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Original research

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

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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

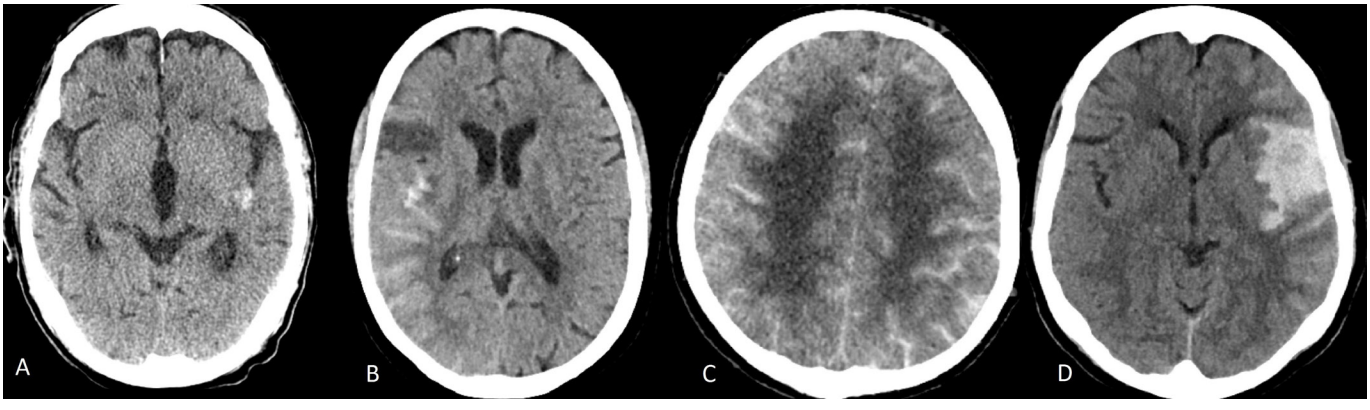

Figure 1 Subarachnoid hemorrhage classification. A: Minor; with hemorrhage within the Sylvian fissure only. This patient had aphasia that recovered after one day. Minor symptoms remained after three months; modified Rankin Scale score (mRS) 1; B: Intermediate, hemorrhage within the Sylvian fissure or 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.

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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.

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SUPPLEMENTAL MATERIAL

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

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Running title: intracranial hemorrhage: intravenous alteplase prior to thrombectomy vs. thrombectomy alone.

