Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke

Olvert A. Berkhemer, MD*; Ivo G.H. Jansen, MD*; Debbie Beumer, MD; Puck S.S. Fransen, MD; Lucie A. van den Berg, MD; Albert J. Yoo, MD; Hester F. Lingsma, PhD; Marieke E.S. Sprengers, MD, PhD; Sjoerd F.M. Jenniskens, MD, PhD; Geert J. Lycklama à Nijeholt, MD, PhD; Marianne A.A. van Walderveen, MD, PhD; René van den Berg, MD, PhD; Joseph C.J. Bot, MD, PhD; Ludo F.M. Beenen, MD; Anna M.M. Boers, MSc; Cornelis H. Slump, PhD; Yvo B.W.E.M. Roos, MD, PhD*; Robert J. van Oostenbrugge, MD, PhD*; Diederik W.J. Dippel, MD, PhD*; Aad van der Lugt, MD, PhD*; Wim H. van Zwam, MD, PhD*; Henk A. Marquering, PhD*; Charles B.L.M. Majoie, MD, PhD*; on behalf of the MR CLEAN Investigators†

Background and Purpose—Recent randomized trials have proven the benefit of intra-arterial treatment (IAT) with retrievable stents in acute ischemic stroke. Patients with poor or absent collaterals (preexistent anastomoses to maintain blood flow in case of a primary vessel occlusion) may gain less clinical benefit from IAT. In this post hoc analysis, we aimed to assess whether the effect of IAT was modified by collateral status on baseline computed tomographic angiography in the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN).

Methods—MR CLEAN was a multicenter, randomized trial of IAT versus no IAT. Primary outcome was the modified Rankin Scale at 90 days. The primary effect parameter was the adjusted common odds ratio for a shift in direction of a better outcome on the modified Rankin Scale. Collaterals were graded from 0 (absent) to 3 (good). We used multivariable ordinal logistic regression analysis with interaction terms to estimate treatment effect modification by collateral status.

Results—We found a significant modification of treatment effect by collaterals (P=0.038). The strongest benefit (adjusted common odds ratio 3.2 [95% confidence intervals 1.7–6.2]) was found in patients with good collaterals (grade 3). The adjusted common odds ratio was 1.6 [95% confidence intervals 1.0–2.7] for moderate collaterals (grade 2), 1.2 [95% confidence intervals 0.7–2.3] for poor collaterals (grade 1), and 1.0 [95% confidence intervals 0.1–8.7] for patients with absent collaterals (grade 0).

Conclusions—In MR CLEAN, baseline computed tomographic angiography collateral status modified the treatment effect. The benefit of IAT was greatest in patients with good collaterals on baseline computed tomographic angiography. Treatment benefit appeared less and may be absent in patients with absent or poor collaterals.

Clinical Trial Registration—URL: http://www.trialregister.nl and http://www.controlled-trials.com. Unique identifier: (NTR)1804 and ISRCTN10888758, respectively.

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From the Departments of Radiology (O.A.B., I.G.H.J., M.E.S.S., R.v.d.B., L.F.M.B., A.M.M.B., C.B.L.M.M.), Neurology (L.A.v.d.B., Y.B.W.E.M.R.), and Biomedical Engineering and Physics (A.M.M.B., H.A.M.), Academic Medical Center, Amsterdam, The Netherlands; Departments of Neurology (O.A.B., P.S.S.F., D.W.J.D.), Radiology (P.S.S.F., A.v.d.L.), and Public Health (H.F.L.), Erasmus MC University Medical Center Rotterdam, The Netherlands; Departments of Neurology (D.B., R.J.v.O.), and Radiology (W.H.v.Z.), Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, The Netherlands; Texas Stroke Institute, TX (A.J.Y.); Department of Radiology, Radboud University Medical Center, Nijmegen, The Netherlands (S.F.M.J.); Department of Radiology, MC Haaglanden, The Hague, The Netherlands (G.J.L.à.N.); Department of Radiology, Leiden University Medical Center, The Netherlands (M.A.A.v.W.); Department of Radiology, VU Medical Center, Amsterdam, The Netherlands (J.C.J.B.); and Department of Robotics & Mechatronics, University of Twente, Enschede, The Netherlands (A.M.M.B., C.H.S.).

*Drs. Berkhemer, Jansen, Roos, van Oostenbrugge, Dippel, van der Lugt, van Zwam, Marquering, and Majoie contributed equally.

†A list of MR CLEAN Investigators (http://www.mrclean-trial.org) is given in the Appendix.

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Correspondence to C.B.L.M. Majoie, MD, PhD, Department of Radiology, C1-426, Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, The Netherlands. E-mail c.b.majoie@amc.uva.nl

Proximal intracranial arterial occlusions account for one third of acute ischemic stroke cases.[1,2] Efficacy of intravenous thrombolysis is limited in patients with a proximal anterior circulation occlusion, with only about one third achieving recanalization, resulting in an overall poor prognosis.[3,4] Recently, the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) demonstrated a clear overall benefit of adding intra-arterial treatment (IAT) to standard care (including intravenous thrombolysis) in patients with acute ischemic stroke caused by proximal arterial occlusion of the anterior circulation, if administered within 6 hours from symptom onset.[5] After publication of the results of MR CLEAN, several randomized controlled trials confirmed the effect of IAT in patients with a proven occlusion on vessel imaging.[6–9] Despite the high recanalization rates after IAT (range 58% to 88%), a substantial proportion of patients did not reach functional independence at 90 days defined as a modified Rankin Scale (mRS) score of ≤2 (range 32%–71%).[5–7,9]

