1.07 (1.02 - 1.12)	0.01	1.05 (0.99 - 1.11)	0.09
History of ischemic stroke	1.01 (0.51 - 1.97)	0.99	-	-	1.36 (0.62 - 2.87)	0.44	-	-
Atrial fibrillation	1.37 (0.86 - 2.17)	0.19	1.42 (0.88 - 2.31)	0.15	2.15 (1.24 - 3.73)	<0.01	1.93 (1.07 - 3.45)	**0.03**
Diabetes Mellitus	1.49 (0.82 - 2.73)	0.19	-	-	1.62 (0.77 - 3.37)	0.2	-	-
Systolic blood pressure per 10 mmHg	0.99 (0.91 - 1.08)	0.82	0.98 (0.9 - 1.08)	0.71	1.02 (1.1 - 1.34)	<0.01	1.17 (1.05 - 1.31)	**<0.01**
Time from stroke onset to randomization per 10 minutes	1.02 (0.99 - 1.05)	0.21	1.02 (0.99 - 1.05)	0.28	1.04 (1 - 1.08)	0.04	1.02 (0.98 - 1.07)	0.23
ASPECTS	0.85 (0.76 - 0.94)	<0.01	0.91 (0.80 - 1.02)	0.1	0.86 (0.76 - 0.99)	0.03	0.91 (0.78 - 1.06)	0.21
Collateral score†								
Moderate collaterals	1.83 (1.07 - 3.12)	0.03	1.69 (0.98 - 2.93)	0.06	1.57 (0.79 - 3.13)	0.2	1.54 (0.75 - 3.17)	0.24
Absent/Poor collaterals	2.40 (1.38 - 4.17)	<0.01	1.88 (1.04 - 3.39)	**0.04**	2.4 (1.2 - 4.81)	0.01	1.77 (0.83 - 3.78)	0.14
Sex	0.87 (0.58 - 1.32)	0.52	-	-	1.2 (0.7 - 2.04)	0.51	-	-
Antiplatelet use	0.97 (0.61 - 1.54)	0.89	0.84 (0.49 - 1.42)	0.5	2.26 (1.32 - 3.86)	<0.01	1.69 (0.91 - 3.15)	0.1
Hypercholesterolemia and statin use	1.19 (0.73 - 1.96)	0.49	1.13 (0.64 - 2.01)	0.67	1.94 (1.09 - 3.45)	0.02	1.26 (0.63 - 2.51)	0.52

Abbreviations: HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; sICH, symptomatic intracranial hemorrhage; EVT, endovascular treatment; NIHSS, (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta stroke Program Early CT Score) indicates early ischemic changes.

All variables with an association with p <0.1 were included in the multivariable regression analysis.

* Control group consists of all patients that did not receive EVT.

† Collateral score with good collaterals as reference level.

Table 3. Univariable and multivariable associations with sICH (binary logistic regression)

	sICH			
	Univariable		Multivariable	
	OR and 95% CI	P value	OR and 95% CI	P value
EVT	1.2 (0.6 - 2.4)	0.6	-	-
Control group*	0.9 (0.34 - 3.12)	0.85	-	-
Age	1.05 (1.02 - 1.08)	<0.01	1.02 (0.99 - 1.06)	0.25
Baseline NIHSS	1.05 (0.99 - 1.12)	0.11	1.05 (0.98 - 1.13)	0.18
History of ischemic stroke	2.27 (0.87 - 5.24)	0.07	1.26 (0.43 - 3.33)	0.66
Atrial fibrillation	1.26 (0.58 - 2.6)	0.54	-	-
Diabetes Mellitus	3.6 (1.61 - 7.65)	<0.01	1.72 (0.67 - 4.15)	0.24
Systolic blood pressure per 10 mmHg	1.32 (1.17 - 1.5)	<0.01	1.28 (1.11 - 1.47)	<0.01
Time from stroke onset to randomization per 10 minutes	1.03 (0.98 - 1.08)	0.2	-	-
ASPECTS	0.95 (0.81 - 1.13)	0.52	-	-
Collateral score†				
Moderate collaterals	1.65 (0.6 - 5.31)	0.36	-	-
Absent/Poor collaterals	2.79 (1.06 - 8.73)	0.05	-	-
Sex	1.17 (0.58 - 2.44)	0.67	-	-
Antiplatelet use	4.28 (2.12 - 8.87)	<0.01	2.6 (1.08 - 6.3)	0.03
Hypercholesterolemia and statin use	3.7 (1.82 - 7.5)	<0.01	1.91 (0.8 - 4.56)	0.14

Abbreviations: sICH, symptomatic intracranial hemorrhage; NIHSS, (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta stroke Program Early CT Score) indicates early ischemic changes.

All variables with an association with p <0.1 were included in the multivariable regression analysis.

* Control group consists of all patients that did not receive EVT

† Collateral score with good collaterals as reference level.

Supplemental material

Supplementary Table I. Clinical and radiological characteristics at baseline of patients with and without HT per treatment group

	EVT					Control group				
	No HT (n=111)	HI (n=63)	P value	PH (n=38)	P value	No HT (n=145)	HI (n=84)	P value	PH (n=37)	P value
Age - median [IQR]	66 [53 - 75]	68 [58 - 78]	0.51	64 [56 - 79]	0.61	64 [53 - 75]	66 [56 - 76]	0.23	69 [60 - 78]	0.13
Baseline NIHSS - median [IQR]	16 [13 - 20]	18 [15 - 21]	0.18	19 [17 - 22]	<0.01	17 [13 - 22]	20 [16 - 23]	<0.01	18 [16 - 22]	0.23
History of ischemic stroke - no. (%)	13 (12)	9 (14)	0.8	6 (16)	0.71	13 (9.0)	6 (7.1)	0.82	4 (10.8)	0.98
Atrial fibrillation - no. (%)	27 (24)	19 (30)	0.51	15 (40)	0.11	31 (21.4)	23 (27.4)	0.39	14 (37.8)	0.06
Diabetes Mellitus - no. (%)	13 (12)	6 (9.5)	0.85	10 (26)	0.06	14 (9.7)	16 (19.0)	0.07	2 (5.4)	0.62
Systolic blood pressure - median [IQR]	140 [130 - 160]	144 [123 - 155]	0.6	147 [135 - 168]	0.06	143 [126 - 160]	140 [126 - 155]	0.42	159 [141 - 168]	<0.01
Time from stroke onset to randomization - median [IQR]	193 [146 - 238]	226 [168 - 292]	0.02	221 [190 - 262]	<0.01	193 [148 - 261]	191 [144 - 264]	0.83	211 [160 - 280]	0.38
ASPECTS - median [IQR]*	9 [8 - 10]	8 [7 - 10]	0.08	8 [5 - 10]	0.03	9 [8 - 10]	9 [7 - 10]	0.03	9 [8 - 10]	0.87
Collateral score - no. (%)†			0.33		0.02			0.01		0.41
Good collaterals	40 (36)	16 (25)		4 (11)		44 (30.8)	12 (14.6)		11 (29.7)	
Moderate collaterals	40 (36)	25 (40)		16 (44)		60 (42.0)	36 (43.9)		12 (32.4)	
Absent/poor collaterals	31 (28)	22 (35)		16 (44)		39 (27.3)	34 (41.5)		14 (37.8)	
Sex (male) - no. (%)	67 (60)	34 (54)	0.51	22 (58)	0.94	86 (59.3)	49 (58.3)	1	26 (70.3)	0.3
Antiplatelet use - no. (%)	26 (23)	14 (22)	1	15 (40)	0.09	40 (27.6)	23 (27.4)	1	18 (48.6)	0.02
Hypercholesterolemia and statin use - no. (%)	25 (23)	10 (16)	0.39	13 (34)	0.23	25 (17)	23 (27)	0.1	11 (30)	0.14

Abbreviations: HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; EVT, endovascular therapy; IVT, intravenous treatment with rtPA; IQR, interquartile range; NIHSS (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta Stroke Program Early CT Score) indicates early ischemic changes;

* ASPECTS was missing for 4 patients.

† Collateral score was assessed on baseline CTA as absent/poor collaterals (0% and >50% filling of occluded are), moderate collaterals (filling of 50% and <100% of occluded area) and good collaterals (100% filling). Collateral score was not available for 6 patients.

Supplementary Table II. Univariable associations with hemorrhagic transformation per treatment group (multinomial logistic regression)

	HI				PH			
	EVT		Control group		EVT		Control group	
	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value
Age	1.01 (0.99 - 1.03)	0.49	1.01 (0.99 - 1.03)	0.23	1 (0.98 - 1.03)	0.71	1.02 (0.99 - 1.05)	0.12
Baseline NIHSS	1.04 (0.98 - 1.1)	0.19	1.09 (1.04 - 1.15)	<0.01	1.12 (1.04 - 1.21)	<0.01	1.03 (0.97 - 1.1)	0.33
History of ischemic stroke	1.26 (0.5 - 3.13)	0.62	0.78 (0.29 - 2.14)	0.63	1.41 (0.5 - 4.02)	0.52	1.23 (0.38 - 4.02)	0.73
Atrial fibrillation	1.34 (0.67 - 2.68)	0.4	1.39 (0.74 - 2.58)	0.3	2.03 (0.93 - 4.43)	0.08	2.24 (1.03 - 4.85)	0.04
Diabetes Mellitus	0.79 (0.29 - 2.2)	0.66	2.2 (1.01 - 4.78)	<0.05	2.69 (1.07 - 6.79)	0.04	0.53 (0.12 - 2.46)	0.42
Systolic blood pressure per 10 mmHg	1.01 (0.89 - 1.15)	0.86	0.97 (0.87 - 1.09)	0.64	1.19 (1.04 - 1.36)	0.01	1.24 (1.07 - 1.44)	<0.01
Time from stroke onset to randomization	1.06 (1.01 - 1.11)	0.02	0.99 (0.96 - 1.03)	0.7	1.07 (1.01 - 1.13)	0.01	1.01 (0.97 - 1.06)	0.58
ASPECTS	0.86 (0.72 - 1.02)	0.08	0.84 (0.73 - 0.96)	0.01	0.76 (0.62 - 0.92)	<0.01	1 (0.81 - 1.23)	1
Collateral score*								
Moderate collaterals	1.56 (0.73 - 3.36)	0.25	2.2 (1.03 - 4.71)	0.04	4 (1.23 - 13.01)	0.02	0.8 (0.32 - 1.98)	0.63
Absent/poor collaterals	1.77 (0.8 - 3.94)	0.16	3.2 (1.46 - 7.02)	<0.01	5.16 (1.57 - 17)	<0.01	1.44 (0.58 - 3.53)	0.43
Sex	0.77 (0.41 - 1.44)	0.41	0.96 (0.56 - 1.66)	0.88	0.9 (0.43 - 1.91)	0.79	1.62 (0.74 - 3.53)	0.22
Antiplatelet use	0.93 (0.45 - 1.96)	0.86	0.99 (0.54 - 1.81)	0.97	2.13 (0.97 - 4.67)	0.06	2.49 (1.19 - 5.21)	0.02
Hypercholesterolemia and statin use	0.65 (0.29 - 1.46)	0.3	1.81 (0.95 - 3.45)	0.07	1.79 (0.8 - 4)	0.16	2.03 (0.89 - 4.64)	0.09

Abbreviations: EVT, endovascular treatment; HI, hemorrhagic infarction; PH, parenchymal hematoma; NIHSS, (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta stroke Program Early CT Score) indicates early ischemic changes.

All variables associated ($p < 0.1$) with hemorrhagic transformation were included in the multivariable regression analysis

*Collateral score with good collaterals as reference level

Supplementary Table III. Clinical and radiological characteristics at baseline of patients with sICH per treatment group

	EVT			Control group		
	Symptomatic ICH			Symptomatic ICH		
	No (n=195)	Yes (n=17)	P value	No (n=248)	Yes (n=18)	P value
Age - median [IQR]	66 [53 - 75]	77 [62 - 81]	<0.01	65 [54 - 75]	72 [62 - 79]	<0.05
Baseline NIHSS - median [IQR]	17 [14 - 21]	19 [17 - 21]	0.13	18 [14 - 22]	19 [18 - 23]	0.23
History of ischemic stroke - no. (%)	25 (13)	3 (18)	0.85	19 (7.7)	4 (22)	0.09
Atrial fibrillation - no. (%)	55 (28)	6 (35)	0.73	63 (25)	5 (28)	1
Diabetes Mellitus - no. (%)	20 (10)	9 (53)	<0.01	30 (12)	2 (11)	1
Systolic blood pressure - median [IQR]	141 [130 - 157]	170 [140 - 189]	<0.01	140 [125 - 160]	156 [144 - 165]	0.01
Time from stroke onset to randomization - median [IQR]	204 [155 - 250]	236 [187 - 294]	0.06	194 [148 - 265]	197 [175 - 247]	0.7
ASPECTS - median [IQR]*	9 [7 - 10]	9 [6 - 10]	0.53	9 [8 - 10]	9 [8 - 9]	0.68
Collateral score - no. (%)†			0.04			0.19
Good collaterals	60 (31)	0 (0.0)		62 (25)	5 (28)	
Moderate collaterals	62 (32)	7 (47)		78 (32)	9 (50)	
Absent/poor collaterals	73 (37)	8 (53)		104 (43)	4 (22)	
Sex (male) - no. (%)	115 (59)	8 (47)	0.49	147 (59)	14 (78)	0.19
Antiplatelet use - no. (%)	45 (23)	10 (59)	<0.01	70 (28)	11 (61)	<0.01
Hypercholesterolemia and statin use - no. (%)	38 (20)	10 (59)	<0.01	52 (21)	7 (39)	0.14
mTICI score‡			0.99			
0	24 (12.3)	2 (11.8)		-	-	-
1	10 (5.1)	1 (5.9)		-	-	-
2	13 (6.7)	2 (11.8)		-	-	-
2a	25 (12.8)	2 (11.8)		-	-	-
2b	62 (31.8)	5 (29.4)		-	-	-
3	43 (22.1)	3 (17.6)		-	-	-

Abbreviations: EVT, endovascular therapy; sICH, symptomatic intracranial hemorrhage; IQR, interquartile range; NIHSS (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta Stroke Program Early CT Score) indicates early ischemic changes; mTICI, modified treatment in cerebral ischemia.

* ASPECTS was missing for 4 patients.

† Collateral score was assessed on baseline CTA as absent/poor collaterals (0% and >50% filling of occluded are), moderate collaterals (filling of 50% and <100% of occluded area) and good collaterals (100% filling). Collateral score was not available for 6 patients.

‡ mTICI scores were not available for the control group.

Supplementary Table IV. Uni- and multivariable analysis of associations with symptomatic ICH per treatment group

	Univariable				Multivariable			
	EVT		Control group		EVT		Control group	
	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value	OR and 95% CI	P value
Age	1.06 (1.02 - 1.12)	<0.01	1.04 (1 - 1.08)	0.06	1.03 (0.98 - 1.09)	0.24	1.02 (0.97 - 1.06)	0.43
Baseline NIHSS	1.08 (0.98 - 1.2)	0.12	1.04 (0.95 - 1.13)	0.4	-	-	-	-
History of ischemic stroke	1.46 (0.32 - 4.86)	0.58	3.44 (0.91 - 10.75)	0.04	-	-	1.74 (3.98 - 6.54)	0.43
Atrial fibrillation	1.39 (0.46 - 3.84)	0.54	1.13 (0.35 - 3.13)	0.82	-	-	-	-
Diabetes Mellitus	9.84 (3.41 - 29.13)	<0.01	0.91 (0.14 - 3.41)	0.9	4.3 (1.22 - 14.94)	0.02	-	-
Systolic blood pressure per 10 mmHg	1.36 (1.16 - 1.62)	<0.01	1.27 (1.06 - 1.54)	<0.01	1.21 (0.99 - 1.47)	0.06	1.25 (1.02 - 1.53)	0.03
Time from stroke onset to randomization	1.07 (0.99 - 1.15)	0.08	1 (0.94 - 1.07)	0.91	1.07 (0.98 - 1.17)	0.16	-	-
ASPECTS	0.88 (0.69 - 1.13)	0.28	1.02 (0.81 - 1.36)	0.87	-	-	-	-
Collateral score*								
Moderate collaterals	-	-	0.48 (0.11 - 1.87)	0.28	-	-	-	-
Absent/poor collaterals	-	-	1.43 (0.47 - 4.86)	0.54	-	-	-	-
Sex (male)	0.62 (0.22 - 1.68)	0.34	2.4 (0.83 - 8.67)	0.13	-	-	-	-
Antiplatelet use	4.76 (1.73 - 13.8)	<0.01	4 (1.51 - 11.25)	<0.01	1.96 (0.52 - 7.46)	0.31	2.84 (0.88 - 9.26)	0.08
Hypercholesteremia and statin use	5.9 (2.13 - 17.23)	<0.01	2.4 (0.85 - 6.4)	0.09	2.64 (0.7 - 9.98)	0.15	1.36 (0.42 - 4.23)	0.6
mTICI score								
0	1.11 (0.17 - 4.12)	0.89	-	-	-	-	-	-
1	1.33 (0.07 - 7.49)	0.79	-	-	-	-	-	-
2	2.05 (0.31 - 8.11)	0.37	-	-	-	-	-	-
2a	1.06 (0.16 - 3.94)	0.94	-	-	-	-	-	-
2b	1.07 (0.35 - 2.77)	0.89	-	-	-	-	-	-
3	0.93 (0.21 - 2.85)	0.91	-	-	-	-	-	-

Abbreviations: sICH, symptomatic intracranial hemorrhage; EVT, endovascular treatment; NIHSS, (National Institute of Health Stroke Scale) indicates stroke severity; ASPECTS (Alberta stroke Program Early CT Score) indicates early ischemic changes.

All variables associated ($p < 0.1$) with hemorrhagic transformation were included in the multivariable regression analysis

*None of the patients with sICH after EVT had good collaterals, therefore conducting an univariable analysis with collateral score was not possible.