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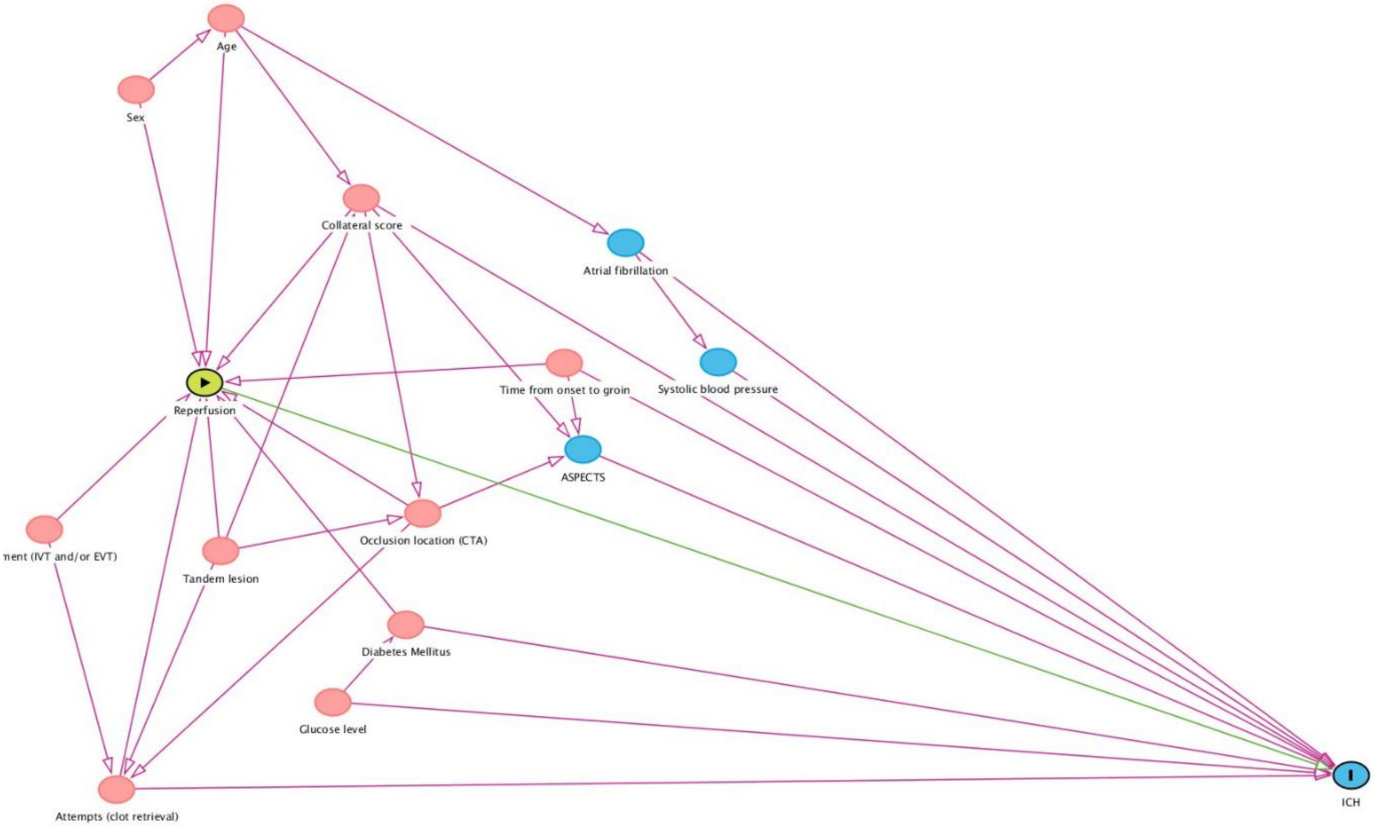
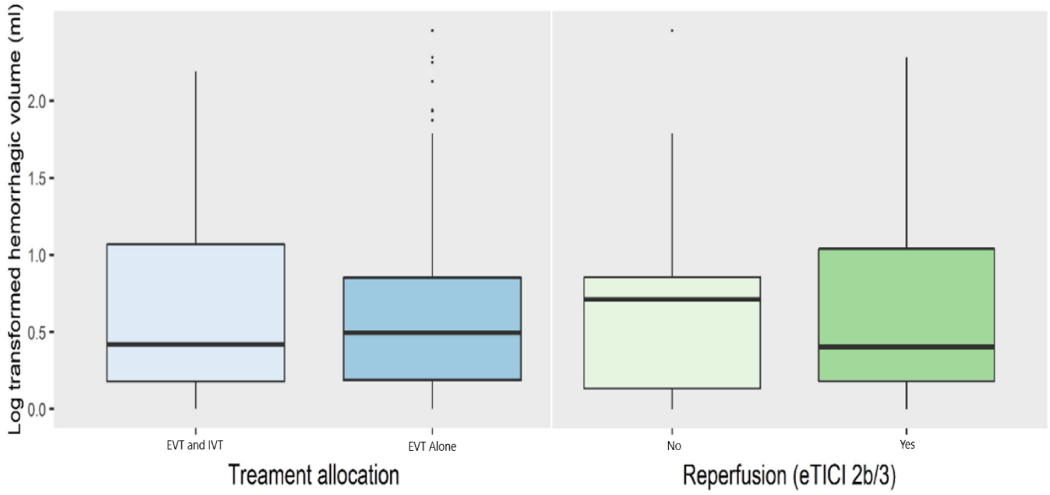
Tables: 3

Figures: 2

Key words: Ischemic stroke (IS), hemorrhagic transformation (HT), intracranial hemorrhage (ICH), endovascular therapy (EVT), thrombolysis



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



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

supplemental table S1. Baseline Characteristics of patients with subarachnoid hemorrhage

