

Absence of Cortical Vein Opacification Is Associated with Lack of Intra-arterial Therapy Benefit in Stroke¹

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Purpose:

To assess the degree of cortical vein opacification in patients with internal carotid artery or middle cerebral artery (MCA) stroke and to evaluate the relationship with treatment benefit from intra-arterial therapy (IAT).

Materials and Methods:

Written informed consent was obtained from all patients in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands. From the trial's database, all patients (recruited from December 2010 until March 2014) with baseline computed tomographic (CT) angiograms were retrospectively included. Enhancement of the vein of Labbé, sphenoparietal sinus, and superficial middle cerebral vein was graded by one neuroradiologist, as follows: 0, not visible; 1, moderate opacification; and 2, full opacification. The sum for the ipsilateral hemisphere was calculated, resulting in the cortical vein opacification score (COVES) (range, 0–6). Primary outcome was the modified Rankin Scale score at 90 days. Association with treatment according to full cortical vein score and different dichotomized cutoff points was estimated with ordinal logistic regression. Interobserver agreement was assessed by two separate observers who reviewed 100 studies each.

Results:

In total, 397 patients were analyzed. Interaction of the cortical vein score with treatment was significant ($P = .044$) when dichotomized COVES was 0 versus more than 0. The adjusted odds ratio for shift toward better functional outcome was 1.0 (95% confidence interval [CI]: 0.5, 2.0) for a COVES of 0 ($n = 123$) and 2.2 (95% CI: 1.6, 4.1) for a COVES greater than 0 ($n = 274$). The multivariate κ value was 0.73.

Conclusion:

In this study, patients with acute middle cerebral artery stroke with absence of cortical vein opacification in the affected hemisphere (COVES = 0) appeared to have no benefit from IAT, whereas patients with venous opacification (COVES >0) were shown to benefit from IAT.

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The benefit of intra-arterial therapy (IAT) for patients with a proven proximal intracranial arterial occlusion treated within a 6-hour time window has recently been shown in several large randomized controlled trials (1–5). However, a substantial number of patients treated with IAT did not reach functional independence after 90 days, despite relatively high recanalization rates in these studies. This underlines the need for simple and more reliable selection of patients who will benefit from IAT.

Cerebral collateral flow has been shown to be associated with IAT effect (6–8). Many studies suggest that patients

with abundant collateral flow have better clinical outcomes and smaller infarct volumes after stroke (9–13). Because of this, collateral flow has been implemented as a patient selection method in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times, or ESCAPE, trial, with the assumption that patients with poor collateral vessels would show minimal benefit from treatment (3).

The degree of opacification of cerebral veins at computed tomographic (CT) angiography in patients with acute ischemic stroke has only sparsely been evaluated (14–16). In patients with acute ischemic stroke, opacification is usually asymmetric to some degree. It has been suggested that reduced venous opacification in the affected hemisphere represents delayed flow through the cerebral microcirculation, which is indicative of extensive local tissue damage (17). The degree of opacification could potentially be a better indicator for tolerance of occlusion than arterial collateral vessel status, as the latter might not give an adequate reflection of the state of the cerebral microcirculation as it only assesses blood flowing into the tissue. The importance of venous drainage as an indicator of adequate collateral and cerebral microcirculation has been acknowledged during balloon test occlusion of the intracranial circulation,

in which symmetry of the cortical veins implies tolerance of occlusion (18).

The purpose of this study was to assess the degree of cortical vein opacification in patients with internal carotid artery (ICA) or middle cerebral artery (MCA) stroke and to evaluate the relationship to treatment benefit from IAT. We hypothesized that diminished or absent cortical vein opacification is associated with reduced treatment benefit from IAT in patients with acute ischemic stroke in the proximal anterior circulation and could therefore potentially be used to guide patient selection for IAT.

Advances in Knowledge

- The cortical vein opacification score (COVES) showed a significant interaction with the effect of intra-arterial therapy (IAT) for patients with an acute proximal occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) when dichotomized between a COVES of 0 (total absence of cortical vein opacification in the affected hemisphere) versus a COVES greater than 0 ($P = .045$).
- In patients with a COVES of 0, there was no shift toward better functional outcome on the modified Rankin scale (adjusted common odds ratio [OR]: 1.0; 95% confidence interval [CI]: 0.5, 2.0), compared with a large shift for a COVES greater than 0 (adjusted common OR: 2.2; 95% CI: 1.6, 4.1).
- The mortality rates in patients with a COVES of 0 at 7 days and 30 days after IAT (18.7% and 26.0%, respectively) were higher than those in patients with a COVES greater than 0 (5.8% and 13.4%, respectively) ($P \leq .001$ at 7 days and $P = .004$ at 30 days).
- Interobserver agreement for the entire COVES was substantial, with a quadratic weighted multirater κ value of 0.73 (95% CI: 0.68, 0.79).