Classifying hemorrhagic transformation after an acute ischemic stroke: B0 echo planar imaging vs. NCCT

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Manuscript in preparation

Abstact

Introduction

Hemorrhagic transformation (HT) is a feared complication after acute ischemic stroke, usually scored with the Heidelberg bleeding classification on non-contrast CT (NCCT) or magnetic resonance imaging (MRI). Commonly used gradient echo MRI sequences are known to overestimate hemorrhages compared to NCCT. Since the B0 series of diffusion weighted echo planar imaging (B0 EPI) has shown to be comparable with NCCT, its usage in trials could reduce modality induced bias. The purpose of this study is to compare HT volume and classification between NCCT and B0 EPI.

Methods

We included patients with both follow-up NCCT and MRI from individual patient datasets from seven pooled trials on endovascular treatment of acute ischemic stroke. HT was classified on NCCT and B0 EPI using the Heidelberg Bleeding classification. Inter-modality agreement was assessed by calculating Cohen's Kappa for HT (all subtypes) and per subtype (yes or no). Hemorrhage volume was measured by manually delineating the hemorrhage.

Results

Of 121 included patients, 57 had HT. Inter-modality agreement between NCCT and B0 EPI was fair for overall HT (κ=0.27), moderate for hemorrhagic infarction type 1 (κ=0.48), slight for hemorrhagic infarction type 2 (κ =0.12) and parenchymal hematoma type 1 (κ=0.08), and good for parenchymal hematoma type 2 (κ=0.7). Hemorrhage volumes were larger when assessed on B0 EPI than NCCT: NCCT median 1.9 ml, interquartile range (IQR) [0.08-8.4] ml, B0 EPI: median 4.6 ml IQR [0.98-10.3] ml, p=0.01).

Discussion

Hemorrhagic transformation assessments of NCCT and B0 EPI are not fully comparable, necessitating standardization of the classification on both modalities to ensure comparability among trials. However, inter modality agreement of the most clinically relevant subtype parenchymal hematoma type 2 was good.

Introduction

Hemorrhagic transformation (HT) after acute ischemic stroke (AIS) occurs frequently and is associated with poor functional outcomes.[1] The ECASS classification was developed to classify HT into four different subtypes.[2] Classifying HT is of importance as PH2 is associated with a direct neurological decline and mortality while the other subtypes are mainly associated with worse functional outcomes three months.[3,4]

Although CT is still the most commonly used imaging modality in AIS, the use of magnetic resonance imaging (MRI) has increased due to its increasing availability and diagnostic advantages.[5–9] In routine clinical practice and clinical trials, the choice of follow up imaging modality can depend on availability and condition of the patient, resulting in some patients receiving MRI and others NCCT.[5–8] This difference in modality can complicate comparing HT after AIS since the extent of hemorrhage might appear different between the two modalities. In particular, gradient echo (GRE) MRI sequences (T2*) and susceptibility weighted imaging (SWI) have a higher sensitivity in detecting hemorrhage as compared to NCCT due to the susceptibility artifact, which is even more pronounced at higher field strength.[10–12] Some HTs appear on MRI but might not even be visible on NCCT.[10] These differences between NCCT and MRI could result in an overestimation of the HT classification on MRI compared to NCCT. Moreover, no specific MRI criteria exist for HT classification. Therefore HT on MRI is usually classified with the CT-based ECASS classification while the classification has not been validated for MRI.[2 13,14]

Diffusion weighted imaging is increasingly used to assess follow-up infarct size after EVT.[15] Previously it was shown that B0-echo planar imaging (B0 EPI) as part of DWI had lower sensitivity for hemorrhage detection than GRE, but was comparable to NCCT.[16] As such usage of B0 EPI to classify HT could result in better comparability to NCCT than GRE sequences. Therefore, the purpose of this study is to compare the ECASS classification and hemorrhage volume as assessed on NCCT compared to B0 EPI.

Methods

Patients

Patients with follow-up imaging on both NCCT and MRI were included from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration and The Multicenter Randomized Clinical trial of Endovascular treatment

for Acute ischemic stroke in the Netherlands (MR CLEAN) NO IV trial.[17–24] The HERMES collaboration consists of pooled data from seven randomized controlled trials that assessed the efficacy of endovascular therapy (EVT) in addition to best medical treatment (including intravenous alteplase treatment (IVT) if eligible) in anterior circulation acute ischemic stroke due to a large vessel occlusion.[17–23] MR CLEAN NO IV is a randomized controlled trial that compared EVT alone versus EVT after intravenous alteplase treatment (IVT).[8] Patients with a stroke onset less than 4.5 hours, eligible for IVT and EVT presenting at an EVT capable center were included in the MR CLEAN NO IV trial.[8]

Imaging protocol

All included patients underwent NCCT and MRI. Scans were made in a multitude of different institutions and scanners. In general, all had 5-mm thin axial NCCT available and MRI with diffusion-weighted imaging. Some, but not all, of the MRI scans also included GRE sequences (T2* n=10 or SWI n=23), but these were not used for this classification comparison study.

Imaging analysis

Follow-up imaging was performed within 7 days of stroke onset. HT was assessed primarily on NCCT by the imaging core lab of HERMES and MR CLEAN NO-IV. The core-lab determined whether HT was visible on follow-up imaging and then classified HT using the European Co-operative Stroke Study (ECASS) criteria which are incorporated in the Heidelberg Bleeding Classification.[25] In one case where one observer scored the hemorrhage as HI1 and another as no HT on NCCT, the MRI was accessed during a third consensus reading to confirm the hemorrhage and uphold the HI1 scored on NCCT. All patients with both NCCT and MRI follow-up imaging and a core-lab confirmed hemorrhage were rescored on B0 EPI sequence. For the classification of HT on B0 EPI, two experienced observers (KMT and MSK, further referred to as observer 1 and 2) blinded to NCCT and clinical findings used B0 EPI and classified HT for half of the population each without T2*nor SWI.

Hemorrhage volume was measured manually by a researcher with experience in hemorrhage volume measurements (KRK) on NCCT and B0 EPI using ITK-snap version 3.4.0.

Due to the time interval between scans, new hemorrhage could have occurred, or the hemorrhage might have grown. Therefore, patients who developed large HT (parenchymal

hematoma (PH) type 1 or 2) between the two scan moments were excluded and patients were excluded when no HT was visible on gradient echo MRI and had any HT on a later NCCT scan. Additionally, patients were excluded if they had undergone neurosurgery between the two scan moments.

Statistical analysis

Inter-modality agreement of the ECASS classification on NCCT and B0 EPI was measured using Cohen's kappa for overall HT (including all subtypes) and per HT subtype (yes or no) of the patients with confirmed hemorrhage by the core-lab. We used a Friedman test to compare hemorrhage volume on NCCT with B0 EPI.
All statistical analyses were conducted using R (R Core Team (V.4.0.0 (2020); R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; used packages ggplot2, and tableone).

Results

Of all 2303 patients from the pooled HERMES and MR CLEAN NO IV trial data, 127 had both follow-up NCCT and MRI performed within a median of 13.5 hours of each other (IQR: 4.2 – 22) hours. Of these 127 patients, 63 patients had HT (as identified by HERMES and MRCLEAN NO-IV core-labs) of which six were excluded. Two patients were excluded because of a substantial increase in hemorrhage that was indicative of new hemorrhage on NCCT imaging acquired after B0 EPI. Two patients were excluded because of HT visible on NCCT imaging acquired after MRI imaging and no visible HT on gradient echo MRI. Last, two patients were excluded because they had an hemicraniectomy between the two scan moments (figure 1).

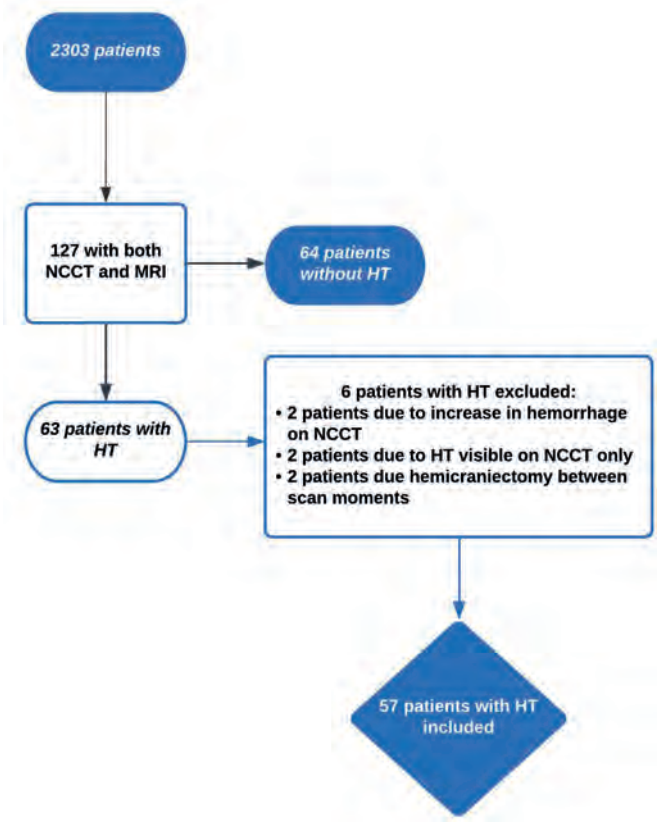

Figure 1. Flowchart of included patients from HERMES and MR CLEAN NO IV.

Abbreviations; NCCT, non-contrast computed tomography; MRI, magnetic resonance imaging; HT, hemorrhagic transformation.

Inter-modality agreement was fair for overall HT (kappa 0.27, 95% CI 0.09-0.44), moderate for HI1 (kappa 0.48, 95% CI 0.46-0.49), slight for HI2 (kappa 0.12, 95%CI 0.11-0.14), slight for PH1 (kappa 0.08, 95% CI 0.06-0.11) and good for PH2 (kappa 0.7, 95% CI 0.68-0.72). Table 1 shows the rates of hemorrhagic transformation classified on NCCT and B0 EPI. Example images of differences between NCCT and B0 EPI and possible explanation of the fair and slight agreement for HI2 and PH1 were shown in figure 2.

Table 1. Rates of hemorrhagic transformation subtypes classified on NCCT and B0 EPI

		B0 EPI						
		No HT	HI1	HI2	PH1	PH2	rPH	Total
NCCT	No HT	0	0	1	0	0	0	1
	HI1	1	10	4	1	0	0	16
	HI2	1	5	10	7	2	0	25
	PH1	0	1	3	2	0	1	7
	PH2	0	0	0	1	4	0	5
	rPH	0	0	0	0	0	1	1
	SAH	1	0	1	0	0	0	2
	Total	3	16	19	11	6	2	57

Abbreviations; NCCT, non-contrast computed tomography; B0 EPI, B0-echo planar imaging ; HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; rPH, remote PH; SAH, subarachnoid hemorrhage.

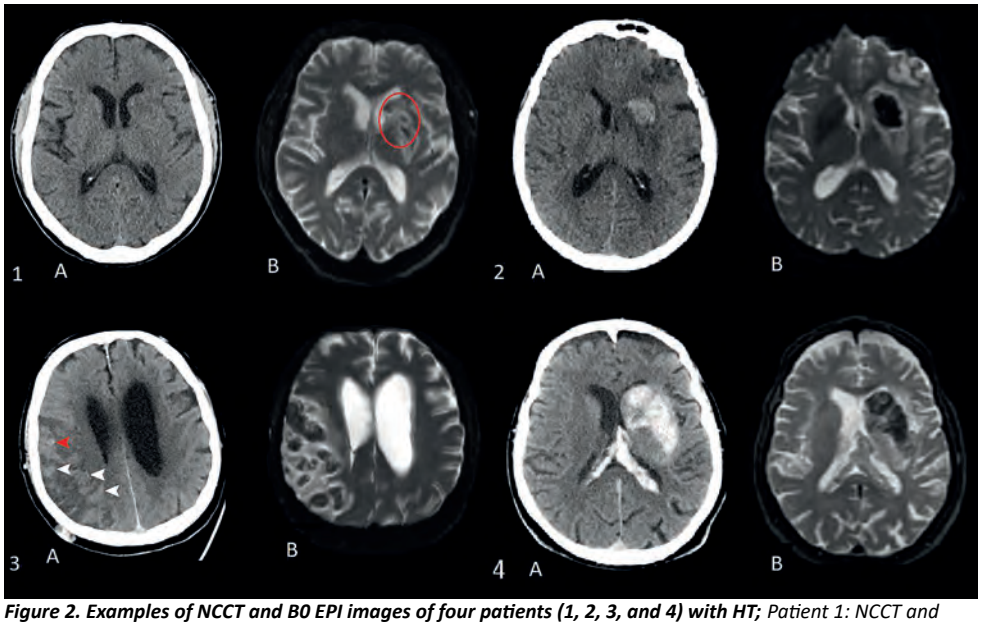

Figure 2. Examples of NCCT and B0 EPI images of four patients (1, 2, 3, and 4) with HT; *Patient 1: NCCT and B0 EPI image with a time interval of 18 minutes of a patient with small HT, A: NCCT shows subtle hypodensity in left caudate and lentiform nucleus without HT (scored by HERMES core-lab). B: small hypointense areas within infarcted tissue on B0 EPI scored as HI2 by observer 2. Patient 2: NCCT image shows confluent hyperdense areas within infarcted tissue consistent with petechial hemorrhage (scored as HI-2 by HERMES core-lab) and clear hypointense area on B0 EPI image (B) (scored as PH2 by observer 1). Patient 3. NCCT and B0 EPI sequence with a time interval of 1 hour and 46 minutes. A: NCCT image of shows isodense areas (white arrows) within infarcted hypodense tissue and one very small hyperdense area (red arrow) scored as HI2 by MR CLEAN NO-IV core-lab. B: B0 EPI hypointense areas within infarcted tissue scored as PH1 by observer 1. Patient 4: time interval of 4 hours and 26 minutes. A: NCCT image shows a large hyperdense area with compression on surrounding brain tissue*

and intraventricular hyperdense area, scored as PH2 by HERMES core-lab. B: B0 EPI shows hypointense area and compression on ventricles with intraventricular isointense area, scored as PH2 by observer 2.

Hemorrhage volume was significantly different between NCCT and B0 EPI (NCCT median 1.9 ml, interquartile range (IQR) [0.08-8.4] ml, B0 EPI: median 4.6 ml IQR [0.98-10.3] ml, p=0.01). We compared the difference in volume between NCCT and B0 EPI over time. No clear trend of time difference between study acquisition and haemorrhage volume difference was seen (Table 2). Time and hemorrhage volume difference are plotted in figure 2.

Table 2. Difference in hemorrhage volume (ml) over time (hours)			
Time between NCCT and B0 EPI (hours)*	≤ -10.0	>-10.0 < 14.9	≥ 14.9
Volume difference (ml) between NCCT and B0 EPI (median [IQR])	1.3 [0.1, 3.8]	0.7 [-0.2, 2.6]	-0.7 [-3.1, 1.9]
*Time difference was divided in three groups based on the interquartile range. Negative times indicate MRI acquisition prior to NCCT acquisition.			

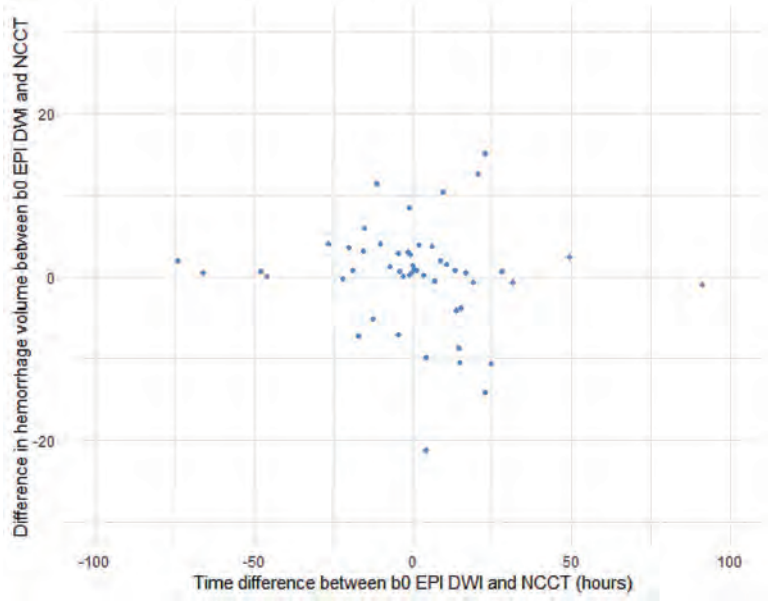

Figure 2. Volume of NCCT and B0 EPI compared with time interval between two scan moments. *Negative time intervals indicate that the B0 EPI was acquired before the NCCT. Negative volume differences indicate that the hemorrhage measured on NCCT was larger than B0 EPI. 5 points were not visualized; 1: Time interval of 118 hours and a volume difference of -0.8 ml, 2: time interval of 21 hours volume difference -83 ml (large volume difference between NCCT and MRI was caused by contrast staining on NCCT), 3: Time interval of -100 hours with a volume*

difference of 2.4 ml, 4: time interval of 811 hours with a volume difference of 2.6 ml, 5: time interval of -1.8 hours with a volume difference of 32.7 ml.

In five of the seven cases where hemorrhage volume on NCCT was larger than B0 EPI, the NCCT was acquired first and this discrepancy was caused by contrast staining. In the other two cases where NCCT was larger than B0 EPI and the B0 EPI was acquired first, the discrepancy was caused by insufficient scan quality of the B0 EPI resulting in an underestimation of the hemorrhage on B0 EPI.

Discussion

This study shows that the inter-modality agreement between NCCT and MRI for assessment of hemorrhagic transformation after AIS was fair for overall HT, moderate for HI1, slight for HI2 and PH1 and good for PH2. Hemorrhage volumes measured on B0 EPI are statistically significantly larger than those measured on NCCT with a mean volume difference of 6 ml.

