Clinical and imaging determinants of collateral status in patients with acute ischemic stroke in MR CLEAN trial and registry

Wiegers, E.J.A.; Mulder, M.J.H.L.; Jansen, I.G.H.; Venema, E.; Compagne, K.C.J.; Berkhemer, O.A.; ... ; Lugt, A. van der

Clinical and Imaging Determinants of Collateral Status in Patients With Acute Ischemic Stroke in MR CLEAN Trial and Registry

Eveline J.A. Wiegers, BSc; Maxim J.H.L. Mulder, MD, PhD; Ivo G.H. Jansen, MD, PhD;
Esmee Venema, MD; Kars C.J. Compagne, BSc; Olvert A. Berkhemer, MD, PhD; Bart J. Emmer, MD, PhD;
Henk A. Marquering, PhD; Adriaan C.G.M. van Es, MD, PhD; Marieke E. Sprengers, MD, PhD;
Wim H. van Zwam, MD, PhD; Robert J. van Oostenbrugge, MD, PhD; Yvo B.W.E.M. Roos, MD, PhD;
Charles B.L.M. Majoie, MD, PhD; Bob Roozenbeek, MD, PhD; Hester F. Lingsma, PhD;
Diederik W.J. Dippel, MD, PhD; Aad van der Lugt, MD, PhD; on behalf of the MR CLEAN Trial and MR
CLEAN Registry Investigators*

Background and Purpose—Collateral circulation status at baseline is associated with functional outcome after ischemic stroke and effect of endovascular treatment. We aimed to identify clinical and imaging determinants that are associated with collateral grade on baseline computed tomography angiography in patients with acute ischemic stroke due to an anterior circulation large vessel occlusion.

Methods—Patients included in the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; n=500) and MR CLEAN Registry (n=1488) were studied. Collateral status on baseline computed tomography angiography was scored from 0 (absent) to 3 (good). Multivariable ordinal logistic regression analyses were used to test the association of selected determinants with collateral status.

Results—In total, 1988 patients were analyzed. Distribution of the collateral status was as follows: absent (7%, n=123), poor (32%, n=596), moderate (39%, n=735), and good (23%, n=422). Associations for a poor collateral status in a multivariable model existed for age (adjusted common odds ratio, 0.92 per 10 years [95% CI, 0.886–0.98]), male (adjusted common odds ratio, 0.64 [95% CI, 0.53–0.76]), blood glucose level (adjusted common odds ratio, 0.97 [95% CI, 0.95–1.00]), and occlusion of the intracranial segment of the internal carotid artery with occlusion of the terminus (adjusted common odds ratio 0.50 [95% CI, 0.41–0.61]). In contrast to previous studies, we did not find an association between cardiovascular risk factors and collateral status.

Conclusions—Older age, male sex, high glucose levels, and intracranial internal carotid artery with occlusion of the terminus occlusions are associated with poor computed tomography angiography collateral grades in patients with acute ischemic stroke eligible for endovascular treatment. (***Stroke***. 2020;51:1493-1502. DOI: 10.1161/STROKEAHA.119.027483.)

Key Words: collateral circulation ■ computed tomography angiography ■ odds ratio ■ stroke ■ thrombosis

Leptomeningeal collateral flow has been considered an important determinant of clinical outcome in patients with acute ischemic stroke. Poor collateral status has been associated with larger follow-up infarct volumes, increased mortality, and poor functional outcome.[1–5] Collateral circulation may prevent the penumbra, at least temporarily, to become infarcted by maintaining a certain level of cerebral blood flow. It has been shown that patients with absent collateral flow

benefit less from endovascular treatment (EVT).[6–9] As a result, several guidelines already recommend collateral status as a method to select patients for EVT.[10,11]

Little is known about the biological mechanisms that leads to the variability in filling pattern of leptomeningeal collaterals. Genetic factors have been suggested to be the strongest determinants of collateral strength.[12] Previous studies demonstrated that higher age, diabetes mellitus, history of hypertension,

high systolic blood pressure, location of the occlusion, presence of extracranial internal carotid artery (ICA) stenosis and poor hydration status are related to worse collateral status.[13–18] Further research on potential determinants for poor collateral status could improve our understanding of the collateral system. Possibly, this might help to find ways to improve collateral status during acute ischemic stroke and thus increase chances of a better clinical outcome.

In this study, we aim to identify clinical and imaging determinants that are associated with collateral status on baseline computed tomography angiography in patients with acute ischemic stroke due to a proximal intracranial occlusion in the anterior circulation.

Methods

The data of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) have been made publicly available at the Virtual International Stroke Trials Archive and can be accessed at http://www.virtualtrialsarchives.org/vista/. Individual patient data of the MR CLEAN Registry cannot be made available under Dutch law, as we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

We used data from the MR CLEAN and the MR CLEAN Registry. Patient selection criteria and methods of the MR CLEAN trial have been reported previously.[19] In short, MR CLEAN was a randomized clinical trial of EVT with usual care (intervention group) versus usual care alone (control group) in patients (n=500) with a proximal intracranial arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 hours after symptom onset. Study-specific inclusion criteria were the presence of an occlusion of the ICA, intracranial carotid artery terminus (ICA-T), middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), as confirmed on computed tomography angiography (CTA).[19,20]

The MR CLEAN Registry is an ongoing, prospective, multicenter, observational monitoring study, including all consecutive patients treated with EVT in the Netherlands since the final inclusion in the MR CLEAN trial. The aim of the MR CLEAN Registry is to monitor the safety and clinical practice of EVT in a well-defined set of patients, who are comparable to the patients in the MR CLEAN trial.[21] Overall, 1628 patients were registered in the MR CLEAN Registry between March 16, 2014 and June 15, 2016. For the current analysis, we applied the same inclusion criteria as in the MR CLEAN trial and therefore we excluded 140 patients, mostly because of occlusion in the posterior circulation or treatment starting after 6.5 hours from the onset of symptoms (Figure I in the Data Supplement). A total of 1488 patients from the MR CLEAN Registry were available for final analysis.

Assessment of Collateral Status

Collateral assessment was performed by 10 observers (each assessed 100–200 different CTAs) from the MR CLEAN Registry imaging core laboratory, who were blinded to the clinical findings. All observers were provided with a training set including relevant definitions. Collateral status was graded on single-phase CTA source images on a 4-point scale according to the visual collateral score using the method of Tan et al, with grade 0 for absent collaterals (0% filling of the occluded vascular territory), grade 1 for poor collaterals (>0% and ≤50% filling of the occluded vascular territory), grade 2 for moderate (>50% and <100% filling of the occluded vascular territory), and grade 3 for good collaterals (100% filling of the occluded vascular territory; Figure 1). This score has shown to be a prognostic marker for outcome.

