ARTICLE CLASS OF EVIDENCE

Association of White Matter Lesions and Outcome After Endovascular Stroke Treatment

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Abstract

Objective

To investigate the association between white matter lesions (WML) and functional outcome in patients with acute ischemic stroke (AIS) and the modification of the effect of endovascular treatment (EVT) by WML.

Methods

We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial and assessed severity of WML on baseline noncontrast CT imaging (NCCT; n = 473) according to the Van Swieten Scale. Poststroke functional outcome was assessed with the modified Rankin Scale. We investigated the association of WML with functional outcome using ordinal logistic regression models adjusted for age, sex, and other relevant cardiovascular and prognostic risk factors. In addition, an interaction term between treatment allocation and WML severity was used to assess treatment effect modification by WML.

Results

We found an independent negative association between more severe WML and functional outcome (adjusted common odds ratio [acOR] 0.77 [95% confidence interval (CI) 0.66–0.90]). Patients with absent to moderate WML had similar benefit of EVT on functional outcome (acOR 1.93 [95% CI 1.31–2.84]) as patients with severe WML (acOR 1.95 [95% CI 0.90–4.20]). No treatment effect modification of WML was found (p for interaction = 0.85).

Conclusions

WML are associated with poor functional outcome after AIS, but do not modify the effect of EVT.

Classification of Evidence

Prognostic accuracy. This study provides Class II evidence that for patients with AIS, the presence of WML on baseline NCCT is associated with worse functional outcomes.

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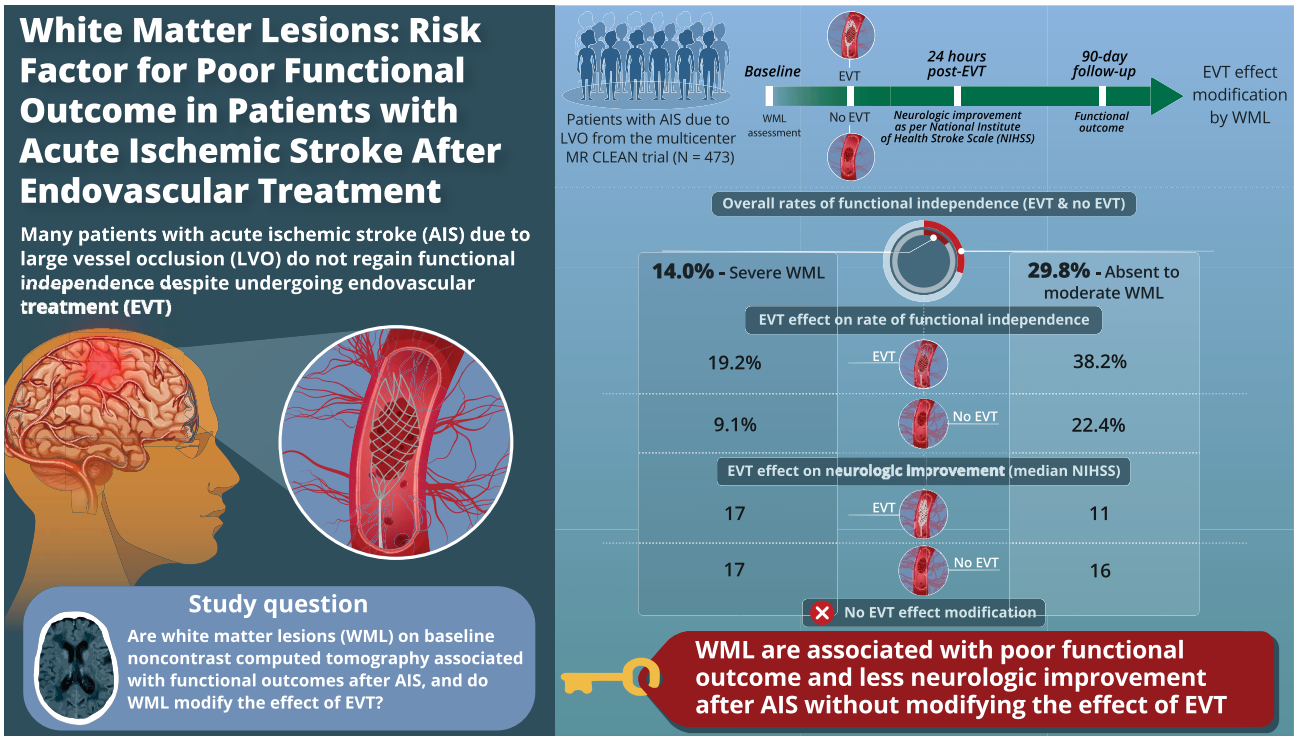
MR CLEAN trial investigators are listed at links.lww.com/WNL/B250.

