

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

Citation for published version (APA):

van Kranendonk, K. R., Treurniet, K. M., Boers, A. M. M., Berkhemer, O. A., van den Berg, L. A., Chalos, V., Lingsma, H. F., van Zwam, W. H., van der Lugt, A., van Oostenbrugge, R. J., Dippel, D. W. J., Roos, Y. B. W. E. M., Marquering, H. A., Majoie, C. B. L. M., & MR CLEAN Investigators (2019). Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *Journal of Neurointerventional Surgery*, *11*(5), 464-468. https://doi.org/10.1136/neurintsurg-2018-014141

Document status and date:

Published: 01/05/2019

DOI: 10.1136/neurintsurg-2018-014141

**Document Version:** Publisher's PDF, also known as Version of record

**Document license:** Taverne

#### Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.

• The final author version and the galley proof are versions of the publication after peer review.

• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

#### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.

• You may not further distribute the material or use it for any profit-making activity or commercial gain

You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

#### Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

# ORIGINAL RESEARCH

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

Katinka R van Kranendonk,<sup>1</sup> Kilian M Treurniet,<sup>9</sup> <sup>1</sup> Anna M M Boers,<sup>9</sup> <sup>1,2,3</sup> Olvert A Berkhemer,<sup>1,4,5</sup> Lucie A van den Berg,<sup>6</sup> Vicky Chalos,<sup>4,5,7</sup> Hester F Lingsma,<sup>7</sup> Wim H van Zwam,<sup>9</sup> <sup>8</sup> Aad van der Lugt,<sup>9</sup> <sup>5</sup> Robert J van Oostenbrugge,<sup>9</sup> <sup>9</sup> Diederik W J Dippel,<sup>9 4</sup> Yvo B W E M Roos,<sup>6</sup> Henk A Marquering,<sup>2</sup> Charles B L M Majoie,<sup>1</sup> the MR CLEAN investigators

For numbered affiliations see end of article.

#### Correspondence to

Katinka R van Kranendonk, Department of Radiology and Nuclear Medicine, Academic Medical Center, Amsterdam, 1100 DD, The Netherlands; k.r. vankranendonk@amc.uva.nl

Received 1 June 2018 Revised 20 August 2018 Accepted 22 August 2018 Published Online First 8 October 2018

#### Check for updates

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: van Kranendonk KR, Treurniet KM, Boers AMM, *et al. J NeuroIntervent Surg* 2019;**11**: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 included in the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic stroke in The Netherlands). **Methods** All patients with follow-up imaging were included. HT was classified on follow-up CT scans according to the European Cooperative Acute Stroke Study 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 as hemorrhagic infarction

type 1, 71 (15%) as hemorrhagic infarction type 2, 36 (8%) as parenchymal hematoma type 1, and 39 (8%) as parenchymal hematoma type 2. Hemorrhagic infarction type 2 (adjusted common OR (acOR) 0.54, 95% CI: 0.32 to 0.89) and parenchymal hematoma type 2 (acOR 0.37, 95% CI 0.17 to 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 parenchymal hematoma type 2 is relevant for functional outcome after an acute ischemic stroke, and smaller HTs might also influence long term functional outcome. **Trail registration number** ISRCTN10888758.

#### INTRODUCTION

Hemorrhagic transformation (HT) manifests as natural progression of acute ischemic stroke (AIS) or a complication of thrombolytic treatment<sup>1 2</sup> and can cause neurological deterioration.<sup>1</sup> With the recent introduction of endovascular treatment (EVT) as standard of care in AIS, the effect of HT on outcome

has gained increased interest.<sup>3-7</sup> Based on the radiological appearance, HT is categorized as hemorrhagic infarction (HI) or parenchymal hematoma (PH).8 Both types have been subdivided into 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 the incidence of sICH between patients treated with and without EVT have been observed.<sup>3–7</sup> The incidence of HT in these patients has not been reported. In most sICHs the underlying hemorrhages are large.<sup>89</sup> Therefore, it has been suggested that the patient's well being is not influenced by the small hemorrhage subtypes, HI1, HI2, and PH1.<sup>10</sup> Some studies even suggest that HI is associated with better functional outcome than patients without HI because it is a sign of early revascularization.<sup>11</sup> <sup>12</sup> However, as some patients with HI show acute neurological deterioration, the impact of HI on functional outcome might be underestimated.<sup>13</sup> Even though, most patients with HI do not show acute neurological deterioration, it could still 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 in the MR CLEAN trial population (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic stroke in The Netherlands).<sup>3</sup>