Clinical and Imaging Parameters

We analyzed patient and imaging characteristics that are expected to influence collateral status, based on expert opinion and recent

literature. These included age, sex, level of glucose at baseline, history of atrial fibrillation, previous ischemic stroke, diabetes mellitus, hypercholesterolemia, hypertension, peripheral arterial disease, myocardial infarction, smoking, systolic and diastolic blood pressures, the current use of statins, antihypertensive drugs and antiplatelets, extracranial carotid stenosis, location of occlusion, and time from symptom onset to CTA. We distinguished 2 subgroups for occlusion location: one subgroup included ICA or ICA-T occlusions, and the other included a segment of the middle cerebral artery and/or anterior cerebral artery.

Acquisition Phase

In an earlier study, CTA acquisition phase appeared to be significantly associated with collateral status.[22] The CTA acquisition phase is evaluated by comparing peak arterial opacification with peak venous opacification. An observer measured the opacification of the contralateral internal carotid artery and the transverse sinus and classified all CTA studies into one of the 5 acquisitions: early arterial (arterial Hounsfield units [HU] higher than venous structure, and venous structure ≤200 HU), peak arterial (arterial HU ≥100 higher than venous structure and venous structure >200 HU), equilibrium (arterial HU <100 higher or equal to venous structure and venous structure >200 HU), peak venous (arterial HU >200 and venous structure higher than artery), or late venous (arterial HU ≤200 and venous vessel higher than artery).[23]

Statistical Analysis

To assess potential nonlinearity of the relation between continuous variables and outcome, we used restricted cubic splines. Ordinal logistic regression analyses were used to test the effect of the selected determinants on the collateral status. The following analyses were performed:

Step 1: univariable analysis with adjustment for CTA acquisition phase[24]

Step 2: univariable analysis of all determinants with a *P* value <0.15 in Step 1, adjusted for age, sex, and CTA acquisition phase

Step 3: multivariable analysis of all determinants with a *P* Value of *P*<0.05 in Step 2, adjusted for study (MR CLEAN trial or MR CLEAN Registry) and CTA acquisition phase.

We performed sensitivity analyses by repeating the analyses in all patients with a M1 or M2 occlusion, after dichotimization of the collateral score into good (grade 2+3) and poor (grade 0+1), in patients who were scanned in acquisition phases 3 or 4, and in women and men separately.

All reported *P* values are 2-sided. Missing values were imputed with multiple imputation on the combined dataset, using the AregImpute function in R statistical software. The imputations (also for missing collateral status) were performed per study (MR CLEAN trial or -Registry) based on relevant covariates and outcome (Table II in the Data Supplement). Statistical analyses were performed in the R software environment (Version 3.2.2 or higher, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

All 500 patients from the MR CLEAN trial (December 2010 to March 2014) and 1488 patients from the MR CLEAN Registry database (March 2014 to June 2016), in total 1988 patients, were included in this analysis. Distribution of the collateral status was as follows: grade 0 (7%, n=123), grade 1 (31.8%, n=596), grade 2 (39.1%, n=734), grade 3 (22.5%, n=422).

Baseline characteristics are reported in Table 1. The median age of the total population was 69 years (interquartile range, 58–79) and 1086 patients (55%) were men. In 113 patients (5.7%), the collateral status was not assessed (Table I in the Data
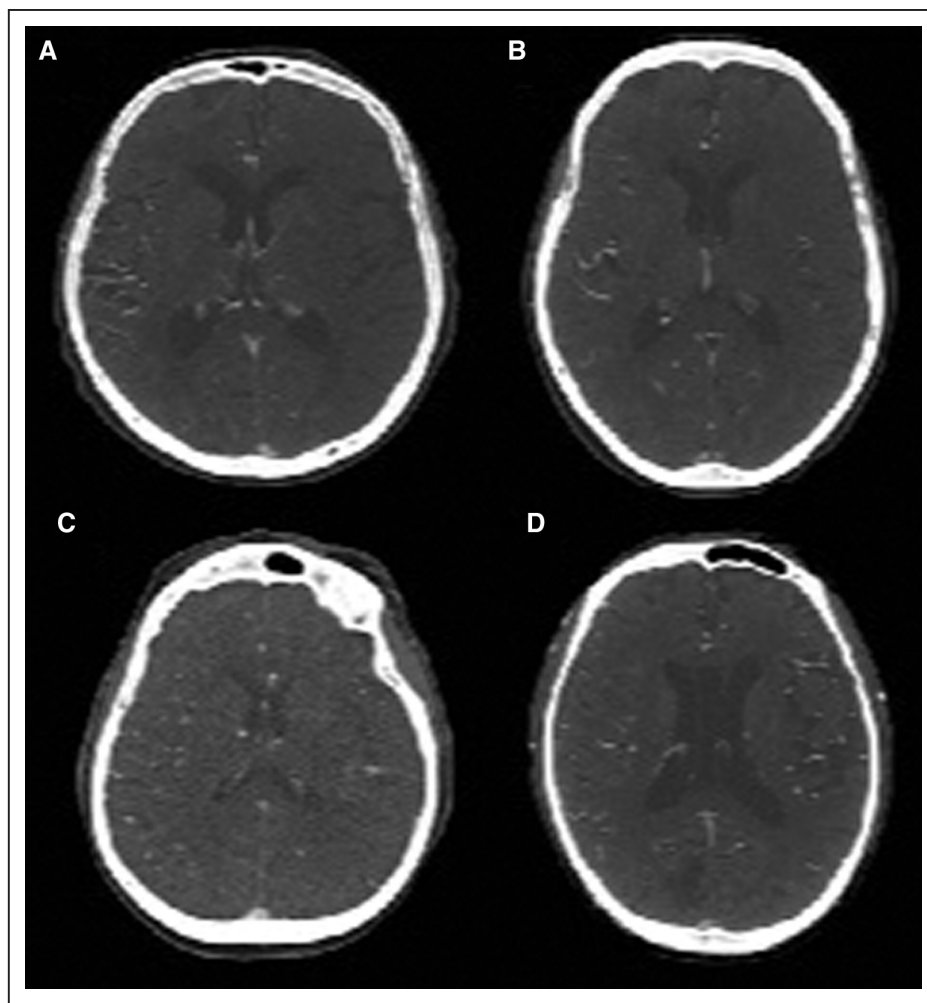
Figure 1. Collateral score grading for each category of the 4-point scale. Left hemisphere was affected in all examples above. **A**, Grade 0, representing absent collaterals (0% filling of the occluded territory). **B**, Grade 1, representing poor collaterals (>0% and ≤50% filling of the occluded territory). **C**, Grade 2, representing moderate (>50% and <100% filling of the occluded territory). **D**, Grade 3, representing good collaterals (100% filling of the occluded territory).