Cerebral collateral flow is believed to be associated with the effect of IAT.[10–13] Collateral flow is defined as blood flow through a network of preexistent vascular anastomoses, which provide varying degrees of blood flow to brain tissue when the primary supply pathways fail. Numerous studies suggest that a good collateral network is of major importance for sustaining the ischemic penumbra. Good collaterals are associated with smaller infarct volumes on follow-up imaging and improved clinical outcomes after both intravenous thrombolysis and IAT.[12,14–18]

Other IAT studies used advanced neuroimaging criteria to select patients for inclusion.[6–9] These selection regimens were used because minimal treatment effect was assumed by the investigators in patients not fulfilling these neuroimaging inclusion criteria. Patients with absent or poor collaterals were not enrolled in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times trial (ESCAPE).[7] In contrast, collateral status was not a selection criterion in MR CLEAN, and the purpose of vessel imaging was to identify an intracranial occlusion. In this post hoc analysis, we aimed to assess whether the effect of IAT was modified by collateral status on baseline computed tomographic angiography (CTA) in MR CLEAN.

Methods

Study Design and Participants

Patient eligibility and methods of MR CLEAN have been reported previously.[5,19] In short, MR CLEAN was a randomized clinical trial of IAT (intervention group) versus no IAT (control group) in patients with a proximal arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 hours after symptom onset. All 500 patients from the MR CLEAN database were eligible for inclusion in this post hoc analysis. Study-specific inclusion criteria were the presence of intracranial carotid artery, intracranial carotid artery terminus, first middle cerebral artery segment (M1) or second middle cerebral artery segment (M2) occlusion as confirmed on CTA, and the sufficient display of the middle cerebral artery region. Collateral status was not an entry criterion for the trial and was assessed by observers blinded for treatment allocation and outcome.

All patients or their legal representatives provided written informed consent before randomization. The study protocol was approved by a central medical ethics committee and the research board of each participating center.

Outcomes

The primary outcome parameter was the score on the mRS at 90 days. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (dead). A score of ≤2 indicates functional independence of the patient.[20] Secondary clinical outcomes included dichotomized mRS score (0–1 versus 2–6; 0–2 versus 3–6, and 0–3 versus 4–6) and the National Institute of Health Stroke Scale (NIHSS) score after 24 hours and at 5 to 7 days or discharge. Secondary radiological outcomes included the modified Thrombolysis in Cerebral Infarction score on digital subtraction angiography, arterial recanalization status on follow-up CTA or magnetic resonance angiogram at 24 hours, and infarct volume on follow-up noncontrast computed tomography at 5 to 7 days after inclusion.[21]

Clinical and Imaging Assessment

A single experienced trial investigator, who was unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or healthcare provider. This interview provided masked reports for the assessment of the mRS by vascular neurologists who remained unaware of the treatment-group assignments.

In MR CLEAN, all neuroimaging data were stored centrally and reanalyzed by a central imaging committee. All CTA data were evaluated by 2 independent experienced neuroradiologists of the MR CLEAN imaging committee, as a part of the overall imaging evaluation. Discrepancies between the initial readers were solved by a third reader. All readers were blinded to clinical findings apart from symptom side. All available slices were used to assess collateral status of the target vessel. On the whole, if different slices expressed different collateral capacities, an average collateral score (CS) over all slices was determined. Collaterals were graded on baseline CTA with a 4-point scale (Figure 1), with 0 for absent collaterals (0% filling of the occluded territory), 1 for poor collaterals (>0% and ≤50% filling of the occluded territory), 2 for moderate (>50% and <100% filling of the occluded territory), and 3 for good collaterals (100% filling of the occluded territory).[22] No fixed CTA protocols were used in MR CLEAN, and protocols varied per center. If patients were transferred from an outside hospital, it was the local investigator's decision to either repeat the CTA or use the CTA of the initial hospital.

Statistical Analysis

The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the mRS, which was estimated with multivariable ordinal logistic regression, in the total population and per collateral grade group. We used multiplicative interaction terms to test for modification of treatment effect by collateral grade. The acOR and all secondary effect parameters were adjusted for potential imbalances in major prespecified prognostic variables adapted from the original trial protocol statistical analysis plan: age, stroke severity (NIHSS) at baseline, time of onset to randomization, presence of previous stroke, atrial fibrillation, diabetes mellitus, and intracranial carotid artery terminus occlusion.

The adjusted and unadjusted common odds ratios were reported with 95% confidence intervals (CI) to indicate statistical precision. Effect of treatment on binary outcomes was analyzed with logistic regression and reported as adjusted and unadjusted odds ratios with 95% CI. Effect of treatment on continuous outcomes was analyzed with linear regression and reported as adjusted and unadjusted betas with 95% CI. We used rank-based tests for continuous data, and χ^2-based tests for categorical data to test for trends in baseline characteristics and trends in secondary outcomes across collateral groups. We assessed interobserver reliability for the collateral assessment by estimating the agreement beyond chance with the quadratic weighted kappa. In addition, we tested for interobserver reliability by calculating the kappa for different collateral grade dichotomizations (grade 0 versus 1–3 and 0–1 versus 2–3). All P values are calculated for 2-sided tests. Statistical analyses were performed with Stata/SE 13.1 (StataCorp, TX).