Follow-up imaging commonly consists of a mix of both NCCT and MRI in trials, depending on availability in different centers, patients' condition or physicians' preference. Few previous studies compared the classification of hemorrhagic transformation between NCCT and MRI.[10,13,26] These studies focussed on the inter-observer agreement and found better agreement with MRI. [10,13,26] If we compare the results of these studies with the inter-modality agreement from our study, the agreement within imaging modalities is better than between modalities. As the inter-observer agreement of the previous studies was at least fair for PH1, the inter-modality agreement of PH1 was only slight.[10,13,26] The quality analysis of Renou et al, (2010) showed difficulties particularly in differentiating between HI2 and PH1, which is confirmed by this study.[26] Previous studies concluded that the ECASS classification for HT based on NCCT imaging can be adapted to MRI although they did not assess the inter-modality agreement.[10,13,26]

This study shows that hemorrhage assessments between NCCT and B0 EPI are not comparable for all subclasses. Particularly the distinction between HI2 and PH1 on B0 EPI is challenging. The key difference between HI2 and PH1 is the presence of petechial hemorrhages versus gross confluent hematoma. Discriminating between confluent petechiae and frank hematoma on a NCCT image is less complicated than on B0 EPI image since the density and distribution of the hemorrhage on a NCCT image aids in the

differentiation. On the contrary, hemorrhage on most MRI sequences (B0 EPI, T2*, SWI) is confluent hypo-intense due to susceptibility (blooming) artefact which increases with gradient strength.[12]

Since hemorrhage volume is a quantitative measure that can be automated it is a promising tool to be used in follow-up imaging assessments in future trials.[27] A previous study showed that hemorrhage volume is associated poor with functional outcome.[28] However, when comparing hemorrhage volume with the classification it only had added value in its association with functional outcome when a PH2 was present.[28] Additionally, information is lost when we would only quantify hemorrhage volume rather than classify hemorrhagic transformation. Isolated quantification of hemorrhage volume does not readily measure space-occupying effect. Especially in the acute setting the space-occupying effect drives the clinical deterioration due to compression, midline shift and even transtentorial herniation, making it the main target for surgical intervention.[29] Hemorrhage volumes on B0 EPI were larger than NCCT. However, it is possible to convert hemorrhage volumes from one modality to another.[30]

Adaptation of the classification could render NCCT and B0 EPI HT assessments more equivalent. This different classification could have three subtypes instead of four. Merging HI2 and PH1 would make classifying HT less complicated. Although it is thought that HI and PH have distinct pathophysiology, the functional outcomes of HI2 and PH1 are similar.[3,4,31] Most studies merged the HI and PH subtypes or examined asymptomatic versus symptomatic intracranial hemorrhage while they assessed possible risk for HT.[32,33] Studies that examined risk factors for HI and PH separately found that risk factors differ between HI and PH.[32,33] It is possible however, that this difference in risk factors between HI and PH is mostly driven by PH2.

This study has several limitations. First, because of the post-hoc nature of this study results should be interpreted with caution. Second, the time interval between scan moments might have had an influence on hemorrhage volumes. To minimize this influence several patients with frank hemorrhage growth or new hemorrhage were excluded. Additionally, we did see a clear trend with larger volume differences between modalities with increasing time intervals between imaging acquisition. As such, the interval between scans might not have had a significant influence on the results. However, we cannot exclude that hemorrhage growth or resorption has influenced the results. Hemorrhage volumes were larger on B0 EPI than NCCT. In some cases, however, the hemorrhage volume was larger

on NCCT than B0 EPI, either due to contrast staining on NCCT or insufficient scan quality of B0 EPI. Last, since we did not perform a double reading on the B0 EPI cases we could not assess the inter-observer variability. Therefore, the inter-modality agreement might be somewhat affected by inter-observer variability, which could have resulted in lower kappa values. However, previous studies showed better inter-observer agreement on MRI than NCCT.[10,13,26]

In conclusion, hemorrhagic transformation assessment on NCCT and B0 EPI are not fully comparable, necessitating standardization of the classification on both modalities to ensure comparability among trials.

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Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone

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J Neurointerv Surg. 2022 Nov 17:jnis-2022-019569. doi: 10.1136/jnis-2022-01956.

Abstract

Background

Intravenous alteplase treatment (IVT) for acute ischemic stroke carries a risk of intracranial hemorrhage (ICH). However, reperfusion of an occluded vessel itself may contribute to the risk of ICH. We determined whether IVT and reperfusion are associated with ICH or its volume in the MR CLEAN-NO IV trial.

Methods

The MR CLEAN-NO IV trial randomized patients with acute ischemic stroke due to large vessel occlusion receive either IVT followed by endovascular treatment (EVT) or EVT alone. ICH was classified according to the Heidelberg bleeding classification on follow-up MRI or CT approximately 8 hours -7 days after stroke. Hemorrhage volume was measured with ITK-snap. Successful reperfusion was defined as extended Thrombolysis in Cerebral Infarction (eTICI) score of 2b-3. Multinomial and binary adjusted logistic regression were used to determine the association of IVT and reperfusion with ICH subtypes.

Results

Of 539 included patients, 173(32%) developed ICH and 30 suffered from sICH(6%). Of patients with ICH, 102 had hemorrhagic infarction, 47 had parenchymal hematoma, 44 had SAH, and 6 had other ICH. Reperfusion was associated with a decreased risk of SAH and IVT was not associated with SAH (eTICI2b-3: adjusted odds ratio(aOR) 0.45, 95%confidence interval(95%CI):0.21-0.97; EVT without IVT:OR:1.6,95%CI:0.91-2.8). Reperfusion status and IVT were not associated with overall ICH, hemorrhage volume, and sICH (sICH: EVT without IVT, OR:0.96,95%CI:0.41-2.25, eTICI2b-3, OR:0.49,95%CI:0.23-1.05).

Conclusion

Neither IVT administration prior to EVT nor successful reperfusion after EVT were associated with ICH, hemorrhage volume, and sICH. SAH occurred more often in patients for whom successful reperfusion was not achieved.

Key messages

What is already know on this topic – When intravenous thrombolysis was introduced as treatment for acute ischemic stroke, intracranial hemorrhage was a feared complication of thrombolytic agents and therefore strict eligibility criteria were introduced.
What this study adds – This study shows that neither administration of intravenous thrombolysis before endovascular therapy nor reperfusion are significantly associated with intracranial hemorrhage. Absence of successful reperfusion was associated with subarachnoid hemorrhage.

How this study might affect research, practice or policy – Patients eligible for treatment with intravenous thrombolysis in addition to thrombectomy should not be withhold from treatment to reduce the risk of intracranial hemorrhage. Subarachnoid hemorrhage is a complication of endovascular therapy that should be considered when the procedure is difficult and more reperfusion attempts are made.

Introduction

Intracranial hemorrhage (ICH) can occur after acute ischemic stroke as a complication of treatment or as natural progression of the disease. ICH can be symptomatic (sICH), when associated with neurological loss of function, or remain asymptomatic. sICH is associated with poor long-term functional outcomes and high mortality rates.[1] Asymptomatic ICH does not cause acute neurological deterioration, but can still impair long-term functional outcome.[2–4] Hemorrhagic transformation (HT) is the most common form of ICH after acute ischemic stroke. HT is categorized based on its radiological appearance as hemorrhagic infarction (HI) or parenchymal hematoma (PH). Both HI and PH are subdivided in small (type 1) and large (type 2) subtypes.[5] PH2 is the most severe HT subtype, consisting of frank parenchymal hemorrhage in more than 30% of the infarcted area with a space-occupying effect.[5] In most cases, sICH is caused by PH2. The definition of sICH varies over scoring systems. The frequently used Heidelberg criteria define sICH as any ICH that is the dominant brain pathology causal for neurological deterioration with a decrease of ≥4 points on the National institutes of Health stroke scale (NIHSS) or ≥2 points in one NIHSS category.[1] Another subtype of ICH is subarachnoid hemorrhage (SAH), which can occur isolated or in combination with HI or PH, it can be a complication of endovascular therapy and has been associated with worse functional outcome.[6]

Treatment with thrombolytic agents is associated with an increased risk of HT and sICH.[7] However, it is still unclear whether the thrombolytic agents or reperfusion of an occluded vessel itself is the main cause of the hemorrhage. Multiple prior analyses have demonstrated a relationship between reperfusion and hemorrhage.[8,9] However, reperfusion with thrombolytic agents might have confounded that relation because thrombolytic agents themselves might induce or exacerbate hemorrhagic transformation.[10,11] Reperfusion can also be achieved with endovascular treatment (EVT), which has, in contrast to the administration of thrombolytic agents, not been associated with HT. [12–18] The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) NO IV trial randomized patients to intravenous alteplase treatment (IVT) followed by EVT or EVT alone, without IVT.[19] This is the first study that is able to separate thrombolytic agents from the relation of reperfusion with hemorrhagic transformation by randomization of patients to EVT with or without prior IVT. In the current substudy, we used data from the MR CLEAN-NO IV trial to determine whether thrombolytic agents or reperfusion were associated with any ICH subtype. Additionally, we determined whether thrombolytic agents were associated with

increased hemorrhage volumes compared to patients receiving EVT without IVT.

Methods

Patients

All patients from the MR CLEAN-NO IV trial were included. MR CLEAN-NO IV was a multicenter randomized controlled trial that assessed the effect of EVT without IVT compared to IVT followed by EVT in patients with an acute ischemic stroke due to a large vessel occlusion of the anterior circulation who presented directly at an EVT capable center.[19] Patients presenting within 4.5 hours of stroke onset and who were eligible for IVT and EVT were included in the trial. The design of the trial has been described in more detail previously.[20] The MR CLEAN NO IV trial was prospectively registered with ISRCTN registry number: ISRCTN80619088.

Imaging

ICH was assessed on follow-up imaging by the MR CLEAN-NO IV imaging core-lab, blinded to treatment allocation. Follow-up imaging (MRI or NCCT) was performed at 5-7 days after stroke onset or at discharge (if discharge occurred earlier). If 5-7 day or discharge imaging was not available, imaging acquired at 8-72 hours after stroke was used. All hemorrhages were assessed according to the Heidelberg bleeding classification.[1] In addition, we classified SAH according to severity: minor in case of hemorrhage limited to the Sylvian fissure, intermediate in case of hemorrhage extending outside of the Sylvian fissure but within one hemisphere, and major in case of hemorrhage in both hemispheres or with mass effect. Hemorrhage volume (ml) was measured manually by an experienced observer (KRK) who delineated the hemorrhage with ITK-snap version 3.4.0 on all available follow-up imaging blinded to clinical data. If necessary, secondary reading with an experienced neuro-radiologist (CBLMM) was performed to resolve difficult cases.

Reperfusion was assessed by the imaging core-lab on final angiogram after EVT, with the extended thrombolysis in cerebral infarction (eTICI) score.[21] This scale ranges from 0 (no reperfusion) to 3 (complete reperfusion), and includes a score of 2C (90-99% reperfusion). A final score of 2B, 2C, or 3 was considered successful reperfusion.[21]

Outcomes

The outcomes evaluated in this study are hemorrhage type and hemorrhage volume. Hemorrhage volume was analyzed as a continuous variable. Hemorrhage type consisted of

three categorical variables, each individually analyzed: (1) HT, including three levels; no HT, HI and PH. To overcome the small sample size and improve statistical power, we merged HI1 with HI2 and PH1 with PH2. (2) sICH (yes or no); and (3) subarachnoid hemorrhage (SAH) (yes or no). SAH can occur separately or adjacent to HT. For the SAH analysis, we included all SAH (isolated and SAH adjacent to HT) and merged the subgroups defined by severity. Because remote PH (rPH), intraventricular hemorrhage (IVH) and subdural hemorrhage (SDH) occur sporadically these were not included in the analysis

Statistical analysis

We report baseline clinical and radiological variables by patients' hemorrhage subtype. Categorical data was presented as counts with percentages, continuous variables as medians and interquartile range (IQR).

The associations between exposures of interest (IVT (treatment allocation) and successful reperfusion) and the outcome variables (hemorrhage type and hemorrhage volume) were tested with regression models. In the IVT analysis, we did not adjust for potential confounders since the data were randomized for this variable. Potential confounders of the association between successful reperfusion and outcomes were identified used a directed acyclic graph (DAG) (Supplemental Figure S1),[22] resulting in the following adjustment variables: ASPECTS (Alberta Stroke Program Early CT Score), age, number of device attempts during EVT, collateral score, diabetes mellitus, time from onset to groin. Causal pathways shown in the DAG were based on multiple publications on factors associated with ICH and/or reperfusion.[23–31]

We used three regression analyses dependent on outcome measure: (1) binary logistic regression for binary outcomes: sICH and SAH resulting in an odds ratio (OR) and adjusted OR (aOR), (2) multinomial logistic regression for categorical variables: HT, (3) linear regression for the continuous outcome: hemorrhage volume resulting in a β value and adjusted β value (aβ). Hemorrhage volume was logarithmically transformed to meet a normal distribution (log10(x+1)). Missing values were imputed for the regression analyses only, with multiple imputation (m=5). A sensitivity analysis was conducted with data that is not imputed and an additional analysis was conducted that excluded SAH caused by a perforation to determine whether the relation of reperfusion and treatment with SAH is not driven by a small group of patients with a perforation.

All statistical analyses were performed with R {R Core Team [V.4.0.5 (2020)]; R: A language

and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; used packages: rms, mice, tableone).

Results

Of the 539 patients included in MR CLEAN-NO IV, 173 patients had any ICH (32%) and 30 suffered from sICH (6%). Of all patients with ICH, 149 patients had HT and 24 had other ICH (Table 1). Twenty-six patients (18%) with HT (HI1, HI2, PH1 or PH2) also had SAH. Of all 44 patients with SAH visible on radiological imaging, 18 patients had SAH limited to the Sylvian fissure (minor), 19 had SAH within and outside the Sylvian fissure but it remained in one hemisphere (intermediate) and 7 patients had large SAH in both hemispheres and/or causing some compression (major) (Figure 1). In 5 cases of which 4 major and 1 intermediate SAH, a perforation during the intervention was reported and all of these 5 patients had sICH. Of the 44 patients with SAH, 18 had isolated SAH and 26 patients had both SAH and HT.

Table 1. Distribution of intracranial hemorrhage classified according to the Heidelberg Bleeding Classification. ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage.

Class	Type	**ICH (n=173)**	**sICH (n=30)**
1	Hemorrhagic transformation of infarcted brain tissue		
1a	HI1 scattered small petechiae, no mass effect	**65** (38%)	**0** (0%)
1b	HI2 Confluent petechiae, no mass effect	**37** (21%)	**1** (3%)
1c	PH1 Hematoma within infarcted tissue, occupying <30%, no substantive mass effect	**23** (13%)	**3** (10%)
2	Intracerebral hemorrhage within and beyond infarcted brain tissue		
	PH2 Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect	**24** (14%)	**17** (57%)
3	Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage		
3a	Parenchymal hematoma remote from infarcted tissue	**4** (2%)	**2** (7%)
3b	Intraventricular hemorrhage	**1** (1%)	**0** (0%)
3c	Subarachnoid hemorrhage*	**18** (10%)	**7** (23%)
3d	Subdural hemorrhage	**1** (1%)	**0** (0%)

**For patients with multiple ICH types the primary (=dominant) hemorrhage type is listed. In addition to the 18 patients with subarachnoid hemorrhage of which 7 were classified as sICH, 26 patients had subarachnoid hemorrhage with other ICH as primary hemorrhage type.*

Baseline and peri-procedural characteristics of patients with HI and PH, compared to those without HT are summarized in Table 2. Patients with PH had a longer time from stroke onset to groin puncture than patients without HT (PH: median 152 minutes, IQR 129-219 vs. no HT: median 130, IQR 104-171, p<0.01) and patients with HT had a higher baseline blood glucose levels than patients without HT (HI: median 7 mmol/L, IQR 6-9, PH: median 8, IQR 6-9 vs. no HT: median 7, IQR: 6-8, p<0.01). Diabetes mellitus was more common among patients with HI than patients without HT (23% vs. 13%, p<0.05). Baseline and peri-procedural characteristics of patients with SAH and sICH are presented in Supplemental Table S1 and S2. In summary, patients with SAH had more passes during EVT (SAH: median 3, IQR 2-5 vs. no SAH: median 2, IQR 2-3, p=0.01), successful reperfusion (eTICI2b3) was less often achieved (SAH: 61% vs. no SAH: 84%, p<0.01) and they were more often treated without prior IVT (EVT without IVT, SAH: 66% vs. no SAH: 49%, p=0.05). Patients with or without sICH were evenly distributed among treatment groups and successful reperfusion rates were not significantly different.

