Maastricht University

Clinical and Imaging Markers Associated With Hemorrhagic Transformation in Patients With Acute Ischemic Stroke

Citation for published version (APA):

van Kranendonk, K. R., Treumiet, K. M., Boers, A. M. M., Berkhemer, O. A., van den Berg, L. A., Chalos, V., Lingsma, H. F., van Zwam, W. H., van der Lugt, A., van Oostenbrugge, R. J., Dippel, D. W. J., Roos, Y. B. W. E. M., Marquering, H. A., Majoie, C. B. L. M., Fransen, P. S. S., Beumer, D., Yoo, A. J., Schonewille, W. J., Vos, J. A., ... MR CLEAN Investigators (2019). Clinical and Imaging Markers Associated With Hemorrhagic Transformation in Patients With Acute Ischemic Stroke. *Stroke*, *50*(8), 2037-2043. https://doi.org/10.1161/STROKEAHA.118.024255

Document status and date:
Published: 01/08/2019

DOI:
10.1161/STROKEAHA.118.024255

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

Document license:
Taverne

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

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

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

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

www.umlib.nl/taverne-license

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

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 20 Mar. 2024

Clinical and Imaging Markers Associated With Hemorrhagic Transformation in Patients With Acute Ischemic Stroke

Katinka R. van Kranendonk, BSc; Kilian M. Treurniet, MD; Anna. M.M. Boers, PhD; Olvert A. Berkhemer, MD, PhD; Lucie A. van den Berg, MD; Vicky Chalos, MD; Hester F. Lingsma, PhD; Wim H. van Zwam, MD, PhD; Aad van der Lugt, MD, PhD; Robert J. van Oostenbrugge, MD, PhD; Diederik W.J. Dippel, MD, PhD; Yvo B.W.E.M. Roos, MD, PhD; Henk A. Marquering, PhD; Charles B.L.M. Majoie, MD, PhD; for the MR CLEAN Investigators

Background and Purpose—Hemorrhagic transformation (HT) after acute ischemic stroke may cause severe neurological deterioration and affects functional outcome. Identifying patients most likely to suffer from this complication could potentially be used for future treatment selection. Reperfusion after endovascular therapy could be associated with different risk factors for HT than intravenous thrombolytics as these treatments largely differ. In this study, we aimed to identify clinical and imaging markers that are associated with HT subtypes in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) population.

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

Results—Of the 478 out of 500 included patients in this subanalysis, 46% had HT (n=222). Of these, 66% had hemorrhagic infarction (n=147) and 34% PH (n=75). Symptomatic intracranial hemorrhage was observed in 7.3% (n=35) of all patients. Baseline National Institutes of Health Stroke Scale (odds ratio [OR], 1.05,95% CI, 1.01–1.09 per point) and absent/poor collaterals (OR, 1.90; 95% CI, 1.05–3.42) were significantly associated with hemorrhagic infarction. Increased systolic blood pressure (OR, 1.17; 95% CI, 1.05–1.31 per 10 mm Hg) and atrial fibrillation (OR, 1.94; 95% CI, 1.08–3.48) were associated with PH. Increased systolic blood pressure (OR, 1.28; 95% CI, 1.12–1.48) and antiplatelet use (OR, 2.6; 95% CI, 1.08–6.3) were associated with symptomatic intracranial hemorrhage.

Conclusions—Clinical and imaging stroke severity parameters were associated with HT, both in hemorrhagic infarction and PH, whereas baseline patients characteristics like systolic blood pressure, atrial fibrillation, and antiplatelet use were only associated with PH or symptomatic intracranial hemorrhage.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN10888758. (***Stroke*****. 2019;50:2037-2043. DOI: 10.1161/STROKEAHA.118.024255.)**

Key Words: atrial fibrillation ■ blood pressure ■ infarction ■ intracranial hemorrhages ■ reperfusion ■ risk factors ■ stroke

Downloaded from http://ahajournals.org by on July 6, 2023

Hemorrhagic transformation (HT) can occur as natural progression of acute ischemic stroke or as a complication of stroke treatment and may result in impaired functional outcome.[1,2] HT ranges from smaller petechial hemorrhagic infarction (HI) to more confluent parenchymal hematoma (PH). Symptomatic intracranial hemorrhage (sICH) is an HT that results in acute neurological deterioration. sICH results in high mortality and is usually a consequence of PH.[3] A small HI is less likely to lead to acute neurological deterioration than PH, although it may still have a negative impact on long-term

Received November 29, 2018; final revision received May 10, 2019; accepted May 30, 2019.