#### METHODS

MR CLEAN was a prospective, multicenter, randomized clinical trial that assessed the efficacy and safety of EVT compared with usual treatment in patients with AIS in The Netherlands. Patients with a proximal intracranial large vessel occlusion of the anterior circulation who could be treated within 6 hours after symptom onset were included in MR CLEAN. The MR CLEAN design and outcomes have been previously presented in detail.<sup>3 15</sup>

A central medical ethics committee and the research boards of all participating centers accepted the MR CLEAN trial. Written informed consent was obtained from all patients or their legal representative.



In this post hoc analysis, all patients with follow-up imaging were eligible for inclusion. HT was classified according to the European Cooperative Acute Stroke Study II (ECASS II) classification.<sup>8</sup> 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.<sup>8</sup> HT was identified by two experienced observers from the core imaging committee. Patients with any ICH and neurological deterioration (increase of 4 points on the National Institute of Health Stroke Scale (NIHSS)) were classified as sICH.<sup>3</sup>

Follow-up imaging acquired at approximately 5 days was examined 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 classification of HT. HI rates at 24 hour and 5 day follow-up imaging were compared to detect possible overestimation of HI due to contrast staining. Functional outcome was defined according to the modified Rankin Scale (mRS) assessed at 90 days ( $\pm$ 14 days) after AIS 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.<sup>8</sup> The effect of HI1, HI2, PH1, and PH2 on functional outcome, with no HT as the reference level, was assessed using 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 OR, which summarizes the shift in the direction of a better outcome on the mRS. Common ORs <1 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.<sup>16</sup> 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. As 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 a secondary outcome we dichotomized 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 CT angiographs to evaluate recanalization rate for 96 patients. With the large amount of missing values, we chose not to include recanalization rate in the multivariable analysis. Recanalization rate is very important 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 X<sup>2</sup> 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 (V.3.4.2 (2017); R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; used packages rms,<sup>17</sup> ggplot2,<sup>18</sup> and tableone<sup>19</sup>).

# RESULTS

Twenty-two patients were excluded because of missing follow-up imaging due to death. Of the remaining 478 patients, 361 (76%) 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 score (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 rates 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%).

# **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% 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 (adjusted common OR (acOR) 0.37, 95% CI 0.17 to 0.78 and 0.54, 95% CI 0.32 to 0.89, respectively). For HI1 and PH1, the point estimates also were in the direction of worse outcome but were not statistically significant (table 2). Patients with HT had larger lesion volumes than patients without HT (P<0.001) figure 2).

Of the patients with sICH, 28 had PH2 (80%), 2 had PH1 (5.7%), 2 had HI2 (5.7%), 1 had HI1 (2.9%), and 2 patients had a subarachnoid hemorrhage (5.7%). Both patients with symptomatic PH1 died, as did one of the patients with symptomatic HI2. The other patient with symptomatic HI2 had a moderately severe disability (mRS 4) as did the patient with symptomatic HI1. Two patients with sICH due to PH2 underwent hemicraniectomy. Of the 37 patients with 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 to 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 to 0.85) and PH2 (acOR 0.22, 95% CI 0.03 to 0.96) were significantly associated with a poor functional outcome (table 2). HI2 and PH1 were not significantly associated with this secondary outcome measure.