Glossary

acOR = adjusted common odds ratio; **AIS** = acute ischemic stroke; **ASPECTS** = Alberta Stroke Program Early CT Score; **CI** = confidence interval; **cSVD** = cerebral small vessel disease; **CTA** = CT angiography; **DSA** = digital subtraction angiography; **EVT** = endovascular treatment; **ICAC** = intracranial carotid artery calcification; **IVT** = IV thrombolysis; **LVO** = large vessel occlusion; **MR CLEAN** = Multicenter Randomized Clinical Trial of Endovascular treatment of Acute Ischemic Stroke in the Netherlands; **mRS** = modified Rankin Scale; **mTICI** = modified Treatment in Cerebral Ischemia; **NCCT** = noncontrast CT; **NIHSS** = NIH Stroke Scale; **sICH** = symptomatic intracranial hemorrhage; **VSS** = Van Swieten Scale; **WML** = white matter lesion.



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Endovascular treatment (EVT) has been proven beneficial across diverse subgroups of patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO).[1] Despite the broad applicability of EVT, a substantial number of treated patients do not regain functional independence. More in-depth knowledge of additional patient characteristics influencing functional outcome after EVT is required to more accurately predict individual patient benefit and aid clinical decision-making regarding eligibility for EVT.

Imaging characteristics at baseline such as collateral status,[2] intracranial carotid artery calcification pattern (ICAC),[3] and in the late time window, the Alberta Stroke Program Early CT Score (ASPECTS)[4] have been shown to influence the effectiveness of EVT in terms of postprocedural functional outcome. Recent studies are suggesting that white matter lesions (WMLs) on baseline noncontrast CT (NCCT) and T2-weighted MRI may adversely impact functional outcome post-EVT.[5–7] In addition, previous studies showed that WML severity is associated with susceptibility to infarct growth,[8] larger cortical infarct volume,[9] and increased risk of intracranial hemorrhage[10] as possible pathophysiologic mechanisms explaining the poor clinical outcomes in these patients. However, these studies were limited by the lack of a control group and were therefore unable to assess whether effect modification of EVT by WML was present.[5–7]

The aim of this post hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN)[11] was to determine whether WML is associated with functional outcome and modifies the effect of EVT.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The MR CLEAN trial (trialregister.nl, unique identifier: NTR1804; isrctn.com, unique identifier: ISRCTN10888758)

was a randomized controlled trial of EVT vs no EVT along with usual clinical care. All patients or their legal representatives provided written informed consent before randomization. Approval for the study protocol was provided by a central ethics committee and the research board of each participating center.

Classification of Evidence

This study addressed the following research questions: (1) Are WMLs on baseline NCCT associated with functional outcome in patients with AIS? (2) Is the effect of EVT on functional outcome modified by WML? Class II level of evidence was assigned to these questions.

Study Population

The current study used data from MR CLEAN, a multicenter trial that included patients with AIS due to LVO in the anterior circulation within 6 hours after symptom onset and randomized them between EVT (intervention) or noEVT (control) along with usual clinical care including IV thrombolysis (IVT). Baseline neuroimaging consisted of NCCT and CT angiography (CTA), which was used to evaluate ASPECTS,[12] location of occlusion, and collateral status.[13] A more detailed overview of all study procedures has been described previously.[14] Baseline NCCT scans were used to assess presence and severity of WML. Patients with scans on which WML could not be assessed reliably due to old infarctions in the asymptomatic hemisphere, artefacts (motion/metal), incomplete data reconstruction, or unavailable data were excluded.

