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

Original research

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

Katinka R van Kranendonk,[1] Manon Kappelhof ,[1] Agnetha A E Bruggeman ,[1] Leon A Rinkel ,[2] Kilian M Treurniet,[1,3] Natalie LeCouffe,[2] Bart J Emmer,[1] Jonathan M Coutinho,[2] Lennard Wolff,[4] Wim H van Zwam ,[5] Robert J van Oostenbrugge,[6] Aad van der Lugt,[4] Diederik W J Dippel ,[7] Yvo B W E M Roos,[2] Henk A Marquering,[1,8] Charles B L M Majoie ,[1] MR CLEAN-NO IV Investigators

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnis-2022-019569).

For numbered affiliations see end of article.

Correspondence to
Katinka R van Kranendonk, Radiology and Nuclear Medicine, Amsterdam UMC Locatie AMC, 1105 AZ Amsterdam, The Netherlands; k.r.vankranendonk@amsterdamumc.nl

Received 25 August 2022
Accepted 1 November 2022

To cite: van Kranendonk KR, Kappelhof M, Bruggeman AAE, *et al*. *J NeuroIntervent Surg* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnis-2022-019569

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 Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)-NO IV trial.

Methods The MR CLEAN-NO IV trial randomized patients with acute ischemic stroke due to large vessel occlusion to 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 symptomatic ICH (sICH) (6%). Of the patients with ICH, 102 had hemorrhagic infarction, 47 had parenchymal hematoma, 44 had SAH, and six had other ICH. Reperfusion was associated with a decreased risk of SAH, and IVT was not associated with SAH (eTICI 2b-3: adjusted OR 0.45, 95% CI 0.21 to 0.97; EVT without IVT: OR 1.6, 95% CI 0.91 to 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 to 2.25; eTICI 2b-3, OR 0.49, 95% CI 0.23 to 1.05).

Conclusion Neither IVT administration before 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.

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 have treatment withheld 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 >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 relation 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 with 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 with 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 elsewhere.[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 non-contrast CT) was performed at 5–7 days after stroke onset or at discharge (if discharge occurred earlier). If 5–7 days 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 neuroradiologist (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) 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 were presented as counts with percentages, continuous variables as medians and 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 using a directed acyclic graph (DAG) (online 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, and 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 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 were 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 was 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).

Table 1 Distribution of intracranial hemorrhage classified according to the Heidelberg bleeding classification

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 seven were classified as sICH, 26 patients had subarachnoid hemorrhage with other ICH as primary hemorrhage type.
ICH, intracranial hemorrhage; sICH, symptomatic intracranial hemorrhage.

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 seven patients had large SAH in both hemispheres and/or causing some compression (major) (figure 1). In five cases, which had four major and one intermediate SAH, a perforation during the intervention was reported and all of these five patients had sICH. Of the 44 patients with SAH, 18 had isolated SAH and 26 patients had both SAH and HT.

Baseline and peri-procedural characteristics of patients with HI and PH, compared with 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 min, IQR 129–219 vs no HT: median 130, IQR 104–171, P<0.01) and patients with HT had a higher baseline blood glucose level 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 online supplemental tables 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 (eTICI 2b-3) 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.

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 (eTICI 2b-3 and eTICI 3c-3) was associated