Implications for Patient Care

- Assessment of cortical vein opacification could provide information about the amount of salvageable brain tissue during an acute proximal occlusion of the ICA or MCA.
- Cortical vein opacification assessment could be applied to patient selection for IAT in patients with an acute proximal occlusion of the ICA or MCA.
- Selecting patients for IAT according to degree of cortical vein opacification could potentially lead to better functional outcome and more brain tissue saved.

Materials and Methods

Study Design and Participants

We used the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the

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Content code: **NR**

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Abbreviations:

CI = confidence interval
 COVES = cortical vein opacification score
 IAT = intra-arterial therapy
 ICA = internal carotid artery
 MCA = middle cerebral artery
 MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
 mRS = modified Rankin Scale
 NIHSS = National Institutes of Health Stroke Scale
 OR = odds ratio

Author contributions:

Guarantors of integrity of entire study, I.G.H.J., A.B.v.V., C.B.L.M.M., R.v.d.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, I.G.H.J., A.B.v.V., H.A.M., R.v.d.B.; clinical studies, I.G.H.J., A.B.v.V., W.H.v.Z., I.R.v.d.W., O.A.B., R.J.v.O., D.W.J.D., M.A.A.v.W., A.v.d.L., Y.B.W.E.M.R., C.B.L.M.M., R.v.d.B.; experimental studies, A.B.v.V., C.H.S.; statistical analysis, I.G.H.J., A.B.v.V., O.A.B., H.F.L., C.H.S., K.M.T.; and manuscript editing, I.G.H.J., A.B.v.V., W.H.v.Z., O.A.B., H.F.L., R.J.v.O., D.W.J.D., M.A.A.v.W., Y.B.W.E.M.R., H.A.M., C.B.L.M.M., R.v.d.B.

Conflicts of interest are listed at the end of this article.

Netherlands (MR CLEAN) dataset for this post hoc analysis. Patient eligibility and methods used for MR CLEAN have been described previously (1), including the provision of informed consent and the approval of the study by a central medical ethics committee and the research board of each participating center.

In MR CLEAN, which ran between December 2010 and March 2014, patients with a proximal arterial occlusion in the anterior circulation demonstrated at vessel imaging who could be treated within 6 hours after symptom onset were randomized to receive IAT (intervention group) or usual care (no IAT) (control group). The median patient age was 66 years (interquartile range, 55–76 years); 58.4% of the 500 patients were men.

Specific inclusion criteria for the present substudy were the presence of ICA, ICA terminus, or MCA (segment M1 or M2) occlusion as confirmed at CT angiography. All included patients were assessed by a neuroradiologist (R.v.d.B., with >10 years of experience) to determine if the timing of CT angiography was adequate for evaluating the venous system, as reflected by evident contrast material opacification of one of the sigmoid sinus jugular bulbs, as well as to determine the location of the occlusion. Patients without adequate timing with solely an occlusion of the anterior cerebral artery were excluded from analysis.

Outcomes

The primary outcome parameter was the modified Rankin scale (mRS) score, a seven-point scale ranging from 0 (no symptoms) to 6 (dead), at 90 days. An mRS score of 2 or less is indicative of functional independence of the patient.

Secondary outcomes were stroke severity after 24 hours (National Institutes of Health Stroke Scale [NIHSS]), recanalization at vessel imaging after 24 hours, and final infarct volume at unenhanced follow-up CT after 3–5 days (or 1 day if this was not available due to death or discharge).