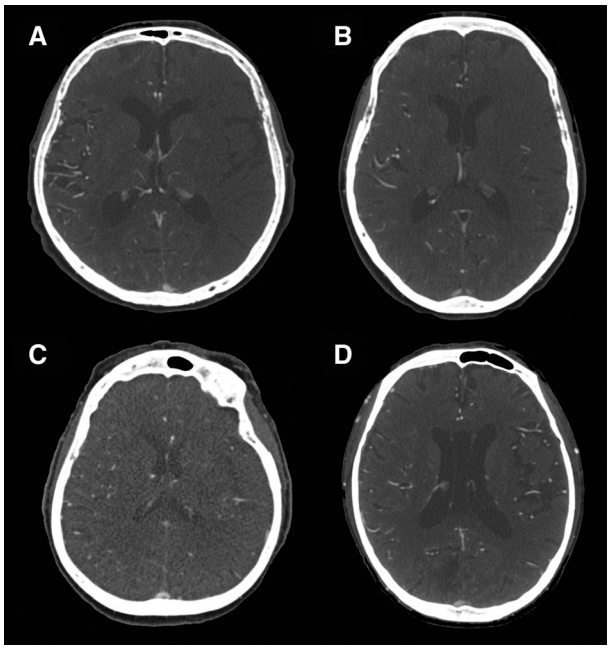

Figure 1. Collateral score grading for each category of the 4-point scale. Left hemisphere was affected in all examples above. **A**, Grade 0, representing absent collaterals (0% filling of the occluded territory). **B**, Grade 1, representing poor collaterals (>0% and ≤50% filling of the occluded territory). **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).

Role of the Funding Source

The trial and this post hoc analysis was designed and executed by members of the trial steering committee, which consists of an executive committee and the local investigators of each participating center. The steering committee had the final responsibility for the decision to submit the article for publication. The study sponsors were not involved in the study design, study conduct, protocol review, or article preparation or review.

Results

Patient Characteristics

Patients were recruited from December 2010 until March 2014. Of the 500 subjects, 233 subjects (47%) were allocated to intervention and 267 subjects (53%) to control. For this analysis, 493 met the study-specific inclusion criteria. Of the 7 excluded patients, 3 had an anterior cerebral artery stroke, 2 patients received baseline magnetic resonance angiography, 1 was excluded because of insufficient vessel coverage on CTA, and 1 patient received no baseline vessel imaging at all.

Baseline characteristics (Table 1 and Table I in the online-only Data Supplement) were evenly distributed across the 4 collateral grade groups, except for trends in age (P=0.012), sex (P=0.031), NIHSS (P<0.001), diabetes mellitus (P=0.032), hyperlipidemia (P=0.016), and Alberta Stroke Program Early Computed Tomography Score (ASPECTS; P=0.018).

In 248 of the 493 assessments (50%) of collateral status, there was no agreement between the first 2 observers, and a third assessment was necessary. The weighted kappa for the agreement between the first 2 observers was 0.60, indicating a moderate agreement. Overall agreement for moderate to good collaterals (grade 2–3) as opposed to poor or absent collaterals (grade 0–1) was 76% (kappa 0.49). Overall agreement for absent (grade 0) as opposed to poor, moderate, and good (grade 1–3) was 95% (kappa 0.59).

Primary Outcome

No patients were lost to follow-up. We found a significant modification of treatment effect on the primary outcome by collateral status (P=0.038), adjusted for age, stroke severity (NIHSS) at baseline, time of onset to randomization, presence of previous stroke, atrial fibrillation, diabetes mellitus, and intracranial carotid artery terminus occlusion according to the original statistical analysis plan. There was a shift in the distribution on the mRS in favor of the intervention group across all collateral grades, except in patients with absent collaterals (grade 0; Table 2 and Figure 2). The strongest shift (acOR 3.2 [95% CI; 1.7–6.2]) was found in patients with good collaterals (grade 3). In the group with moderate collaterals (grade 2), the acOR was 1.6 [95% CI; 1.0–2.7]. The acOR was 1.2 [95% CI; 0.7–2.3] in patients with poor collaterals (grade 1) and 1.0 [95% CI; 0.1–8.7] in patients with absent collaterals (grade 0).

Secondary Outcomes

When functionally independent status at 90 days (mRS 0–2) was considered as outcome, the modification of treatment effect by collateral status was significant (P=0.018). Patients with collateral grade 3 had a 29.5% (95% CI; 13.5%–45.5%) absolute increase in the chance of becoming functionally independent at 90 days (mRS 0–2) compared with controls (adjusted odds ratio 4.2 [95% CI; 1.9–9.3]; Table 2). For collateral grade 2, the absolute risk difference for functional independence was 15.0% (95% CI; 3.7%–27.3%; adjusted odds ratio 2.2 [95% CI; 1.1–4.5]). In collateral grade group 1, the absolute risk difference was 1.7% (95% CI; −14.2% to 18.8%) in favor of the control group (adjusted odds ratio 0.8 [95% CI; 0.3–2.3]). In patients with absent collaterals (grade 0), none of the patients in the control or intervention group were functionally independent at 90 days (Table 2 and Figure 2).