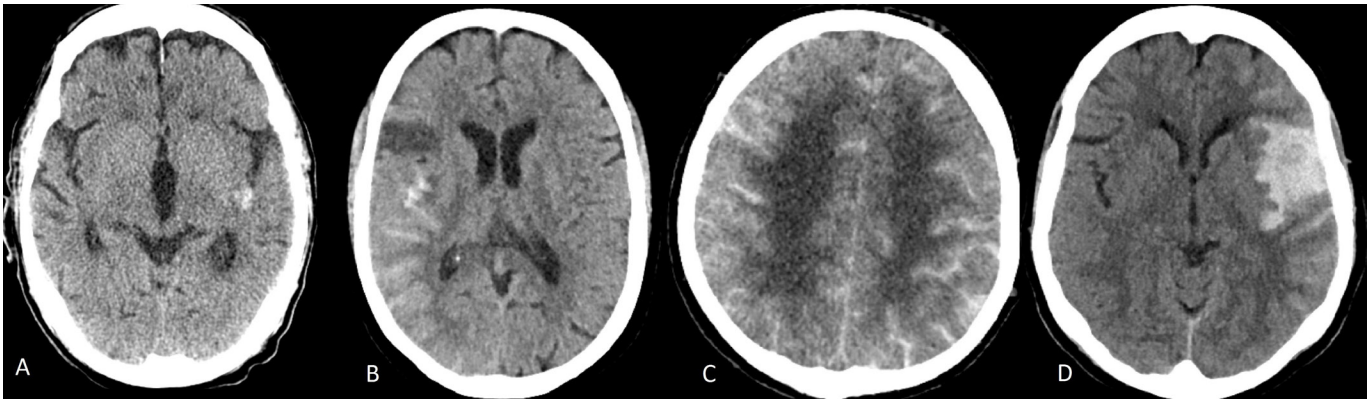

Figure 1 Subarachnoid hemorrhage classification. A: Minor; with hemorrhage within the Sylvian fissure only. This patient had aphasia that recovered after one day. Minor symptoms remained after three months; modified Rankin Scale score (mRS) 1; B: Intermediate, hemorrhage within the Sylvian fissure or 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 mm Hg (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 <100%)	135 (41%)	45 (44%)	22 (49%)	
3 (100% of occluded area)	83 (25%)	18 (18%)	6 (13%)	
Reperfusion (eTICI 2b-3) n (%)	249 (82%)	79 (80%)	35 (85%)	45 (9%)
Reperfusion (eTICI 2c-3) n (%)	185 (61%)	50 (51%)	24 (57%)	45 (9%)
Total attempts (median (IQR))	2 (2–3)	3 (2–4)	2 (2–4)	
Anesthesia 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 anesthesia	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 at 24 hours FU n (%)	246 (82%)	70 (79%)	25 (78%)	62 (13%)

A2, anterior cerebral artery segment 2; ASPECTS, Alberta Stroke Program Early CT Score; DSA, digital subtraction angiography; eTICI, extended Thrombolysis In Cerebral Infarction; EVT, endovascular therapy; FU, follow-up; HI, hemorrhagic infarction; HT, hemorrhagic transformation; ICA, internal carotid artery; ICA-T, tandem occlusion of internal carotid artery; INR, international normalized ratio; IVT, intravenous alteplase treatment; M1, medial cerebral artery segment 1; M2, medial cerebral artery segment 2; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma; SR, stent retriever; TOAST, trial of ORG 10172 in Acute Stroke Treatment.

Table 3 Association of treatment modality and reperfusion with HT, sICH and hemorrhage volume

	HI	PH	SAH	sICH	Hemorrhage volume
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	β (95% CI)
Univariable					
EVT without IVT	0.95 (0.62 to 1.44)	0.94 (0.62 to 1.71)	1.76 (0.92 to 3.35)	0.96 (0.41 to 2.25)	−0.08 (−0.17 to 0)
eTICI 2b-3	0.9 (0.54 to 1.53)	0.89 (0.37 to 2.15)	0.41 (0.19 to 0.86)	0.47 (0.23 to 0.98)	−0.05 (−0.16 to 0.06)
eTICI 2c-3	0.76 (0.51 to 1.15)	0.85 (0.42 to 1.73)	0.47 (0.26 to 0.87)	0.54 (0.29 to 0.99)	0.01 (−0.08 to 0.1)
Multivariable					
eTICI 2b-3	0.95 (0.56 to 1.62)	0.99 (0.42 to 2.36)	0.45 (0.21 to 0.97)	0.49 (0.23 to 1.05)	−0.04 (−0.14 to 0.05)
eTICI 2c-3	0.79 (0.52 to 1.22)	0.91 (0.44 to 1.89)	0.53 (0.29 to 0.99)	0.56 (0.3 to 1.05)	0.01 (−0.07 to 0.1)

Missing values where imputed using multiple imputations (M=5).
Adjusted for the following potential confounders; age, attempts, collateral score, time from stroke onset to groin, treatment allocation.
eTICI, extended Thrombolysis In Cerebral Infarction; EVT, endovascular therapy; HI, hemorrhagic infarction; HT, hemorrhagic transformation; IVT, intravenous alteplase treatment; PH, parenchymal hematoma; SAH, subarachnoid hemorrahge; sICH, symptomatic intracranial hemorrhage.

with sICH; however, this association was not significant in the multivariable analysis. Hemorrhage volume per treatment group and reperfusion status are presented in online supplemental figure S2. IVT before 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 to 3.88) and this association remained significant after excluding patients with SAH due to a perforation (OR 2.05, 95% CI 1.04 to 4.2) (online supplemental table S3).