Imaging Assessment

All CT angiography protocols are provided in Table E1 (online). Three veins

were analyzed, enabling evaluation of the representative venous outflow network of the MCA territory. These were the superficial middle cerebral vein, the vein of Labbé, and the sphenoparietal sinus. These veins were chosen because they account for nearly all venous drainage from the MCA territory and show a limited anatomic variability compared with other cortical veins. In case of absence of opacification of a cortical vein on the contralateral side owing to an anatomic variation, this was reflected in a lower maximum venous score. On the affected side, however, anatomic variations could not be determined with certainty, especially in case of complete absence of cortical vein opacification. Cortical vein opacification was graded per vein with baseline CT angiography by using a three-point scale, as follows: 0, complete absence of cortical vein opacification; 1, moderate opacification (defined as approximately half the attenuation of one of the target veins on the contralateral side); and 2, full opacification. For the affected hemisphere, the sum of the grades for all three veins resulted in the cortical vein opacification score (COVES) and could add up to a maximum of six (all veins fully opacified). The total absence of venous opacification in a hemisphere was reflected by a score of 0. Examples of COVES assessment are shown in Figures 1 and 2. Isolated opacification of only the most medial part of the sphenoparietal sinus in close proximity to the cavernous sinus (without opacification of the more lateral part of the sphenoparietal sinus or the superficial middle cerebral vein) was not considered as venous filling. All baseline CT angiograms were graded by one neuroradiologist (R.v.d.B.). The reader was blinded to clinical findings.

Association with Treatment Effect

We tested for interaction between COVES and treatment effect, using the full range of 0–6, and by using different dichotomous cutoff values (grade 0 vs grade >0; grade 0–1 vs grade >1; grade 0–2 vs grade >2; and grade 0–3 vs grade >3). Because of the possibility of anatomic variations,

no dichotomization was performed for higher cutoff values. We tested model fit for all cutoff values and for the linear and categorical full COVES on the basis of the Akaike Information Criterion and the log likelihood (Table E2 [online]). We selected the model with the best fit for further analysis.

Interobserver Analysis

A random subset of 100 scans was graded by two additional observers (neuroradiologist W.v.Z., with >10 years of experience, and neurologist I.v.d.W., with <5 years of experience). Agreement beyond chance was estimated by using quadratic weighted multirater Fleiss κ statistics on the full range COVES, with correction for the κ paradox (19). Disagreement entailed a difference of one category between observers. Agreement for dichotomous cutoff values was estimated by using unweighted κ statistics.

Statistical Analysis

Differences in baseline parameters were assessed by using the χ^2 test for categorical variables or the Student *t* test or Mann-Whitney *U* test for continuous variables. The primary effect parameter was the adjusted common odds ratio (OR) for a shift in the direction of a better outcome on the mRS, which was estimated with multivariable ordinal logistic regression analysis. The adjusted common OR and all secondary effect parameters were adjusted for major prespecified prognostic variables adapted from the original trial protocol statistical analysis plan: age, NIHSS at baseline, time of onset to randomization, presence of previous stroke, atrial fibrillation, diabetes mellitus, and ICA terminus occlusion. The unadjusted and adjusted common ORs were reported with 95% confidence intervals (CIs) to indicate statistical precision. Binary outcomes were analyzed with logistic regression and reported as unadjusted and adjusted common ORs with 95% CIs. *P* < .05 was considered indicative of a statistically significant difference. All *P* values were calculated for two-sided tests. Statistical analyses were performed with software (SPSS,