The median NIHSS scores in surviving patients at 24 hours were 23, 17, 14 and 12 for grades 0, 1, 2 and 3, respectively (P<0.001; Table 3). The median NIHSS scores in surviving patients at 5 to 7 days or at discharge were 18, 16, 11, 7.5 for grades 0, 1, 2 and 3, respectively (P<0.001). Neurological improvement on the NIHSS was in favor of intervention in all subgroups after 24 hours and after 5 to 7 days or discharge (Table 2 and 3). We found no significant modification of treatment effect by collateral status when NIHSS at 24 hours (P=0.26) or NIHSS 5 to 7 days or discharge (P=0.63) was used as an outcome.

Collateral status did not modify the treatment effect of IAT on recanalization rate (P=0.19). Recanalization rate on follow-up imaging was higher in the intervention group compared with the control group, which was consistent for all collateral subgroups. Rate of good revascularization on post-treatment digital subtraction angiography (modified Thrombolysis in Cerebral Infarction score 2B-3) only measured in patients undergoing IAT was not significantly different between collateral grades (P=0.89). Good angiographic revascularization

Table 1. Clinical Characteristics at Baseline per Collateral Grade

	Grade 0 (N=26)	Grade 1 (N=136)	Grade 2 (N=198)	Grade 3 (N=133)
Age, median (IQR)	72.5 (58.9–77.0)	67.3 (56.9–77.5)	65.8 (55.0–76.0)	63.1 (52.2–73.8)
Male sex, n (%)	18 (69.2)	84 (61.8)	120 (60.6)	67 (50.4)
NIHSS, median (IQR)	21 (17–24)	19 (16–23)	17 (14–21)	16 (12–19)
Clinical localization: Left hemisphere, n (%)	13 (50.0)	71 (52.2)	104 (52.5)	74 (55.6)
Atrial fibrillation, n (%)	10 (38.5)	36 (26.5)	52 (26.3)	37 (27.8)
History of ischemic stroke, n (%)	1 (3.8)	24 (17.6)	17 (8.6)	12 (9.0)
History of hypertension, n (%)	11 (42.3)	75 (55.1)	75 (37.9)	62 (46.6)
History of diabetes mellitus, n (%)	7 (26.9)	24 (17.6)	19 (9.6)	16 (12.0)
History of myocardial infarction, n (%)	5 (19.2)	25 (18.4)	27 (13.6)	18 (13.5)
History of peripheral artery disease, n (%)	0 (–)	12 (8.8)	8 (4.0)	4 (3.0)
History of hyperlipidemia, n (%)	5 (19.2)	52 (38.2)	43 (21.7)	27 (20.3)
History of smoking, n (%)*	6 (23.1)	39 (28.7)	53 (26.8)	42 (31.6)
Current statin use, n (%)	6 (23.1)	57 (41.9)	42 (21.2)	36 (27.1)
Current anticoagulant use, n (%)	2 (7.7)	13 (9.6)	10 (5.1)	14 (10.5)
Current antiplatelet use, n (%)	7 (26.9)	50 (36.8)	52 (26.3)	33 (24.8)
Systolic blood pressure, mean mm Hg (SD)†	152.2 (27.4)	146.7 (23.9)	143.3 (25.8)	144.7 (24.0)
Prestroke modified Rankin Scale score, n (%)				
0	20 (76.9)	103 (75.7)	167 (84.3)	108 (81.2)
1	3 (11.5)	14 (10.3)	21 (10.6)	12 (9.0)
≥2	3 (11.5)	19 (14.0)	10 (5.1)	13 (9.8)
Treatment with IV alteplase, n (%)	23 (88.5)	121 (89.0)	179 (90.4)	117 (88.0)
Onset to IV alteplase in min, median (IQR)	90 (73–110)	85 (70–110)	83 (65–113)	90 (64–113)
ASPECTS‡				
0–4	3 (11.5)	13 (9.6)	11 (5.7)	2 (1.5)
5–7	8 (30.8)	27 (20.0)	38 (19.2)	19 (14.3)
8–10	15 (57.7)	95 (70.4)	149 (75.3)	112 (84.2)
Level of occlusion, n (%)				
ICA	0 (–)	0 (–)	1 (0.5)	3 (2.3)
ICA-T	8 (30.8)	46 (33.8)	52 (26.3)	27 (20.3)
M1	15 (57.7)	82 (60.3)	128 (64.6)	92 (69.2)
M2	3 (11.5)	8 (5.9)	17 (8.6)	11 (8.3)
Onset to randomization in min, median (IQR)§	201 (159–244)	193 (148–246.5)	196 (150–262)	217 (158–268)
Onset to groin puncture in min, median (IQR)	220 (199–278)	265 (210–331)	260 (210–305)	256 (220–305)
Onset to reperfusion or last angiogram in min, median (IQR)	308 (272–341)	334 (275–411)	339 (277–388)	341 (274–387)

ASPECTS indicates Alberta Stroke Program Early CT Score, range 0 to 10, higher scores indicate less early ischemic changes; ICA, internal carotid artery (intracranial segment); ICA-T, internal carotid artery with involvement of the M1 segment; IQR, interquartile range; IV, intravenous; M1/2, middle cerebral artery segments; NIHSS, National Institutes of Health Stroke Scale range 0 to 42, higher scores indicate more severe neurological deficits; and SD, standard deviation.

*Current smoking status was missing in 23 patients in MR CLEAN.

†Systolic blood pressure at baseline was missing in 1 patient in MR CLEAN.

‡ASPECTS was not available in 1 patient in MR CLEAN.