Supplement), and therefore 1875 patients were eligible for analysis. In total, 1639 values (3.9%) were missing at baseline and subsequently imputed. Except for time to CTA (n=1351, 68%) and smoking status (n=1645, 83%), all other determinants were in >95% complete (Table II in the Data Supplement).

Acquisition Phase

Distribution of the acquisition phase was as follows: phase 1 (25.7%, n=483), phase 2 (16.4%, n=308), phase 3 (27.2%, n=510), phase 4 (20.2%, n=380), and phase 5 (10.5%, n=197). In phase 1, more patients had a collateral grade of 1 compared with other phases. Most patients whom were scanned during phase 3 or phase 4 had a collateral grade of 2 (Figure 2).

Associations With Collateral Status

The following determinants had a *P* value <0.15 in Step 1 and were therefore considered in Step 2: age, sex, diastolic and systolic blood pressures, glucose level, a history of hypercholesterolemia, hypertension, myocardial infarction, peripheral arterial disease and ischemic stroke, the use of statins, antiplatelets and antihypertensives, ICA-T occlusion, and time to

CTA (Table 2). None of the continuous variables appeared to be nonlinear.

After adjustment for, age, sex, and CTA acquisition phase in Step 2, diastolic blood pressure, glucose, history of peripheral arterial disease, and occlusion in the ICA-(T) were significantly associated with collateral status (Table 2).

An independent association with worse collateral status in Step 3 was observed for higher age (adjusted common odds ratio, 0.92 [95% CI, 0.86–0.98] per 10 years, *P*=0.01), men (adjusted common odds ratio, 0.64 [95% CI, 0.53–0.83], *P*=0.76), higher glucose levels (adjusted common odds ratio, 0.97 [95% CI 0.95–1.00] per mmol/L, *P*=0.02), and an occlusion of the ICA-T segment (adjusted common odds ratio, 0.50 [95% CI, 0.41–0.61], *P*<0.001) in the multivariable model (Table 2; Figure II in the Data Supplement).

No additional determinants could be identified in sensitivity analysis in patients with an M1 or M2 occlusion, after dichotimization of the collateral score, or patients who were scanned in acquisition phase 3 or 4. Reanalysis in men and women separately revealed that in men, age and glucose were no longer associated with collateral status, but the use of antiplatelets was associated with worse collateral status. In

Table 1.   Clinical and Imaging Characteristics at Baseline per Collateral Status

|	Total (n=1988)	Grade 0 (n=123)	Grade 1 (n=596)	Grade 2 (n=734)	Grade 3 (n=422)	P Value
Clinical						
Age, y; median (IQR)	69 (58–79)	72 (60–79)	71 (61–80)	68 (58–78)	67 (56–77)	<0.001
Men, no. (%)	1086 (55)	81 (66)	355 (60)	392 (53)	199 (47)	<0.001
NIHSS; median (IQR)	16 (12–20)	19 (15–23)	18 (14–22)	16 (12–19)	14 (10–18)	<0.001
SBP, mm Hg; mean (SD)	149 (25)	154 (25)	149 (25)	148 (25)	148 (24)	0.04
DBP, mm Hg; mean (SD)	82 (15)	85 (15)	82 (16)	81 (15)	81 (16)	0.01
Glucose at baseline, mmol/L; median (IQR)	6.7 (5.9–8.0)	7.1 (6.0–8.5)	6.8 (6.0– 8.1)	6.7 (5.8– 7.9)	6.5 (5.8–7.8)	0.01
Atrial fibrillation, n (%)	462 (24)	34 (28)	134 (23)	180 (25)	87 (21)	0.24
Hypercholesterolemia, n (%)	560 (29)	35 (29)	185 (32)	192 (27)	111 (27)	0.19
Hypertension, n (%)	973 (49)	59 (48)	315 (53)	334 (46)	199 (48)	0.06
Diabetes mellitus, n (%)	323 (16)	26 (21)	91 (15)	120 (16)	61 (15)	0.33
Myocardial infarction, n (%)	302 (15)	19 (16)	100 (17)	107 (15)	54 (13)	0.34
Peripheral artery disease, n (%)	159 (8.1)	8 (6.6)	66 (11)	58 (8.0)	22 (5.3)	0.01
Ischemic stroke, n (%)	304 (15)	21 (17)	108 (18)	104 (14)	54 (13)	0.08
Prestroke modified Rankin Scale score, n (%)						0.10
0	1395 (71)	81 (68)	409 (69)	524 (72)	302 (73)	
1	240 (12)	19 (16)	64 (11)	90 (12)	51 (12)	
2	135 (6.9)	10 (8)	47 (8)	46 (6)	24 (6)	
>2	190 (10)	10 (8)	69 (12)	65 (9)	39 (9)	
Current smoking, n (%)	481 (29)	27 (22)	146 (25)	180 (25)	113 (27)	0.50
Statin use, n (%)	666 (34)	44 (36)	232 (40)	221 (30)	128 (31)	<0.01
Antiplatelet use, n (%)	638 (32)	37 (30)	235 (40)	209 (29)	121 (29)	<0.001
Antihypertensive medication use, n (%)	1004 (51)	59 (50)	338 (57)	353 (49)	194 (47)	<0.01
Intravenous alteplase treatment, n (%)	1607 (81)	95 (77)	485 (81)	598 (81)	338 (80)	0.52
Imaging						
Level of occlusion on noninvasive vessel imaging, n (%)						<0.001
ICA	86 (4.5)	2 (1.6)	21 (3.5)	31 (4.3)	27 (6.4)	
ICA-T	447 (23)	46 (37)	176 (30)	157 (22)	64 (15)	
M1	1144 (60)	63 (51)	333 (56)	452 (61)	271 (64)	
M2	214 (11)	12 (10)	60 (10)	88 (12)	52 (12)	
ASPECTS on NCCT—median (IQR)	9 (7–10)	8 (6–10)	8 (7–10)	9 (7–10)	9 (8–10)	<0.001
Other						
Time from onset to CTA—median (IQR)	105 (72–171)	106 (66–183)	99 (72–160)	104 (72–174)	115 (80–189)	0.23

Collateral status was missing in 113 patients. We performed χ² test for categorical variables and ANOVA and Kruskal-Wallis testing for continuous variables. CTA indicates computed tomography angiography; DBP, diastolic blood pressure; ICA, intracranial carotid artery; ICA-T, intracranial carotid artery terminus; IQR, interquartile range; NCCT, noncontract computerized tomography; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

women, age was no longer associated with collateral status, but a history of peripheral arterial disease was associated with worse collateral status (Table III in the Data Supplement).