Figure 1

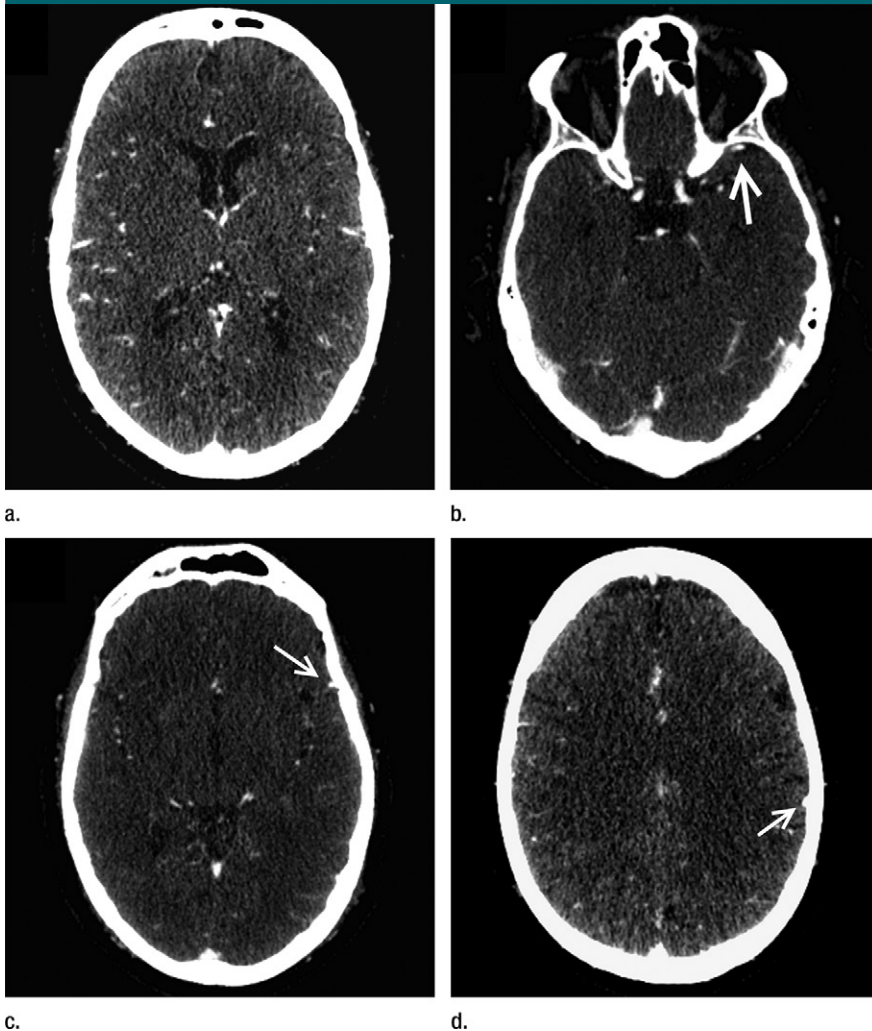


Figure 1: Images from baseline CT angiography in 61-year-old man with right-sided segment M1 occlusion. (a) Image shows abundant arterial collateral flow in affected hemisphere (grade 3). Patient had moderate disability 90 days after IAT (mRS score, 4). (b–d) Images in unaffected hemisphere show full opacification (arrow) of sphenoparietal sinus (b), superficial middle cerebral vein (c), and vein of Labbé (d). However, opacification was absent in all three cortical veins in affected hemisphere. This resulted in a COVES of 0 for this patient.

Table 1

Results of Interaction Analysis with Different Cutoff Values

COVES Cutoff Value	Unadjusted Analysis	Adjusted Analysis*
Full COVES	.070	.179
0 (<i>n</i> = 123) vs > 0 (<i>n</i> = 274)	.005	.044
0–1 (<i>n</i> = 203) vs > 1 (<i>n</i> = 194)	.190	.276
0–2 (<i>n</i> = 293) vs > 2 (<i>n</i> = 104)	.192	.262
0–3 (<i>n</i> = 335) vs > 3 (<i>n</i> = 62)	.784	.941

Note.—Data are *P* values. One hundred twenty-three patients had COVES of 0, 80 had COVES of 1, 90 had COVES of 2, 42 had COVES of 3, 32 had COVES of 4, 17 had COVES of 5, and 13 had COVES of 6.

* Adjusted for prespecified prognostic variables.

Figure 2

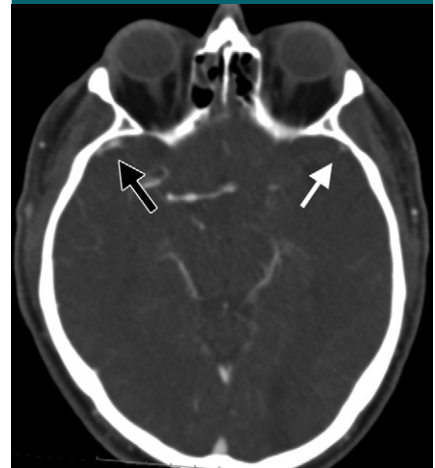


Figure 2: Image from baseline CT angiography in 61-year-old man with left-sided occlusion. In affected hemisphere, sphenoparietal sinus is moderately opacified, resulting in opacification grade of 1 (white arrow). In unaffected hemisphere, sphenoparietal sinus is fully opacified, with opacification grade of 2 (black arrow).

version 22.0 for Windows; IBM, Armonk, NY).

Results

Patients were recruited from December 2010 until March 2014. For this post hoc analysis, 397 patients met the study specific inclusion criteria—216 (54%) in the intervention group and 181 (46%) in the control group. In 101 excluded patients, timing of CT angiography hindered good assessment of the cortical venous system. Two patients were excluded because they only had anterior cerebral artery occlusion.