§Randomization time was missing in 2 patients in MR CLEAN.

was reached in 50%, 54%, 70%, and 49% for grades 0, 1, 2 and 3, respectively (Table 3).

The median final infarct volumes on 5 to 7 day noncontrast computed tomography (range 3–9 days) were 212 mL, 114 mL, 56 mL, and 39 mL for grades 0, 1, 2 and 3, respectively (P<0.001). We found no significant (P=0.71) treatment effect modification by collaterals status when follow-up infarct volume was used as secondary outcome (Table 2 and 3). Follow-up infarct volume was smaller in the intervention group across all collateral subgroups (Table 2 and 3).

Serious Adverse Events and Safety Parameters

We found a difference in overall mortality (P<0.001) across the different collateral subgroups (Table 4 and Table II in the online-only Data Supplement). The proportion of patients with at least one serious adverse event was higher if patients had

Table 2. Primary and Secondary Effect Parametes per Collateral Grade

Outcome	Effect Parameter	Grade 0 Unadjusted Effect	Grade 0 Adjusted Effect	Grade 1 Unadjusted Effect	Grade 1 Adjusted Effect	Grade 2 Unadjusted Effect	Grade 2 Adjusted Effect	Grade 3 Unadjusted Effect	Grade 3 Adjusted Effect	*P* Value (Unadjusted)*	*P* Value (Adjusted)*
Primary											
mRS at 90 days	cOR (95% CI)	0.8 (0.2 to 4.1)	1.0 (0.1 to 8.7)	1.4 (0.8 to 2.6)	1.2 (0.7 to 2.3)	1.7 (1.0 to 2.8)	1.6 (1 to 2.7)	2.9 (1.5 to 5.4)	3.2 (1.7 to 6.2)	0.094	0.038
Secondary: clinical											
mRS 0–1	OR (95% CI)	n/a	n/a	1.2 (0.3 to 5.6)	1.4 (0.2 to 8.2)	2 (0.8 to 5.2)	1.6 (0.6 to 4.7)	2.8 (0.9 to 8.7)	3.2c (1.0 to 10.2)	0.458	0.457
mRS 0–2	OR (95% CI)	n/a	n/a	0.9 (0.3 to 2.2)	0.8 (0.3 to 2.3)	2.2 (1.1 to 4.2)	2.2 (1.1 to 4.5)	3.6 (1.7 to 7.4)	4.2 (1.9 to 9.3)	0.037	0.018
mRS 0–3	OR (95% CI)	n/a	n/a	1.2 (0.6 to 2.5)	1.3 (0.6 to 2.8)	2.1 (1.2 to 3.7)	2.1 (1.1 to 4)	2.9 (1.4 to 6.0)	3.6 (1.6 to 8.2)	0.213	0.158
NIHSS after 24 h†	β (95% CI)	2.1 (–6.6 to 10.7)	n/a	–2.3 (–5.0 to 0.5)	–2.2 (–4.7 to 0.2)	–2.8 (–4.9 to –0.6)	–2.4 (–4.4 to –0.4)	–3.2 (–6.0 to –0.5)	–3.2 (–5.4 to –1.0)	0.358	0.264
NIHSS at 5–7 days or discharge†	β (95% CI)	–10.6 (–20.9 to –0.4)	n/a	–0.8 (–4.0 to 2.3)	–1.5 (–4.4 to 1.5)	–4.1 (–6.4 to –1.9)	–3.5 (–5.6 to –1.4)	–3.9 (–6.6 to –1.2)	–3.6 (–6.0 to –1.1)	0.490	0.626
Secondary: radiological											
Recanalization on follow-up vessel imaging at 24 h	OR (95% CI)	15 (1.0 to 229.0)	n/a	9.8 (3.9 to 24.8)	22.6 (6.2 to 82.1)	5.1 (2.5 to 10.1)	5.2 (2.5 to 10.9)	5.9 (2.6 to 13.3)	6.3 (2.6 to 15.2)	0.311	0.190
Final infarct volume in milliliters‡	β (95% CI)	–60.0 (–282.3 to 166.3)	n/a	–26.9 (–62.6 to 8.8)	–27.4 (–64.5 to 9.7)	–17.1 (–42.1 to 7.9)	–10.7 (–36.8 to 15.4)	–30.0 (–50.7 to –9.3)	–26.0 (–46.6 to –5.5)	0.938	0.710

This table lists 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-T occlusion. β indicates beta coefficient; cOR, common odds ratio; OR, odds ratio; mRS, modified Rankin Scale; n/a, not enough data available to calculate statistical parameter; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

**P* value of interaction term.

†NIHSS was measured in survivors only.

‡Final infarct volume on NCCT after 5 days (range 3–9 days).

poorer collaterals ($P<0.001$). There was no trend ($P=0.080$) for proportion of patients with symptomatic intracranial hemorrhage across collateral subgroups; however, the absolute difference in patients with collateral grade 2 was higher in the intervention group compared with the control group (7.5%; $P=0.028$; Table II in the online-only Data Supplement). In addition, progression of ischemic stroke ($P<0.001$) increased if patients had poorer collateral grades.

Discussion

In this post hoc analysis of MR CLEAN, baseline CTA collateral status modified the effect of IAT. The benefit of IAT was robust in patients with good collaterals on baseline CTA. Treatment benefit could not be established in patients with absent or poor collaterals. These results are pathophysiologically plausible. Our findings expand on earlier reports from ESCAPE, which demonstrated that patients with moderate to good collaterals have improved functional outcome when treated with IAT.[7] ESCAPE could not examine the treatment effect in patients with poor or absent collaterals because these patients were excluded by design.