From the Department of Radiology and Nuclear Medicine (K.R.v.K., K.M.T., A.M.M.B., O.A.B., C.B.L.M.M.), Department of Biomedical Engineering and Physics (A.M.M.B., H.A.M.), and Department of Neurology (L.A.v.d.B., Y.B.W.E.M.R.), Amsterdam UMC, location AMC, University of Amsterdam, the Netherlands; Department of Robotics and Mechatronics, University of Twente, Enschede, the Netherlands (A.M.M.B.); Department of Neurology (O.A.B., V.C., D.W.J.D.), Department of Radiology and Nuclear Medicine (O.A.B., V.C., A.v.d.L.), and Department of Public Health, Center for Medical Decision Making (V.C., H.F.L.), Erasmus MC-University Medical Center Rotterdam, the Netherlands; and Department of Radiology (W.H.v.Z.) and Department of Neurology (R.J.v.O.), Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, the Netherlands.

*A list of all MR CLEAN Investigators is given in the Appendix.

Guest Editor for this article was Giuseppe Lanzino, MD.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.024255.

Correspondence to Katinka R. van Kranendonk, BSc, Department of Radiology and Nuclear Medicine, Amsterdam UMC, location AMC, G1-230, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. Email k.r.vankranendonk@amc.uva.nl

© 2019 American Heart Association, Inc.

functional outcome.[4,5] Various risk factors associated with the occurrence of HT have been identified. These include: treatment with thrombolytic agents, age, hyperglycemia, hypertension, use of antiplatelet agents, large infarct size, early ischemic changes on computed tomography (CT), and cholesterol level.[6–9] Most studies have examined risk factors for HT after treatment with intravenous thrombolysis (IVT).[6] Recently, endovascular therapy (EVT) has become part of usual care for patients with acute ischemic stroke due to intracranial large vessel occlusions. It is not clear whether risk factors for HT differ after treatment with EVT.[10–14] By determining factors that contribute to the development of HT, we may be able to identify patients at risk for developing HT and alter treatment to decrease this risk.

In this study, we aimed to identify clinical and imaging markers that are associated with the occurrence of HI, PH, and sICH in the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands).[10] In addition, we explored whether the association of these characteristics would differ per treatment group.

Methods

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

Study Design

Data was obtained from MR CLEAN, a prospective multicenter randomized trial assessing the safety and effect of additional EVT compared with usual care only. Acute ischemic stroke patients with a proximal intracranial occlusion who could be treated with EVT within 6 hours of stroke onset were included for randomization. Patients who endured a previous stroke within 6 weeks before stroke onset were excluded, as were patients with a blood pressure exceeding 185 out of 110 mm Hg before start of treatment. Additionally, patients with a history of intracranial hemorrhage were specifically excluded for intraarterial treatment with alteplase, but not for EVT. More specific inclusion and exclusion criteria can be found in the MR CLEAN study protocol.[15]

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

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

Statistical Analysis

For the statistical analysis, 2 analyses were performed: (1) patients with HI (HI1 and HI2) and patients with PH (PH1 and PH2) were both compared with patients without HT; (2) patients with any sICH were compared with patients without sICH. We assessed the relation of clinical and radiological characteristics with the occurrence of HI and PH using multinomial logistic regression analysis and sICH using binary logistic regression analysis. Univariable tests were used to identify variables associated with HI, PH, and sICH. Variables with an association with $P<0.10$ were included in the multivariable regression analysis. The following variables collected at baseline were explored for their association with HI, PH, and sICH: Alberta Stroke Program Early CT Score (ASPECTS), admission collateral score, EVT, administration of intravenous thrombolytics, age, sex, systolic blood pressure (measured on admission), NIHSS, known hypercholesterolemia and statin use, antiplatelet use, atrial fibrillation, time from onset to randomization, diabetes mellitus, and previous stroke. Criteria for diagnosing diabetes mellitus in the Netherlands are diabetes symptoms (polyuria and polydipsia) and a venous plasma glucose concentration ≥1≥1.1 mmol/L or a fasting plasma glucose concentration ≥≥7.0 mmol/L.