Association with Treatment Effect

The results of the interaction analysis for the COVES and the different dichotomized cutoff values are shown in Table 1. The distribution of patients on the full range of the COVES was as follows: COVES 0, 123 patients; COVES 1, 80 patients; COVES 2, 90 patients; COVES 3, 42 patients; COVES 4, 32 patients; COVES 5, 17 patients; and COVES 6, 13 patients. For a COVES of 0 (*n* = 123) versus a COVES greater than 0 (*n* = 271), the association with IAT

Table 2

Patient Characteristics at Baseline for the Optimal Cutoff Value of COVES 0 versus COVES Greater Than 0

Characteristic	COVES 0*	COVES >0*	PValue
No. of patients	123	274	
No. of men	74 (60.2)	155 (56.2)	.456
Median age (y) [†]			
All patients	66 (54, 74)	65 (54, 76)	.955
Men	65 (53, 73)	63 (54, 74)	.594
Women	69 (56, 77)	66 (53, 77)	.633
Median NIHSS [‡]	20 (17, 23)	16 (13, 20)	<.001
Left hemisphere	61 (49.6)	155 (56.2)	.224
Level of occlusion			.001
ICA	0 (0.0)	3 (1.1)	
ICA-T	47 (38.2)	64 (23.4)	
Segment M1	73 (59.4)	177 (64.6)	
Segment M2	3 (2.4)	30 (10.9)	
Treatment with intravenous alteplase	112 (91.1)	245 (88.8)	.493
Median onset to intravenous alteplase administration (min) [‡]	90 (66, 122)	83(65, 110)	.055
Median onset to randomization (min) ^{††}	199 (148, 256)	205 (151, 266)	.818
Collateral vessel score			<.001
Grade 0	8 (6.5)	5 (1.8)	
Grade 1	55 (44.7)	46 (16.7)	
Grade 2	53 (43.1)	112 (40.7)	
Grade 3	7 (5.7)	111 (40.5)	
ASPECTS subgroups [§]			.039
0–4	8 (6.6)	14 (5.1)	
5–7	32 (26.2)	44 (16.1)	
8–10	82 (67.2)	216 (78.8)	
Prestroke mRS score			.410
0	100 (81.3)	225 (81.5)	
1	8 (6.5)	27 (9.8)	
≥2	15 (12.2)	24 (8.7)	
Mean systolic blood pressure (mm Hg)	145 (26)	145 (25)	.874
Atrial fibrillation	40 (32.5)	63 (22.8)	.048
History of diabetes mellitus	18 (14.6)	32 (11.6)	.398
History of hypertension	52 (42.3)	127 (46.0)	.489
History of ischemic stroke	15 (12.2)	27 (9.8)	.470
History of myocardial infarction	17 (13.8)	35 (12.7)	.755
History of peripheral artery disease	8 (6.5)	12 (4.3)	.363
History of hyperlipidemia	28 (22.8)	67 (24.3)	.744
History of smoking [#]	40 (32.5)	80 (29.0)	.478
Current statin use	29 (23.6)	78 (28.3)	.331
Current anticoagulant use	8 (6.5)	20 (7.2)	.789
Current antiplatelet use	33 (26.8)	76 (27.5)	.884

Note.—ASPECTS = Alberta Stroke Program Early CT Score (range, 0–10, with higher scores indicating less early ischemic changes), ICA-T = ICA terminus.

* Except where indicated, data are numbers of patients, with percentages in parentheses.

[†] Numbers in parentheses are interquartile ranges.

[‡] Randomization time was missing in two patients.

[§] ASPECTS was not available in one patient.

^{||} Systolic blood pressure at baseline was missing in one patient. Numbers in parentheses are standard deviations.

[#] Current smoking status was missing in 23 patients.

treatment effect was significant ($P = .005$). This effect remained after adjustment for the predefined baseline variables ($P = .045$). Model performance was similar for a grade of 0 versus a grade greater than 0 and the full linear scale (Table E2 [online]). Because of greater clinical applicability of a two-level score than a seven-level score, we chose to use the cutoff value 0 versus greater than 0. For this threshold, additional data analysis was performed.

Baseline Characteristics

At baseline, significant differences between patients with a COVES of 0 and those with a COVES higher than 0 included NIHSS ($P < .001$), Alberta Stroke Program Early CT Score ($P = .039$), and history of atrial fibrillation ($P = .048$) (Table 2). Especially notable is the difference in collateral vessel status between both groups ($P < .001$). As can be appreciated in Table 2, 60 patients (48.8%) with COVES of 0 had moderate or good collateral vessel status (grade 2 or 3) at baseline. The level of occlusion was also significantly different, with more patients with a COVES of 0 having a proximal occlusion ($P = .001$). None of the other baseline characteristics showed a significant difference.