In recently published exploratory analyses of the Interventional Management of Stroke (IMS) III trial, maximal benefit of treatment was seen in patients with moderate collaterals, some in patients with good collaterals, but none in patients with poor collaterals. This IMS III post hoc analysis showed no significant modification of treatment effect by collateral status, but the sample size was relatively small (N=185).[23] In addition, post hoc effect modification analyses in neutral trials have to be interpreted with care.[24,25] In IMS III, maximal benefit of endovascular therapy was present in the group with moderate collaterals on CTA. In contrast, our study showed maximum benefit of IAT for patients with good collaterals. In agreement with IMS III, patients with absent collaterals on baseline CTA do not seem to benefit from IAT in MR CLEAN. Previous work has shown that absent collaterals in a substantial territory downstream from an occlusion is associated with large infarcts on concurrent diffusion-weighted imaging and may further identify patients who are unlikely to benefit but do not yet demonstrate extensive ischemic changes on noncontrast computed tomography.[26] Although we have only limited diffusion-weighted imaging data in MR CLEAN, we also demonstrated this relationship based on the noncontrast computed tomography ASPECTS score.

Limitations

In the majority of patients in MR CLEAN, we used single-phase CTA, which lacks adequate temporal information. This could lead to mislabeling patients in the lower collateral categories.[17,27] The use of multiphase CTA, an imaging technique that gives better temporal information about collateral filling, could help to reduce this problem.[28] Another option to evaluate this slow collateral filling is to derive a so-called timing-invariant CTA from acquired computed tomography perfusion data.[29,30] Even though we have confidence in these new techniques, a flow-limiting proximal stenosis could still delay

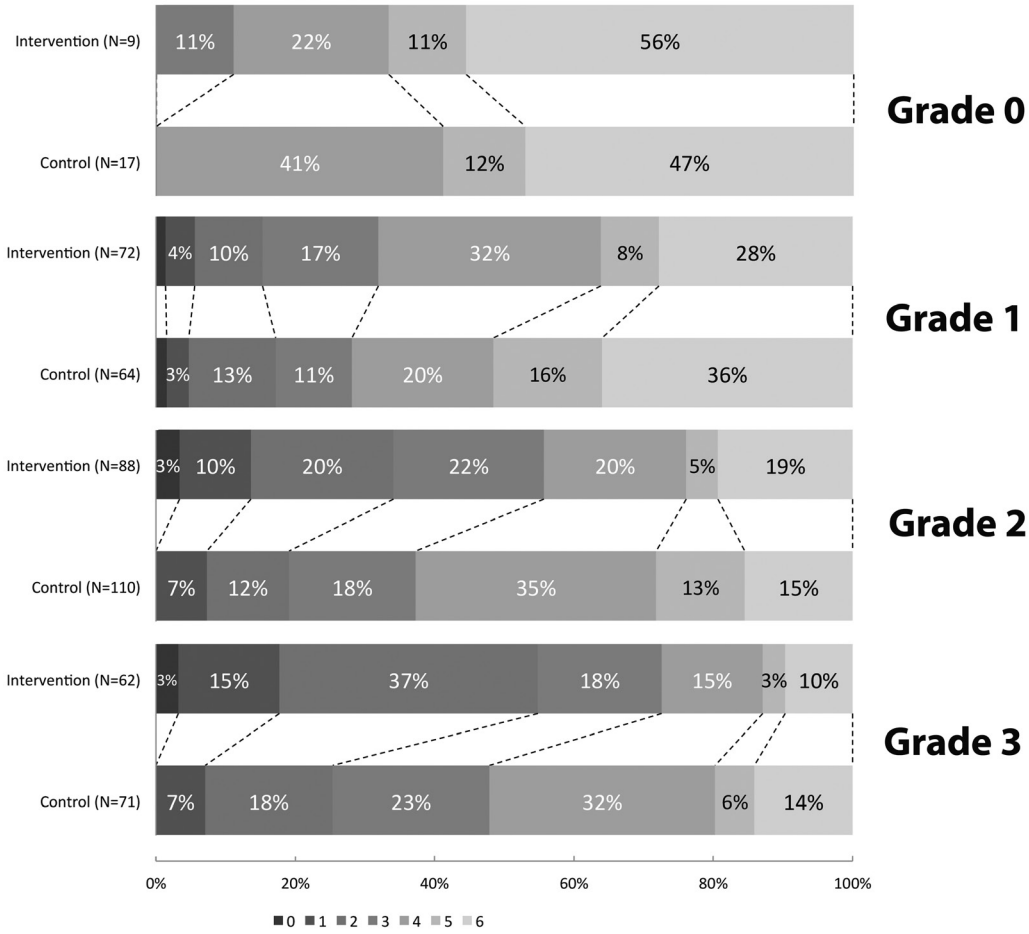

Figure 2. Modified Rankin Scale (mRS) scores at 90 days per collateral grade. Distribution of scores on the modified Rankin Scale (mRS). Scores range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (patient is able to function without assistance but is unable to carry out all previous activities); 3, moderate disability (patient requires some help but is able to walk unassisted); 4, moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (patient requires constant nursing care and attention); and 6, death. We found a significant modification of treatment effect by collaterals (P=0.038). There was a shift in the distribution on the mRS in favor of the intervention group across all collateral grades, except in patients with absent or poor collaterals.

contrast filling and influence interpretation of the collateral status. Implementation and standardization of these new techniques in everyday practice will take a considerable amount of time.[31]

Collateral status assessment on CTA can be prone to moderate interobserver agreement; however, for the scoring method used in this study, reported agreement is high.[22] In our study, interobserver agreement was moderate.The fact that we nevertheless found an interaction with treatment suggest that improvements in assessment and classification might lead to a stronger influence on treatment effect and, thus, more efficient selection of patients for IAT.