DISCUSSION

In this population of patients randomized to undergo either 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 with 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 dataset, where IVT administration before 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 it was 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 with 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 SAHs 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, and 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; this is 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. In contrast, 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 before 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.

Author affiliations
[1]Radiology and Nuclear Medicine, Amsterdam UMC Location AMC, Amsterdam, Noord-Holland, The Netherlands
[2]Neurology, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, The Netherlands
[3]Radiology, Haaglanden Medical Center Bronovo, Den Haag, Zuid-Holland, The Netherlands
[4]Radiology & Nuclear Medicine, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[5]Radiology, Maastricht University Cardiovascular Research Institute Maastricht, Maastricht, Limburg, The Netherlands
[6]Neurology, Maastricht University Cardiovascular Research Institute Maastricht, Maastricht, Limburg, The Netherlands
[7]Neurology, Erasmus MC, Rotterdam, Zuid-Holland, The Netherlands
[8]Biomedical Engineering and Physics, Amsterdam UMC Location AMC, Amsterdam, North Holland, The Netherlands

Collaborators List of MR CLEAN-NO IV Investigators, Collaborators, and Affiliations. Principal investigators: Yvo Roos (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Charles Majoie (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Study coordinators Kilian Treurniet (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Jonathan Coutinho (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Bart Emmer (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Natalie LeCouffe (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Manon Kappelhof (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Leon Rinkel (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Agnetha Bruggeman (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Local principal investigators: Bob Roozenbeek (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Adriaan van Es (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Inger de Ridder (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Wim van Zwam (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Bart van der Worp (MD, PhD) (University Medical Center Utrecht, Brain Center, Utrecht, the Netherlands), Rob Lo (MD, PhD) (University Medical Center Utrecht, Brain Center, Utrecht, the Netherlands), Koos Keizer (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Rob Gons (MD), Lonneke Yo (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Jelis Boiten (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Ido van den Wijngaard (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Geert Lycklama à Nijeholt (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Jeannette Hofmeijer (MD, PhD) (Rijnstate Hospital, Arnhem, the Netherlands), Jasper Martens (MD) (Rijnstate Hospital, Arnhem, the Netherlands), Wouter Schonewille (MD, PhD) (St Antonius Hospital, Nieuwegein, the Netherlands), Jan Albert Vos (MD, PhD) (St Antonius Hospital, Nieuwegein, the Netherlands), Anil Tuladhar (MD, PhD) (Radboud University Medical Center, Nijmegen, the Netherlands), Floris Schreuder (MD, PhD) (Radboud University Medical Center, Nijmegen, the Netherlands), Jeroen Boogaarts (MD, PhD) (Radboud University Medical Center, Nijmegen, the Netherlands), Sjoerd Jenniskens (MD) (Radboud University Medical Center, Nijmegen, the Netherlands), Karlijn de Laat (MD, PhD) (HagaZiekenhuis, the Hague, the Netherlands), Lukas van Dijk (MD, PhD) (HagaZiekenhuis, the Hague, the Netherlands), Heleen den Hertog (MD, PhD) (Isala Klinieken, Zwolle, the Netherlands), Boudewijn van Hasselt (MD) (Isala Klinieken, Zwolle, the Netherlands), Paul Brouwers (MD, PhD) (Medisch Spectrum Twente, Enschede, the Netherlands), Emiel Sturm (MD) (Medisch Spectrum Twente, Enschede, the Netherlands), Tomas Bulut (MD) (Medisch Spectrum Twente, Enschede, the Netherlands), Michel Remmers (MD) (Amphia Hospital, Breda, the Netherlands), Anouk van Norden (MD) (Amphia Hospital, Breda, the Netherlands), Thijs de Jong (MD) (Amphia Hospital, Breda, the Netherlands), Anouk Rozeman (MD) (Albert Schweitzer Hospital, Dordrecht, the Netherlands), Otto Elgersma (MD, PhD) (Albert Schweitzer Hospital, Dordrecht, the Netherlands), Maarten Uyttenboogaart (MD, PhD) (University Medical Center Groningen, the Netherlands), Reinoud Bokkers (MD, PhD) (University Medical Center Groningen, the Netherlands), Julia van Tuijl (MD) (Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands), Issam Boukrab (MD) (Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands), Hans Kortman (MD) (Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands), Vincent Costalat (MD, PhD) (Centre Hospitalier Universitaire de Montpellier, Montpellier, France), Caroline Arquizan (MD, PhD) (Centre Hospitalier Universitaire de Montpellier, Montpellier, France), Robin Lemmens (MD, PhD) (Universitair Ziekenhuis Leuven, Leuven, Belgium), Jelle Demeestere (MD, PhD) (Universitair Ziekenhuis Leuven, Leuven, Belgium), Philippe Desfontaines (MD, PhD) (Centre Hospitalier Chrétien, Liège, Belgium), Denis Brisbois (MD, PhD) (Centre Hospitalier Chrétien, Liège, Belgium), Frédéric Clarençon (MD, PhD) (Pitié-Salpêtrière Hospital, Paris, France), Yves Samson (MD, PhD) (Pitié-Salpêtrière Hospital, Paris, France), Local trial collaborators: Executive and writing committee Yvo Roos (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Charles Majoie (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Adriaan van Es (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Wim van Zwam (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Jelis Boiten (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Geert Lycklama à Nijeholt (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Lonneke Yo (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Koos Keizer (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Jonathan Coutinho (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Bart Emmer (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Kilian Treurniet (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Natalie LeCouffe (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Manon Kappelhof (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Data Safety Monitoring Board: Martin Brown (MD) – Chair (National Hospital for Neurology and Neurosurgery, London, UK), Phil White (MD, PhD) (Institute of Neuroscience and Newcastle University Institute for Ageing, Newcastle University, Newcastle, UK), John Gregson (MD, PhD) (London School of Hygiene and Tropical Medicine, London, UK), Independent trial statistician Daan Nieboer (MSc) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), CONTRAST clinical trial collaborators: Research leaders: Diederik Dippel (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Charles Majoie (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Consortium coordinator: Rick van Nuland (PhD) (Lygature, Utrecht, the Netherlands), Imaging assessment committee: Charles Majoie (MD, PhD) – Chair (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Aad van der Lugt (MD, PhD) – Chair (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Wim van Zwam (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Linda Jacobi (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), René van den Berg (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Ludo Beenen (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Bart Emmer (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Adriaan van Es (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Pieter-Jan van Doormaal (MD) (Erasmus MC University Medical Center,