WML Assessment

Presence and severity of WML was assessed according to the Van Swieten Scale (VSS), which is a visual scale separately grading the white matter on NCCT around the anterior horns of the lateral ventricles and posterior part of the cella media and centrum semiovale.[15] Assessment was done in the asymptomatic hemisphere following a 3-point scale: grade 0 for no lesions; grade 1 for multiple punctate white matter lesions; grade 2 for confluent white matter lesions extending from the ventricles to the cortex. Subsequently, summation of the anterior and posterior grades provided a cumulative VSS score of 0–4. Graded VSS scores were dichotomized into absent to moderate (0–2) vs severe (3–4) WML for comparisons with prior studies.[5,6] All scans were graded by an observer (S.P.R.L.) who was blinded for clinical characteristics and outcome during assessment. In addition, an expert neuroradiologist (A.C.G.M.v.E.) with >9 years of experience graded a randomly selected subset of scans (n = 100) in order to define the level of interobserver agreement. Interobserver agreement for graded and dichotomized VSS scores was determined by calculating the proportion of agreement and by means of kappa statistics. Interobserver agreement was almost perfect (weighted $\kappa = 0.83$; 59% agreement) for graded VSS scores and substantial for dichotomized VSS scores ($\kappa = 0.76$; 91% agreement). Patients with graded VSS scores that were decisive for dichotomization (i.e., VSS 2 or 3; n = 136) were assessed by a second observer and in case of disagreement consensus was reached.

Assessment of Covariables

Information on cardiovascular risk and prognostic factors was obtained at admission to the hospital as previously described.[14] ICACs were manually segmented on NCCT scans and subsequently used to compute ICAC volumes.[3] ICAC pattern was divided into either intimal or medial calcification pattern using a visual scoring method.[3,16] ASPECTS was graded on baseline NCCT according to previously described methods.[17] Assessment of baseline collateral status was done following a 4-point scale based on CTA imaging: grade 0 for absent collaterals (0% filling of the occluded territory), grade 1 for poor collaterals (>0% and ≤50% filling of the occluded territory), grade 2 for moderate collaterals (>50% and <100% filling of the occluded territory), and grade 3 for good collaterals (100% filling of the occluded territory).[13]

Primary and Secondary Outcomes

The primary outcome was functional outcome at 90 days follow-up assessed by the modified Rankin Scale (mRS)[18] by an independent research nurse who was blinded for treatment allocation. Secondary outcomes included the stroke severity measured by the NIH Stroke Scale (NIHSS) score after 24 hours, the recanalization status on follow-up CTA after 24 hours evaluated by the modified arterial occlusive lesion score,[19] and the follow-up infarct volume on NCCT after 5–7 days using validated semiautomatic segmentation software.[20] In patients receiving EVT, recanalization was also assessed on posttreatment digital subtraction angiography (DSA) according to the modified Treatment in Cerebral Ischemia (mTICI) scale. Finally, symptomatic intracranial hemorrhage (sICH) was defined as an increase of 4 points or more on the NIHSS and evidence of intracranial hemorrhage on neuroimaging.

Statistical Analysis

The association of WML severity (absent to moderate vs severe WML) with functional outcome (mRS score 0–6) was assessed with ordinal logistic regression. In the first model, adjustments for age and sex were made. In the second model, we also adjusted for cardiovascular risk factors: smoking, diabetes mellitus, atrial fibrillation, myocardial infarction, and history of hypertension. In the third model, for a true estimation of the effect of WML on functional outcome, we adjusted for additional proven predictors of functional outcome including prestroke mRS, NIHSS at baseline, occlusion of the internal carotid terminus, ASPECTS on baseline NCCT, collateral status on baseline CTA, and time to randomization.[21] Modification of EVT treatment effect by severity of WML was assessed using a multiplicative interaction term. Associations of WML severity with secondary outcome measures including NIHSS at 24 hours, recanalization grade at 24 hours, and follow-up infarct volume at 5–7 days were assessed with ordinal and linear regression models. We performed a sensitivity analysis in which we assessed effect modification of EVT by WML using the graded VSS (0–4) instead of the dichotomized VSS to investigate whether the results changed. All analyses were conducted according to the intention-to-treat principle. Cases with missing data of