Hypercholesterolemia is defined as a total cholesterol of ≥≥6.5 mmol/L.

An additional analysis was conducted to explore possible differences in associations with HI, PH, and sICH between patients treated with EVT or not treated with EVT. Therefore, the groups HI, PH, and sICH were all divided per treatment, patients treated with EVT, and control group, respectively. The control group consisted of all patients that did not receive EVT. Revascularization rate assessed with modified Treatment in Cerebral Ischemia (mTICI) scores was available for patients treated with EVT; therefore, we added this variable to the analysis of patients with sICH after EVT.

As discriminating HI from contrast staining may be difficult on a 24-hour CT scan, HI rates on scans acquired at 24 hours or 5 to 7 days were compared.

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

Results

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

Of all 478 patients, 46% had an HT (n=222). Of the patients with HT, 66% had HI (n=147), and 34% had PH (n=75). sICH was observed in 35 patients (7.3%). In the sICH group, 2 patients had a subarachnoid hemorrhage. Both patients with a subarachnoid hemorrhage had undergone EVT. HI was found in 36 of 117 (31%) patients on 24-hour imaging and in 111 of 361 (31%) patients on 5-day follow-up imaging.

Characteristics at baseline for patients with HI, PH, and sICH compared with patients without HT are presented in Table 1. Occurrence of any HT or sICH was evenly distributed among all 4 possible treatments: EVT+intravenous alteplase, intravenous alteplase, EVT only, and patients without treatment. Compared with patients without any HT, patients with HI had a higher median NIHSS score (19 versus 17, $P<0.01$) and lower median ASPECTS score (9 [7–10] versus 9 [8–10], $P<0.01$). In the multivariable regression analysis presented in Table 2, HI was significantly associated with baseline NIHSS score (odds ratio [OR], 1.05; 95% CI, 1.01–1.09 [per point]) and with absent/poor collaterals (OR, 1.88; 95% CI, 1.04–3.39).

Downloaded from http://ahajournals.org by on July 6, 2023

Table 1. Clinical and Radiological Characteristics at Baseline

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

ASPECTS denotes early ischemic changes and NIHSS denotes stroke severity. ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, CT-angiography; EVT, endovascular therapy; HI, hemorrhagic infarction; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; IQR, interquartile range; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and PH, parenchymal hematoma.

*ASPECTS was missing for 4 patients.

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

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

Of the 35 patients diagnosed with sICH, 30 patients had PH, 3 patients had HI, and 2 patients had subarachnoid hemorrhage. Patients with sICH were older (75 versus 65 years, *P*<0.001), had a higher NIHSS score (19 versus 17, *P*<0.01), had more often diabetes mellitus (31% versus 11%, *P*<0.01), and had a higher systolic blood pressure (158 versus 140, *P*<0.01) than patients without sICH. Pretreatment antiplatelet use was more common among patients with sICH (60% versus 26%, *P*<0.01) as was hypercholesterolemia and statin use (49% versus 20%, *P*<0.01). In the multivariable regression analysis presented in Table 3, sICH was significantly associated with systolic blood pressure (OR, 1.28; 95% CI, 1.11–1.47 [per 10 mm Hg]) and antiplatelet use (OR, 2.6; 95% CI, 1.08–6.3).