Rotterdam, the Netherlands), Geert Lycklama (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Ido van den Wijngaard (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Albert Yoo (MD, PhD) (Texas Stroke Institute, Plano, Texas, USA), Lonneke Yo (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Jasper Martens (MD, PhD) (Rijnstate Hospital, Arnhem, the Netherlands), Bas Hammer (MD, PhD) (HagaZiekenhuis, the Hague, the Netherlands), Stefan Roosendaal (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Anton Meijer (MD, PhD) (Radboud University Medical Center, Nijmegen, the Netherlands), Menno Krietemeijer (MD) (Catharina Hospital, Eindhoven, the Netherlands), Reinoud Bokkers (MD, PhD) (University Medical Center Groningen, the Netherlands), Anouk van der Hoorn (MD, PhD) (University Medical Center Groningen, the Netherlands), Dick Gerrits (MD) (Medisch Spectrum Twente, Enschede, the Netherlands), Adverse event committee: Robert van Oostenbrugge (MD, PhD) – Chair (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Bart Emmer (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Jonathan Coutinho (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Ben Jansen (MD, PhD) (Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands), Outcome assessment committee: Yvo Roos (MD, PhD) – Chair (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Sanne Manschot (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Diederik Dippel (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Henk Kerkhof (MD, PhD) (University Medical Center Utrecht, Brain Center, Utrecht, the Netherlands), Ido van den Wijngaard (MD, PhD) (Haaglanden Medical Center, the Hague, the Netherlands), Jonathan Coutinho (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Peter Koudstaal (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Koos Keizer (MD, PhD) (Catharina Hospital, Eindhoven, the Netherlands), Data management group Hester Lingsma (PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Diederik Dippel (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Vicky Chalos (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Olvert Berkhemer (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Imaging data management Aad van der Lugt (MD, PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Charles Majoie (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Adriaan Versteeg (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Lennard Wolff (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Jiahang Su (MSc) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Manon Tolhuisen (MSc) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Henk van Voorst (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Biomaterials and translational group: Hugo ten Cate (MD, PhD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Moniek de Maat (PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Samantha Donse-Donkel (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Heleen van Beusekom (PhD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Aladdin Taha (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Local collaborators: Vicky Chalos (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Kilian Treurniet (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Sophie van den Berg (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Natalie LeCouffe (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Rob van de Graaf (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Robert-Jan Goldhoorn (MD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Aladdin Taha (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Samantha Donse-Donkel (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Wouter Hinsenveld (MD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Anne Pirson (MD) (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Lotte Sondag (MD) (Radboud University Medical Center, Nijmegen, the Netherlands), Manon Kappelhof (MD, PhD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Rik Reinink (MD) (University Medical Center Utrecht, Brain Center, Utrecht, the Netherlands), Manon Tolhuisen (MSc) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Josje Brouwer (MD) (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Lennard Wolff (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Sabine Collette (University Medical Center Groningen, the Netherlands), Wouter van der Steen (MD) (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Research nurses: Rita Sprengers (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands), Martin Sterrenberg (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Naziha El Ghannouti (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Sabrina Verheesen (Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands), Wilma Pellikaan (St Antonius Hospital, Nieuwegein, the Netherlands), Kitty Blauwendraat (St Antonius Hospital, Nieuwegein, the Netherlands), Yvonne Drabbe (HagaZiekenhuis, the Hague, the Netherlands), Joke de Meris (Haaglanden Medical Center, the Hague, the Netherlands), Michelle Simons (Rijnstate Hospital, Arnhem, the Netherlands), Hester Bongenaar (Catharina Hospital, Eindhoven, the Netherlands), Anja van Loon (Amphia Hospital, Breda, the Netherlands), Eva Ponjee (Isala Klinieken, Zwolle, the Netherlands), Rieke Eilander (Isala Klinieken, Zwolle, the Netherlands), Suze Kooij (Albert Schweitzer Hospital, Dordrecht, the Netherlands), Marieke de Jong (University Medical Center Groningen, the Netherlands), Esther Santegoets (Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands), Suze Roodenburg (Albert Schweitzer Hospital, Dordrecht, the Netherlands), Ayla van Ahee (Amsterdam UMC location, University of Amsterdam, Amsterdam the Netherlands),5 Marinette Moynier (Centre Hospitalier Universitaire de Montpellier, Montpellier, France), Annemie Devroye (Universitair Ziekenhuis Leuven, Leuven, Belgium), Evelyn Marcis (Universitair Ziekenhuis Leuven, Leuven, Belgium), Ingrid Iezzi (Centre Hospitalier Chrétien, Liège, Belgium), Annie David (Centre Hospitalier Chrétien, Liège, Belgium), Atika Talbi (Pitié-Salpêtrière Hospital, Paris, France), Study monitors: Leontien Heiligers (Erasmus MC University Medical Center, Rotterdam, the Netherlands), Yvonne Martens (Erasmus MC University Medical Center, Rotterdam, the Netherlands).

Contributors CBLM, HAM, YB, DWJD, AvdL, RJvO, WHvZ, LW, JMC, BJE, NL, KMT, LAR, AAEB and MK designed the MR CLEAN NO IV trial. MK, AAEB, LAR, KMT, NL, LW collected and prepared the data for the trial. KRvK, MK, AAEB, LAR and KMT prepared data for this study. KRvK performed the statistical analysis, interpreted the results and drafted the paper with assistance from MK, KMT, HAM and CBLM. The article was critically revised by AAEB, LAR, NL, BJE, JMC, LW, WHvZ, RJvO, AvdL, DWJD, YBWR, HAM and CBLM. CBLM acts as guarantor for the article. All authors contributed to the submitted version.