Primary Outcome

No patients were lost to clinical follow-up. In patients without venous opacification in the affected hemisphere (COVES 0), there was no shift on the mRS (adjusted common OR, 1.0; 95% CI: 0.5, 2.0). However, a large shift on the mRS was seen in favor of the intervention group for patients with any degree of opacification on the affected side (COVES >0) (adjusted common OR, 2.2; 95% CI: 1.6, 4.1) (Table 3).

Secondary Outcomes

Patients in the intervention group with a COVES greater than 0 had a significantly higher chance (27%) of becoming functionally independent at 90 days (mRS, 0–2) (adjusted common OR, 3.0; 95% CI: 1.7, 5.4), compared with 1% of patients with a COVES of 0 (adjusted common OR, 1.4; 95% CI: 0.5,

Table 3

Primary and Secondary Effect Parameters according to COVES

Outcome	COVES 0 (n = 123)		COVES >0 (n = 274)		P Value*	
	Unadjusted Effect	Adjusted Effect	Unadjusted Effect	Adjusted Effect	Unadjusted	Adjusted
Primary outcome: mRS score at 90 days [†]	0.9 (0.5, 1.6)	1.0 (0.5, 2.0)	2.8 (1.8, 4.3)	2.2 (1.4, 3.5)	.005	.044
Secondary outcome: clinical						
mRS 0–2 [‡]	1.1 (0.5, 2.6)	1.4 (0.5, 3.6)	3.6 (2.1, 6.1)	3.0 (1.7, 5.4)	.024	.13
NIHSS after 24 hours [§]	0.5 (–2.5, 3.5)	0.024 (–2.8, 2.8)	–4.1 (–6.0, –2.2)	–2.6 (–4.2, –1.0)	.010	.069
Secondary outcome: radiologic						
Recanalization on follow-up vessel images at 24 hours [†]	6.1 (2.5, 15.5)	9.4 (3.1, 28.8)	6.3 (3.5, 11.3)	6.0 (3.3, 11.1)	.62	.97
Final infarct volume in milliliters	–0.1 (–0.5, 0.4)	–0.1 (–0.5, 0.3)	–0.4 (–6.7, –0.1)	–0.4 (–6.7, –0.1)	.25	.49

Note.—This table lists the type of effect parameter (OR or linear regression coefficient), unadjusted and adjusted for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus, and presence of ICA terminus occlusion. Numbers in parentheses are 95% CIs.

* P value of interaction term.

[†] Data are ORs.

[‡] Data are β coefficients.

[§] NIHSS was measured in survivors only.

^{||} Final infarct volume (log transformed) at unenhanced CT after 5 days (range, 3–9 days).

3.6). However, interaction with treatment effect did not reach statistical significance (adjusted $P = .13$) (Table 3). For patients with a COVES greater than 0, NIHSS after 24 hours was lower in patients treated with IAT (β coefficient, -2.6 ; 95% CI: $-4.2, -1.0$), and the difference was statistically significant. This was not the case in the patients with a COVES of 0 (β coefficient, 0.024 ; 95% CI: $-2.8, 2.8$). Here too, no significant interaction was found (adjusted $P = .069$). The effect of IAT on recanalization or final infarct volume was comparable in the different groups.

Serious Adverse Events and Death

We found a significant difference in both 7- and 30-day mortality between the two groups ($P \leq .001$) (Table 4). The mortality rates in patients with a COVES of 0 at 7 days and 30 days after IAT (18.7% and 26.0%, respectively) were higher than those in patients with a COVES greater than 0 (5.8% and 13.4%, respectively) ($P \leq .001$ at 7 days and $P = .004$ at 30 days). For grade greater than 0, a smaller proportion of patients experienced a serious adverse event or stroke progression. There was no significant difference in

the number of symptomatic intracranial hemorrhages between both groups (Table 4, Table E3 [online]).

Interobserver Analysis

Interobserver agreement for the full COVES was substantial, with a quadratic weighted multirater κ value of 0.73 (95% CI: $0.68, 0.79$) (20). Agreement for the COVES cutoff value of 0 versus greater than 0 was moderate, with an unweighted κ value of 0.62 (95% CI: $0.45, 0.80$). The observers agreed in 83 of 100 cases.