Future Directions

Additional research is warranted to further elucidate the role of collaterals regarding selection of patients for IAT, in particular those with absent and poor collaterals, because more accurately identifying these patients could further improve efficacy and cost effectiveness of IAT in acute ischemic stroke. As suggested by previous work, a collateral scoring system that focuses on poor collateral grades predictive of treatment futility may be more relevant clinically and may have better reliability.[26] Reported interobserver variability varies across studies ranging from fair to substantial agreement.[26,30] Further research is needed into more uniform reporting, easier interpretable scoring systems, and implementation in an emergency before collaterals can be used in clinical setting to select patients for IAT. With the development of new computed tomography-techniques, for example, 4D CTA and time-invariant CTA, collateral grading accuracy will in all likelihood improve. Finally, our results suggest that strong benefit can be expected for patients with moderate and, especially, good collaterals. It can be argued that the compensating effect of collaterals may delay conversion from hypoperfused but salvageable tissue into infarct core, and one may anticipate a treatment benefit beyond the current 6-hour time window. This justifies further exploration in new trials. On the other side of the spectrum, it is theoretically possible that early treatment may lead to substantial benefits in patients with absent collaterals. In our opinion,

Table 3. Secondary Outcomes per Collateral Grade in Intervention and Control

Outcome	Grade 0 Intervention (N=9)	Grade 0 Control (N=17)	Grade 1 Intervention (N=72)	Grade 1 Control (N=64)	Grade 2 Intervention (N=88)	Grade 2 Control (N=110)	Grade 3 Intervention (N=62)	Grade 3 Control (N=71)
Secondary: clinical								
NIHSS after 24 h, median (IQR; N)*	24 (6–37; 7)	23 (16–24; 15)	16 (11–21; 69)	18 (14–23; 62)	12 (6–18; 84)	16 (12–19.5; 104)	9 (4–18; 62)	15 (8–18; 71)
NIHSS at 5–7 days or discharge, median (IQR; N)*	11 (3–18; 4)	22 (15–25; 11)	15 (7–21; 60)	17 (9–19; 49)	7 (2–13; 74)	14 (7–18; 99)	3 (1–10; 57)	13 (4–17;67)
Secondary: radiological								
Recanalization on follow-up vessel imaging, n/total n (%)	3/5 (60)	1/11 (9)	44/57 (77)	11/43 (26)	53/70 (76)	35/92 (38)	40/54 (74)	19/58 (33)
Revascularization on DSA (mTICI 2B-3), n/total n (%)	4/8 (50)	n/a	34/63 (54)	n/a	50/71 (70)	n/a	26/53 (49)	n/a
Final infarct volume on NCCT, Median mL (IQR; N)†	156 (46–266; 2)	212 (164–264; 4)	96 (49–156; 48)	131 (71–227; 34)	42 (23–73; 50)	71 (33–111; 71)	25 (10–52; 44)	67 (27–95; 50)

DSA indicates digital subtraction angiography; mTICI, modified Thrombolysis in Cerebral Infarction; NCCT, noncontrast computed tomography; and NIHSS, National Institutes of Health Stroke Scale.

*NIHSS was measured in survivors only.

†Final infarct volume on NCCT after 5 days (range 3–9 days).

exclusion of all patients with absent collaterals from treatment is not justified. The interaction between time from symptom onset to start of treatment and collateral status has to be studied further, and our results have to be validated in independent studies.

Conclusions

In MR CLEAN, baseline CTA collateral status modified the treatment effect. The benefit of IAT was greatest in patients with good collaterals on baseline CTA. Treatment benefit appeared less and may be absent in patients with absent or poor collaterals.