Funding MR CLEAN NO_IV was funded through the CONTRAST consortium, which acknowledges the support from the Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation (CVON2015-01: CONTRAST), and from the Brain Foundation Netherlands (HA2015.01.06). The collaboration project is additionally financed by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships (LSHM17016). This work was funded in part through unrestricted funding by Stryker, Medtronic and Cerenovus.

Disclaimer The funding sources were not involved in study design, monitoring, data collection, statistical analyses, interpretation of results, or manuscript writing.

Competing interests CBLM reports grants from CVON/Dutch Heart Foundation and Stryker (related and paid to institution), and TWIN Foundation, European Commission, Health Evaluation Netherlands (outside the submitted work and paid to institution); and is shareholder of Nico.lab. HAM is cofounder and shareholder of Nico.lab. DWJD and Van der Lugt report grants from Dutch Heart Foundation, Dutch Brain Foundation, Health Holland, Stryker, Medtronic Penumbra, Cerenovus and Thrombolytic Science Inc, all paid to the institution. YDWR is shareholder of Nico.lab. JMC reports research support from Medtronic (paid to institution). All other authors have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the trial protocol was approved by the Dutch, Belgian, and French central ethical committees and by research boards at each participating center. Medical Ethics Committee Erasmus MC University Medical Centre Rotterdam, 19-10-2017, ref: MEC-2017-368. Deferred consent was taken from participants or their legal representatives.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request after approval by the CONTRAST data access and writing committee.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Manon Kappelhof http://orcid.org/0000-0001-5250-8955
Agnetha A E Bruggeman http://orcid.org/0000-0002-6873-2545
Leon A Rinkel http://orcid.org/0000-0002-0291-8515
Wim H van Zwam http://orcid.org/0000-0003-1631-7056
Diederik W J Dippel http://orcid.org/0000-0002-9234-3515
Charles B L M Majoie http://orcid.org/0000-0002-7600-9568