# **Recanalization rate**

In the sensitivity analysis in which recanalization rate was included in the analysis, in the analysis using the full mRS scale, HI2 (acOR 0.37, 95% CI 0.21 to 0.67) and PH2 (acOR 0.21, 95% CI 0.08 to 0.53) were significantly associated with a worse functional outcome. In the analysis using the mRS as

| Table 1 Patient characteristics                                   |                  |               |               |               |               |          |
|---|------------------|---------------|---------------|---------------|---------------|----------|
|   | No HT<br>(n=256) | HI1<br>(n=76) | HI2<br>(n=71) | PH1<br>(n=36) | PH2<br>(n=39) | P values |
| EVT (n (%))   | 111 (43.4)       | 28 (36.8)     | 35 (49.3)     | 21 (58.3)     | 17 (43.6)     | 0.286    |
| Treatment with IV alteplase (n (%))                               | 228 (89.1)       | 66 (86.8)     | 65 (91.5)     | 33 (91.7)     | 36 (92.3)     | 0.398    |
| Age (years) (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 (n (%))                                | 26 (10.2)        | 7 (9.2)       | 8 (11.3)      | 1 (2.8)       | 9 (23.1)      | 0.233    |
| Atrial fibrillation (n (%))                                       | 58 (22.7)        | 17 (22.4)     | 25 (35.2)     | 15 (41.7)     | 14 (35.9)     | 0.003    |
| Diabetes mellitus (n (%))   | 27 (10.5)        | 13 (17.1)     | 9 (12.7)      | 5 (13.9)      | 7 (17.9)      | 0.192    |
| Systolic blood pressure (mm Hg) (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 min (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 (n (%))†   |                  |               |               |               |               | 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 (n (%))§                                      |                  |               |               |               |               | 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 (n (%))   | 2 (0.8)          | 1 (1.3)       | 2 (2.8)       | 2 (5.6)       | 28 (72)       |          |

\*ASPECTS was missing for four patients

+Collateral score was assessed on baseline CT angiography 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 six patients.

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

\$24 hour follow-up CT angiography to evaluate recanalization rate was not available for 96 patients due to death, decreased kidney function, or insufficient scan quality. Mean and SD are used to summarize normally distributed variables; for non-normally distributed variables, median and IQR are used.

ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; HI, hemorrhagic infarction; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma.



**Figure 1** Functional outcome defined by the modified Rankin Scale score per group. HI, hemorrhagic infarction; mRS, modified Rankin Scale HT, hemorrhagic transformation; PH, parenchymal hematoma.

#### Table 2 Adjusted and unadjusted ORs of the association of hemorrhage with functional outcome

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

This table lists the primary outcome which was the association of HT with the full scale mRS score for patients without hemorrhage as the reference. The secondary outcome was the association of HT with good functional outcome (mRS 0–2). An additional analysis was conducted where recanalization rate was added to the adjusted analysis.

Adjusted for age, diabetes mellitus, systolic blood pressure, intravenous thrombolysis, endovascular treatment, time from stroke onset to randomization, previous stroke, atrial fibrillation, and follow-up lesion volume.

HT, hemorrhagic transformation; HI, hemorrhagic infarction; mRS, modified Rankin Scale; PH, parenchymal hematoma.

dichotomous scale, HI1 and PH2 were significantly associated with a poor functional outcome (aOR 0.34, 95% CI 0.12 to 0.90 and aOR 0.15, 95% CI 0.02 to 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 with patients without HT. However, point estimates for all types of HT were in the direction of worse functional outcome. After adjusting for revascularization rate, the results largely did not change 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 a few studies have reported an association of HI1 or HI2 with functional outcome. Nogueira *et al* reported a significant

association of HI and PH with worse functional outcome.<sup>20</sup> Further, Dzialowski et al reported that HI2, PH1, and PH2 were significantly associated with worse functional outcome compared with patients without HT.<sup>14</sup> Other studies did not find an association of HI or PH1 with worse functional outcome.9-12 21-24 This difference might be explained by smaller sample sizes in some studies<sup>11</sup> <sup>12</sup> <sup>22</sup> <sup>24</sup> or by a lower incidence of HT compared with our study.<sup>9 10 23</sup> Treatment with IVT might be the reason for this difference in incidence because IVT increases the risk of developing HT.<sup>25 26</sup> In our population, 90% of patients received IVT whereas these rates were much lower in other studies.<sup>9 10 23</sup> Additionally, the high incidence of HT in our study might be explained by the broad inclusion criteria of the MR CLEAN trial. Patients with early signs of infarction on CT indicating severe strokes were not excluded, in contrast with other studies with a lower incidence of HT.<sup>9 10 23</sup>



**Figure 2** Follow-up lesion volume per group. Follow-up lesion volume includes hemorrhage and infarct volume. Patients with any subtype of hemorrhagic transformation (HT) have larger lesion volumes than patients without HT (P<0.001). HI, hemorrhagic infarction; PH, parenchymal hematoma.