Table 1 Baseline Characteristics of Analyzed Patients

	Intervention group (n = 222)	Control group (n = 251)	*p* Value
Age, y	66 (55–76)	65 (54–76)	0.78
Male sex	131 (59.0)	147 (58.6)	0.92
Previous stroke	24 (10.8)	18 (7.2)	0.17
Atrial fibrillation	61 (27.5)	68 (27.1)	0.93
Diabetes mellitus	31 (14)	30 (12)	0.52
Smoking	64 (28.8)	72 (28.7)	0.97
Myocardial infarction	29 (13.1)	41 (16.3)	0.32
Hypertension	93 (41.9)	118 (47.0)	0.26
Prestroke mRS ≤2	212 (95.5)	242 (96.4)	0.89
NIHSS at baseline	17 (14–21)	18 (14–22)	0.53
Systolic blood pressure at baseline, mm Hg	145 (130–159)	142 (128–160)	0.97
Treatment with IV alteplase	195 (87.8)	228 (90.8)	0.29
ASPECTS on baseline NCCT[a]	9 (7–10)	9 (8–10)	0.13
Location of intracranial occlusion on baseline CTA			0.80
ICA	1 (0.5)	3 (1.2)	
ICA-T	57 (25.7)	71 (28.4)	
M1	146 (65.8)	154 (61.6)	
M2	17 (7.7)	20 (8.0)	
A1 or A2	1 (0.5)	2 (0.8)	
Collateral status on baseline CTA[b]			0.09
Absent collaterals	9 (4.1)	15 (6.1)	
Poor collaterals	71 (32.3)	55 (22.3)	
Moderate collaterals	83 (37.7)	108 (43.7)	
Good collaterals	57 (25.9)	69 (27.9)	
Extracranial ICA ≥50% stenosis	28 (12.6)	29 (11.6)	0.72
Extracranial ICA occlusion	18 (8.1)	20 (8.0)	0.96
ICAC at symptomatic side of stroke	116 (77.9)	140 (78.2)	0.94
ICAC volume at symptomatic side of stroke, mm^3	30 (1–122)	34 (1–117)	0.96
ICAC pattern at symptomatic side of stroke			0.53
No calcification	33 (22.1)	39 (21.8)	
Intimal calcification	57 (38.3)	59 (33.0)	
Medial calcification	59 (39.6)	81 (45.3)	
Graded Van Swieten score			0.03
0	109 (49.1)	128 (51.0)	
1	40 (18.0)	26 (10.4)	
2	21 (9.5)	42 (16.7)	
3	29 (13.1)	26 (10.4)	
4	23 (10.4)	29 (11.6)	
Dichotomized Van Swieten score			0.70
Absent to moderate (0–2)	170 (76.6)	196 (78.1)	
Severe (3–4)	52 (23.4)	55 (21.9)	
Time from stroke onset to randomization, min[c]	202 (151–250)	204 (150–268)	0.71

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CTA = CT angiography; ICA = intracranial carotid artery; ICAC = intracranial carotid artery calcification; mRS = modified Rankin Scale; NCCT = noncontrast CT; NIHSS = NIH Stroke Scale.
Values are median (interquartile range) or n (%).
[a] ASPECTS missing for 3 patients.
[b] Collateral status missing for 6 patients.
[c] Time from stroke onset to randomization missing for 2 patients.

baseline characteristics and outcomes were included in the analysis and the number of missing data was reported for each variable. Results are expressed as adjusted common odds ratios (acOR) or adjusted β values with 95% confidence intervals (CIs). Statistical analyses were performed using R statistical software (version 3.6.1) using packages rms, foreign, ggplot2, MASS, irr, gvlma, haven, and Rcpp.

Data Availability

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

Results

We used the data of 473 of 500 patients (95%) who had been included in the MR CLEAN trial; 27 patients were excluded for the following reasons: old infarctions in the asymptomatic hemisphere (n = 14), artefacts on NCCT due to motion or metal (n = 8), incomplete image reconstruction (n = 1), or unavailable data (n = 4).

The intervention group contained more patients with a graded VSS score of 1, whereas the control group contained more patients with a graded VSS score of 2 (table 1). Consequently, dichotomized VSS scores were evenly distributed

Table 2 Characteristics of Patients According to White Matter Lesion (WML) Severity