Discussion

In this analysis, we found that worse collateral status in patients with acute ischemic stroke with a large vessel occlusion was associated with the following clinical and imaging determinants: higher age, male, glucose level at baseline, and ICA-T occlusion segment.

The results of our multivariable analysis suggest that a higher age has a direct negative effect on collateral status. A possible explanation has been described as pruning of collaterals with increasing age, involving a decline in vessel diameter and increase in vessel tortuosity.[25] Previous studies suggested that the association of age and collateral status is mediated through other age-related factors such as hyperlipidemia or systolic blood pressure.[12,21] However, we did not find an effect of systolic blood pressure or a history of hypercholesterolemia on collateral status.
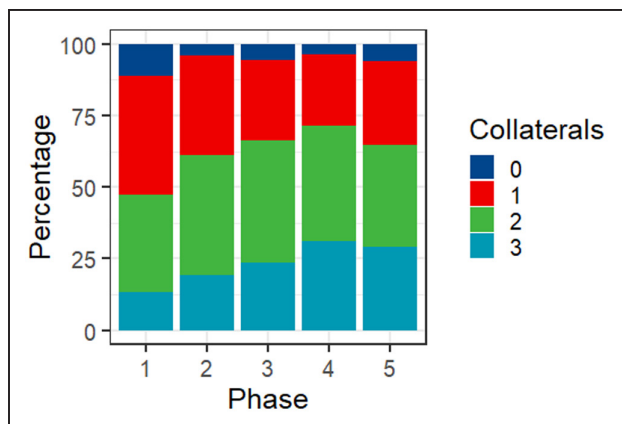
Figure 2. Distribution of collateral grades per computed tomography angiography (CTA) acquisition phase. The contrast density in Hounsfield units in the unaffected hemisphere of the M1 segment of the MCA territory (arterial structure) and the confluence of sinuses (venous structure) was measured to determine the CTA acquisition phase. On the basis of these contrast measurements, all CTA studies were classified into 1 of the 5 acquisition phases: 1 (early arterial), 2 (peak arterial), 3 (equilibrium), 4 (peak venous), and 5 (late venous).

We found poorer collateral status in men then in women, although it is reported that women have worse stroke outcomes than men. The main explanation for these sex differences are said to be attributable to a difference in sex hormones.[26–28] Sex differences in the collateral circulation in mice have been investigated by a recent study. However, the authors concluded that the cerebral collateral circulation was not different between male and female mice.[29] Further research is needed to investigate possible anatomic differences related to cerebral collaterals between men and women.

We found an association of a higher level of glucose at baseline and worse collateral status. Among patients without a history of diabetes mellitus, admission hyperglycemia may be resulting from previously undiagnosed diabetes mellitus or glucose intolerance, stress response mediated by cortisol and noradrenaline, or combination of these.[30,31] Earlier studies showed that hyperglycemia, whether acute or chronic, impairs nitrogen oxide availability and endothelium-dependent vasodilation and enhances the production of endothelial-derived vasoconstrictor prostanoids.[32,33] In a recent pooled-data meta-analysis, it was found that treatment effects of thrombectomy were larger at lower glucose levels.[34] Together with our finding, this implicates that appropriate testing whether tight glucose control is needed to further improve outcomes after EVT.

Finally, ICA-T occlusions have worse collaterals compared with ICA occlusions, M1 and M2 occlusion because an ICA-T occlusion leads to an occlusion of both the A1 segment

Table 2.   Univariable and Multivariable Effects of the Studied Determinants on Collateral Status

	Univariable		Univariable+Age and Sex		Multivariable Model	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age, y*	0.92 (0.87–0.97)	0.01	0.90 (0.85–0.96)	<0.01	0.92 (0.86–0.98)	0.01
Male sex	0.67 (0.56–0.79)	<0.001	0.65 (0.55–0.77)	–	0.64 (0.53–0.76)	<0.001
Systolic blood pressure	0.97 (0.94–1.01)	0.11	0.99 (0.95–1.02)	–		
Diastolic blood pressure†‡	0.94 (0.89–0.99)	0.03	0.95 (0.89–1.00)	0.07		
Glucose at baseline‡	0.97 (0.94–0.99)	0.02	0.97 (0.94–1.00)	0.02	0.97 (0.95–1.00)	0.02
Atrial fibrillation	0.95 (0.77–1.16)	0.59				
History of hypercholesterolemia	0.90 (0.75–1.09)	0.28				
History of hypertension	0.91 (0.78–1.08)	0.29				
History of diabetes mellitus	0.84 (0.66–1.07)	0.21				
History of myocardial infarction	0.83 (0.66–1.04)	0.10	0.92 (0.73–1.16)	0.47		
History of peripheral arterial disease	0.66 (0.50–0.89)	0.01	0.71 (0.53–0.96)	0.02	0.76 (0.56–1.04)	0.09
History of ischemic stroke	0.9 (0.62–1.01)	0.06	0.82 (0.65–1.05)	0.11		
Current smoking	0.93 (0.83–1.05)	0.25				
Current statin use	0.79 (0.66–0.95)	0.01	0.86 (0.71–1.03)	0.11		
Current antiplatelet use	0.78 (0.66–0.93)	0.01	0.84 (0.70–1.00)	0.06		
Current antihypertensive use	0.84 (0.71–1.00)	0.05	0.86 (0.71–1.03)	0.09		
Extracranial carotid stenosis	1.19 (0.85–1.68)	0.32				
ICA-T occlusion	0.50 (0.41–0.61)	<0.001	0.50 (0.41–0.61)	<0.001	0.50 (0.41–0.61)	<0.001
Time from onset to CTA§	1.04 (0.98–1.11)	0.23				

All determinants with an association with P<0.15 in Step 1 were included in Step 2. All determinants with a significant association (P<0.05) in Step 2 were included in the multivariable analysis (Step 3). All models were adjusted for acquisition phase. CTA indicates computed tomography angiography; and ICA-T, intracranial carotid artery terminus.

*Per 10 y.