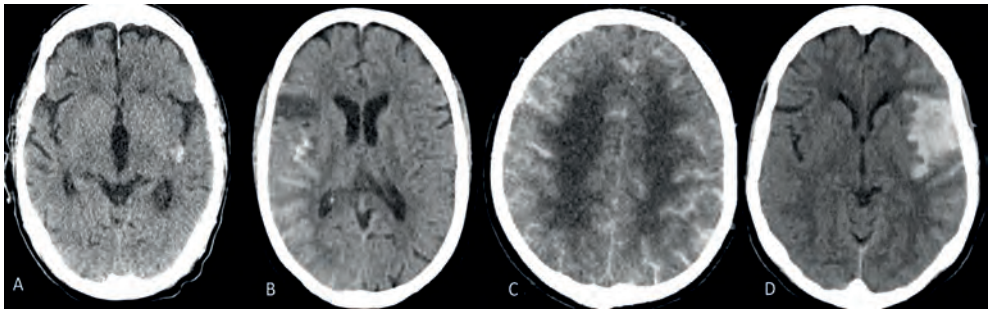


***Figure 1. Subarachnoid hemorrhage classification**. A: Minor; with hemorrhage within the Sylvian fissure only. This patient had aphasia that recovered after one day. Minor symptoms remained after three months; modified Rankin Scale score (mRS) 1; B: Intermediate, hemorrhage within the Sylvian fissure or spread over the sulci of one hemisphere without mass effect. Three-month outcome for this patient was slight disability, mRS 2; C: Major, distributed over the sulci of both hemispheres, 90-day mRS 2; D: Major, with compression on surrounding tissue, 90-day mRS 0.*

Table 2. Baseline characteristics of patients with hemorrhagic transformation				
	No HT	HI	PH	NA
n	340	102	47	50 (10%)
Treatment group = EVT without IVT (%)	175 (52%)	52 (51%)	22 (47%)	
age (median (IQR))	70 [61, 78]	72 [62, 79]	71 [62, 80]	
sex = Male (%)	194 (57%)	58 (57%)	25 (53%)	
Time from onset to groin (min) (median [IQR])	130 [104, 171]	144 [111, 182]	152 [129, 219]	19 (4%)
Previous stroke (%)	53 (16%)	19 (19%)	9 (19%)	
Baseline NIHSS (median [IQR])	16 [9, 20]	16 [11, 21]	17 [13, 21]	
Atrial fibrillation (%)	36 (11%)	10 (10%)	6 (13%)	
Diabetes mellitus (%)	45 (13%)	23 (23%)	9 (19%)	
Hypertension (%)	149 (44%)	59 (58%)	20 (43%)	
Antiplatelet use (%)	111 (33%)	46 (45%)	16 (34%)	
Baseline systolic blood pressure mmHg (median [IQR])	148 [130, 169]	152 [136, 163]	156 [135, 177]	2 (0.4%)
Hypercholesterolemia (%)	85 (25%)	35 (34%)	15 (32%)	
Blood glucose mmol/L (median [IQR])	6.5 [5.8, 7.6]	6.8 [5.9, 9.0]	7.7 [6.2, 9.3]	5 (1%)
INR (median [IQR])	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	70 (14%)
Peri-procedural characteristics of patients with hemorrhagic transformation				
Baseline ASPECTS (median [IQR])	9 [8, 10]	9 [7, 10]	9 [8, 10]	
Occlusion location n (%)				1 (0.2%)
– ica	2 (1%)	2 (2%)	0 (0%)	
– ica-t	68 (20%)	23 (23%)	9 (19%)	
– M1	212 (63%)	58 (57%)	28 (60%)	
– M2	54 (16%)	19 (19%)	8 (17%)	
– none	3 (1%)	0 (0%)	2 (4%)	
first device type n (%)				45 (9%)
– Aspiration First	67 (22%)	21 (21%)	6 (15%)	
– SR	234 (78%)	78 (78%)	34 (85%)	
Collateral score n (%)				11 (2%)
– 0 (absent collaterals)	17 (5%)	8 (8%)	5 (11%)	
– 1 (filling ≤50% of occluded area)	96 (29%)	31 (30%)	12 (27%)	
– 2 (>50% but less <100%)	135 (41%)	45 (44%)	22 (49%)	
– 3 (100% of occluded area)	83 (25%)	18 (18%)	6 (13%)	
Reperfusion (eTICI2b3) n (%)	249 (82%)	79 (80%)	35 (85%)	45 (9%)
Reperfusion (eTICI2c3) n (%)	185 (61%)	50 (51%)	24 (57%)	45 (9%)

Total attempts (median [IQR])	2 [2, 3]	3 [2, 4]	2 [2, 4]	
Anaesthesia deepest n (%)				23 (5%)
– 0 - None (local only)	209 (65%)	58 (57%)	25 (57%)	
– 1 - None with bolus short working opiates	29 (9%)	6 (6%)	5 (11%)	
– 2 - Moderate sedation	26 (9%)	19 (19%)	8 (18%)	
– 3 - Deep sedation	5 (2%)	1 (1%)	1 (2%)	
– 4 - General anaesthesia	49 (15%)	17 (17%)	5 (11%)	
TOAST n (%)				
– Cardioembolic	83 (24%)	28 (28%)	12 (26%)	
– Large artery atherosclerosis	41 (12%)	21 (21%)	9 (19%)	
– Other determined	2 (1%)	0 (0%)	0 (0%)	
– Undetermined etiology	200 (59%)	49 (48%)	25 (53%)	
– Undetermined etiology: more than one cause	14 (4%)	4 (4%)	1 (2%)	
Recanalization on 24h FU n (%)	246 (82%)	70 (79%)	25 (78%)	62 (13%)
Abbreviations: HT, hemorrhagic transformation; HI, hemorrhagic infarction; PH, parenchymal hematoma; EVT, endovascular therapy; IVT, Intravenous alteplase treatment; NIHSS, national institute of health stroke scale; ASPECTS, Alberta stroke program early CT score; IQR, interquartile range; ICA-T, tandem occlusion of carotid internal artery; M1, medial cerebral artery segment 1; M2, medial cerebral artery segment 2; SR, stent retriever; DSA, digital subtraction angiography; A2, anterior cerebral artery segment 2; eTICI, extended thrombolysis in cerebral infarction; TOAST, trial of ORG 10172 in Acute Stroke Treatment. INR, international normalized ratio; IQR, interquartile range.				

Regression analysis

In the regression analyses, treatment allocation (prior IVT: yes/no) and successful reperfusion were not significantly associated with the occurrence of any HT subtype or with hemorrhage volume (Table 3). Additionally, treatment allocation was not significantly associated with sICH. In the univariable analyses, successful reperfusion (eTICI2b/3 and eTICI3c/3) was associated with sICH, however this association was not significant in the multivariable analysis. Hemorrhage volume per treatment group and reperfusion status are presented in Supplemental figure S2. IVT prior to EVT was not significantly associated with SAH. Successful reperfusion was significantly associated with a decreased risk of SAH in the uni- and multivariable analysis. The sensitivity analysis with the unimputed data shows similar results, although EVT without IVT was significantly associated with SAH (OR: 1.98, 95%CI: 1.05 – 3.88) and this association remained significant after excluding patients with SAH due to a perforation (OR: 2.05, 95%CI: 1.04 – 4.2)(supplemental table S3).

Table 3. Association of treatment modality and reperfusion with HT, sICH and hemorrhage volume.					
	HI	PH	SAH	sICH	Hemorrhage volume
Univariable	OR and 95&CI	OR and 95&CI	OR and 95&CI	OR and 95&CI	β and 95&CI
EVT without IVT	0.95 (0.62 - 1.44)	0.94 (0.62 - 1.71)	1.76 (0.92 - 3.35)	0.96 (0.41 - 2.25)	-0.08 (-0.17 - 0)
eTICI2b/3	0.9 (0.54 - 1.53)	0.89 (0.37 - 2.15)	0.41 (0.19 - 0.86)	0.47 (0.23 - 0.98)	-0.05 (-0.16 - 0.06)
eTICI2c/3	0.76 (0.51 - 1.15)	0.85 (0.42 - 1.73)	0.47 (0.26 - 0.87)	0.54 (0.29 - 0.99)	0.01 (-0.08 - 0.1)
Multivariable					
eTICI2b/3	0.95 (0.56 - 1.62)	0.99 (0.42 - 2.36)	0.45 (0.21 - 0.97)	0.49 (0.23 - 1.05)	-0.04 (-0.14 - 0.05)
eTICI2c/3	0.79 (0.52 - 1.22)	0.91 (0.44 - 1.89)	0.53 (0.29 - 0.99)	0.56 (0.3 - 1.05)	0.01 (-0.07 - 0.1)
Abbreviations: HI, hemorrhagic infarction; PH, parenchymal hematoma; SAH, subarachnoid hemorrahge; sICH, symptomatic intracranial hemorrhage; EVT, endo-vascular therapy; eTICI, extended thrombolysis in cerebral infarction.					
Missing values where imputed using multiple imputations (M=5)					
Adjusted for following potential confounders; age, attempts, collateral score, time from stroke onset to groin, treatment allocation					

Discussion

In this population of patients randomized to either undergo IVT followed by EVT or EVT without IVT, neither treatment with IVT nor successful reperfusion after EVT were associated with HT, sICH , or hemorrhage volume. However, SAH was more commonly observed in patients with a lack of reperfusion after EVT.

Recently published randomized trials that compared EVT alone with EVT followed by IVT (DIRECT-MT, SKIP, DEVT, SWIFT DIRECT, DIRECT SAFE) found similar results regarding the associations between IVT and ICH compared to ours.[32–36] In these trials, sICH rates were not significantly different between treatment arms. In contrast to our study however, the DEVT and SKIP trials did observe less asymptomatic ICH in the EVT without IVT group.[33,34] Only the DEVT and SWIFT DIRECT trials reported SAH rates, in the DEVT trial they observed only two patients with SAH in both treatment groups and SAH rates in the SWIFT DIRECT trial were similar to ours.[34,36]

Since the start of stroke treatment with IVT, ICH has been the most feared complication of stroke treatment.[37,38] With EVT as standard of care since 2015, it became possible to study whether IVT, or reperfusion of ischemic tissue by any revascularization method is associated with ICH. Especially in the MR CLEAN-NO IV data set, where IVT administration prior to EVT was randomized, a comparison unaffected by IVT indication bias was possible. However, the results of our study do not answer this question as we would have expected: neither IVT nor reperfusion seem to have a clear association with HT, sICH or hemorrhage volume. Several reasons could explain our findings. First, the overall ICH rate was relatively low. All patients were treated within 4.5 hours after stroke onset whereas ICH rates increase when treatment is initiated after a longer time from stroke onset.[39] Compared with the MR CLEAN trial[12], the MR CLEAN-NO IV trial has a 15% reduction of ICH rates, probably due to the improved workflow and inclusion of patients presenting with stroke at EVT capable centers only, further decreasing treatment delays by interhospital transfer. Second, successful reperfusion was relatively high. Successful reperfusion was achieved in almost all patients which resulted in a small group of patients without successful reperfusion to compare ICH rates. Last, the higher rate of SAH in the EVT without IVT group could mask potential differences with regard to HT.

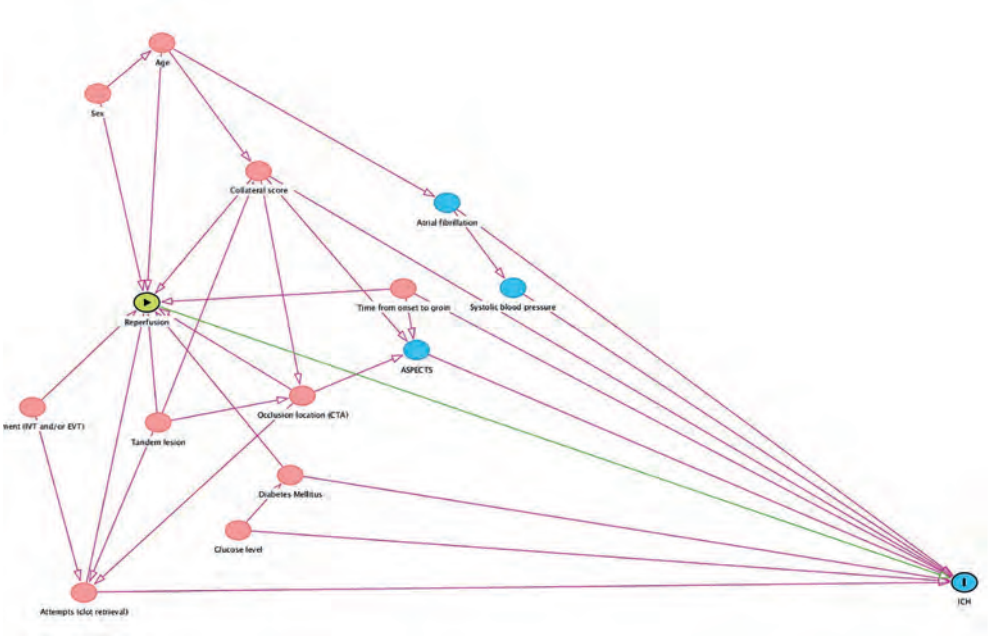
In most cases, no frank perforation was observed in patients with SAH after EVT and therefore not likely to be the underlying cause of all SAH. It has been hypothesized that

manipulation and stent retrieval during EVT might stretch perforating arterioles and venules in the subarachnoid space, resulting in hemorrhage.[40] This hypothesis is partly supported by our results, as we observed that in patients with SAH more thrombus retrieval attempts were made during EVT, and more patients did not reach successful reperfusion. Additionally, SAH was more commonly observed in the EVT without IVT group which is also reported by a previously published study.[6] It is possible that the procedure in these patients with SAH was more complex which might partially be caused by omitting IVT, which targets fibrin. Fibrin rich clots are stiff, eliciting more friction with the endothelium during clot removal.[41] Perhaps the superficial effect of IVT on the fibrin rich clot referred to as "thinning" might facilitate clot removal during EVT, or prior IVT helps to reduce the overall thrombus load, facilitating clot removal.[42,43] Moreover, SAH after stroke treatment is distributed differently in the subarachnoid space compared to SAH caused by a ruptured aneurysm.[44] In most cases, SAH after EVT is small and peripheral, remaining within the Sylvian fissure or spread over the sulci of one hemisphere and without mass effect (minor or intermediate severity SAH). However, it is unclear what the clinical relevance is of these isolated minor and intermediate SAHs (SAH without HT). Good functional outcomes after those isolated SAHs have been reported previously.[45] Some cases of SAH are more severe, with hemorrhage spread out over the sulci of both hemispheres or even with some mass effect (major SAH). In our study, a few patients had major SAH and most of these major SAH were classified as sICH.

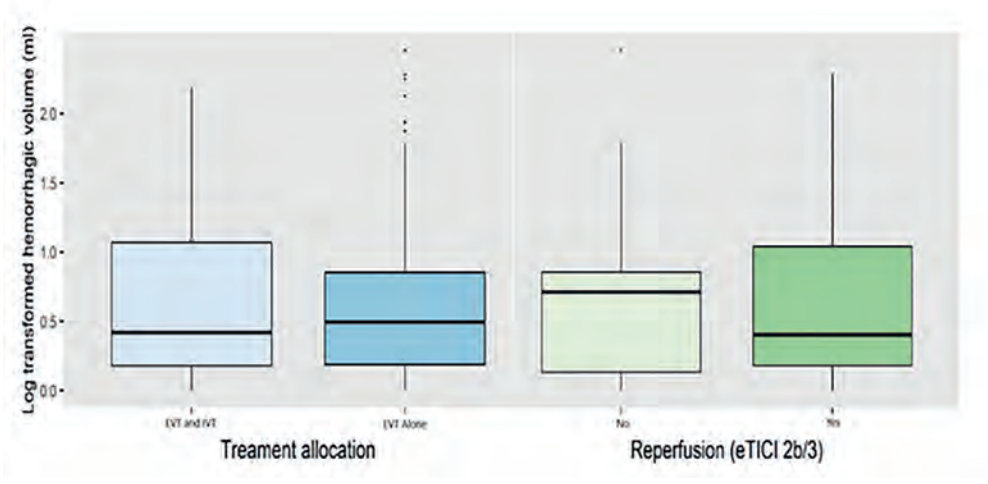
Our study has several limitations. Due to a relatively small sample size of patients per ICH subtype, we merged HI1 and 2, PH1 and 2, using HI and PH instead. Additionally, we merged the SAH subtypes and excluded IVH, rPH and SDH from the entire analysis. This results in some loss of information about the specific ICH subtypes. However, it improved power to determine the association of IVT and reperfusion with HI, PH and SAH. Hemorrhage volume was measured on CT or MRI, when follow-up CT was not available. This could have resulted in a higher rate of small HT cases, and larger hemorrhage volumes, since MRI is more sensitive to hemorrhage and hemorrhages appear larger on MRI than on CT.[46] Because of missing follow-up imaging of 50 patients, we imputed the missing data on HT classification. Imputation affected the results significantly, which was shown with the sensitivity analysis. However, the results from the sensitivity analysis should be interpreted with caution as they could be biased because one of the reasons for the missing data might be due to death before follow-up imaging could be acquired and an underlying ICH could not be confirmed or excluded. Contrary, patients whose symptoms completely recovered might have been discharged before follow-up imaging would have taken place and an underlying ICH would be very unlikely.

In conclusion, neither IVT administration prior to EVT nor successful reperfusion after EVT were significantly associated with HI, PH, sICH, or hemorrhage volume. SAH however, occurred significantly more often in patients without successful reperfusion.

Supplemental material



Supplemental figure S1: Directed acyclic graph (DAG) of the relation of reperfusion with ICH. According to this DAG minimal sufficient adjustment for estimating the effect of reperfusion on ICH should be made for; age, attempts, collateral score, time from stroke onset to groin and treatment allocation.



Supplemental figure S2. Logarithmically transformed hemorrhage volume per treatment allocation and reperfusion.
Abbreviations: EVT, endovascular therapy; IVT, intravenous alteplase; eTICI, extended thrombolysis in cerebral infarction.

Supplemental table S1. Baseline Characteristics of patients with subarachnoid hemorrhage		
	No SAH	SAH
n	445	44
Treatment group = EVT without IVT (%)	220 (49%)	29 (66%)
age (median [IQR])	70 [61, 78]	72 [61, 80]
sex = Male (%)	252 (57%)	25 (57%)
Time from onset to groin (min)	132 [105, 175]	146 [120, 208]
Previous stroke (%)	73 (16%)	8 (18%)
Baseline NIHSS (median [IQR])	16 [10, 20]	16 [11, 20]
Atrial fibrillation (%)	43 (10%)	9 (20%)
Diabetes mellitus (%)	70 (16%)	7 (16%)
Hypertension (%)	207 (47%)	21 (48%)
Antiplatelet use (%)	161 (36%)	12 (27%)
Baseline systolic blood pressure mmHg (median [IQR])	150 [132, 169]	139 [130, 160]
Hypercholesterolemia (%)	123 (27%)	12 (27%)
Blood glucose mmol/L (median [IQR])	6.6 [5.9, 7.8]	6.7 [5.8, 7.9]
INR (median [IQR])	1.0 [1.0, 1.1]	1.0 [1.0, 1.2]
Peri-procedural characteristics		
Baseline ASPECTS (median [IQR])	9 [8, 10]	9 [8, 10]
Occlusion location (%)		
– ica	4 (1%)	0 (0%)
– ica-t	91 (21%)	9 (21%)
– M1	273 (62%)	25 (57%)
– M2	72 (16%)	9 (21%)
– none	4 (1%)	1 (2%)
first device type (%)		
– Aspiration First	88 (22%)	6 (15%)
– SR	313 (78%)	33 (85%)
Collateral score (%)		
– 0 (absent collaterals)	24 (6%)	6 (15%)
– 1 (filling ≤50% of occluded area)	128 (29%)	11 (26%)
– 2 (>50% but less <100%)	192 (44%)	10 (24%)
– 3 (100% of occluded area)	92 (21%)	15 (36%)
Reperfusion (eTICI2b3) n (%)	338 (84%)	25 (61%)
Reperfusion (eTICI2b3) n (%)	244 (61%)	15 (37%)

Total attempts (median [IQR])	2 [2, 3]	3 [2, 5]
Anesthesia deepest (%)		
– 0 - None (local only)	268 (63%)	24 (57%)
– 1 - None with bolus short working opiates	38 (9%)	2 (5%)
– 2 - Moderate sedation	48 (11%)	8 (19%)
– 3 - Deep sedation	7 (2%)	0 (0%)
– 4 - General anesthesia	63 (15%)	8 (19%)
TOAST (%)		
– Cardioembolic	112 (25%)	11 (25%)
– Large artery atherosclerosis	63 (14%)	8 (18%)
– Other determined	2 (0%)	0 (0%)
– Undetermined etiology	252 (57%)	22 (50%)
– Undetermined etiology: more than one cause	16 (4%)	3 (7%)
Recanalization on 24h FU = Yes (%)	318 (82%)	23 (74%)

Abbreviations: SAH, subarachnoid hemorrhage; EVT, endovascular therapy; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, national institute of health stroke scale; INR, international normalized ratio; ICA, internal carotid artery; ICA-T, tandem occlusion of carotid internal artery; M1, medial cerebral artery segment 1; M2, medial cerebral artery segment 2; SR, stent retriever; DSA, digital subtraction angiography; A2, anterior cerebral artery segment 2; eTICI, extended thrombolysis in cerebral infarction; TOAST, trial of ORG 10172 in Acute Stroke Treatment.