Table 4. Safety Parameters and Serious Adverse Events

	Grade 0 (N=26)	Grade 1 (N=136)	Grade 2 (N=198)	Grade 3 (N=133)
Safety parameters				
Death within 7 days, n (%)	10 (38.5)	27 (19.9)	18 (9.1)	3 (2.3)
Death within 30 days, n (%)	11 (42.3)	39 (28.7)	27 (13.6)	14 (10.5)
Hemicraniectomy, n (%)	4 (15.4)	8 (5.9)	9 (4.5)	6 (4.5)
Serious adverse events				
Patients with at least one SAE, n (%)*	19 (73.1)	78 (57.4)	87 (43.9)	37 (27.8)
Symptomatic ICH, n (%)	1 (3.8)	16 (11.8)	12 (6.1)	5 (3.8)
Parenchymal hematoma type 1 (PH1), n (%)†	0 (–)	2 (1.5)	0 (–)	0 (–)
Parenchymal hematoma type 2 (PH2), n (%)†	1 (3.8)	12 (8.8)	10 (5.1)	4 (3.0)
Hemorrhagic infarction type 1 (HI1), n (%)‡	0 (–)	1 (0.7)	0 (–)	0 (–)
Hemorrhagic infarction type 2 (HI2), n (%)‡	0 (–)	0 (–)	1 (0.5)	1 (0.8)
Subarachnoid hemorrhage, n (%)	0 (–)	1 (0.7)	1 (0.5)	0 (–)
Recurrent ischemic stroke, n (%)	0 (–)	7 (5.1)	3 (1.5)	4 (3.0)
Progression of ischemic stroke, n (%)	13 (50.0)	37 (27.2)	30 (15.2)	14 (10.5)
Pneumonia, n (%)	6 (23.1)	22 (16.2)	29 (14.6)	13 (9.8)
Other infection, n (%)	1 (3.8)	9 (6.6)	12 (6.1)	4 (3.0)
Cardiac ischemia, n (%)	1 (3.8)	0 (–)	3 (1.5)	1 (0.8)
Extracranial hemorrhage, n (%)	0 (–)	1 (0.7)	1 (0.5)	0 (–)
Allergic reaction, n (%)	0 (–)	0 (–)	1 (0.5)	0 (–)
Other complication, n (%)	4 (15.4)	14 (10.3)	31 (15.7)	15 (11.3)

ICH indicates intracerebral hemorrhage; and SAE, serious adverse event.

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

†Parenchymal hematoma defined as PH1 blood clot(s) ≤30% of infarct area with some mild space-occupying effect; PH2 blood clots >30% of infarct area with significant mild space-occupying effect.

‡Hemorrhagic infarcts defined as HI1 small petechiae along the margins of the infarct; HI2 with more confluent petechiae within the infarct area.

Appendix

Local Principal Investigators and Committee Members

Wouter J. Schonewille; Jan-Albert Vos; Paul J. Nederkoorn; Marieke J.H. Wermer; Julie Staals; Jeannette Hofmeijer; Jacques A. van Oostayen; Jelis Boiten; Patrick A. Brouwer; Bart J. Emmer; Sebastiaan F. de Bruijn; Lukas C. van Dijk; L. Jaap Kappelle; Rob H. Lo; Ewoud J. van Dijk; Joost de Vries; Paul L.M. de Kort; Jan S.P. van den Berg; Boudewijn A.A.M. van Hassel; Leo A.M. Aerden; René J. Dallinga; Marieke C. Visser; Patrick C. Vroomen; Omid Eshghi; Tobien H.C.M.L. Schreuder; Roel J.J. Heijboer; Koos Keizer; Alexander V. Tielbeek; Heleen M. den Hertog; Dick G. Gerrits; Renske M. van den Berg-Vos; Giorgos B. Karas; Peter J. Koudstaal; H. Zwenneke Flach; Ewout W. Steyerberg; Martin M. Brown; Thomas Liebig; Theo Stijnen

List of Affiliations

Departments of Neurology (W.J.S.) and Radiology (J.A.V.), Sint Antonius Hospital, Nieuwegein, The Netherlands; Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands (P.J.N.); Departments of Neurology (M.J.H.W.) and Medical Statistics and Bioinformatics (T.S.), Leiden University Medical Center, Leiden, The Netherlands; Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), The Netherlands (J.S.); Departments of Neurology (J.H.) and Radiology (J.A.v.O.), Rijnstate Hospital, Arnhem, The Netherlands; Department of Neurology, MC Haaglanden, The Hague, The Netherlands (J.B.); Departments of Radiology (P.A.B., B.J.E.), Neurology (P.J.K.), and Public Health (E.W.S.), Erasmus MC University Medical Center, The Netherlands; Departments of Neurology (S.F.d.B.) and Radiology (L.C.v.D.), HAGA Hospital, The Hague, The Netherlands; Departments of Neurology (L.J.K.) and Radiology (R.H.L.), University Medical Center Utrecht, The Netherlands; Departments of Neurology (E.J.v.D.) and Neurosurgery (J.d.V.), Radboud University Medical Center, Nijmegen, The Netherlands; Department of Neurology, Sint Elisabeth Hospital, Tilburg, The Netherlands (P.L.M.d.K.); Departments of Neurology (J.S.P.v.d.B.) and Radiology (B.A.A.M.v.H., H.Z.F.), Isala Klinieken, Zwolle, The Netherlands; Departments of Neurology (L.A.M.A.) and Radiology (R.J.D.), Reinier de Graaf Gasthuis, Delft, The Netherlands; Department of Neurology, VU Medical Center, Amsterdam, The Netherlands (M.C.V.); Departments of Neurology (P.C.V.) and Radiology (O.E.), University Medical Center Groningen, The Netherlands; Departments of Neurology (T.H.C.M.L.S.) and Radiology (R.J.J.H.), Atrium Medical Center, Heerlen, The Netherlands; Departments of Neurology (K.K.) and Radiology (A.V.T.), Catharina Hospital, Eindhoven, The Netherlands; Departments of Neurology (H.M.d.H.) and Radiology (D.G.G.), Medical Spectrum Twente, Enschede, The Netherlands; Departments of Neurology (R.M.v.d.B.-V.) and Radiology (G.B.K.), Sint Lucas Andreas Hospital, Amsterdam, The Netherlands; UCL Institute of Neurology (M.M.B.), National Hospital for Neurology and Neurosurgery, London, United Kingdom; and Med. Fakultät (T.L.), Uniklinik Köln, Germany.

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