†Per 10 mm Hg.

‡Per 1 mmol/L.

§Per 60 min.

of the anterior cerebral artery and the M1 segment of the middle cerebral artery and collateral flow may occur via the AComA and the cortical branches of the anterior cerebral artery to the middle cerebral artery branches. However, in this situation, collateral flow is dependent on a patent AComA. This dependency also exists in case of an ICA occlusion, but collateral flow may directly occur via the AComA, to the A1 segment and subsequently to the M1 segment. In a middle cerebral artery occlusion, collateral flow is independent of a patent AComA.

In single-phase CTA, collateral assessment is influenced by the time of the CTA snapshot. Acquiring CTA too early after contrast bolus administration runs the risk of underestimating collateral capacity, while a delayed venous phase scan may hamper detection of the primary occlusion. Also, delayed venous phase cannot discriminate between fast and slow collaterals.[35] Previous studies suggest single-phase CTA might underestimate collateral status in some patients.[36,37] As collateral status is used as a predictor in various prediction models for patients with acute ischemic stroke, this further supports the need to implement newer techniques like multiphase CTA, time-invariant CTA, or 4D-CTA.[37–39]

Furthermore, several factors were associated with collateral status in univariable analysis but not in the multivariable analysis in which we adjusted for age and sex. These included history of myocardial infarction, history of ischemic stroke, the current use of antihypertensive medication, and time to CTA. In the final multivariable analysis, the association with collaterals disappeared for diastolic blood pressure, history of peripheral arterial disease, the use of statins, and the use of antiplatelets. For all these variables, this could suggest that cardiovascular-related factors as age and history of peripheral arterial disease moderate the association.[15,40–42]

The role of pathophysiological factors in augmenting or diminishing collateral status is still mostly unclear. In the literature, several factors have been studied. The presence and luminal diameter of both primary collaterals (arterial segments of the circle of Willis) and secondary collaterals (ophthalmic artery and leptomeningeal vessels), formed during prenatal period, are considered the most important determinants.[14,18,43–45] This was however beyond the scope of our current study.

Limitations

Collateral status assessment is prone to interobserver variability, although all images were assessed by highly experienced and trained assessors.[46] A range of different scanner protocols was used, which could have added to the variability. However, we think this heterogeneity adds to the generalizability of our study. Furthermore, all our patients underwent single phase CTA, which could have led to underestimation of collateral status in the case of delayed filling in combination with an early acquisition phase. However, the sensitivity analysis in which we restricted the analysis to scans acquired with optimal timing revealed the same results. Selection bias might have appeared, since we were unable to assess the collateral status in 113 patients. Since multiple imputation was used to handle this missing data, we assume that our results could be safely interpreted. The golden standard for assessing collateral status is digital subtraction angiography. However, we aimed to represent the acute clinical setting, in which multivessel digital subtraction angiography is not performed. Furthermore, we did not have any information on ethnicity. It is known that ethnicity groups show differences in prevalence in acute ischemic stroke, and some studies also indicate possible differences in rates of collateralization.[47,48]

Finally, important to note is that the associations with collateral status do not necessarily imply a causal relationship. For example, the association we found with higher glucose level could be the cause of poor collateral status but may also be the result of poor collateral status. Further studies to investigate the causality of associations with collateral status are pivotal.

Conclusions

In conclusion, this study shows that higher age, male sex, higher glucose levels, and occlusion of the ICA-T are associated with poor CTA collateral grades in patients with acute ischemic stroke eligible for EVT. No clear modifiable determinants of collateral status could be identified.

Appendix

Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center), Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Yvo B.W.E.M. Roos (Department of Neurology, Amsterdam UMC, University of Amsterdam), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Jan Albert Vos (Department of Neurology, Haaglanden MC, the Hague); Study coordinators: Josje Brouwer (Department of Neurology, Amsterdam UMC, University of Amsterdam), Sanne J. den Hartog (Department of Neurology, Department of Radiology, and Department of Public Health, Erasmus MC University Medical Center), Wouter H. Hinsenveld (Department of Neurology and Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Manon Kappelhof (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Kars C.J. Compagne (Department of Radiology, Erasmus MC University Medical Center), Robert-Jan B. Goldhoorn (Department of Neurology and Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Maxim J.H.L. Mulder (Department of Neurology and Department of Radiology, Erasmus MC University Medical Center), Ivo G.H. Jansen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam); Local principal investigators: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University