Supplemental table 2. Baseline Characteristics of patients with sICH

	No	Yes
n	459	30
Treatment group = EVT without IVT (%)	233 (51%)	16 (53%)
age (median [IQR])	70 [61, 78]	72 [62, 82]
sex = Male (%)	261 (57%)	16 (53%)
Time from onset to groin (min)	130 [105, 174]	170 [135, 249]
Previous stroke (%)	73 (16%)	8 (27%)
Baseline NIHSS (median [IQR])	16 [10, 20]	16 [11, 20]
Atrial fibrillation (%)	47 (10%)	5 (17%)
Diabetes mellitus (%)	70 (15%)	7 (23%)
Hypertension (%)	212 (46%)	16 (53%)
Antiplatelet use (%)	161 (35%)	12 (40%)
Baseline systolic blood pressure mmHg (median [IQR])	150 [132, 167]	160 [139, 180]
Hypercholesterolemia (%)	128 (28%)	7 (23%)
Blood glucose mmol/L (median [IQR])	6.6 [5.8, 7.8]	7.3 [6.3, 8.5]
INR (median [IQR])	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]
Peri-procedural characteristics		
Baseline ASPECTS (median [IQR])	9 [8, 10]	9 [8, 10]
Occlusion location (%)		
– ica	4 (1%)	0 (0%)
– ica-t	95 (21%)	5 (17%)
– M1	283 (62%)	15 (50%)
– M2	74 (16%)	7 (23%)
– none	2 (0%)	3 (10%)
first device type (%)		
– Aspiration First	89 (21%)	5 (20%)
– SR	326 (78%)	20 (80%)
Collateral score (%)		
– 0 (absent collaterals)	30 (7%)	0 (0%)
– 1 (filling ≤50% of occluded area)	132 (29%)	7 (24%)
– 2 (>50% but less <100%)	190 (42%)	12 (41%)
– 3 (100% of occluded area)	97 (21%)	10 (35%)
Reperfusion (eTICI2b3) n (%)	344 (83%)	19 (73%)
Reperfusion (eTICI2b3) n (%)	247 (59%)	12 (46%)

Total attempts (median [IQR])	2 [2, 3]	2 [2, 4]
Anesthesia deepest (%)		
– 0 - None (local only)	278 (63%)	14 (52%)
– 1 - None with bolus short working opiates	36 (8%)	4 (15%)
– 2 - Moderate sedation	52 (12%)	4 (15%)
– 3 - Deep sedation	6 (1%)	1 (4%)
– 4 - General anesthesia	67 (15%)	4 (15%)
TOAST (%)		
– Cardioembolic	117 (26%)	6 (20%)
– Large artery atherosclerosis	66 (14%)	5 (17%)
– Other determined	2 (0%)	0 (0%)
– Undetermined etiology	257 (56%)	17 (57%)
– Undetermined etiology: more than one cause	17 (4%)	2 (7%)
Recanalization on 24h FU = Yes (%)	329 (81%)	12 (80%)

Abbreviations: sICH, symptomatic intracranial hemorrhage; EVT, endovascular therapy; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, national institute of health stroke scale; INR, international normalized ratio; ICA, internal carotid artery; ICA-T, tandem occlusion of carotid internal artery; M1, medial cerebral artery segment 1; M2, medial cerebral artery segment 2; SR, stent retriever; DSA, digital subtraction angiography; A2, anterior cerebral artery segment 2; eTICI, extended thrombolysis in cerebral infarction; TOAST, trial of ORG 10172 in Acute Stroke Treatment.

Supplementary table S3. Association of treatment modality and reperfusion with HT, SAH, sICH and hemorrhage volume (multinominal, binary logistic and linear regression with original data)

	HI	PH	SAH	SAH (excluding perfo-rations)	sICH	Hemorrhage volume
Univariable	OR and 95&CI	OR and 95&CI	OR and 95&CI	OR and 95&CI	OR and 95&CI	β and 95&CI
EVT without IVT	0.98 (0.63 - 1.53)	0.83 (0.45 - 1.53)	1.98 (1.05 - 3.88)	2.05 (1.04 - 4.2)	1.11 (0.53 - 2.35)	-0.08 (-0.16 - 0)
eTICI2b/3	0.86 (0.48 - 1.52)	1.26 (0.51 - 3.16)	0.3 (0.15 - 0.59)	0.34 (0.16 - 0.71)	0.58 (0.24 - 1.52)	-0.07 (-0.19 - 0.04)
eTICI2c/3	0.65 (0.41 - 1.03)	0.9 (0.46 - 1.75)	0.37 (0.19 - 0.72)	0.41 (0.2 - 0.82)	0.59 (0.26 - 1.31)	0.02 (-0.07 - 0.11)
Multivariable						
eTICI2b/3	1.02 (0.55 - 1.12)	1.4 (0.52 - 3.76)	0.31 (0.14 - 0.67)	0.4 (0.18 - 0.94)	0.53 (0.2 - 1.58)	-0.08 (-0.2 - 0.04)
eTICI2c/3	0.69 (0.4 - 1.11)	0.92 (0.45 - 1.89)	0.4 (0.19 - 0.82)	0.49 (0.22 - 1.05)	0.57 (0.23 - 1.4)	0.01 (-0.08 - 0.11)

Abbreviations: HI, hemorrhagic infarction; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage; EVT, endovascular therapy; eTICI, extended thrombolysis in cerebral infarction.

Adjusted for following potential confounders; age, attempts, collateral score, time from stroke onset to groin, treatment allocation

Hemorrhage volume was logarithmically transformed to meet a normal distribution (log10(x+1))

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7

General discussion and future perspectives

General discussion

It was at the end of 2014, a few months before the MR CLEAN trial was published, when I first got in contact with stroke research. At the time I was a second year medical student assisting the stroke research group in Amsterdam and unaware of the implications this pivotal trial would have. I was mainly focused on infarct segmentations on follow-up imaging when I noticed many patients also had a hemorrhage. When I noted that that almost half of the population developed a hemorrhage after an ischemic stroke treated with EVT, a large number of questions came up. I still remember this as if it happened yesterday. When I addressed my questions to Prof. Dr. H.A. Marquering he answered: "Why don't you try to figure it out". Consequently, I decided that I was going to follow up on his suggestion.

A few years later I applied for a MD/PhD scholarship that was granted by the Amsterdam University Medical Center to conduct research to answer my questions. I could alternate research and clinical internships in order to achieve my medical degree and learn more about the subject. When I started my PhD, I was particularly astonished that for almost half of the patients with a stroke and hemorrhage on follow-up imaging, this hemorrhage would not affect their functional outcome. More-over, despite the immense improvements to functional outcomes as a result of EVT in addition to medical treatment as standard of care for an anterior circulation acute ischemic stroke, hemorrhagic complications occurred frequently.[1–7] However, before we can determine how to treat or prevent hemorrhagic transformation it is necessary to determine what the risk factors for hemorrhagic transformation are, and what its impact is on functional outcome.

First, we assessed the impact of hemorrhagic transformation on functional outcome (chapters 2, 3 and 4). The next step was to determine which patients have an increased risk for hemorrhagic transformation (chapter 5). After, we assessed whether the classification of hemorrhagic transformation on NCCT is comparable with MRI (chapter 6). Finally, we assessed the association of reperfusion therapy with hemorrhagic transformation (chapter 7). In this general discussion, the findings of this thesis will be addressed further and in consideration of these findings future research will be discussed.

Hemorrhagic transformation and functional outcome

When MR CLEAN and the other randomized controlled trials established the effect of EVT in addition to medical treatment, it made an enormous impact on stroke treatment. [1–7] As such, every aspect of stroke treatment became of increased interest, including hemorrhagic transformation. Before this new stroke era, only the largest hemorrhagic transformation subtype (parenchymal hematoma type 2) was feared as in most cases it directly affected a patient's functional outcome.[8–10] In chapters 2 and 3, we assessed whether any hemorrhagic transformation subtype was associated with functional outcome after three months of stroke onset. In chapter 2 we used data form the MR CLEAN trial to assess the association of hemorrhagic transformation with functional outcome.[1] Since larger infarcts were associated with increased rates of hemorrhagic transformation and poor outcomes, we performed both analyses adjusted and unadjusted for follow-up lesion size.[8] We found that not only parenchymal hematoma type 2 was associated with functional outcome after three months of stroke onset but also, also smaller hemorrhagic transformation subtypes. Without adjustment for final lesion size, all hemorrhagic transformation subtypes were associated with functional outcome. However, after adjustment for lesion size, not the larger parenchymal hematoma type 1 but smaller hemorrhagic infarction type 2 remained associated with functional outcome.

In chapter 3, we performed a similar analysis with data from seven randomized controlled trials that established the effect of EVT in addition to medical treatment. [1–7] We assessed the association of all hemorrhagic transformation subtypes with follow-up lesion volume and functional outcome. Additionally, we determined whether patients with hemorrhagic transformation still benefitted from treatment with EVT. While the population was larger than the MR CLEAN trial alone, results were comparable to chapter 2. The results showed that all hemorrhagic transformation subtypes were associated with functional outcome assessed with the mRS on an ordinal scale. However, only hemorrhagic infarction type 2 and parenchymal hematoma type 2 were associated with functional outcome independent of follow-up lesion volume. Additionally, the results showed that treatment with EVT was always of benefit, even after hemorrhagic transformation.

The seemingly unexpected finding that hemorrhagic infarction type 2 and not parenchymal hemorrhage type 1 were associated with poor outcomes could be a result of the manner how follow-up lesion volume is determined. Follow-up lesion volumes incorporate

both the infarct and hemorrhage since they are difficult to segment separate from each other. Still, we still considered adjustment for follow-up lesion volume necessary since it is a potential confounder.[8] Another explanation for the observation that hemorrhagic infarction type 2 and not parenchymal hematoma type 1 was associated with functional outcome independent of follow-up lesion volume could be the used classification. Especially distinction between hemorrhagic infarction type 2 and parenchymal hematoma type 1 can be difficult.[11] Therefore we assessed the prognostic value of hemorrhage volume quantification in chapter 4. We measured hemorrhage volumes and assessed the association between hemorrhage volume with functional outcome. We added the hemorrhagic transformation classification to determine which measure would be a stronger predictor of outcome. Our results showed that hemorrhage volume was associated with functional outcome. When the hemorrhagic transformation classification was added to the analysis, the association of parenchymal hematoma type 2 with functional outcome was less pronounced while the other hemorrhagic transformation subtypes had a stronger association with functional outcome than hemorrhage volume. Additionally, the sensitivity analysis showed that only the volume of parenchymal hematoma type 2 was associated with functional outcome. Therefore, hemorrhage volume could have an added prognostic value but only when a parenchymal hematoma type 2 is present. Since PH2 have a substantial mass effect, larger hemorrhages constitute to an even greater mass effect on surrounding healthy brain tissue resulting in poor functional outcomes.

Together, chapter 2, 3 and 4 showed that not only parenchymal hematoma type 2 is associated with functional outcome but the smaller subtypes are associated with functional outcome as well. However, it is not entirely clear whether this association of hemorrhagic infarction type 1, 2 and parenchymal hematoma type 1 with functional outcome is caused by hemorrhage or infarct volume. This difficulty is also represented in previous literature. Previous studies that have shown an association of all hemorrhagic transformation subtypes with functional outcome did not adjust for follow-up lesion volume in their analysis.[12] On the contrary, when follow-up lesion was added to the analysis, only larger hemorrhagic transformation subtypes remain associated with functional outcome.[13] While it is clear those large hemorrhages such as parenchymal hematoma type 2 could cause brain tissue damage due to mass effect; this is not the case for the smaller hemorrhagic transformation subtypes. However, the association of the smaller hemorrhagic transformation with functional outcome might be caused by secondary brain tissue damage due to neurotoxic blood products, such as haem, iron

and thrombin.[14] It is questionable, however, whether these neurotoxic blood products would damage brain tissue that is already damaged by ischemia. It would be interesting to determine whether the location of hemorrhagic transformation relative to the infarct would influence the association with functional outcome. If the hemorrhage is located near healthy brain tissue and not within infarcted brain tissue, it might cause more damage due to its neurotoxic blood products and would impair a patient's functional outcome.

Clinical and imaging markers associated with hemorrhagic transformation

It is necessary to determine which baseline clinical or imaging characteristics are associated with hemorrhagic transformation to identify patients with an increased risk for hemorrhagic transformation after reperfusion therapy with EVT. In chapter 5, we determined the association of several clinical and imaging factors with hemorrhagic transformation. At the time we conducted the study, EVT was a relatively new treatment and risk factors for hemorrhagic transformation after reperfusion therapy with EVT were yet to be determined. Our results showed that several markers indicative for large infarcts, such as high NIHSS and poor collateral scores were associated with hemorrhagic infarction. Furthermore, clinical markers, such as increased admission systolic blood pressure, atrial fibrillation and antiplatelet use were associated with parenchymal hematoma and symptomatic intracranial hemorrhage. From these associated parameters, blood pressure is the most interesting, as blood pressure lowering could be a possible medical intervention.

Several studies determined an association of blood pressure with hemorrhagic transformation and/or symptomatic intracranial hemorrhage.[15–22] The timing and type of blood pressure measurements varied between studies. For example, in chapter 5 an increased systolic blood pressure measured on admission was associated with parenchymal hematoma and symptomatic intracranial hemorrhage. The Multicenter rt-PA Acute Stroke Survey, showed that an elevated pretreatment mean blood pressure was associated with hemorrhagic transformation and symptomatic intracranial hemorrhage.[17] Additionally, the SITS-ISTR trial showed that increased systolic blood pressures 2-24 hours after treatment with IVT is associated with symptomatic intracranial hemorrhage.[19] In a MR CLEAN registry sub-study, maximum systolic blood pressure in the first six hours after treatment with EVT was associated with symptomatic intracranial hemorrhage.[23]

Altogether, there is a large amount of evidence of an association of increased blood pressure with hemorrhagic transformation and/or symptomatic intracranial hemorrhage.[15–21] Therefore, the ENCHANTED trial determined whether intensive blood pressure lowering would improve functional recovery and reduce the risk of hemorrhagic transformation after an acute ischemic stroke.[24] However, rapid reduction of blood pressure before reperfusion is established could result in exacerbation of hypo perfusion. In turn, this could increase the risk for ischemia eventually resulting in poor functional outcomes.[16,25–27] For this reason, intensive blood pressure lowering during the ENCHANTED trial was started after reperfusion therapy with IVT.[24] Blood pressure lowering with a target systolic blood pressure of 130-140 mmHg was compared with a guideline-recommended systolic blood pressure < 180 mmHg. Surprisingly, the study showed no significant difference in symptomatic intracranial hemorrhage or functional outcome between the groups. However, hemorrhagic transformation was less often observed in the intensive blood pressure lowering group.[24] The Blood Pressure target trial took the blood pressure lowering measures even further with a systolic blood pressure target of 100-129 mmHg after reperfusion therapy with EVT compared to the standard systolic blood pressure target of 130-185 mmHg.[28] Interestingly, the results showed no difference in occurrence of hemorrhagic transformation between the two groups.[28] The ENCHANTED 2 trial randomized stroke patients with a persistent elevated blood pressure (>140 mmHg for > 10 min) after successful reperfusion to intensive blood pressure lowering (systolic blood pressure target <120 mmHg) or less intensive (140-180 mmHg).[29] In the intensive blood pressure lowering group, patients had worse functional outcomes than the less intensive blood pressure lowering group. However, rates of symptomatic intracranial hemorrhage did not differ between the groups.[29] With the previously discussed observational studies that showed an association with blood pressure and hemorrhagic transformation, the results of the ENCHANTED 1/2 and Blood Pressure target trial might seem unexpected. However, the trials only had a slight difference in mean blood pressure between treatment groups < 10 mmHg which could be somewhat explanatory.[24,28,29]

Blood pressure is not only important because it is a possible target for medical intervention; it is also an important baseline characteristic that could help identify patients at risk for hemorrhagic transformation. Based on associations of clinical and imaging markers with hemorrhagic transformation as described in chapter 4, several prediction tools have been developed.[30–36] These prediction tools could help identify patients at risk for hemorrhagic transformation. If we can identify patients at risk for hemorrhagic

transformation, patient-tailored care could be applied, where we could increase the frequency of medical checks or even start with possible medication preventive for hemorrhagic transformation when it becomes available in the future. Most prediction tools are developed to predict symptomatic intracranial hemorrhage since it is the most feared form of hemorrhagic transformation.[31–36] The prediction scores are all based on different clinical and imaging characteristics, however most scores included age, NIHSS, systolic blood pressure, baseline glucose level and early ischemic changes on NCCT.[30–36] Machine learning algorithms could help determine which markers are most predictive for hemorrhagic transformation and/or symptomatic intracranial hemorrhage.[30]

Imaging of hemorrhagic transformation

Classifying hemorrhagic transformation can be challenging, especially when some hemorrhages seem to fit more than one classification. Additionally, the use of both NCCT and MRI as follow-up imaging (sometimes in the same trial) will complicate classifying hemorrhagic transformation even further as they visualize hemorrhage transformation differently. Because both modalities are used in clinical trials,[37–40] we assessed in chapter 6 whether hemorrhagic transformation is comparable between NCCT and B0 echo planar diffusion weighed imaging (B0 EPI) MRI. We compared the ECASS classification and hemorrhage volume between NCCT and B0 EPI. B0 EPI was used to compare NCCT with because it is suitable for detecting hemorrhagic transformation and is less susceptible to susceptibility artifacts, potentially causing less overestimation than T2* or susceptibility weighted imaging.[42] The results showed that the inter-modality agreement for overall hemorrhagic transformation was fair, moderate for hemorrhagic infarction type 1 and slight for hemorrhagic infarction type 2 and parenchymal hematoma type 1. The inter-modality agreement for PH2 was good. Hemorrhage volumes were larger on B0 EPI than NCCT. Therefore, hemorrhagic transformation between NCCT and B0 EPI are not comparable except for when it matters most, in case of a parenchymal hematoma type 2.