Differences Per Treatment

Clinical and imaging characteristics at baseline of patients with HI and PH differed per treatment group and are presented in Table I in the online-only Data Supplement. In the control group, that consisted of all patients that did not receive EVT, patients with HI had higher baseline NIHSS score than patients without HT (20 versus 17, *P*<0.01). In contrast, patients with HI in the EVT group did not have a significant higher baseline NIHSS score than patients without HI. PH was in the control group associated with an increased systolic blood pressure compared with patients without HT (159 versus 143, *P*<0.01). In the EVT group, the association with systolic blood pressure and PH was not apparent. The univariable analyses of HI and PH per treatment group are presented in Table II in the online-only

Downloaded from http://ahajournals.org by on July 6, 2023

Table 2. Univariable and Multivariable Associations With HT (Multinomial Logistic Regression)

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

All variables with an association with $P<0.1$ were included in the multivariable regression analysis. ASPECTS denotes early ischemic changes and NIHSS denotes stroke severity. ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular therapy; HI, hemorrhagic infarction; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PH, parenchymal hematoma.

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

†Collateral score with good collaterals as reference level.

Downloaded from http://ahajournals.org by on July 6, 2023

Data Supplement. In the univariable analysis, systolic blood pressure was associated with PH in both groups, EVT (OR, 1.19; 95% CI, 1.04–1.36 [per 10 mm Hg]), and control group (OR, 1.24; 95% CI, 1.07–1.44 [per mm Hg]), respectively.

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

Discussion

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

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

When considering all effect estimates, including nonsignificant associations, our study seems to confirm presumed different underlying mechanisms for different hemorrhage types.[26] Hemorrhage development per se (HI and PH) is more likely in patients with risk factors for large infarcts (ie, worse collateral scores and higher NIHSS score). The paradoxical effect estimate for ASPECTS can probably be explained by inclusion of both ASPECTS and collateral score in the same model, 2 variables very much related.[27] Larger hemorrhages that are more likely to be symptomatic (PH and sICH) might more likely develop if an additional risk factor is present: an increased hydrostatic pressure (blood pressure), impaired

Table 3. Univariable and Multivariable Associations With sICH (Binary Logistic Regression)

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

All variables with an association with $P<0.1$ were included in the multivariable regression analysis. ASPECTS denotes early ischemic changes, and NIHSS denotes stroke severity. ASPECTS indicates Alberta Stroke Program Early CT Score; EVT endovascular therapy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and sICH, symptomatic intracranial hemorrhage.

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

†Collateral score with good collaterals as reference level.

Downloaded from http://ahajournals.org by on July 6, 2023

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

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

In agreement with previous studies,[8,21,25] neither IVT or EVT were significantly associated with HT in our study. As pretreatment with IVT is standard of care in eligible patients,[32] all patients without IVT had contraindications for IVT. Therefore, no reliable estimate of the true effect of tPA (tissue-type plasminogen activator) on hemorrhage rates can be made. Ongoing trials that randomize between IVT followed by EVT and EVT alone (MR CLEAN-NO IV [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands], SWIFT DIRECT [Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke], DIRECT-SAFE [A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset], and DIRECT MT [Parallel Group, Randomized Clinical Trial of Direct Intra-arterial Thrombectomy Versus Intravenous Thrombolysis With Intra-arterial Thrombectomy for Patients With Large Vessel Occlusion of the Anterior Circulation]) will give us valuable information about the actual impact of IVT on HT.[33–36]

Our study had several limitations. First, our purpose of this study was to identify variables associated with HT, and therefore, we did not adjust for potential confounders. Consequently, the associated variables in this study should not be interpreted as causal factors for HT. Second, not all follow-up CT scans at 5 days could be retrieved due to death

(n=52) or other reasons, which resulted in the use of follow-up CT scans at 2 different moments.[10] This might have influenced the categorization of HI because it is complicated to distinguish HI from contrast staining resulting in an overestimation of HI at the first scan moment (24-hour CT scan). However, HI rates were not different between the 2 scan moments. If some HIs were misinterpreted contrast staining, the actual HI-rate could be higher on the 5-day follow-up CT scans. Dual-energy CT can differentiate between contrast staining and HI, but dual-energy CT was not part of our imaging protocol. Third, we used baseline systolic blood pressure measured on admission, which only represents a snap-shot in time. Multiple measurements of blood pressure were not available. However, in previous studies, as well as in this analysis, baseline systolic blood pressure had a stronger relation with outcome and HT than diastolic blood pressure or known hypertension.[37] Furthermore, this was a post hoc study, and therefore, results should be interpreted carefully. Last, although we selected variables with care, it should be considered that some associations might have occurred by chance due to the large number of variables that were included in the analysis.[38]