Discussion

In this post hoc analysis of MR CLEAN, the degree of venous opacification in the affected hemisphere, as evaluated with baseline CT angiography, was associated with the effect of IAT in patients with MCA stroke. The presence of cortical vein opacification was related to a treatment benefit of IAT. Patients without venous opacification had no benefit from treatment.

Our study identifies an association between cortical vein asymmetry and IAT benefit. We were able to determine if the COVES, or one of its proposed

cutoff values, could be considered associated with treatment effect. Because a COVES of 0 versus greater than 0 was the optimal cutoff value in this study, this was the focus of our further analyses.

Of the comparable studies performed until now, three used a multivein scoring method at baseline or dynamic CT angiography, one was focused on the internal cerebral vein asymmetry at baseline CT angiography, and one was focused on deep medullary vein asymmetry at susceptibility-weighted MR imaging (14–16,21,22). One of these studies included a small proportion of our current study population (16). Although a cortical vein score was also proposed in that study, it included only 46 patients from two centers (out of the 500 patients in the 17 MR CLEAN centers). Furthermore, the association of the proposed scoring method with IAT benefit, which we believe to be essential, was not analyzed in that study. Finally, as with previous studies, there is at least in part a focus on analysis of veins draining the deep cerebral systems (14–16,21,22). We believe the superficial venous system to be more relevant as it more accurately reflects the status of the microcirculation in the

Table 4

Serious Adverse Events and Deaths

Event	COVES 0			COVES 0			COVES >0		
	(n = 123)*	(n = 274)*	PValue	Intervention Group (n = 62)*	Control Group (n = 61)*	PValue	Intervention Group (n = 99)*	Control Group (n = 156)*	PValue
Death within 7 days	23 (18.7)	16 (5.8)	<.001	13 (21.0)	10 (16.4)	.65	8 (6.7)	8 (5.1)	.61
Death within 30 days	32 (26.0)	37 (13.4)	.004	18 (29.0)	14 (23.0)	.54	14 (11.7)	23 (14.7)	.48
Hemicraniectomy	11 (8.9)	9 (3.3)	.024	5 (8.1)	6 (9.8)	.76	3 (2.5)	6 (3.8)	.74
Patients with at least one SAE†	69 (56.1)	104 (37.7)	.001	37 (59.7)	32 (52.5)	.47	44 (36.7)	60 (38.5)	.80
Symptomatic ICH	9 (7.3)	15 (5.4)	.50	7 (11.3)	2 (3.3)	.16	4 (3.3)	11 (7.1)	.28
Progression of ischemic stroke	42 (25.9)	30 (12.7)	.001	17 (27.4)	19 (31.1)	.70	17 (14.2)	19 (12.2)	.72

Note.—ICH = intracerebral hemorrhage, SAE = serious adverse event.

* Data are numbers of patients, with percentages in parentheses.

† Only first events of one type are listed. Patients experiencing multiple events of one type have been counted once.

MCA territory. We therefore omitted the deep cerebral venous system from the cortical vein score. Despite this fundamental difference and relatively small number of patients included in the other studies, an association between venous opacification and clinical outcome after IAT was reported. Our results confirm this association.

Our data support the expected worse outcome in patients with a proximal or distal ICA occlusion. These patients are less likely to sustain venous drainage due to the decreased chance of having leptomeningeal collateral vessels from the anterior cerebral artery territory backward to the MCA territory. The only chance of filling the anterior circulation in ICA terminus occlusions is through an adequate anterior communicating artery from the contralateral side. Conversely, patients with segment M2 occlusion are more likely to exhibit venous drainage, as the still-patent MCA territory will continue to provide parenchymal blood flow with subsequent filling of the cortical venous territories.

Also of interest is the fact that a substantial proportion of patients with a COVES of 0 exhibited good collateral flow. We can speculate that microcirculation function, as well as possibly altered autoregulatory processes, hampers local tissue perfusion, resulting in absent venous flow despite a good arterial collateral status. In a study in the same population, a strong association

between arterial collateral flow and IAT benefit was found (7). However, the group that did not benefit at all from IAT could not be conclusively identified. By applying the cortical vein score, it was possible to identify a group of patients who did not benefit from IAT. Additional analysis is required to combine patient-specific data on arterial collateral vessel score and cortical vein score, allowing a better determination of the combined effect of use of both scoring systems.