The susceptibility effect is one of the causes for the overestimation of the classification of hemorrhagic transformation on gradient echo MRI compared to NCCT. Susceptibility weighted imaging is especially sensitive for paramagnetic compounds such as deoxyhemoglobin.[43–45] A previous study showed that it is possible to convert hemorrhage volume from one modality to another by using a formula.[46] However, hemorrhage volumes are usually not measured in clinical practice or even trials. Instead the Heidelberg bleeding classification is commonly used.[47] Our results showed that especially distinction between

hemorrhagic infarction type 2 and parenchymal hematoma type 1 was complicated and that the other subtypes had at least a moderate inter-modality agreement. Estimating functional outcome is the main reason for classifying hemorrhagic transformation and several studies showed that the functional outcome between hemorrhagic infarction type 2 and parenchymal hematoma type 1 is similar.[12,13,48–50] Therefore, merging these hemorrhagic transformation subtypes would not significantly affect their association with functional outcome. However, future studies should determine whether merging hemorrhagic infarction type 2 and parenchymal hematoma type 1 would improve the inter-observer and/or inter-modality agreement.

Hemorrhagic transformation and reperfusion therapy

Several decades ago, when IVT was introduced as effective treatment for an acute ischemic stroke, hemorrhagic transformation was more commonly observed among patients treated with IVT.[51–57] Therefore, strict eligibility criteria were introduced for treatment with IVT. For example, WHO guidelines recommended a time from stroke onset to treatment of less than 4.5 hours.[58] When EVT was introduced as treatment for acute ischemic stroke, rates of hemorrhagic transformation did not increase in patients treated with EVT after IVT compared with IVT alone.[1–7] Therefore, the MR CLEAN NO-IV trial and several other randomized clinical trials determined the effect of EVT without IVT compared with IVT followed by EVT.[37–40,59,60] Because of these trials, it became possible to determine whether reperfusion or IVT was associated with hemorrhagic transformation.[37–40,59,60] We assessed this subject in chapter 7 by determining the association of IVT and reperfusion with hemorrhagic transformation, hemorrhage volume and symptomatic intracranial hemorrhage. The results showed no association with hemorrhagic transformation, hemorrhage volume or symptomatic intracranial hemorrhage of IVT or degree of reperfusion. However, more patients with subarachnoid hemorrhage were observed in the group of patients that did not receive IVT before EVT. Additionally, unsuccessful reperfusion was associated with subarachnoid hemorrhage.

Although we did not show an association of IVT with hemorrhagic transformation in chapter 7, a meta-analysis of the six randomized controlled trials that determined the effect of EVT without IVT compared to EVT after administration of IVT did show an association with any hemorrhagic transformation.[61] More hemorrhages were observed in the group that received IVT prior to EVT.[61] Rates of symptomatic intracranial hemorrhage

did not differ statistically significantly between the groups. In most cases, alteplase is used as treatment with IVT. However, other IVT medications could give better results than alteplase. For example, tenecteplase is associated with better functional outcomes compared to alteplase in patients with large vessel occlusion eligible for EVT.[62–66] However, the used dose of tenecteplase is of importance. While a dose 0.25 mg/kg tenecteplase did not show increased rates of symptomatic intracranial hemorrhage, trials investigating a higher 0.40 mg/kg dose did observe more frequent symptomatic intracranial hemorrhages.[62–67] This led to one trial being stopped due to safety concerns.[67]

Subarachnoid hemorrhage is a complication of EVT that can occur due to wire perforation. However, manipulation during EVT or stent retrieval could also stretch perforating arterioles and venules resulting in (often less pronounced) subarachnoid hemorrhage.[68] EVT in patients not treated with IVT could make the procedure more difficult as partial lysis of the clot did not occur without IVT resulting in more friction during clot retrieval.[69] However, in the post-hoc analysis of the DIRECT-MT trial more patients with subarachnoid hemorrhage were observed in the group that received both IVT and EVT.[70]

In the MR CLEAN NO-IV trial, we observed 44/539 (8%) patients with subarachnoid hemorrhage.[40] This number is even larger in the DIRECT-MT trial, where they observed 88/633 (14%) patients with subarachnoid hemorrhage. [70] Compared with the MR CLEAN trial this is a very significant increase, as we only observed 2/478 (0.4%) patients with subarachnoid hemorrhage in that population.[1] It is possible that the awareness for bleeding complications after EVT has increased, resulting in more accurate scoring of hemorrhages. For example, of those 44 subarachnoid hemorrhages described in chapter 7, 26 patients had subarachnoid hemorrhage with another primary hemorrhage subtype. Before the introduction of the Heidelberg bleeding classification, subarachnoid hemorrhage would not be classified separately when another primary hemorrhage type was present.[47] What the impact is on functional outcome of subarachnoid hemorrhage after EVT is still unclear. As described in chapter 7, subarachnoid hemorrhage after EVT appears differently than subarachnoid hemorrhage that occurred due to a ruptured aneurysm.[71] In most cases, the subarachnoid hemorrhage after EVT was small and limited to the Sylvian fissure of one hemisphere. Therefore, these hemorrhages might not have a negative impact on functional outcome.[72] However, subarachnoid hemorrhage is a complication of EVT that should not be ignored and could be related to the technique or device that is used during EVT.

In chapter 7 and the meta-analysis that included all six randomized trials that determined the effect of EVT without IVT, no significant association of IVT or reperfusion with hemorrhage volume or symptomatic intracranial hemorrhage was shown.[61] IVT with alteplase or tenecteplase may not increase the risk of symptomatic intracranial hemorrhage when it is administered within 4.5 hours of stroke onset.[62] However, in the the MR CLEAN MED trial administration of unfractionated heparin or aspirin during EVT were associated with higher rates of symptomatic intracranial hemorrhage.[73] The MR CLEAN MED trial was stopped early due to safety concerns and routine peri-procedural administration of unfractionated heparin or aspirin is not advised.[73,74]

Future perspectives

Many advances with regard to stroke treatment have been made and many studies on hemorrhagic transformation are conducted. Still, several aspects around hemorrhagic transformation need to be investigated further, for example, refining the identification of patients at risk for hemorrhagic transformation and search for preventive medication that could decrease risk of hemorrhagic transformation. Additionally, the adaptation of stroke treatment with a decreased risk for hemorrhagic transformation or even the possibility for treatment of hemorrhagic transformation should be investigated further.

Many clinical and imaging markers have been examined and found to be associated with hemorrhagic transformation such as, blood pressure, ASPECTS, antiplatelet use, collateral score and age.[12,15,83–85,75–82] It is still difficult, however, to predict which stroke patients will develop hemorrhagic transformation. Previously developed prediction scores discriminate poorly between low and high risk for symptomatic intracranial hemorrhage and hemorrhagic transformation.[86] New studies could provide new insights on predictor variables for hemorrhagic transformation. For example, CTP parameters could be valuable for predicting hemorrhagic transformation.[87–93] The hypo perfusion intensity ratio is a measure of microvascular collateral flow derived from CTP imaging.[94] Recently, a study showed that a low hypo perfusion intensity ratio is associated with parenchymal hematoma.[95] Additionally, ischemic core location such as subcortical infarcts assessed by CTP are associated with hemorrhagic transformation and subcortical infarct volume was associated with symptomatic intracranial hemorrhage.[96] Therefore, CTP parameters could aid in identifying patients at risk for hemorrhagic transformation and/or symptomatic intracranial hemorrhage.

Additionally, several imaging techniques, such as, dynamic contrast-enhanced CT or MRI and single photo-emitting computed tomography could measure BBB permeability which might aid in identifying patients at risk for hemorrhagic transformation.[97] Machine learning algorithms could use these CTP parameters and BBB permeability measure together with known clinical and imaging predictors to develop an accurate prediction tool for hemorrhagic transformation and maybe even its subtypes.[30] Also, a previous study developed a mathematical model of hemorrhagic transformation using a microvascular network.[98] An expansion of this mathematical model of hemorrhagic transformation could help predict the extent of hemorrhagic transformation.[98] However, for such a tool to serve a purpose, prevention strategies or preventive medication should exist to act on their results.
Several targets exist with regard to preventive medication for hemorrhagic transformation, neuroprotective medication or blood pressure lowering for example. Although, several studies on blood pressure lowering have already been conducted, it is still unclear what the preferred systolic blood pressure target is after successful reperfusion.[24,28,29]

Several ongoing trials are going to investigate this subject further. The ongoing BEST-II (NCT04116112), OPTIMAL-BP (NCT04205305), DETECT (NCT04484350) and CRISIS-I (NCT04775147) trials will assess the association of systolic blood pressure targets of 120-180 mmHg with hemorrhagic transformation and/or functional outcome.[99–102]

Neuroprotective agents refer to any agent reducing ischemic brain injury on a molecular level, e.g. inhibiting neuronal cell death.[103] Some of these neuroprotective agents are designed to reduce ischemia induced inflammation that would damage the blood-brain barrier and attribute to hemorrhagic transformation.[103] Rat models of neuroprotective therapy are promising, however many human trials failed to show an effect,[104,105] due to unsuccessful reperfusion.[106] Therefore, neuroprotective agents became of increased interest after the introduction of EVT as standard of care.[1,106] Several ongoing trials will determine the efficacy and safety of neuroprotective agents that could reduce the risk of hemorrhagic transformation by stabilizing the blood-brain barrier (OPENS-2, NCT04681651), potentially reduce inflammation (RESCUE, NCT04693715) and reduce cerebral edema (CHARM, NCT02864953).[107–109]

Stroke treatment with EVT does not increase the risk of hemorrhagic transformation. However, the meta-analysis that included six randomized controlled trials that determined the effect of EVT without prior administration of IVT compared with EVT after IVT,

showed less hemorrhagic transformation rates in the group with EVT without IVT.[61] Although, hemorrhagic transformation rates were increased in the EVT with prior IVT group, functional outcomes in the EVT with IVT group were slightly better than EVT without IVT. Therefore, IVT before EVT is advised as stroke treatment.[61] Since IVT is still a very effective and important stroke treatment,[61] alternative IVT medications with the same effectiveness but a decreased risk for hemorrhagic transformation could improve functional outcomes after an acute ischemic stroke. An ongoing trial assesses the safety and efficacy of dual thrombolytic treatment with mutant pro-urokinase and a low dose alteplase compared with usual treatment with alteplase alone for acute ischemic stroke (DUMAS, NCT04256473).[110] It is hypothesized that mutant pro-urokinase has an improved safety profile and might decrease the risk for hemorrhagic transformation.[110]

Surgery in ischemic stroke patients has a role, exclusively, in case of malignant middle cerebral artery infarction.[111] Although, decompressive hemicraniectomy is a lifesaving treatment, most patients that survive have a moderately severe disability.[111] For hemorrhagic stroke patients with spontaneous intracerebral hemorrhage, which might be somewhat comparable to patients with hemorrhagic transformation after ischemic stroke, no medical or surgical treatments with proven benefit are available.[112–114] However, the Dutch Intracerebral hemorrhage Surgery Trial (DIST, NCT03608423) aims to determine the safety and effect of minimal invasive endoscopy-guided surgery for patients with supratentorial intracerebral hemorrhage.[115] When the DIST trial shows positive result, future trials could determine whether minimal invasive surgery might have a role for treatment of gross hemorrhagic transformation after acute ischemic stroke.

Conclusion

Hemorrhagic transformation occurs after an acute ischemic stroke as a complication of treatment or as stroke progresses. Studies included in this thesis highlighted different aspects of hemorrhagic transformation: impact of hemorrhagic transformation on functional outcome, clinical and imaging makers associated with hemorrhagic transformation, comparison of NCCT and MRI in visualizing hemorrhagic transformation and the association of reperfusion therapy with hemorrhagic transformation. We showed that hemorrhagic transformation is associated with a poor functional outcome after three months. Several markers associated with large infarcts were also associated with hemorrhagic infarction while clinical markers, such as blood pressure, atrial fibrillation and antiplatelet use were associated with parenchymal hematoma and symptomatic

intracranial hemorrhage. Hemorrhagic transformation visualized on NCCT and B0 EPI is not fully interchangeable, necessitating standardization of the classification on both modalities. Patients treated within 4.5 hours after stroke onset do not have an increased risk for hemorrhagic transformation after treatment with IVT compared with EVT without IVT.

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Appendices

Summary

Summary

Hemorrhagic transformation in acute ischemic stroke

An acute ischemic stroke is one of the most common causes of morbidity and mortality worldwide. In the last decade, many advances have been made in stroke treatment. Especially endovascular therapy (EVT) immensely improved functional outcomes after an acute ischemic stroke due to a large vessel occlusion. Despite this major improvement, approximately half of the patients with an acute ischemic stroke has a poor functional outcome.

Hemorrhagic transformation of an ischemic stroke can occur as stroke progresses or as a complication of stroke treatment. Hemorrhagic transformation varies in severity and is divided into four subtypes. Small petechial bleedings along the margins of the infarct constitute hemorrhagic infarction (HI) type 1, with more confluent petechial bleeding constituting HI type 2. Parenchymal hematomas (PH) are frank hematomas that are categorized in hemorrhages that consist of less than 30% of the infarct area without substantial mass effect (PH type 1) or consist of more than 30% of the infarct area with a space occupying effect (PH type 2). Some large hematomas result in acute neurological deterioration with high mortality rates; these hemorrhages causing acute neurological deterioration are classified as symptomatic intracranial hemorrhage (sICH). In most of these cases PH2 is the underlying hemorrhagic transformation subtype. Smaller hemorrhages have no or less apparent clinical consequences than large hemorrhages and their precise impact on outcome remains unclear. Additionally, it is unclear which patients are at increased risk for hemorrhagic transformation and whether that risk is modifiable.

The association with outcome of hemorrhagic transformation subtypes was assessed in chapters 2 and 3. In chapter 4 the association of hemorrhage volume with functional outcome was investigated, and additionally we assessed whether volume was of added value to existing hemorrhage classifications. Then factors that might be associated with the occurrence of hemorrhagic transformation (chapter 5) and differences regarding imaging and assessment of hemorrhagic transformation (chapter 6) were discussed. Finally, in chapter 7 we assessed the association with hemorrhagic transformation of both intravenous thrombolysis with alteplase before endovascular treatment and reperfusion status after endovascular treatment. Findings and future perspectives are discussed in the general discussion (chapter 8).

hemorrhagic transformation and functional outcome

In **chapter 2, 3** and **4** the functional outcome of patients with hemorrhagic transformation was studied. Large space-occupying hematomas (PH2) that cause acute neurological deterioration are often classified as sICH. Smaller hemorrhages, such as HI1 and 2, are thought to have no or less apparent clinical consequence and do not cause acute neurological deterioration. While these smaller hemorrhages might not cause acute neurological deterioration, they could have an impact on functional outcome.

In **chapter 2**, we used data from the MR CLEAN trial to assess the association of hemorrhagic transformation with functional outcome. Our results showed that not only PH2 was associated with functional outcome after three months of stroke onset but also all the smaller hemorrhagic transformation subtypes were associated with functional outcome. In **chapter 3**, we conducted a similar analysis in a larger population consisting of data from seven randomized controlled trials which all established the effect of EVT in addition to medical treatment. We assessed the association of all hemorrhagic transformation subtypes with follow-up lesion volume and functional outcome. Additionally, we determined whether patients with hemorrhagic transformation still had benefit from treatment with EVT. Results were comparable to those reported in **chapter 2** and showed that all hemorrhagic transformation subtypes were associated with functional outcome if no adjustment was made for follow-up lesion volume. However, large infarcts are associated with poor functional outcomes and more common hemorrhagic transformation. Therefore, the association of hemorrhagic transformation with functional outcome is probably influenced by the association of large infarcts with functional outcome. To determine whether the association of hemorrhagic transformation with functional outcome is influenced by large infarcts, we adjusted for follow-up lesion volume. Follow-up lesion volume is a measure that includes both infarct volume and hemorrhage volume since they are not easily separated during segmentation. Our results showed that the association of HI1 with functional outcome was likely confounded by large infarct size. However, HI2 was associated with functional outcome independent of follow-up lesion volume. Due to the larger contribution of hematoma to the follow-up lesion volume in the PH subgroups, the inclusion of follow-up lesion volume in the associative models could have resulted in overadjustment. That PH2 and not PH1 was associated with functional outcome independent of follow-up lesion volume is probably due to the substantial space occupying effect of PH2. The resulting compression on healthy brain

tissue often results in neurological deterioration and high mortality rates.

In **chapter 4**, we assessed the prognostic value of quantified hemorrhage volume. We measured hemorrhage volume and assessed the association between hemorrhage volumes and functional outcome in comparison with the hemorrhagic transformation classification. We found that both hemorrhage volume and the hemorrhage classification were associated with functional outcome independent of each other. However, when follow-up lesion volume was added to the analysis, hemorrhage volume was not and the HI2 and PH2 classifications were associated with functional outcome. However, in the PH2 subgroup hemorrhage volume was found to be associated with functional outcome. Since PH2 hemorrhages were already determined to have substantial mass effect, larger hemorrhage volume likely constitutes to a greater mass effect on surrounding tissue in this subgroup and would have more impact on functional outcome. Therefore, the hemorrhage volume of a PH2 has added prognostic value beside its classification.