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

Appendix

MR CLEAN Investigators: Olvert A. Berkhemer, Amsterdam UMC, location AMC, the Netherlands and Erasmus MC-University Medical Center Rotterdam, the Netherlands. Puck S.S. Fransen, Erasmus MC-University Medical Center Rotterdam, the Netherlands. Debbie Beumer, Erasmus MC-University Medical Center Rotterdam, the Netherlands and Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), the Netherlands. Berkhemer, Fransen and Beumer contributed equally. Lucie A. van den Berg, Amsterdam UMC, location AMC, the Netherlands. Hester F. Lingsma, Erasmus MC-University Medical Center Rotterdam, the Netherlands. Albert J. Yoo, Massachusetts General Hospital, Boston, United States of America. Wouter J. Schonewille, Sint Antonius Hospital, Nieuwegein, the Netherlands. Jan Albert Vos, MD, Sint Antonius Hospital, Nieuwegein, the Netherlands. Paul J. Nederkoorn, Amsterdam UMC, location AMC, the Netherlands. Marieke J.H. Wermer and Marianne A.A. van Walderveen, Leiden University Medical Center, the Netherlands. Julie Staals, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), the Netherlands. Jeannette Hofmeijer and Jacques A. van Oostayen, Rijnstate Hospital, Arnhem, the Netherlands. Geert J. Lycklama à Nijeholt and Jelis Boiten, MC Haaglanden, the Hague, the Netherlands. Patrick A. Brouwer and Bart J. Emmer, Erasmus MC-University Medical Center Rotterdam, the Netherlands. Sebastiaan F. de Bruijn and Lukas C. van Dijk, HAGA Hospital, the Hague, the Netherlands. L. Jaap Kappelle, University Medical Center Utrecht, the Netherlands. Rob H. Lo, University Medical Center Utrecht, the Netherlands. Ewoud J. van Dijk and Joost de Vries, Radboud University Medical Center, Nijmegen, the Netherlands. Paul L.M. de Kort and Willem Jan J. van Rooij, Sint Elisabeth Hospital, Tilburg, the Netherlands. Jan S.P. van den Berg and Boudewijn A.A.M. van Hasselt, Isala Klinieken, Zwolle, the Netherlands. Leo A.M. Aerden and René J. Dallinga, Reinier de Graaf Gasthuis, Delft, the Netherlands. Marieke C. Visser and Joseph C.J. Bot, Amsterdam UMC, location VU, Amsterdam, the Netherlands. Patrick C. Vroomen and Omid Eshghi, University Medical Center Groningen, the Netherlands. Tobien H.C.M.L. Schreuder and Roel J.J. Heijboer, Atrium Medical Center, Heerlen, the Netherlands. Koos Keizer and Alexander V. Tielbeek, Catharina Hospital, Eindhoven, the Netherlands. Heleen M. den Hertog and Dick G. Gerrits, Medical Spectrum Twente, Enschede, the Netherlands. Renske M. van den Berg-Vos and Giorgos B. Karas, Sint Lucas Andreas Hospital, Amsterdam, the Netherlands. Ewout W. Steyerberg, Erasmus MC-University Medical Center Rotterdam, the Netherlands. H. Zwenneke Flach, Isala Klinieken, Zwolle, the Netherlands. Henk A. Marquering and Marieke E.S. Sprengers, Amsterdam UMC, location AMC, the Netherlands. Sjoerd F.M. Jenniskens, Radboud University Medical Center, Nijmegen, the Netherlands. Ludo F.M. Beenen and René van den Berg, Amsterdam UMC, location AMC, the Netherlands. Peter J. Koudstaal and Wim H. van Zwam, Erasmus MC-University Medical Center Rotterdam, the Netherlands. Yvo B.W.E.M. Roos, Amsterdam UMC, location AMC, the Netherlands. Aad van der Lugt, Erasmus MC-University Medical Center Rotterdam, the Netherlands. Robert J. van Oostenbrugge, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), the Netherlands. Charles B.L.M. Majoie, Amsterdam UMC, location AMC, the Netherlands. Diederik W.J. Dippel, Erasmus MC-University Medical Center Rotterdam, the Netherlands. van Zwam, Roos, van der Lugt, van Oostenbrugge, Majoie and Dippel contributed equally.