The association between cortical vein opacification and IAT benefit in our study is not surprising if we take into account the already acknowledged value of venous asymmetry as seen during balloon test occlusion of the ICA. A study in patients undergoing balloon occlusion for ICA aneurysms already showed a strong association between symmetrical venous opacification and neurologic tolerance of permanent occlusion (18). In that study, it was frequently seen that the delay from the arterial phase to the venous phase increases over time, which emphasizes the potential of venous assessment as a surrogate marker for local microcirculation function.

Our study has limitations. The main analysis was performed by one observer, and the analysis of interobserver agreement was performed only on a random subset of 100 patients, showing agreement in our final dichotomous outcome in only 83 of the 100 patients. Second, we chose to use a

threshold score of greater than 0 after data were analyzed. Thus, this threshold might not perform optimally in other populations. Additional prospective investigations are needed to assess the reproducibility and clinical utility of the COVES. Third, a large variation in venous anatomy is commonly seen among patients. This could have influenced our results, as some patients could have missing veins that would normally have been scored, and therefore did not add up to a COVES of 6. However, in the dichotomous analysis this issue does not play a role. More important, for assessment of cortical vein opacification, timing of CT angiography through the entire venous phase is crucial. In MR CLEAN, most patients underwent single-phase CT angiography. Single-phase CT angiography is widely available and routinely used in clinical stroke work-up. This leads to clinical applicability of the COVES. However, because patients with inadequate imaging timing were excluded, this could have created a selection bias in this post hoc analysis, owing to, for instance, exclusion of patients with a poor cardiac status. The use of time-resolved CT angiography techniques like multiphase or dynamic CT angiography could help minimize these limitations in future research (16).

The results of our analysis show a strong association between the opacification of cortical veins from an occluded territory and benefit from IAT.

Our cortical vein scoring method is simple and has substantial interobserver agreement. Moreover, it could potentially be a stronger predictor of IAT benefit than arterial collateral vessel status because it better reflects microcirculation function. In the future, the COVES may play a role in the further refinement of patient selection for IAT. In conclusion, patients with acute MCA stroke with absence of cortical vein opacification in the affected hemisphere appeared to have no benefit from IAT, whereas patients with venous opacification were shown to benefit from IAT.

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Errata

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Immediate Allergic Reactions to Gadolinium-based Contrast Agents: A Systematic Review and Meta-Analysis

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Erratum in:

Radiology 2018;286(2):731
DOI:10.1148/radiol.2018174037

Abstract, second sentence of Results should read as follows: The overall and severe rates of GBCA allergic-like adverse events were 9.2 and **0.52** per 10000 administrations, respectively: 81% (539 of 662) were mild, 13% (86 of 662) were moderate, and 6% (37 of 662) were severe reactions.

Second paragraph of Results, first sentence should read as follows: The overall rate of patients who had immediate allergic-like reactions was 9.2 per 10000 administrations and the overall rate of severe immediate allergic-like reactions was **0.52** per 10000 administrations.

Third paragraph of Discussion, first sentence should read as follows: The favorable low reaction rate for nonionic linear GBCAs stands in contrast to their worrisome lower kinetic stability, which is thought to increase the risk of nephrogenic systemic fibrosis and gadolinium **retention** in the brain (22,43–45).

Fifth paragraph of Discussion, second sentence should read as follows: This greater rate of allergic-like reactions must be considered with other aspects of safety including the favorable stability of macrocyclic agents that reduces risk of nephrogenic systemic fibrosis and gadolinium **retention** in the brain (43,47,48).

Table 3, under the column Comparison, fourth row head should read as follows: **Non-protein binding linear vs macrocyclic**

Table 5, under column Jung et al (7), the overall bias should be **Moderate**

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Absence of Cortical Vein Opacification is Associated with Lack of Intra-arterial Therapy Benefit in Stroke

Ivo G. H. Jansen, Annemieke B. van Vuuren, Wim H. van Zwam, Ido R. van den Wijngaard, Olvert A. Berkhemer, Hester F. Lingsma, Cornelis H. Slump, Robert J. van Oostenbrugge, Kilian M. Treurniet, Diederik W. J. Dippel, Marianne A.A. van Walderveen, Aad van der Lugt, Yvo B. W. E. M. Roos, Henk A. Marquering, Charles B. L. M. Majoie, René van den Berg, for the MR CLEAN Trial Investigators

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The legend for Figure 1b–d should read as follows: Images in unaffected hemisphere show full opacification (arrow) of **sphenoparietal sinus (b)**, superficial middle cerebral vein (**c**), and vein of Labbé (**d**).