Clinical and imaging markers associated with hemorrhagic transformation

To identify patients with an increased risk for hemorrhagic transformation after reperfusion therapy with EVT, It is necessary to determine which baseline clinical or imaging characteristics are associated with hemorrhagic transformation. In **chapter 5**, we determined the association of clinical and imaging factors with hemorrhagic transformation. Of all included patients, 46% had any hemorrhagic transformation. Our results showed that several markers indicative for large infarcts, such as high NIHSS and poor collateral scores were associated with HI. Clinical markers, such as high admission systolic blood pressure and atrial fibrillation were associated with PH. More-over, high admission systolic blood pressure and antiplatelet use were associated with sICH. Of these markers blood pressure is of interest since it potentially could be a modifiable risk factor.

Imaging of hemorrhagic transformation

NCCT and MRI are both used as follow-up imaging after an acute ischemic stroke. Hemorrhagic transformation appears differently on NCCT than MRI. Especially susceptibility weighted imaging and gradient echo MRI sequences are more sensitive for hemorrhage than NCCT. The use of both NCCT and MRI in clinical trials could therefore hamper comparison of hemorrhagic transformation classification across studies. B0 series

of echo planar diffusion weighted imaging (B0 EPI) MRI is known to have less susceptibility artifacts than gradient echo sequences and could be more accurate in depicting hemorrhage compared to T1, T2 and FLAIR sequences. Therefore, B0 EPI could be more comparable to NCCT than gradient echo MRI sequences when classifying hemorrhagic transformation. We assessed whether hemorrhagic transformation classification and volume measurement is comparable between NCCT and B0 EPI **chapter 6**. We found that the inter-modality agreement for overall hemorrhagic transformation that included all subtypes is fair (κ=0.27), moderate for HI1 (κ=0.48) and slight for both HI2 (κ=0.12) and PH1 (κ=0.08). The inter-modality agreement for PH2 was good (κ=0.7). Last, hemorrhage volumes appear larger on B0 EPI than NCCT. Therefore, we concluded that hemorrhagic transformation classification is not readily comparable between NCCT and B0 EPI except for when it matters most: in case of a PH2.

Hemorrhagic transformation and stroke reperfusion therapy

If patients are eligible, current standard practice is to treat patients with a large vessel occlusion stroke with both intravenous thrombolysis (IVT) and endovascular treatment. However, reperfusion rates after sole IVT are low compared to EVT, and early IVT trials showed increased hemorrhage rates. The MR CLEAN NO-IV trial and several other randomized clinical trials compared EVT without IVT compared to IVT followed by EVT. Due to the randomized nature of these trials it became possible to determine whether IVT is associated with an increased risk of hemorrhagic transformation. Additionally, we could assess whether reperfusion rates were associated with hemorrhage development. We assessed this subject in **chapter 7** by determining the association of IVT and reperfusion with hemorrhagic transformation, hemorrhage volume and sICH in the MR CLEAN NO-IV population. We found no significant association of IVT before EVT with hemorrhagic transformation, hemorrhage volume or sICH. Additionally, reperfusion was also not statistically significantly associated with these outcomes. Unsuccessful reperfusion was, however, associated with subarachnoid hemorrhage. Patients with subarachnoid hemorrhage were also more often treated with EVT without IVT (SAH: 66% vs no SAH: 49%, P=0.05), and more clot retrieval attempts were made during EVT (SAH: median 3, IQR 2–5 vs. no SAH: median 2, IQR 2–3, P=0.01). As such, EVT without IVT could potentially be more complicated in some patients due to the lack of (partial) lysis of the clot, resulting in more friction with the vessel wall during retrieval. This could lead to more stretching of the vessel and potential rupture of small perforating arteries, resulting in subarachnoid

hemorrhage.

Conclusion

Hemorrhagic transformation occurs after an acute ischemic stroke as a complication of treatment or as stroke progresses. We showed that hemorrhagic transformation is associated with a poor functional outcomes. Several markers of large final infarcts such as poor collateral score and high NIHSS were associated with HI while clinical markers such as blood pressure and atrial fibrillation were associated with PH and sICH. Hemorrhagic transformation classified on NCCT and B0 EPI are not readily comparable. Last, patients treated within 4.5 hours after stroke onset do not have an increased risk for hemorrhagic transformation after treatment with IVT compared with EVT without IVT. Patients without successful reperfusion and IVT were more prone to developing subarachnoid hemorrhage.

Nederlandse samenvatting

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Hemorragische transformatie bij een accuut herseninfarct

Een acuut herseninfarct is een van de meest voorkomende oorzaken van morbiditeit en mortaliteit wereldwijd. In de afgelopen decennia is er veel vooruitgang geboekt in de behandeling van een herseninfarct. Endovasculaire behandeling verbetert de functionele uitkomsten na een herseninfarct door een occlusie van een groot vaatbed aanzienlijk. Ondanks deze grote verbetering heeft ongeveer de helft van de patiënten met een herseninfarct een slechte functionele uitkomst.

Hemorragische transformatie van ischemisch beschadigd hersenweefsel kan optreden naarmate het herseninfarct vordert of als complicatie van de behandeling van het herseninfarct. Hemorragische transformatie varieert in ernst en is verdeeld in vier subtypen. Hemorragische infarcten (HI) zijn kleine bloedingen langs de randen van het infarct (HI type 1) of meer samenvloeiende kleine bloedingen (HI type 2). Parenchymale bloedingen bestaan uit minder dan 30% van het infarctgebied (PH type 1) of meer dan 30% van het infarctgebied met een compressie op gezond hersenweefsel (PH type 2). Sommige grote bloedingen kunnen leiden tot acuut neurologische achteruitgang en hoge mortaliteitscijfers; deze bloedingen worden geclassificeerd als symptomatische intracraniale bloedingen (sICH). In de meeste gevallen is PH2 het onderliggende hemorragische transformatie subtype die als sICH is geclassificeerd. Kleinere bloedingen hebben geen of minder uitgesproken klinische gevolgen en hun precieze impact op de uitkomst blijft onduidelijk. Bovendien is onduidelijk bij welke patiënten het risico op hemorragische transformatie verhoogd is en of dit risico te verminderen is.

Deze thesis begint met een algemene introductie en richt zich op de impact van hemorragische transformatie in hoofdstuk 2 en 3. In hoofdstuk 4 werd de associatie tussen bloedvolume met functionele uitkomst onderzocht. Deze thesis rapporteert over risico factoren voor het krijgen van hemorragische transformatie (hoofdstuk 5) en problemen met betrekking tot beeldvorming en beoordeling van hemorragische transformatie (hoofdstuk 6). Tot slot beschrijft deze scriptie de associatie tussen de behandeling van het herseninfarct en reperfusie met hemorragische transformatie (hoofdstuk 7). Alle bevindingen en toekomst perspectieven worden verder bediscussieerd in de algemene discussie (hoofdstuk 8).

Hemorragische transformatie en functionele uitkomst

In hoofdstuk 2, 3 en 4 is de functionele uitkomst van patiënten met hemorragische transformatie bestudeerd. Grote ruimte-innemende hematomen (PH2) worden vaak geclassificeerd als sICH. Kleinere bloedingen, zoals HI1 en 2, lijken geen of minder zichtbare klinische gevolgen te hebben en veroorzaken geen acute neurologische verslechtering. Hoewel deze kleinere bloedingen mogelijk geen acute neurologische verslechtering veroorzaken, kunnen ze wel een impact hebben op de functionele uitkomst.

In hoofdstuk 2 maakten we gebruik van gegevens uit de MR CLEAN-studie om de associatie tussen hemorragische transformatie en functionele uitkomst te beoordelen. Onze resultaten lieten zien dat niet alleen PH2 geassocieerd was met functionele uitkomst na drie maanden na het herseninfarct, maar ook alle kleinere subtypen van hemorragische transformatie waren geassocieerd met functionele uitkomst. Na het corrigeren voor follow-up laesie volume van de afwijking, wat een maat is die zowel de grootte van de infarct als de bloeding omvat, waren PH2 en HI2 geassocieerd met functionele uitkomst. In hoofdstuk 3 worden de resultaten van een meta-analyse met gegevens uit zeven gerandomiseerde onderzoeken gericht op de effecten van EVT naast medische behandeling gerapporteerd. We beoordeelden de associatie van alle subtypen van hemorragische transformatie met het follow-up laesie volume en de functionele uitkomst. Bovendien bepaalden we of patiënten met hemorragische transformatie nog steeds baat hadden bij behandeling met EVT. Zelfs na het onderzoeken van een populatie met meer patiënten waren de resultaten vergelijkbaar met hoofdstuk 2. De resultaten lieten de resultaten zien dat behandeling met EVT altijd voordelig was, zelfs na hemorragische transformatie. Daarnaast lieten de resultaten zien dat alle subtypen van hemorragische transformatie geassocieerd waren met functionele uitkomst wanneer niet werd gecorrigeerd voor follow-up laesie volume. Echter, een groot herseninfarct is geassocieerd met een slechte functionele uitkomst en hemorragische transformatie komt vaker voor na een groot herseninfarct. De associatie van hemorragische transformatie met functionele uitkomst is waarschijnlijk beïnvloed door de grootte van het herseninfarct. Om te bepalen of de associatie van hemorragische transformatie werd beïnvloed door infarct grootte hebben we gecorrigeerd voor follow-up laesie volume. Follow-up laesie volume is een maat die zowel bloedvolume als infarct volume omvat, gezien het vrijwel niet mogelijk is om deze apart te segmenteren. Onze resultaten toonden aan dat de associatie van HI1 met functionele uitkomst waarschijnlijk wordt veroorzaakt door de grootte van

het infarct, terwijl HI2 was geassocieerd met functionele uitkomst onafhankelijk van het follow-up laesie volume. Doordat het bloedvolume vrij groot is bij de PH subtypes bestaat het follow-up laesie volume voornamelijk uit het bloedvolume. Wanneer er dan ook wordt gecorrigeerd voor follow-up laesie volume in het geval van PH1 en PH2, resulteert dat in over correctie. Dat PH2 en niet PH1 geassocieerd was met functionele uitkomst onafhankelijk van het volume van de follow-up laesie volume, komt door het substantiële ruimte-innemend effect van PH2. Het ruimte innemend effect van een PH2 veroorzaakt compressie op gezond hersenweefsel, wat vaak leidt tot neurologische achteruitgang en hoge mortaliteitscijfers.

In hoofdstuk 4 beoordeelden we de prognostische waarde van het kwantificeren van het bloedvolume. We meetten het bloedvolume en beoordeelden de associatie tussen het bloedvolume en functionele uitkomst. We voegden de classificatie van hemorragische transformatie toe aan het model van het bloedvolume om te bepalen welke maat de sterkste voorspeller van functionele uitkomst zou zijn. De resultaten toonden aan dat de classificatie van HI1, HI2 en PH1 sterkere voorspellers van functionele uitkomst waren dan hun volume. Integendeel, het bloedvolume was geassocieerd met functioneel resultaat wanneer een PH2 aanwezig was. Grote bloedvolumes van een PH2 zouden een grotere massa-effect op omringend weefsel hebben dan kleinere PH2's en zouden daardoor meer invloed hebben op functionele uitkomst. Daarom heeft het bloedvolume van een PH2 naast zijn classificatie toegevoegde waarde bij de voorspelling van functionele uitkomst.
Klinische en beeldvormende markers geassocieerd met hemorragische transformatie

Het is noodzakelijk om te bepalen welke klinische of beeldvormende kenmerken geassocieerd zijn met hemorragische transformatie om patiënten te identificeren met een verhoogd risico op hemorragische transformatie na behandeling met EVT. In hoofdstuk 5 hebben we de associatie van klinische en beeldvormende factoren met hemorragische transformatie bepaald. Onze resultaten lieten zien dat verschillende markers die aangeven voor grote beroertes, zoals een hoge NIHSS slechte collaterale vaten score geassocieerd waren met HI. Klinische markers, zoals verhoogde systolische bloeddruk tijdens opname en atriumfibrilleren waren geassocieerd met PH. Daarnaast waren een verhoogde systolische bloeddruk tijdens opname en antistollingsbehandeling geassocieerd met sICH. Van deze klinische en beeldvormende markers die geassocieerd zijn met hemorragische transformatie, is bloeddruk het meest interessant omdat verlaging van de bloeddruk een mogelijke medische ingreep zou kunnen zijn.

Beeldvorming van hemorragische transformatie

NCCT en MRI worden beide gebruikt als follow-up beeldvorming na een acuut herseninfarct. Hemorragische transformatie ziet er anders uit op NCCT dan MRI. MRI is gevoeliger voor bloedingen dan NCCT en de bloeding lijkt groter op MRI. Vooral susceptibility gewogen imaging en gradient echo MRI zijn sequenties die gevoelig zijn voor bloedingen vanwege het susceptability artefact. Omdat zowel NCCT als MRI in klinische onderzoeken worden gebruikt, kan dit de vergelijking van hemorragische transformatie aantallen tussen studies belemmeren. De B0 serie van echo planar diffusie gewogen (B0 EPI) MRI wordt minder beïnvloed door het susceptability artefact dan gradient echo sequentie maar is accurater in het visualiseren van bloeding dan de algemene T1, T2 en FLAIR sequenties. Daarom zou B0 EPI vergelijkbaarder kunnen zijn met NCCT dan gradient echo met betrekking tot het classificeren van hemorragische transformatie. Daarom hebben we in hoofdstuk 6 bekeken of hemorragische transformatie vergelijkbaar is tussen NCCT en B0 EPI. De resultaten lieten zien dat de inter-modaliteitsovereenkomst voor de algehele hemorragische transformatie classifcatie redelijk was (κ=0.27). De inter-modaliteitsovereenkomst voor HI1 was gemiddeld (κ=0.48) en voor HI2 (κ =0.12) en PH1 gering (κ =0.08). De inter-modaliteitsovereenkomst voor PH2 was goed (κ=0.7). Bloedvolumes waren groter op B0 EPI dan op NCCT. Daarom is hemorragische transformatie niet direct vergelijkbaar tussen NCCT en MRI, behalve wanneer het het meest van belang is; in het geval van een PH2.

Hemorragische transformatie en behandeling van een herseninfarct

Het is de standaard praktijk om patiënten die een herseninfarct hebben door een verstopping in een groot cerebraal vat, ze te behandelen middels intraveneuze thrombolyse (IVT) en EVT wanneer ze daarvoor in aanmerking komen. Echter, in vergelijking tot EVT zijn de behandelresultaten van IVT minder goed en eerdere IVT studies lieten zien dat er meer hemorragische transformatie ontstaat na IVT in vergelijking tot geen behandeling. De MR CLEAN NO-IV-trial en verschillende andere gerandomiseerde klinische trials bepaalden het effect van EVT zonder IVT in vergelijking met IVT gevolgd door EVT. Door deze trials werd het mogelijk om te bepalen of het reperfusie of IVT is wat geassocieerd is met een verhoogd risico op hemorragische transformatie. In hoofdstuk 7 hebben we dit onderwerp onderzocht door de associatie van behandeling

en reperfusie met hemorragische transformatie, bloedingsvolume en sICH te bepalen aan de hand van gegevens uit de MR CLEAN NO-IV-trial. De resultaten lieten geen significante associatie zien tussen IVT vóór EVT of reperfusie na EVT met hemorragische transformatie, bloedingsvolume of sICH. Onsuccesvolle reperfusie was wel geassocieerd met een subarachnoïdale bloeding. Daarnaast waren patiënten met een subarachnoïdale bloeding vaker behandeld met EVT zonder IVT (subarachnoïdale bloeding: 66% vs geen subarachnoïdale bloeding: 49%, P=0.05) en werden er meer pogingen gedaan om het bloedstolsel tijdens EVT te kunnen verwijderen (subarachnoïdale bloeding: mediaan 3, IQR 2–5 vs. geen subarachnoïdale bleding: mediaan 2, IQR 2–3, P=0.01). EVT zonder IVT zou in sommige patiënten ingrijpender kunnen zijn omdat de oplossing van het stolsel niet heeft kunnen optreden. Daarom werden er meer pogingen gedaan om het stolsel te kunnen verwijderen wanneer er geen succesvolle reperfusie was, waardoor een subarachnoïdale bloeding kon ontstaan.

Conclusie

Hemorragische transformatie treedt op na een acute herseninfarct als gevolg van behandeling of wanneer het herseninfarct vordert. We hebben aangetoond dat hemorragische transformatie geassocieerd is met een slechte functionele uitkomst na drie maanden. Verschillende markers die aangeven dat er sprake zou kunnen zijn van een groot infarct, waren geassocieerd met HI, terwijl klinische markers zoals bloeddruk en atriumfibrilleren geassocieerd waren met PH en sICH. Hemorragische transformatie zichtbaar op NCCT is niet eenvoudig te vergelijken met MRI. Tenslotte hebben patiënten die binnen 4,5 uur na het ontstaan van het herseninfarct worden behandeld, geen verhoogd risico op hemorragische transformatie na behandeling met IVT in vergelijking met EVT zonder IVT. Patiënten zonder succesvolle reperfusie waren gevoeliger voor het ontwikkelen van een subarachnoïdale bloeding.

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List of publications

List of publications

In this thesis:

van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, van den Berg LA, Chalos V, Lingsma HF, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Dippel DWJ, Roos YBWEM, Marquering HA, Majoie CBLM; MR CLEAN investigators. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. J Neurointerv Surg. 2019 May;11(5):464-468. doi: 10.1136/neurintsurg-2018-014141. Epub 2018 Oct 8. PMID: 30297537.

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van der Steen W, van der Ende NA, **van Kranendonk KR**, Chalos V, Brouwer J, van Oostenbrugge RJ, van Zwam WH, van Doormaal PJ, van Es AC, Majoie CB, van der Lugt A, Dippel DW, Roozenbeek B. Timing of symptomatic intracranial hemorrhage after endovascular stroke treatment. Eur Stroke J. 2022 Dec;7(4):393-401. doi: 10.1177/23969873221112279. Epub 2022 Aug 3. PMID: 36478761; PMCID: PMC9720857.