Medical Center), Bob Roozenbeek (Department of Neurology, Erasmus MC University Medical Center), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center), Adriaan C.G.M. van Es (Department of Radiology, Erasmus MC University Medical Center), Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Yvo B.W.E.M. Roos (Department of Neurology, Amsterdam UMC, University of Amsterdam), Bart J. Emmer (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Jonathan M. Coutinho (Department of Neurology, Amsterdam UMC, University of Amsterdam), Wouter J. Schonewille (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Jan Albert Vos (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Marieke J.H. Wermer (Department of Neurology, Leiden University Medical Center), Marianne A.A. van Walderveen (Department of Radiology, Leiden University Medical Center), Julie Staals (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Sebastiaan F. de Bruijn (Department of Neurology, HAGA Hospital, the Hague), Lukas C. van Dijk (Department of Radiology, HAGA Hospital, the Hague), H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht), Rob H. Lo (Department of Radiology, University Medical Center Utrecht), Ewoud J. van Dijk (Department of Neurology, Radboud University Medical Center, Nijmegen), Hieronymus D. Boogaarts (Department of Neurosurgery, Radboud University Medical Center, Nijmegen), J. de Vries (Department of Neurology, Isala Klinieken, Zwolle), Paul L.M. de Kort (Department of Neurology, Sint Elisabeth Hospital, Tilburg), Julia van Tuijl (Department of Neurology, Sint Elisabeth Hospital, Tilburg); Jo Jo P. Peluso (Department of Radiology, Sint Elisabeth Hospital, Tilburg), Puck Fransen (Department of Neurology, Isala Klinieken, Zwolle), Jan S.P. van den Berg (Department of Neurology, Isala Klinieken, Zwolle), Boudewijn A.A.M. van Hasselt (Department of Radiology, Isala Klinieken, Zwolle), Leo A.M. Aerden (Department of Neurology, Reinier de Graaf Gasthuis, Delft), René J. Dallinga (Department of Radiology, Reinier de Graaf Gasthuis, Delft), Maarten Uyttenboogaart (Department of Neurology, University Medical Center Groningen), Omid Eschgi (Department of Radiology, University Medical Center Groningen), Reinoud P.H. Bokkers (Department of Radiology, University Medical Center Groningen), Tobien H.C.M.L. Schreuder (Department of Neurology, Atrium Medical Center, Heerlen), Roel J.J. Heijboer (Department of Radiology, Atrium Medical Center, Heerlen), Koos Keizer (Department of Neurology, Catharina Hospital, Eindhoven), Lonneke S.F. Yo (Department of Radiology, Catharina Hospital, Eindhoven), Heleen M. den Hertog (Department of Neurology, Isala Klinieken, Zwolle), Emiel J.C. Sturm (Department of Neurology, Medical Spectrum Twente, Enschede), Paul Brouwers (Department of Neurology, Medical Spectrum Twente, Enschede); Imaging assessment committee: Charles B.L.M. Majoie (chair; Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Marianne A.A. van Walderveen (Department of Radiology, Leiden University Medical Center), Marieke E.S. Sprengers (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Sjoerd F.M. Jenniskens (Department of Radiology, Radboud University Medical Center, Nijmegen), René van den Berg (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Albert J. Yoo (Department of Radiology, Texas Stroke Institute, TX), Ludo F.M. Beenen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Alida A. Postma (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Stefan D. Roosendaal (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Bas F.W. van der Kallen (Department of Radiology, Haaglanden MC, the Hague), Ido R. van den Wijngaard (Department of Radiology, Haaglanden MC, the Hague), Adriaan C.G.M. van Es (Department of Radiology, Erasmus MC University Medical Center), Bart J. Emmer (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), Lonneke S.F. Yo (Department of Radiology, Catharina Hospital, Eindhoven), Jan Albert Vos (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Joost Bot (Department of Radiology, Amsterdam UMC, Vrije Universiteit van Amsterdam), Pieter-Jan van Doormaal (Department of Radiology, Erasmus MC University Medical Center), Anton Meijer (Department of Radiology, Radboud University Medical Center, Nijmegen), Elyas Ghariq (Department of Radiology, Haaglanden MC, the Hague), Reinoud P.H. Bokkers (Department of Radiology, University Medical Center Groningen), Marc P. van Proosdij (Department of Radiology, Noordwest Ziekenhuisgroep, Alkmaar), G. Menno Krietemeijer (Department of Radiology, Catharina Hospital, Eindhoven), Jo P. Peluso (Department of Radiology, Sint Elisabeth Hospital, Tilburg), Hieronymus D. Boogaarts (Department of Neurosurgery, Radboud University Medical Center, Nijmegen), Rob Lo (Department of Radiology, University Medical Center Utrecht), Dick Gerrits (Department

of Neurology, Medical Spectrum Twente, Enschede), Wouter Dinkelaar (Department of Radiology, Erasmus MC University Medical Center), Auke P.A. Appelman (Department of Radiology, University Medical Center Groningen), Bas Hammer (Department of Radiology, HAGA Hospital, the Hague), Sjoert Pegge (Department of Radiology, Radboud University Medical Center, Nijmegen), Anouk van der Hoorn (Department of Radiology, University Medical Center Groningen), Saman Vinke (Department of Neurosurgery, Radboud University Medical Center, Nijmegen); Writing committee: Diederik W.J. Dippel (chair; Department of Neurology, Erasmus MC University Medical Center), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center), Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Yvo B.W.E.M. Roos (Department of Neurology, Amsterdam UMC, University of Amsterdam), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Jan Albert Vos (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Wouter J. Schonewille (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht), Rob H. Lo (Department of Radiology, University Medical Center Utrecht); Adverse event committee: Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), (chair), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), H. Zwenneke Flach (Department of Radiology, Isala Klinieken, Zwolle); Trial methodologist: Hester F. Lingsma (Department of Public Health, Erasmus MC University Medical Center); Research nurses / local trial coordinators: Naziha el Ghannouti (Department of Neurology, Erasmus MC University Medical Center), Martin Sterrenberg (Department of Neurology, Erasmus MC University Medical Center), Corina Puppels (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Wilma Pellikaan (Department of Neurology, Sint Antonius Hospital, Nieuwegein), Rita Sprengers (Department of Neurology, Amsterdam UMC, University of Amsterdam), Marjan Elfrink (Department of Neurology, Rijnstate Hospital, Arnhem), Michelle Simons (Department of Neurology, Rijnstate Hospital, Arnhem), Marjolein Vossers (Department of Radiology, Rijnstate Hospital, Arnhem), Joke de Meris (Department of Neurology, Haaglanden MC, the Hague), Tamara Vermeulen (Department of Neurology, Haaglanden MC, the Hague), Annet Geerlings (Department of Neurology, Radboud University Medical Center, Nijmegen), Gina van Vemde (Department of Neurology, Isala Klinieken, Zwolle), Tiny Simons (Department of Neurology, Atrium Medical Center, Heerlen), Cathelijn van Rijswijk (Department of Neurology, Sint Elisabeth Hospital, Tilburg), Gert Messchendorp (Department of Neurology, University Medical Center Groningen), Nynke Nicolaij (Department of Neurology, University Medical Center Groningen), Hester Bongenaar (Department of Neurology, Catharina Hospital, Eindhoven), Karin Bodde (Department of Neurology, Reinier de Graaf Gasthuis, Delft), Sandra Kleijn (Department of Neurology, Medical Spectrum Twente, Enschede), Jasmijn Lodico (Department of Neurology, Medical Spectrum Twente, Enschede), Hanneke Droste (Department of Neurology, Medical Spectrum Twente, Enschede), Maureen Wollaert (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Sabrina Verheesen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), D. Jeurrissen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Erna Bos (Department of Neurology, Leiden University Medical Center), Yvonne Drabbe (Department of Neurology, HAGA Hospital, the Hague), Michelle Sandiman (Department of Neurology, HAGA Hospital, the Hague), Marjan Elfrink (Department of Neurology, Rijnstate Hospital, Arnhem), Nicoline Aaldering (Department of Neurology, Rijnstate Hospital, Arnhem), Berber Zweedijk (Department of Neurology, University Medical Center Utrecht), Mostafa Khalilzada (Department of Neurology, HAGA Hospital, the Hague), Jocova Vervoort (Department of Neurology, Sint Elisabeth Hospital, Tilburg), Hanneke Droste (Department of Neurology, Medical Spectrum Twente, Enschede), Nynke Nicolaij (Department of Radiology, Erasmus MC University Medical Center), Michelle Simons (Department of Neurology, Hospital, Arnhem), Eva Ponjee (Department of Neurology, Isala Klinieken, Zwolle), Sharon Romviel (Department of Neurology, Radboud University Medical Center, Nijmegen), Karin Kanselaar (Department of Neurology, Radboud University Medical Center, Nijmegen), Erna Bos (Department of Neurology, Leiden University Medical Center), Denn Barning (Department of Radiology, Leiden University Medical Center); PhD/Medical students: Esmee Venema (Department of Public Health, Erasmus MC University Medical Center), Vicky Chalos (Department of Neurology and Department of Public Health, Erasmus MC University Medical Center), Ralph R. Geuskens (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Tim van Straaten (Department of Neurology, Radboud University Medical Center, Nijmegen, Saliha Ergezen (Department of Neurology, Erasmus MC University Medical Center), Roger R.M. Harmsma (Department of Neurology, Erasmus MC University Medical Center), Daan Muijres (Department of Neurology, Erasmus MC University Medical Center), Anouk de Jong (Department of Neurology, Erasmus MC University Medical Center), Olvert A. Berkhemer (Department of Neurology, Erasmus MC University Medical Center; Department of Radiology