	Absent to moderate WML (n = 366)	Severe WML (n = 107)	*p* Value
Allocation to intervention group	170 (46.4)	52 (48.6)	0.70
Age, y	61 (52–70)	79 (72–84)	<0.01
Male sex	220 (60.1)	58 (54.2)	0.28
Previous stroke	23 (6.3)	19 (17.8)	<0.01
Atrial fibrillation	85 (23.2)	44 (41.1)	<0.01
Diabetes mellitus	42 (11.5)	19 (17.8)	0.09
Smoking	119 (32.5)	17 (15.9)	<0.01
Myocardial infarction	47 (12.8)	23 (21.5)	0.03
Hypertension	140 (38.3)	71 (66.4)	<0.01
Prestroke mRS ≤2	361 (98.6)	93 (86.9)	0.01
NIHSS at baseline	17 (14–21)	19 (15–23)	0.09
Systolic blood pressure at baseline, mm Hg	140 (125–158)	155 (140–170)	<0.01
Treatment with IV alteplase	328 (89.6)	95 (88.8)	0.81
ASPECTS on baseline NCCT[a]	9 (8–10)	9 (7–10)	0.07
Location of intracranial occlusion on baseline CTA			0.07
ICA	2 (0.5)	2 (0.5)	
ICA-T	104 (28.5)	24 (22.4)	
M1	233 (63.8)	67 (62.6)	
M2	23 (6.3)	14 (13.1)	
A1 or A2	3 (0.8)	0 (0)	
Collateral status on baseline CTA[b]			0.01
Absent collaterals	13 (3.6)	11 (10.4)	
Poor collaterals	91 (25.2)	35 (33.0)	
Moderate collaterals	152 (42.1)	39 (36.8)	
Good collaterals	105 (29.1)	21 (19.8)	
Extracranial ICA ≥50% stenosis	42 (11.5)	15 (14.0)	0.48
Extracranial ICA occlusion	27 (7.4)	11 (10.3)	0.33
ICAC at symptomatic side of stroke	175 (70.9)	81 (100.0)	<0.01
ICAC volume at symptomatic side of stroke, mm^3	16 (0–101)	106 (37–271)	<0.01
ICAC pattern at symptomatic side of stroke			<0.01
No calcification	71 (28.7)	1 (1.2)	
Intimal calcification	89 (36.0)	27 (33.3)	
Medial calcification	87 (35.2)	53 (65.4)	
Time from stroke onset to randomization, min[c]	200 (150–260)	207 (148–268)	0.52
Time from stroke onset to groin puncture, min[d]	255 (210–299)	300 (206–331)	0.07

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CTA = CT angiography; ICA = intracranial carotid artery; ICAC = intracranial carotid artery calcification; mRS = modified Rankin Scale; NCCT = noncontrast CT; NIHSS = NIH Stroke Scale.
Values are median (interquartile range) or n (%).
[a] ASPECTS missing for 3 patients.
[b] Collateral status missing for 6 patients.
[c] Time from stroke onset to randomization missing for 2 patients.
[d] Time reported for 205 patients in the intervention group, data missing for 17 patients.

between both groups ($p = 0.70$). Patients with severe WML were older (respectively, 79 vs 61 years; $p < 0.01$), were less often smokers (respectively, 15.9% vs 32.5%; $p < 0.01$) and functionally independent (respectively, 86.9% vs 98.6%; $p = 0.01$), and more often reported a history of stroke (respectively, 17.8% vs 6.3%; $p < 0.01$), myocardial infarction (respectively, 21.5% vs 12.8%; $p = 0.03$), atrial fibrillation (respectively, 41.1% vs 23.2%; $p < 0.01$), hypertension (respectively, 66.4% vs 38.3%; $p < 0.01$), ICAC at symptomatic side of stroke (respectively, 100% vs 47.8%; $p < 0.01$), and more often had a poorer collateral status at baseline ($p = 0.01$) (table 2). Further evaluation with ordinal analysis showed that more severe WML (per VSS increment) was independently associated with poorer collateral status on baseline CTA (acOR 0.82 [95% CI 0.69–0.96]). Baseline characteristics of patients according to WML severity were evenly distributed between treatment groups (data not shown).

WML and Functional Outcome

Overall, increasing WML burden (per VSS increment) was negatively associated with functional outcome at 90 days follow-up (acOR 0.77 [95% CI 0.66–0.90]). Rates of functional independence (mRS ≤2) were higher in patients with absent to moderate WML compared to patients with severe WML (respectively, 29.8% vs 14.0%; $p < 0.01$), and mortality rates were lower (respectively, 15.6% vs 39.3%; $p < 0.01$; table 3).