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van der Steen W, van der Ende NAM, **van Kranendonk KR**, Chalos V, van Oostenbrugge RJ, van Zwam WH, Roos YBWEM, van Doormaal PJ, van Es ACGM, Lingsma HF, Majoie CBLM, van der Lugt A, Dippel DWJ, Roozenbeek B; MR CLEAN Trial and MR CLEAN Registry Investigators. Determinants of Symptomatic Intracranial Hemorrhage After Endovascular Stroke Treatment: A Retrospective Cohort Study. Stroke. 2022 Jun 8:101161TROKEAHA121036195. doi: 10.1161/STROKEAHA.121.036195. Epub ahead of print. PMID: 35674042.

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decision trees for predicting poor outcome after endovascular treatment for acute ischemic stroke. Comput Biol Med. 2021 Jun;133:104414. doi: 10.1016/j.compbiomed.2021.104414. Epub 2021 Apr 21. PMID: 33962154.

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PhD portfolio and CV

PhD portfolio and CV

Name PhD student: K.R. van Kranendonk
PhD period: December 2016 – June 2023
Name PhD supervisors: C.B.L.M. Majoie/H.A. Marquering/Y.B.W.E.M. Roos/K.M. Treurniet

1. PhD training

	Year	Workload (Hours/ ECTS)
General courses		
– Scientific Writing in English for publication	2017	1.5
– Practical Biostatistics	2017	1.1
– Computing in R	2017	0.4
– Basic Course Legislation and Organization – eBROK	2018	0.9
– Didactical skills	2018	0.4
– Observational Clinical Epidemiology Effects & Effectiveness	2018	0.6
– MRI: Basic understanding for (bio)medical research	2018	1.0
– Advanced topics in Biostatistics	2019	2.1
– Clinical epidemiology: Evaluation of Medical Tests	2021	0.9
Seminars, workshops and master classes		
– Ischemic stroke meeting (monthly)	2016-2023	2.0
– Masterclass prof. Demchuk	2016	0.2
– Masterclass prof. Goyal	2018	0.2
– MR CLEAN Registry national meeting	2018	0.2
– CONTRAST Consortium meeting	2018	0.2
– CONTRAST Consortium meeting	2019	0.2
– MR CLEAN Registry national meeting	2019	0.2
Oral Presentations		
– European Stroke Organisation Conference, Prague: Associations with hemorrhagic transformation in acute ischemic stroke.	2017	0.5
– European Stroke Organisation Conference, Milan: Hemorrhage volume in patients with hemorrhagic transformation after acute ischemic stroke.	2019	0.5

– International Stroke Conference, Los Angeles: Hemorrhagic transformation after acute ischemic stroke due to a large vessel occlusion is associated with less treatment benefit.	2020	0.5
– European Stroke Organisation Conference, Digital: Association between intracranial hemorrhage after acute ischemic stroke with thrombolytic agents and revascularization. Results from the MR CLEAN-NO IV	2021	0.5

(Inter)national conferences

– European Stroke Organisation Conference, Prague	2017	0.75
– Annual Meeting Amsterdam Neuroscience	2018	0.25
– European Stroke Organisation Conference, Milan	2019	0.75
– Institute QuantiVision Conference	2019	0.25
– International Stroke Conference, Los Angeles	2020	0.75
– European Stroke Organisation Conference, Digital	2021	0.25
– Annual Meeting Amsterdam Neuroscience	2021	0.25

2. Teaching

	Year	Workload (Hours/ ECTS)
Lecturing		
– Keuzeonderwijs: cardiovascular research & care	2019	0.2
– Keuzeonderwijs: cardiovascular research & care	2020	0.2
Supervising		
– Student Public Health: J van Genuchten	2019	1.0
– Student Medische natuurwetenschappen: M Allaoui	2021-2022	1.0

3. Parameters of Esteem

	Year
Grants	
– Junior investigators travel award	2020
– MD/PhD scholarship	2016

Curriculum vitae

Personal data

First name(s):	Katinka Rebekka
Surname:	van Kranendonk
Address:	Wethouder Maartje Biermanstraat 5
ZIP code and city:	1474 KG Oosthuizen
Country:	The Netherlands
E-mail address:	krvankranendonk@outlook.com
Date of birth:	20th April 1991
Place of birth:	Purmerend, The Netherlands
Sex:	Female
Nationality:	Dutch

Education

2016 – present	**University of Amsterdam** PhD candidate Amsterdam UMC, location AMC Department of Radiology and Nuclear Medicine *Subject:* Hemorrhagic transformation in patients with acute ischemic stroke.
2016 – 2020	**University of Amsterdam** Master of Science in Medicine (graduated) Amsterdam, The Netherlands *Main Modules:* Clinical internships *Final clinical internship*: Neurosurgery
2013 – 2016	**University of Amsterdam** Bachelor of Science in Medicine (graduated) Amsterdam, The Netherlands *Main Modules:* Disease Pathogenesis, Metabolic Disorders, Hormonal Disorders and Pharmacology, Infectious Diseases,

Immunity and inflammation, Reproduction and Development, Lung Diseases and Gas Exchange Disorders, Cardiovascular Disorders, Gastrointestinal and Liver Disease, Musculoskeletal System Disorders, Nervous System Disorders, Diseases of the Kidney and Urinary Tract, Psychiatric Disorders, Oncology, Disease, Health Care and Society.

2009 – 2013 **University of Amsterdam** Bachelor of Science in Psychobiology (graduated)
Amsterdam, The Netherlands
Main Modules: Neuro Anatomy and Physiology, Academic Fundamental Competences, Basic Statistics, Perception & Visual Consciousness, Pathophysiology of the Nervous System, Practicals, Statistics and Experimental Design & Academic Skills, Professional Ethics.
Optional Modules: Neuropharmacology, Social Neuro Cognition & Neuro Economy.
Thesis subject: The role of P-glycoprotein on the Blood-Brain Barrier in Pharmacoresistant Epilepsy.

2003 – 2009 **Jan van Egmond College** Pre-University Secondary Education (graduated)
Purmerend, The Netherlands
Main Modules: Biology, Physics, Chemistry, Mathematics.

Work experience

12/2022 – present **Dijklanderziekenhuis, location Hoorn and Purmerend**
Department of Orthopaedic surgery
Physician (ANIOS)

08/2021 – 01/2022 **Amsterdam UMC, location AMC and VUmc**
Department of Neurosurgery
Physician (ANIOS)

01/2021 – 11/2022	**Amsterdam Medical Research bv**
05/2020 – 07/2020	Department of Radiology and Nuclear Medicine
07/2018 – 05/2019	Medical Researcher, PhD candidate
	Subject: Hemorrhagic transformation in patients with acute ischemic stroke.

Publications

See list of publications

Honors and Awards:

02/2020 **Junior investigators travel award**

An honorarium of $1000,- won with the abstract: Hemorrhagic transformation after acute ischemic stroke due to a large vessel occlusion is associated with less treatment benefit.

11/2016 **MD/PhD Scholarship winner**

The MD/PhD program at the AMC combines the medical Master's degree program with funded PhD research.

Relevant courses CS50's introduction to artificial intelligence with python

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Languages Dutch (native)
English (fluent)

Activities Stand up paddling, Skiing, cycling and inline skating.
Designing and manufacturing clothes.

References Available on request

Dankwoord

Dankwoord

Dankwoord

Dit avontuur wat begon als een leuk klein project naast de studie en wat uitliep in een promotie heb ik uiteraard niet alleen gedaan. Er zijn vele mensen die mij onderweg hebben geholpen en eraan hebben bijgedragen in hoe ver ik nu ben gekomen. Van de grote groep mensen die hebben bijgedragen aan mijn proefschrift zou ik er een aantal expliciet willen benoemen. Om te beginnen met mijn (co-)promotoren **Prof. Dr. Majoie**, **Prof. Dr. Marquering**, **Prof. Dr. Roos** en **Dr. Treurniet.**

Charles, bedankt voor alle hulp, aandacht en wijsheid ten aanzien van het proefschrift. Als ik met vrienden of familie sprak over mijn werk als onderzoeker beschreef ik jou als mijn “opperbaas”, het grote brein achter mijn werk. Ik heb natuurlijk meer bazen maar er is er maar één de opperbaas en ik weet dat ik van geluk mag spreken dat ik jou als mijn opperbaas had. Jij heb mij altijd gesteund in mijn ideeën, of dat nou ging om een idee voor een studie, beursaanvraag of tussen mijn promotie door even klinische ervaring opdoen op de afdeling neurochirurgie. Niks was te gek en daar ben ik je ontzettend dankbaar voor.

Henk, zonder jouw hulp was het boekje nooit zo mooi geworden. Jij was degene die mij altijd hielp herinneren waarom ik een bepaald onderzoek deed, dat vergat ik zelf wel eens maar jij stuurde mij de goede richting in als ik weer eens afdwaalde. Daarnaast heb ik echt genoten van het sparren over statistische analyses, stond jij altijd klaar voor vragen en gaf jij zeer waardevolle feedback op mijn stukken wat het echt mooier maakte. Je enthousiasme toen ik te horen kreeg dat ik het MD/PhD scholarship toegekend kreeg werkte aanstekelijk, hierdoor kon ik met volle vertrouwen starten met het traject.

Yvo, bedankt voor alle inspirerende colleges waar ik ontzettend veel van heb geleerd. Je bent altijd zo druk geweest tijdens mijn tijd als onderzoeker maar wanneer het echt nodig was, wist je ondanks je drukke schema toch tijd vrij te maken voor vragen of feedback.

Kilian, wat hebben wij een bijzondere tijd achter de rug. Eigenlijk begon het ermee dat jij mijn begeleider was en mij stimuleerde om van mijn studieprojectje een promotieonderzoek te maken. Hierdoor werd jij al snel mijn collega, waarbij wij eindeloos konden brainstormen of eigenlijk discussiëren over stukken. Regelmatig eindigde de discussie met meer vragen dan antwoorden, ik kon daar van genieten want dan had ik weer nieuwe stof om over na te denken. Na onze mooie tijd als collega’s en al jouw

waardevolle bijdragen aan de onderzoeken die we deden ben ik ontzettend trost om jou mijn co-promoter te noemen. Ik hoop dat wij in de toekomst onze samenwerking door kunnen zetten.

Graag zou ik alle leden van de promotie commissie, **Prof. Dr. Vandertop**, **Prof. Dr. Daemen**, **Dr. Uyttenboogaart**, **Prof. Dr. van Bavel**, **Dr. Sprengers** en **Prof. Dr. Hendrikse** willen bedanken voor hun tijd die ze in het lezen van het proefschrift hebben gestoken en hun bereidheid om de verdediging bij te wonen.

Ook wil ik mijn dank uitten aan de andere grote bazen van de MR CLEAN groep, **Prof. van Zwam**, **Prof. Dippel**, **Prof. Van der Lugt**, **Prof. van Oostenbrugge** zonder jullie was dit proefschrift niet tot stand gekomen en daarnaast ben ik jullie dankbaar voor alle nuttige feedback die jullie op mijn stukken hebben geleverd wat de kwaliteit van het proefschrift zeker ten goede is gekomen.

Hester Lingsma, bedankt voor de statistische ondersteuning die je hebt geboden, de informatie die je hebt gegeven was onmisbaar voor dit proefschrift.

Olvert, ik denk dat ik het MR CLEAN artikel inmiddels zo vaak heb gelezen dat ik het praktisch blind woord voor woord kan opschrijven. Bedankt voor al je hulp en zeker ook je tip voor het bezoeken van de Phong Nha caves in Vietnam, dat was een ervaring die ik nooit zal vergeten.

Gezien ik zeer lang heb rondgelopen op de afdeling zijn er een groot aantal G1 collega's die ik wil noemen, om te beginnen met al mijn (semi-)kamergenoten. **Charlotte**, jij was als een warme deken op G1, door jou voelde ik mij er thuis en had ik het naar mijn zin. Jij zorgde echt voor de hele afdeling en het wekelijks invullen en bespreken van het mood bord waren een hoogtepunt van de week. **Anouk**, mijn mede MD/PhD'er, wat vond ik het ontzettend fijn om de kamer te delen met iemand (en vooral jou) die hetzelfde traject volgde waardoor we alle hoogtepunten en soms ook dieptepunten konden delen. Ik kijk met een grote glimlach terug naar onze tijd samen in kamer G1-230. **Onno**, jij bracht altijd bijzondere dingen mee naar de kamer, op sterk water of voor aan de muur maar één ding is zeker, jij zorgde voor gezelligheid. **Fabiano**, I liked sharing the room with you in the last few months of my PhD. After the Covid period, which meant working at home, it was nice to share stories with such a kind roommate.
Dan zijn er natuurlijk alle andere G1 collega's waarmee ik zo veel mooie momenten heb

meegemaakt, **Ivo**, **Miou**, **Ali**, **Floortje**, **Laura**, **Marloes**, **Sofieke**, **Maadrika**, **Anne-Sophie**, **Ruud**, **Rik**, **Matthias**, **Kerensa**, **Kyra**, **Marieke**, **Kim**, **Agnetha**, **Floris**, **Anke, Jihtsa, Manon** bedankt. Sinterkerst, de gezellige borrels en natuurlijk het jaarlijkse kerstdiner waren nooit zo leuk zonder jullie. **AJ**, het was leuk om iemand met iemand te sparren die gelijktijdig zijn/haar promotiedatum had gepland.

Collega's van BMEP, **Praneeta,** I enjoyed working with you, you are a friend and I like sharing thoughts with you. **Nerea**, **Mahsa** and **Henk**, you are alle very good colleges and I really enjoyed working with you. **Merel**, met jou kwam ik in contact in de prille tijd van mijn onderzoek. Zonder jouw vraag om segmentaties was het mij waarschijnlijk niet opgevallen dat zo veel patiënten hemorragische transformatie hadden wat leidde tot dit proefschrift.

Ik wil de vakgroep orthopedie van het Dijklanderziekenhuis bedanken, **de Boer**, **Huitema**, **Hillen**, **Steens**, **Amaya**, **Damen**, **Kraaneveld**, **Bouman, Stadhouder, van Kampen** en **Wijgman**. Zonder jullie begrip, flexibiliteit en aandacht was het nooit gelukt om de puntjes op de i te zetten ten aanzien van dit proefschrift.

Neurochirurgen ten tijde van mijn ANIOS functie, **Vandertop, Hoefnagels, Buis, Schuurman, van den Munckhof, Hoogmoed, Court, Lequin, Mandl, Bot, Feller, Idema, Baaijen, Noske, Peerdeman, de Witt Hamer, Verburg**, bedankt voor alle aandacht die jullie in mijn leerproces hebben gestoken.

Susanne, ik heb het zo naar mijn zin als wij iets hebben afgesproken, dat zijn alle ritjes naar Rotterdam meer dan waard.

Lieve **Kim en Kris**, jullie zijn zulke waardevolle vrienden en we beleven zo veel verschillende avonturen, van skiën tot airsoften tot F1 tot verbouwen, met jullie is het gegarandeerd een fantastische ervaring.

Lotte, jij bent mijn alleroudste vriendin, wij begrijpen elkaar. Altijd. Ik ben ontzettend blij en dankbaar dat jij mij hebt geholpen met het proefschrift. Het zou er nooit zo mooi uit hebben gezien zonder jou.

Mijn schoonfamilie, **Manuela**, **Mariska**, **Rini** en **Kelsey**, ik ben gek op jullie. **Frans**, jouw gezelligheid en vriendelijkheid zal ik koesteren en altijd blijven onthouden.

Dankwoord

Mijn oom en tante, **Wouter & Antoinette**, wat ben ik blij geweest om in jullie zomerhuis te kunnen overnachten/leven/logeren/wonen ten tijde van de verbouwing. Ik heb daar een groot deel van dit proefschrift in alle rust kunnen schrijven en daar ben ik jullie zeer dankbaar voor.

Mireille, Mir, ik ben erg dankbaar voor jouw steun tijdens zware tijden. Onze (minstens) tweejaarlijkse fashion gerelateerde meetings hoop ik oneindig voort te zetten.

Petra, bedankt voor alle fijne telefoontjes, ik weet dat ik altijd op jou kan rekenen voor een goed gesprek.

Oma, wat ben ik blij dat jij dit meemaakt, ik hoop dat je geniet van de verdediging. Ik zal onze zwempartijen in de Noordzee nooit vergeten, “je moet je laten drijven” vertelde jij aan mij.

Mijn allerliefste zussen, **Tamara** en **Roxane**. Behalve zussen, zijn wij ook beste vriendinnen. Onze band is zo hecht, daar kan niets tegenop. Ik geniet van onze zussenmiddagen en samen kunnen wij de mooiste dingen creëren of organiseren. Zo kijk ik erg uit naar de promotie datum, ik weet zeker dat mijn twee paranymfen iets moois voor mij in petto hebben.

Hedwig, mijn lieve moeder, ik weet zeker dat jij dit moment zo graag had mee willen maken. Ik denk elke dag nog aan je en weet dat je trots op mij bent.

Pa, oftewel **Marcus,** jij hebt mij zo ontzettend veel meegegeven. Nog steeds kan ik genieten van al onze gesprekken over politiek, geschiedenis en economie. Dankzij jou heb ik een brede algemene kennis en daar ben ik je zeer dankbaar voor. **Marjanne**, ik ben blij dat jij er voor pa bent, ik hoop dat jij hem altijd blijft ondersteunen.

Lieve **Tim**, mijn prins op het witte paard (zonder wit paard), jij bent mijn grootste steun. Wij hebben samen al zo veel meegemaakt, veel hoogtepunten maar ook dieptepunten. Samen kunnen wij alles aan. Ik ben ontzettend blij, trots en dankbaar dat jij mij zo hebt gesteund de afgelopen jaren. Het is zwaar geweest met de verbouwing van ons droomhuis en dat ik vaak niet beschikbaar was. Ik hoop daar nu verandering in te brengen, zodat we ons paleisje kunnen voltooien. **Ik houd van jou**.