	No SAH	SAH
n	445	44
Treatment group = EVT without IVT (%)	220 (49%)	29 (66%)
age (median [IQR])	70 [61, 78]	72 [61, 80]
sex = Male (%)	252 (57%)	25 (57%)
Time from onset to groin (min)	132 [105, 175]	146 [120, 208]
Previous stroke (%)	73 (16%)	8 (18%)
Baseline NIHSS (median [IQR])	16 [10, 20]	16 [11, 20]
Atrial fibrillation (%)	43 (10%)	9 (20%)
Diabetes mellitus (%)	70 (16%)	7 (16%)
Hypertension (%)	207 (47%)	21 (48%)
Antiplatelet use (%)	161 (36%)	12 (27%)
Baseline systolic blood pressure mmHg (median [IQR])	150 [132, 169]	139 [130, 160]
Hypercholesterolemia (%)	123 (27%)	12 (27%)
Blood glucose mmol/L (median [IQR])	6.6 [5.9, 7.8]	6.7 [5.8, 7.9]
INR (median [IQR])	1.0 [1.0, 1.1]	1.0 [1.0, 1.2]
Peri-procedural characteristics		
Baseline ASPECTS (median [IQR])	9 [8, 10]	9 [8, 10]
Occlusion location (%)		
– ica	4 (1%)	0 (0%)
– ica-t	91 (21%)	9 (21%)
– M1	273 (62%)	25 (57%)
– M2	72 (16%)	9 (21%)
– none	4 (1%)	1 (2%)
first device type (%)		
– Aspiration First	88 (22%)	6 (15%)
– SR	313 (78%)	33 (85%)
Collateral score (%)		
– 0 (absent collaterals)	24 (6%)	6 (15%)
– 1 (filling ≤50% of occluded area)	128 (29%)	11 (26%)
– 2 (>50% but less <100%)	192 (44%)	10 (24%)
– 3 (100% of occluded area)	92 (21%)	15 (36%)
Reperfusion (eTICI2b3) n (%)	338 (84%)	25 (61%)
Reperfusion (eTICI2b3) n (%)	244 (61%)	15 (37%)
Total attempts (median [IQR])	2 [2, 3]	3 [2, 5]
Anesthesia deepest (%)		
– 0 - None (local only)	268 (63%)	24 (57%)
– 1 - None with bolus short working opiates	38 (9%)	2 (5%)
– 2 - Moderate sedation	48 (11%)	8 (19%)
– 3 - Deep sedation	7 (2%)	0 (0%)
– 4 - General anesthesia	63 (15%)	8 (19%)
TOAST (%)		
– Cardioembolic	112 (25%)	11 (25%)

– Large artery atherosclerosis	63 (14%)	8 (18%)
– Other determined	2 (0%)	0 (0%)
– Undetermined etiology	252 (57%)	22 (50%)
– Undetermined etiology: more than one cause	16 (4%)	3 (7%)
Recanalization on 24h FU = Yes (%)	318 (82%)	23 (74%)

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

Supplemental table 2. Baseline Characteristics of patients with sICH

	No	Yes
n	459	30
Treatment group = EVT without IVT (%)	233 (51%)	16 (53%)
age (median [IQR])	70 [61, 78]	72 [62, 82]
sex = Male (%)	261 (57%)	16 (53%)
Time from onset to groin (min)	130 [105, 174]	170 [135, 249]
Previous stroke (%)	73 (16%)	8 (27%)
Baseline NIHSS (median [IQR])	16 [10, 20]	16 [11, 20]
Atrial fibrillation (%)	47 (10%)	5 (17%)
Diabetes mellitus (%)	70 (15%)	7 (23%)
Hypertension (%)	212 (46%)	16 (53%)
Antiplatelet use (%)	161 (35%)	12 (40%)
Baseline systolic blood pressure mmHg (median [IQR])	150 [132, 167]	160 [139, 180]
Hypercholesterolemia (%)	128 (28%)	7 (23%)
Blood glucose mmol/L (median [IQR])	6.6 [5.8, 7.8]	7.3 [6.3, 8.5]
INR (median [IQR])	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]
Peri-procedural characteristics		
Baseline ASPECTS (median [IQR])	9 [8, 10]	9 [8, 10]
Occlusion location (%)		
– ica	4 (1%)	0 (0%)
– ica-t	95 (21%)	5 (17%)
– M1	283 (62%)	15 (50%)
– M2	74 (16%)	7 (23%)
– none	2 (0%)	3 (10%)
first device type (%)		
– Aspiration First	89 (21%)	5 (20%)
– SR	326 (78%)	20 (80%)
Collateral score (%)		
– 0 (absent collaterals)	30 (7%)	0 (0%)
– 1 (filling ≤50% of occluded area)	132 (29%)	7 (24%)
– 2 (>50% but less <100%)	190 (42%)	12 (41%)
– 3 (100% of occluded area)	97 (21%)	10 (35%)
Reperfusion (eTICI2b3) n (%)	344 (83%)	19 (73%)
Reperfusion (eTICI2b3) n (%)	247 (59%)	12 (46%)
Total attempts (median [IQR])	2 [2, 3]	2 [2, 4]
Anesthesia deepest (%)		
– 0 - None (local only)	278 (63%)	14 (52%)
– 1 - None with bolus short working opiates	36 (8%)	4 (15%)
– 2 - Moderate sedation	52 (12%)	4 (15%)
– 3 - Deep sedation	6 (1%)	1 (4%)
– 4 - General anesthesia	67 (15%)	4 (15%)
TOAST (%)		
– Cardioembolic	117 (26%)	6 (20%)
– Large artery atherosclerosis	66 (14%)	5 (17%)

– Other determined	2 (0%)	0 (0%)
– Undetermined etiology	257 (56%)	17 (57%)
– Undetermined etiology: more than one cause	17 (4%)	2 (7%)
Recanalization on 24h FU = Yes (%)	329 (81%)	12 (80%)