There was a shift in distribution on the mRS in favor of intervention in both patients with absent to moderate WML (acOR 1.93 [95% CI 1.31–2.84]) and patients with severe WML (acOR 1.95 [95% CI 0.90–4.20]) (table 4 and figure). We found no treatment effect modification by WML on functional outcome (p for interaction = 0.85; table 5). Also, in the sensitivity analysis in which we replaced the dichotomized

Table 3 Outcome Measures According Treatment Allocation and White Matter Lesion (WML) Severity

	Absent to moderate WML		Severe WML	
	Intervention (n = 170)	Control (n = 196)	Intervention (n = 52)	Control (n = 55)
mRS ≤2 at 90 days	65 (38.2)	44 (22.4)	10 (19.2)	5 (9.1)
Mortality at 90 days	25 (14.7)	32 (16.3)	20 (38.5)	22 (40.0)
NIHSS after 24 hours[a]	11 (5–18)	16 (11–20)	17 (7–23)	17 (13–23)
Successful recanalization on DSA (mTICI 2B–3)[b]	88 (61.1)	n/a	22 (52.4)	n/a
Infarct volume at 5–7 days[c]	51 (17–117)	77 (32–144)	87 (30–200)	80 (30–168)

Abbreviations: DSA = digital subtraction angiography; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; mTICI = modified Thrombolysis in Cerebral Infarction.
Values are median (interquartile range) or n (%).
[a] NIHSS at 24 hours missing for 19 patients.
[b] mTICI score missing for 36 patients treated with endovascular treatment.
[c] Follow-up infarct volume on NCCT at 5–7 days was missing for 46 patients.

VSS with the graded VSS, we found no evidence for effect modification of EVT by WML (p for interaction = 0.83).

WML and Secondary Outcomes

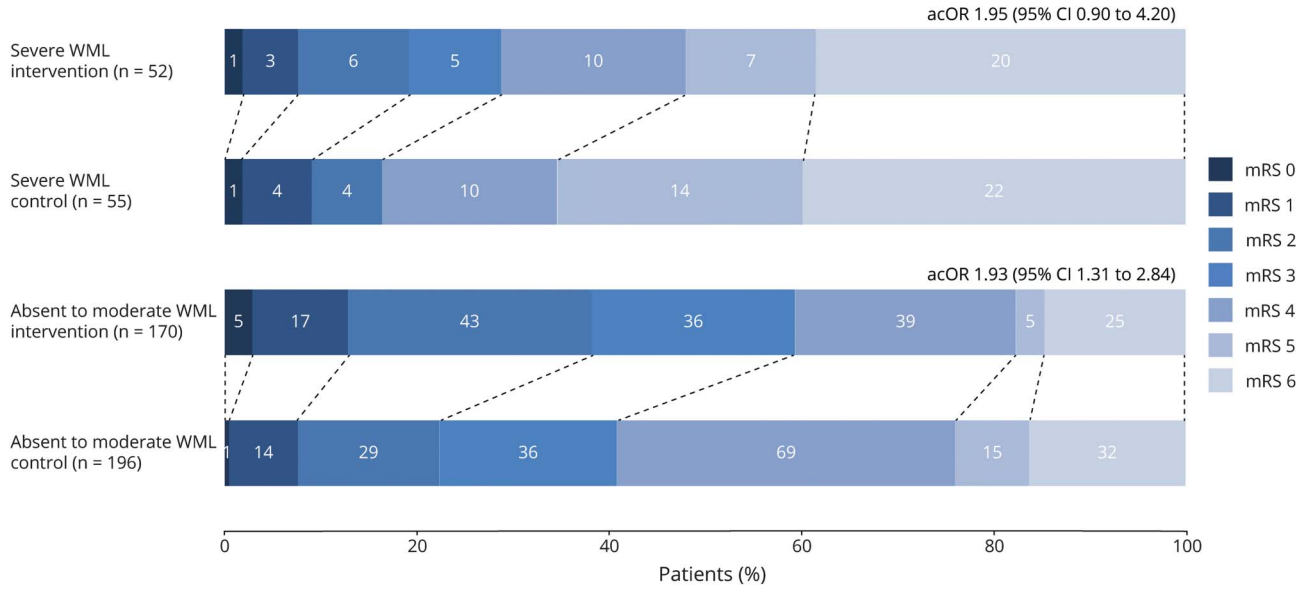
Patients with absent to moderate WML had better neurologic improvement after 24 hours post-EVT compared to patients with severe WML (respectively, median NIHSS, 11 vs 17; p = 0.01; table 3), although no significant treatment effect modification was found (p for interaction = 0.29; table 5). As well in patients with absent to moderate WML as in patients with severe WML, recanalization grades on CTA at 24 hours were significantly higher in the intervention group. Rates of successful recanalization on post-treatment DSA (mTICI 2B–3) were similar in patients with absent to moderate and