and Nuclear Medicine, Amsterdam UMC, University of Amsterdam; Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht [CARIM]), Anna M.M. Boers (Department of Radiology and Nuclear Medicine and Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam), J. Huguet (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), P.F.C. Groot (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Marieke A. Mens (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Katinka R. van Kranendonk (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Kilian M. Treurniet (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Ivo G.H. Jansen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Manon L. Tolhuisen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam), Heitor Alves (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Annick J. Weterings (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Eleonora L.F. Kirkels (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Eva J.H.F. Voogd (Department of Neurology, Rijnstate Hospital, Arnhem), Lieve M. Schupp (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam), Sabine Collette (Department of Neurology and Department of Radiology, University Medical Center Groningen), Adrien E.D. Groot (Department of Neurology, Amsterdam UMC, University of Amsterdam), Natalie E. LeCouffe (Department of Neurology, Amsterdam UMC, University of Amsterdam), Praneeta R. Konduri (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam), Haryadi Prasetya (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam), Nerea Arrarte-Terreros (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam), Lucas A. Ramos (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam).

Sources of Funding

Disclosures

References

1. Lima FO, Furie KL, Silva GS, Lev MH, Camargo EC, Singhal AB, et al. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. *Stroke*. 2010;41:2316–2322. doi: 10.1161/STROKEAHA.110.592303

2. Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. *Stroke*. 2009;40:3001–3005. doi: 10.1161/STROKEAHA.109.552513

3. Menon BK, Smith EE, Modi J, Patel SK, Bhatia R, Watson TW, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. *AJNR Am J Neuroradiol*. 2011;32:1640–1645. doi: 10.3174/ajnr.A2564

4. Nambiar V, Sohn SI, Almekhlafi MA, Chang HW, Mishra S, Qazi E, et al. CTA collateral status and response to recanalization in patients with acute ischemic stroke. *AJNR Am J Neuroradiol*. 2014;35:884–890. doi: 10.3174/ajnr.A3817

5. Ramaiah SS, Mitchell P, Dowling R, Yan B. Assessment of arterial collateralization and its relevance to intra-arterial therapy for acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2014;23:399–407. doi: 10.1016/j.jstrokecerebrovasdis.2013.03.012

6. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, et al; MR CLEAN Investigators. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. *Stroke*. 2016;47:768–776. doi: 10.1161/STROKEAHA.115.011788

7. Liebeskind DS, Tomsick TA, Foster LD, Yeatts SD, Carrozzella J, Demchuk AM, et al; IMS III Investigators. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke*. 2014;45:759–764. doi: 10.1161/STROKEAHA.113.004072

8. Bang OY, Saver JL, Kim SJ, Kim GM, Chung CS, Ovbiagele B, et al. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. *Stroke*. 2011;42:693–699. doi: 10.1161/STROKEAHA.110.595256

9. Boers AM, Jansen IG, Berkhemer OA, Yoo AJ, Lingsma HF, Slump CH, et al; MR CLEAN Investigators. Collateral status and tissue

outcome after intra-arterial therapy for patients with acute ischemic stroke. *J Cereb Blood Flow Metab*. 2017;37:3589–3598. doi: 10.1177/0271678X16678874

10. Venema E, Mulder MJHL, Roozenbeek B, Broderick JP, Yeatts SD, Khatri P, et al. Selection of patients for intra-arterial treatment for acute ischaemic stroke: development and validation of a clinical decision tool in two randomised trials. *BMJ*. 2017;357:j1710. doi: 10.1136/bmj.j1710

11. Casaubon LK, Boulanger JM, Blacquiere D, Boucher S, Brown K, Goddard T, et al; Heart and Stroke Foundation of Canada Canadian Stroke Best Practices Advisory Committee. Canadian Stroke Best Practice Recommendations: hyperacute stroke care guidelines, update 2015. *Int J Stroke*. 2015;10:924–940. doi: 10.1111/ijs.12551

12. Chung JW, Kim SJ, Bang OY, Kim KH, Ki CS, Jeon P, et al. Determinants of basal collaterals in moyamoya disease: clinical and genetic factors. *Eur Neurol*. 2016;75:178–185. doi: 10.1159/000445348

13. Beard DJ, Murtha LA, McLeod DD, Spratt NJ. Intracranial pressure and collateral blood flow. *Stroke*. 2016;47:1695–1700. doi: 10.1161/STROKEAHA.115.011147

14. Chalothorn D, Faber JE. Formation and maturation of the native cerebral collateral circulation. *J Mol Cell Cardiol*. 2010;49:251–259. doi: 10.1016/j.yjmcc.2010.03.014

15. Chan SL, Sweet JG, Bishop N, Cipolla MJ. Pial collateral reactivity during hypertension and aging: understanding the function of collaterals for stroke therapy. *Stroke*. 2016;47:1618–1625. doi: 10.1161/STROKEAHA.116.013392

16. Chang SW, Huang YC, Lin LC, Yang JT, Weng HH, Tsai YH, et al. Effect of dehydration on the development of collaterals in acute middle cerebral artery occlusion. *Eur J Neurol*. 2016;23:494–500. doi: 10.1111/ene.12841

17. Lazzaro MA, Chen M, Christoforidis GA, Mohammad Y. The impact of diabetes on the extent of pial collaterals in acute ischemic stroke patients. *J Neurointerv Surg*. 2011;3:242–245. doi: 10.1136/jnis.2010.004507