Sources of Funding

The MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) was partly funded by the Dutch Heart Foundation grant number 2008T30 and by unrestricted grants from AngioCare BV, Medtronic/Covidien/EV3, MEDAC Gmbh/LAMEPRO, Penumbra, Inc, Stryker, and Top Medical/Concentric.

Disclosures

Academic medical center Amsterdam received funds from Stryker for consultations by Dr Majoie, Roos, and Berkhemer. Dr Majoie received research grants from Cardiovasculair Onderzoek Nederland (CVON)/Dutch Heart Foundation, European Commission, Twin Foundation and Stryker (all paid to institution). Dr Marquering, Dr Boers, Dr Majoie and Dr Roos are shareholders of Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. Erasmus University Medical Center received funds from Bracco Imaging for consultations by Dr Dippel. Erasmus University Medical Center received funds from CVON/Dutch Heart Foundation, European Commission, Stryker, Penumbra, and Medtronic for the execution of stroke trials by Drs Dippel and van der Lugt. Maastricht University Medical Center received funds from Stryker and Cerenovus for consultations by Dr Zwam. The other authors report no conflicts.

References

1. Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction–a prospective study. *Stroke*. 1986;17:179–185.
2. Hommel M, Cornu C, Boutitie F, Boissel JP; Multicenter Acute Stroke Trial–Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med*. 1996;335:145–150. doi: 10.1056/NEJM199607183350301
3. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. 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. doi: 10.1161/STR.0000000000000152
4. Dzialowski I, Pexman JH, Barber PA, Demchuk AM, Buchan AM, Hill MD; CASES Investigators. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian

Downloaded from http://ahajournals.org by on July 6, 2023

alteplase for stroke effectiveness study registry. *Stroke*. 2007;38:75–79. doi: 10.1161/01.STR.0000251644.76546.62
5. van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, van den Berg LA, Chalos V, 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.
6. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. 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;43:2904–2909. doi: 10.1161/STROKEAHA.112.665331
7. Nogueira RG, Gupta R, Jovin TG, Levy EI, Liebeskind DS, Zaidat OO, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. *J Neurointerv Surg*. 2015;7:16–21. doi: 10.1136/neurintsurg-2013-010743
8. Sugiura Y, Yamagami H, Sakai N, Yoshimura S; Committee of Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism (RESCUE)-Japan Study Group. Predictors of symptomatic intracranial hemorrhage after endovascular therapy in acute ischemic stroke with large vessel occlusion. *J Stroke Cerebrovasc Dis*. 2017;26:766–771. doi: 10.1016/j.jstrokecerebrovasdis.2016.10.015
9. Hao Y, Yang D, Wang H, Zi W, Zhang M, Geng Y, et al; ACTUAL Investigators (Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry). Predictors for symptomatic intracranial hemorrhage after endovascular treatment of acute ischemic stroke. *Stroke*. 2017;48:1203–1209. doi: 10.1161/STROKEAHA.116.016368
10. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
11. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
12. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
13. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
14. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
15. Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Lingsma H, van der Lugt A, et al; MR CLEAN Investigators. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. *Trials*. 2014;15:343. doi: 10.1186/1745-6215-15-343
16. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.
17. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525–531. doi: 10.3174/ajnr.A1408
18. Venables WN, Ripley BD. *Modern applied statistics with S*. New York, NY: Springer; 2002.
19. Harrell FE. rms: Regression Modeling Strategies. R package version 5.1-3. 2017. https://CRAN.R-project.org/package=rms. Accessed April 8, 2019.
20. Yoshida K, Bohn J. Create "Table 1" to Describe Baseline Charachteristics. R package version 0.10.0. 2019. http://CRAN.R-project.org/package=tableone. Accessed April 8, 2019.
21. Kaesmacher J, Kaesmacher M, Maegerlein C, Zimmer C, Gersing AS, Wunderlich S, et al. Hemorrhagic transformations after thrombectomy: risk factors and clinical relevance. *Cerebrovasc Dis*. 2017;43:294–304. doi: 10.1159/000460265
22. Kass-Hout T, Kass-Hout O, Sun CJ, Kass-Hout TA, Nogueira R, Gupta R. Longer procedural times are independently associated with symptomatic intracranial hemorrhage in patients with large vessel occlusion stroke undergoing thrombectomy. *J Neurointerv Surg*. 2016;8:1217–1220. doi: 10.1136/neurintsurg-2015-012157
23. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.
24. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587. doi: 10.1056/NEJM199512143332401
25. Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Dávalos A, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR Studies. *JAMA Neurol*. 2017;74:268–274. doi: 10.1001/jamaneurol.2016.5374
26. Thomalla G, Sobesky J, Köhrmann M, Fiebach JB, Fiehler J, Zaro Weber O, et al. Two tales: hemorrhagic transformation but not parenchymal hemorrhage after thrombolysis is related to severity and duration of ischemia: MRI study of acute stroke patients treated with intravenous tissue plasminogen activator within 6 hours. *Stroke*. 2007;38:313–318. doi: 10.1161/01.STR.0000254565.51807.22
27. Jadhav AP, Diener HC, Bonafe A, Pereira VM, Levy EI, Baxter BW, et al; SWIFT PRIME Investigators. Correlation between clinical outcomes and baseline CT and CT angiographic findings in the SWIFT PRIME trial. *AJNR Am J Neuroradiol*. 2017;38:2270–2276. doi: 10.3174/ajnr.A5406
28. Simard JM, Kent TA, Chen M, Tarasov KV, Gerzanich V. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. *Lancet Neurol*. 2007;6:258–268. doi: 10.1016/S1474-4422(07)70055-8
29. Maier IL, Tsogkas I, Behme D, Bähr M, Knauth M, Psychogios MN, et al. High systolic blood pressure after successful endovascular treatment affects early functional outcome in acute ischemic stroke. *Cerebrovasc Dis*. 2018;45:18–25. doi: 10.1159/000484720
30. Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos YBWEM, Beumer D, et al; MR CLEAN Investigators. Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke. *Stroke*. 2017;48:1299–1305. doi: 10.1161/STROKEAHA.116.016071
31. Chamorro Á, Brown S, Amaro S, Hill MD, Muir KW, Dippel DWJ, et al; HERMES Collaborators. Glucose modifies the effect of endovascular thrombectomy in patients with acute stroke. *Stroke*. 2019;50:690–696. doi: 10.1161/STROKEAHA.118.023769
32. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
33. ISRCTN. ISRCTN80619088: Is Intravenous Alteplase Still of Added Benefit in Patients with Acute Ischaemic Stroke Who Undergo Intra-Arterial Treatment? http://www.isrctn.com/ISRCTN80619088. Accessed February 16, 2019.
34. NCT03192332. Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke. https://clinicaltrials.gov/ct2/show/NCT03192332. Accessed February 16, 2019.
35. NCT03494920. DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval. https://clinicaltrials.gov/ct2/show/NCT03494920. Accessed February 16, 2019.
36. NCT03469206. Direct Intra-arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals. https://clinicaltrials.gov/ct2/show/NCT03469206. Accessed February 19, 2019.
37. Mulder MJHL, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, et al; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) Investigators. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). *Stroke*. 2017;48:1869–1876. doi: 10.1161/STROKEAHA.116.016225
38. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165:710–718. doi: 10.1093/aje/kwk052
39. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, et al; ENCHANTED Investigators and Coordinators. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet*. 2019;393:877–888. doi: 10.1016/S0140-6736(19)30038-8

Downloaded from http://ahajournals.org by on July 6, 2023