REFERENCES

1 von Kummer R, Broderick JP, Campbell BCV, *et al*. The Heidelberg bleeding classification. *Stroke* 2015;46:2981–6.
2 Dzialowski I, Pexman JHW, 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.
3 Park JH, Ko Y, Kim W-J, *et al*. Is asymptomatic hemorrhagic transformation really innocuous? *Neurology* 2012;78:421–6.
4 van Kranendonk KR, Treurniet KM, Boers AMM, *et al*. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *J Neurointerv Surg* 2019;11:464-468.
5 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.
6 Lee H, Qureshi AM, Mueller-Kronast NH, *et al*. Subarachnoid hemorrhage in mechanical thrombectomy for acute ischemic stroke: analysis of the STRATIS registry, systematic review, and meta-analysis. *Front Neurol* 2021;12.
7 Wardlaw JM, Murray V, Berge E, *et al*. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014:CD000213.
8 Fiehler J, Remmele C, Kucinski T, *et al*. Reperfusion after severe local perfusion deficit precedes hemorrhagic transformation: an MRI study in acute stroke patients. *Cerebrovasc Dis* 2005;19:117–24.
9 Horsch AD, Dankbaar JW, van der Graaf Y, *et al*. Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. *Neuroradiology* 2015;57:1219–25.
10 Wang X, Tsuji K, Lee S-R, *et al*. Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. *Stroke* 2004;35:2726–30.
11 Khatri R, McKinney AM, Swenson B, *et al*. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. *Neurology* 2012;79:S52–7.
12 Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
13 Campbell BCV, Mitchell PJ, Kleinig TJ, *et al*. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009–18.
14 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.
15 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.
16 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.
17 Muir KW, Ford GA, Messow C-M, *et al*. Endovascular therapy for acute ischaemic stroke: the pragmatic ischaemic stroke thrombectomy evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2017;88:38–44.
18 Bracard S, Ducrocq X, Mas JL, *et al*. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138–47.
19 LeCouffe NE, Kappelhof M, Treurniet KM, *et al*. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;385:1833–44.
20 Treurniet KM, LeCouffe NE, Kappelhof M, *et al*. MR CLEAN-NO IV: intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion-study protocol for a randomized clinical trial. *Trials* 2021;22:141.
21 Liebeskind DS, Bracard S, Guillemin F, *et al*. eTICI reperfusion: defining success in endovascular stroke therapy. *J Neurointerv Surg* 2019;11:433–8.
22 Williams TC, Bach CC, Matthiesen NB, *et al*. Directed acyclic graphs: a tool for causal studies in paediatrics. *Pediatr Res* 2018;84:487–93.
23 Whiteley WN, Slot KB, Fernandes P, *et al*. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. *Stroke* 2012;43:2904–9.
24 Álvarez-Sabín J, Maisterra O, Santamarina E, *et al*. Factors influencing haemorrhagic transformation in ischaemic stroke. *Lancet Neurol* 2013;12:689–705.
25 Yaghi S, Willey JZ, Cucchiara B, *et al*. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017;48:e343-e361.
26 van Kranendonk KR, Treurniet KM, Boers AMM, *et al*. Clinical and imaging markers associated with hemorrhagic transformation in patients with acute ischemic stroke. *Stroke* 2019;50:2037–43.
27 Maïer B, Desilles JP, Mazighi M. Intracranial hemorrhage after reperfusion therapies in acute ischemic stroke patients. *Front Neurol* 2020;11:599908.
28 Charbonnier G, Bonnet L, Biondi A, *et al*. Intracranial bleeding after reperfusion therapy in acute ischemic stroke. *Front Neurol* 2020;11:629920.
29 Constant Dit Beaufils P, Preterre C, De Gaalon S, *et al*. Prognosis and risk factors associated with asymptomatic intracranial hemorrhage after endovascular treatment of large vessel occlusion stroke: a prospective multicenter cohort study. *Eur J Neurol* 2021;28:229–37.
30 Bai X, Zhang X, Wang J, *et al*. Factors influencing recanalization after mechanical thrombectomy with first-pass effect for acute ischemic stroke: a systematic review and meta-analysis. *Front Neurol* 2021;12:628523.
31 Groot AE, Treurniet KM, Jansen IGH, *et al*. Endovascular treatment in older adults with acute ischemic stroke in the MR CLEAN registry. *Neurology* 2020;95:e131–9.
32 Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med Overseas Ed* 2020;382:1981–93.
33 Suzuki K, Matsumaru Y, Takeuchi M, *et al*. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke. *JAMA* 2021;325:244.
34 Zi W, Qiu Z, Li F, *et al*. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234.
35 Mitchell PJ, Yan B, Churilov L, *et al*. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 H of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022;400:116–25.
36 Fischer U, Kaesmacher J, Strbian D, *et al*. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022;400:104–15.
37 The 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.
38 Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke, 2009. Available: http://dx.doi.org/101056/NEJMoa0804656
39 Molina CA, Montaner J, Abilleira S, *et al*. Timing of spontaneous recanalization and risk of hemorrhagic transformation in acute cardioembolic stroke. *Stroke* 2001;32:1079–84.
40 Yoon W, Jung MY, Jung SH, *et al*. Subarachnoid hemorrhage in a multimodal approach heavily weighted toward mechanical thrombectomy with Solitaire stent in acute stroke. *Stroke* 2013;44:414–9.
41 Jolugbo P, Ariëns RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. *Stroke* 2021;52:1131–42.
42 Krajíčková D, Krajina A, Šteiner I, *et al*. Fibrin clot architecture in acute ischemic stroke treated with mechanical thrombectomy with stent-retrievers—cohort study. *Circ J* 2018;82:866–73.
43 Dwivedi A, Glynn A, Johnson S, *et al*. Measuring the effect of thrombosis, thrombus maturation and thrombolysis on clot mechanical properties in an in-vitro model. *J Biomech* 2021;129:110731.
44 Hijdra A, Brouwers PJ, Vermeulen M, *et al*. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. *Stroke* 1990;21:1156–61.
45 Qureshi AI, Saleem MA, Aytac E. Postprocedure subarachnoid hemorrhage after endovascular treatment for acute ischemic stroke. *J Neuroimaging* 2017;27:493–8.
46 Arnould M-C, Grandin CB, Peeters A, *et al*. Comparison of CT and three MR sequences for detecting and categorizing early (48 hours) hemorrhagic transformation in hyperacute ischemic stroke. *AJNR Am J Neuroradiol* 2004;25:939–44.