18. Zhang H, Prabhakar P, Sealock R, Faber JE. Wide genetic variation in the native pial collateral circulation is a major determinant of variation in severity of stroke. *J Cereb Blood Flow Metab*. 2010;30:923–934. doi: 10.1038/jcbfm.2010.10

19. 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

20. 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

21. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry Investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949

22. Boers AMM, Sales Barros R, Jansen IGH, Berkhemer OA, Beenen LFM, Menon BK, et al; MR CLEAN Investigators. Value of quantitative collateral scoring on CT angiography in patients with acute ischemic stroke. *AJNR Am J Neuroradiol*. 2018;39:1074–1082. doi: 10.3174/ajnr.A5623

23. Rodriguez-Luna D, Dowlatshahi D, Aviv RI, Molina CA, Silva Y, Dzialowski I, et al; PREDICT/Sunnybrook ICH CTA Study Group. Venous phase of computed tomography angiography increases spot sign detection, but intracerebral hemorrhage expansion is greater in spot signs detected in arterial phase. *Stroke*. 2014;45:734–739. doi: 10.1161/STROKEAHA.113.003007

24. Akaike H. Statistical predictor identification. *Ann Inst Stat Math*. 1970;22:203–217.

25. Schirmer SH, van Nooijen FC, Piek JJ, van Royen N. Stimulation of collateral artery growth: travelling further down the road to clinical application. *Heart*. 2009;95:191–197. doi: 10.1136/hrt.2007.136119

26. Appelros P, Stegmayr B, Terént A. A review on sex differences in stroke treatment and outcome. *Acta Neurol Scand*. 2010;121:359–369. doi: 10.1111/j.1600-0404.2009.01258.x

27. Spaander FH, Zinkstok SM, Baharoglu IM, Gensicke H, Polymeris A, Traenka C, et al; Thrombolysis in Ischemic Stroke Patients Collaborators (TrISP). Sex differences and functional outcome after intravenous thrombolysis. *Stroke*. 2017;48:699–703. doi: 10.1161/STROKEAHA.116.014739

28. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7:915–926. doi: 10.1016/S1474-4422(08)70193-5

29. Faber JE, Moore SM, Lucitti JL, Aghajanian A, Zhang H. Sex differences in the cerebral collateral circulation. *Transl Stroke Res*. 2017;8:273–283. doi: 10.1007/s12975-016-0508-0

30. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773–778. doi: 10.1016/S0140-6736(99)08415-9

31. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care*. 2013;17:305. doi: 10.1186/cc12514

32. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation*. 1998;97:1695–1701.

33. Tesfamariam B, Brown ML, Deykin D, Cohen RA. Elevated glucose promotes generation of endothelium-derived vasoconstrictor prostanoids in rabbit aorta. *J Clin Invest*. 1990;85:929–932. doi: 10.1172/JCI114521

34. 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

35. van den Wijngaard IR, Holswilder G, Wermer MJ, Boiten J, Algra A, Dippel DW, et al. Assessment of collateral status by dynamic CT angiography in acute MCA stroke: timing of acquisition and relationship with final infarct volume. *AJNR Am J Neuroradiol*. 2016;37:1231–1236. doi: 10.3174/ajnr.A4746

36. Jansen IG, Mulder MJ, Goldhoorn RB, Boers AM, van Es AC, Yo LS, et al; MR CLEAN Registry Investigators. Impact of single phase CT angiography collateral status on functional outcome over time: results from the MR CLEAN Registry. *J Neurointerv Surg*. 2019;11:866–873. doi: 10.1136/neurintsurg-2018-014619

37. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology*. 2015;275:510–520. doi: 10.1148/radiol.15142256

38. Frölich AM, Wolff SL, Psychogios MN, Klotz E, Schramm R, Wasser K, et al. Time-resolved assessment of collateral flow using 4D CT angiography in large-vessel occlusion stroke. *Eur Radiol*. 2014;24:390–396. doi: 10.1007/s00330-013-3024-6

39. Smit EJ, Vonken EJ, van Seeters T, Dankbaar JW, van der Schaaf IC, Kappelle LJ, et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. *Stroke*. 2013;44:2194–2199. doi: 10.1161/STROKEAHA.111.000675

40. Arsava EM, Vural A, Akpinar E, Gocmen R, Akcalar S, Oguz KK, et al. The detrimental effect of aging on leptomeningeal collaterals in ischemic stroke. *J Stroke Cerebrovasc Dis*. 2014;23:421–426. doi: 10.1016/j.jstrokecerebrovasdis.2013.03.014

41. Malik N, Hou Q, Vagal A, Patrie J, Xin W, Michel P, et al. Demographic and clinical predictors of leptomeningeal collaterals in stroke patients. *J Stroke Cerebrovasc Dis*. 2014;23:2018–2022. doi: 10.1016/j.jstrokecerebrovasdis.2014.02.018

42. Faber JE, Zhang H, Lassance-Soares RM, Prabhakar P, Najafi AH, Burnett MS, et al. Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. *Arterioscler Thromb Vasc Biol*. 2011;31:1748–1756. doi: 10.1161/ATVBAHA.111.227314

43. Liebeskind DS. Collateral circulation. *Stroke*. 2003;34:2279–2284. doi: 10.1161/01.STR.0000086465.41263.06

44. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol*. 2011;10:909–921. doi: 10.1016/S1474-4422(11)70195-8

45. Hoksbergen AW, Fülesdi B, Legemate DA, Csiba L. Collateral configuration of the circle of Willis: transcranial color-coded duplex ultrasonography and comparison with postmortem anatomy. *Stroke*. 2000;31:1346–1351. doi: 10.1161/01.str.31.6.1346

46. Mair G, von Kummer R, Adami A, White PM, Adams ME, Yan B, et al; IST-3 Collaborative Group. Observer reliability of CT angiography in the assessment of acute ischaemic stroke: data from the Third International Stroke Trial. *Neuroradiology*. 2015;57:1–9. doi: 10.1007/s00234-014-1441-0

47. Liu Z, Pericak-Vance MA, Goldschmidt-Clermont P, Seo D, Wang L, Rundek T, et al. Coronary collateralization shows sex and racial-ethnic differences in obstructive artery disease patients. *PLoS One*. 2017;12:e0183836. doi: 10.1371/journal.pone.0183836

48. Howard G, Kissela BM, Kleindorfer DO, McClure LA, Soliman EZ, Judd SE, et al. Differences in the role of black race and stroke risk factors for first vs. recurrent stroke. *Neurology*. 2016;86:637–642. doi: 10.1212/WNL.0000000000002376