As large infarct volumes are associated with worse functional outcome and with HT, a large underlying infarct could drive an observed association of HT with functional outcome.<sup>10</sup> 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, it may be complicated to separate them statistically. Also, lesion volume includes 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 the outcome measure (ie, dichotomized or full mRS) both HI1 and HI2 were significantly associated with poor functional outcome. Additionally, all point estimates were in the direction of 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 with patients without HT. However, due to the alternating statistical significance it is difficult to determine their actual influence on functional outcome.

HI1, HI2, and PH2 were 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 with the similarly common PH2. The point estimate, however, indicated 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.<sup>27</sup> Our study suggests otherwise. While patients with PH2 are likely to show acute neurological deterioration in contrast with patients with other subtypes of HT, we found that PH2 was not the only condition relevant for functional outcome. The smaller subtypes of HT were associated with worse functional outcome after approximately 90 days of stroke onset and should therefore 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 conventional 24 hour CT scans. Although these patients with contrast staining have 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 may 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 impaired functional outcome, resulting in a more positive functional outcome for patients with HI. However, the rates of HI were not different between the 24 hour and 5 day CT scans.

In conclusion, we found that not only PH2 is relevant for functional outcome after AIS but smaller types of HT may influence functional outcome. However, it is difficult 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 will randomize periprocedural anti-thrombotic drugs and aims to improve microvascular reperfusion might further improve our knowledge regarding HT risk.<sup>28</sup> Additionally, other upcoming trials that will randomize treatment with thrombolytic agents (MR CLEAN-NO IV, SWIFT DIRECT, DIRECT-SAFE, and DIRECT MT) may clarify whether EVT alone will reduce the risk of HT and improve functional outcome after AIS.<sup>29–32</sup>

#### Author affiliations

<sup>1</sup>Department of Radiology and Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

<sup>2</sup>Department of Biomedical Engineering and Physics, Academic Medical Center, Amsterdam, The Netherlands

<sup>3</sup>Department of Robotics and Mechatronics, University of Twente, Enschede, The Netherlands

<sup>4</sup>Department of Neurology, Erasmus MC-University Medical Rotterdam, Amsterdam, The Netherlands

<sup>5</sup>Department of Radiology and Nuclear Medicine, Erasmus MC-University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>6</sup>Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands <sup>7</sup>Department of Public Health, Center for Medical Decision Making, Erasmus MC-University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>8</sup>Department of Radiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands <sup>9</sup>Department of Neurology, Cardiovascular Research Institute Maastricht (CARIM),

Maastricht University Medical Center, Maastricht, The Netherlands

**Contributors** The MR CLEAN trial was designed by WHvZ, AvdL, RJvO, DWJD, YBWEMR, and CBLMM. OAB collected and prepared the data for the trial. OAB, AMMB, KMT, and KRvK prepared the data for this study. KRvK and KMT conducted the statistical analysis, interpreted the results, and drafted the paper. HAM assisted with the statistical analysis, interpretation of the results, and drafting the paper. AMMB, OAB, LAvdB, VC, HFL, WHvZ, AvdL, RJvO, DWJD, YBWEMR, and CBLMM critically revised the paper. All authors approved the version to be published.

**Funding** The MR CLEAN trial was partly funded by the Dutch Heart Foundation, grant No 2008T30, and by unrestricted grants from AngioCare BV, Medtronic/ Covidien/EV3, MEDAC Gmbh/LAMEPRO, Penumbra Inc, Stryker, and Top Medical/ Concentric.

**Competing interests** Academic Medical Center Amsterdam received funds from Stryker for consultations by CBLMM, YBWEMR, and OAB. CBLMM received research grants from CVON/Dutch Heart Foundation, European Commission, and Twin Foundation. HAM, AMMB, and CBLMM are shareholders of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Erasmus MC received funds from Stryker for consultations by DWJD and AvdL, and Bracco Imaging for consultations by DWJD. Maastricht University Medical Center received funds from Stryker for consultations by WHvZ. WHvZ had speaking engagements with Stryker and Cerenovus.