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

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

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

Abbreviations: HI, hemorrhagic infarction; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; sICH, symptomatic intracranial hemorrhage; EVT, endovascular therapy; eTICI, extended thrombolysis in cerebral infarction.
Adjusted for following potential confounders; age, attempts, collateral score, time from stroke onset to groin, treatment allocation
Hemorrhage volume was logarithmically transformed to meet a normal distribution (log10(x+1))

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Date: 10/28/2021

Your Name: Aad van der Lugt

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

Manuscript Number (if known): jnis-2022-019569.R1

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		Penumbra	Funding for research paid to institution
		Medtronic	Funding for research paid to institution
		Cerenovus	Funding for research paid to institution
		Thrombolytic Science LLC	Funding for research paid to institution
		Dutch Heart Foundation	Funding for research paid to institution
		Brain Foundation Netherlands	Funding for research paid to institution
		The Netherlands Organization for Health Research and Development, Health Holland Top Sector Life Sciences & Health,	Funding for research paid to institution
		The Netherlands Organization for Health Research and Development,	Funding for research paid to institution
		Health Holland Top Sector Life Sciences & Health	Funding for research paid to institution

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		Escape -MEVO	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		Research leader of CONTRAST consortium	unpaid
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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Your Name: B.J. Emmer

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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		Netherlands Organisation for Health Research and Development	Paid to institution
		Nicolab B.V.	Paid to Institution
3	Royalties or licenses	☒ **None**	

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6	Payment for expert testimony	☒ **None**	
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8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		Dutch Delegate UEMS Neuroradiology	Unpaid
		Board member Neuroradiology Dutch Society of Radiology	Unpaid

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13	Other financial or non-financial interests	☒ **None**	

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Your Name: Robert J van Oostenbrugge

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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Your Name: Agnetha Bruggeman

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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Date: 10/21/2022

Your Name: Charles Majoie

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
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11	Stock or stock options	☐ **None**	
		Nico-lab	Minority interest owned by me
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Date: 10/26/2022

Your Name: Diederik Dippel

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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		Dutch Heart Foundation	Grant for research, paid to institution
		Brain Foundation Netherlands	Grant for research, paid to institution
		The Netherlands Organisation for Health Research and Development	Grant for research, paid to institution
		Health Holland Top Sector Life Sciences & Health	Grant for research, paid to institution
		Stryker	Unrestricted grant for research, paid to institution
		Medtronic	Unrestricted grant for research, paid to institution
		Cerenovus	Unrestricted grant for research, paid to institution
		Thrombolytic Science	Unrestricted grant for research, paid to institution

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
		Penumbra	Unrestricted grant for research, paid to institution
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety	☒ **None**	

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	Monitoring Board or Advisory Board	DSMC LATE-MT	No payments
		DSMC TESLA trial	No payments
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		Research leader of CONTRAST consortium	No payments
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

ICMJE DISCLOSURE FORM

Date: 10/21/2022

Your Name: Henk Marquering

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☐ **None**	
		cofounder and shareholder of Nicolab	
		cofounder and shareholder of TrianecT	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/21/2022

Your Name: K.M. Treurniet

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/27/2022

Your Name: Katinka Rebekka van Kranendonk

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/21/2022

Your Name: Leon A. Rinkel

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/23/2022

Your Name: Lennard Wolff

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☐ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/20/2022

Your Name: Manon Kappelhof

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/22/2022

Your Name: N.E. LeCouffe

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Oral presentation at AAN for the MR CLEAN NO IV trial	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

van Kranendonk KR, *et al. J NeuroIntervent Surg* 2022;0:1–8. doi: 10.1136/jnis-2022-019569

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/20/2022

Your Name: Wim H. van Zwam

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☐ **None**	
		Philips	Paid to institution
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Stryker	Paid to institution
		Cerenovus	Paid to institution
		NicoLab	Paid to institution
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 10/20/2022

Your Name: Yvo Roos

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

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Time frame: Since the initial planning of the work			
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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☐ **None**	
		Minor share-holder of Nico-Lab	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 9/21/2022

Your Name: Jonathan Coutinho

Manuscript Title: Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone.

Manuscript Number (if known): jnis-2022-019569.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Boehringer	Honoraria for membership steering committee. All fees paid to my institution
		Bayer	Honoraria for membership steering committee. All fees paid to my institution
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		The Netherlands Organisation for Health Research and Development (ZonMw, grant number 10430072110005)	Honoraria for membership steering committee. All fees paid to my institution
		Dr. C.J. Vaillant Foundation	Honoraria for membership steering committee. All fees paid to my institution
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3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board,	☒ **None**	

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	society, committee or advocacy group, paid or unpaid		
11	Stock or stock options	☐ **None**	
		Trianect	Dr Coutinho is a shareholder of Trianect BV
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.