Patient consent Obtained.

Ethics approval A central medical ethics committee and the research boards of all participating centers accepted the MR CLEAN trial.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Because of the sensitive nature of the data collected for this study, requests to access the data set may be sent to the MR CLEAN executive committee (https://www.mrclean-trial.org/).

# REFERENCES

- Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction-a prospective study. *Stroke* 1986;17:179–85.
- 2 Hommel M, Cornu C, Boutitie F, et al. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996;335:145–50.
- 3 Berkhemer OA, Fransen PS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
- 4 Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–30.

# Ischemic Stroke

- 5 Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–18.
- 6 Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296–306.
- 7 Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–95.
- 8 Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245–51.
- 9 Fiorelli M, Bastianello S, von Kummer R, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999;30:2280–4.
- Berger C, Fiorelli M, Steiner T, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001;32:1330–5.
- 11 Molina CA, Alvarez-Sabín J, Montaner J, et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. Stroke 2002;33:1551–6.
- 12 Kablau M, Kreisel SH, Sauer T, *et al.* Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011;32:334–41.
- 13 The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. *Stroke* 1997;28:2109–18.
- 14 Działowski I, Pexman JH, Barber PA, *et al*. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. *Stroke* 2007;38:75–9.
- 15 Fransen PS, Beumer D, Berkhemer OA, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. *Trials* 2014;15:343.
- 16 Boers AM, Marquering HA, Jochem JJ, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. AJNR Am J Neuroradiol 2013;34:1522–7.
- 17 Harrell FE, 2017. rms: regression modeling strategies. R package version 5.1-0 https:// CRAN.R-project.org/package=rms (accessed 2 Feb 2018).
- Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag, 2009.
- 19 Yoshida K, Bohn J, 2015. Tableone: create table 1 to describe baseline charachteristics. R package version 0.7.3 https://CRAN.R-project.org/package=tableone (accessed 2 Feb 2018).

- 20 Nogueira RG, Gupta R, Jovin TG, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointerv Surg 2015;7:16–21.
- 21 Dávalos A, Toni D, Iweins F, et al. Neurological deterioration in acute ischemic stroke: potential predictors and associated factors in the European cooperative acute stroke study (ECASS) I. Stroke 1999;30:2631–6.
- 22 Bayramoğlu M, Karataş M, Leblebici B, *et al*. Hemorrhagic transformation in stroke patients. *Am J Phys Med Rehabil* 2003;82:48–52.
- 23 Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 2008;39:2249–56.
- 24 Loh Y, Liebeskind DS, Towfighi A, et al. Preprocedural basal ganglionic infarction increases the risk of hemorrhagic transformation but not worse outcome following successful recanalization of acute middle cerebral artery occlusions. World Neurosurg 2010;74:636–40.
- 25 Hacke W, *et al.* Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* 1995;274:1017.
- 26 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–8.
- 27 von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg bleeding classification. Stroke 2015;46:2981–6.
- 28 ISRCTN ISRCTN76741621. Endovascular treatment for acute ischemic stroke; the use of periprocedural heparin or antiplatelet agents. http://www.isrctn.com/ ISRCTN76741621 (acessed 16 Aug 2018).
- 29 ISRCTN ISRCTN80619088. Is intravenous alteplase still of added benefit in patients with acute ischaemic stroke who undergo intra-arterial treatment? http://www.isrctn. com/ISRCTN80619088 (accessed 16 Aug 2018).
- 30 NCT03192332. Bridging thrombolysis versus direct mechanical thrombectomy in acute ischemic stroke. https://clinicaltrials.gov/ct2/show/NCT03192332 (accessed 22 May 2018).
- 31 NCT03494920. DIRECT-SAFE: a randomized controlled trial of direct endovascular clot retrieval versus standard bridging thrombolysis with endovascular clot retrieval. https://clinicaltrials.gov/ct2/show/NCT03494920 (accessed 22 May 2018).
- 32 NCT03469206. Direct intra-arterial thrombectomy in order to revascularize ais patients with large vessel occlusion efficiently in Chinese Tertiary Hospitals. https:// clinicaltrials.gov/ct2/show/NCT03469206 (accessed 22 May 2018).