Table 4 Association of Treatment Allocation With Functional Outcome, NIH Stroke Scale (NIHSS) Score at 24 Hours, Recanalization, and Follow-Up infarct Volume According to White Matter Lesion (WML) Severity

	Functional outcome, acOR (95% CI)	NIHSS 24 hours,[a] aβ (95% CI)	Recanalization,[b] acOR (95% CI)	Follow-up infarct volume,[c] aβ (95% CI)
Intervention vs control group				
Total sample (n = 473)				
Model 1	1.69 (1.22–2.34)	−2.73 (−4.21 to −1.25)	5.05 (3.29–7.74)	−0.24 (−0.49 to 0.01)
Model 2	1.68 (1.21–2.33)	−2.74 (−4.22 to −1.26)	5.13 (3.33–7.90)	−0.25 (−0.50 to 0.00)
Model 3	1.84 (1.32–2.59)	−2.52 (−3.76 to −1.28)	5.47 (3.51–8.52)	−0.25 (−0.47 to −0.03)
Absent to moderate WML (n = 366)				
Model 1	1.82 (1.26–2.65)	−3.18 (−4.79 to −1.57)	5.09 (3.14–8.25)	−0.35 (−0.63 to −0.08)
Model 2	1.81 (1.24–2.64)	−3.27 (−4.88 to −1.64)	5.20 (3.18–8.51)	−0.37 (−0.65 to −0.10)
Model 3	1.93 (1.31–2.84)	−2.90 (−4.22 to −1.57)	5.42 (3.26–9.04)	−0.37 (−0.61 to −0.12)
Severe WML (n = 107)				
Model 1	1.49 (0.74–3.00)	−1.48 (−5.01 to 2.05)	4.95 (1.95–12.53)	0.15 (−0.40 to 0.70)
Model 2	1.44 (0.71–2.92)	−1.51 (−5.12 to 2.10)	5.67 (2.14–15.03)	0.24 (−0.32 to 0.80)
Model 3	1.95 (0.90–4.20)	−1.89 (−5.11 to 1.33)	9.33 (3.05–28.58)	0.19 (−0.33 to 0.71)

Abbreviations: aβ = adjusted β; acOR = adjusted common odds ratio; CI = confidence interval.
Model 1 = adjusted for age and sex; model 2 = model 1 plus adjustments for smoking, diabetes mellitus, atrial fibrillation, myocardial infarction, and history of hypertension; model 3 = model 2 plus adjustments for prestroke modified Rankin Scale score, NIHSS at baseline, occlusion of the internal carotid terminus, Alberta Stroke Program Early CT Score on baseline noncontrast CT (NCCT), collateral status on baseline CT angiography (CTA), and time to randomization.
[a] NIHSS at 24 hours missing for 19 patients.
[b] Recanalization on follow-up CTA at 24 hours was missing for 106 patients.
[c] Follow-up infarct volume on NCCT at 5–7 days was missing for 46 patients.

Figure Modified Rankin Scale (mRS) Score at 90 Days Follow-Up According to Treatment Allocation and White Matter Lesions (WML) Severity



White numbers in the bars indicate absolute number of patients per subgroup. Effect measure is the adjusted common odds ratio (acOR) for a shift in distribution on the mRS in favor of intervention. CI = confidence interval.

severe WML who received EVT (respectively, 61% vs 52%; p = 0.31; table 3). In patients with absent to moderate WML, EVT resulted in smaller follow-up infarct volumes compared to controls (respectively, median volume, 51 vs 77 mL; p = 0.02; table 3). In patients with severe WML, no difference in follow-up infarct volumes was observed between the intervention and control group (respectively, median volume, 87 vs 80 mL; p = 0.74; table 3). As a result, we found a strong indication for the presence of effect modification by WML on follow-up infarct volume (p for interaction = 0.05; table 5). Rates of serious adverse events were higher in patients with severe WML (table 6), but we observed no significant difference in the occurrence of sICH compared to patients with absent to moderate WML (p = 0.66).

Discussion

This study shows that patients with more severe WML have worse functional outcomes after AIS due to an LVO. Recent studies have described a similar adverse association between WML severity and functional outcome in patients post-EVT.[5–7] Given the lack of a control group, however, they were unable to determine whether patients with severe WML could still benefit from EVT. Or, in other words, modification of treatment effect by WML could not be assessed. Previous post hoc analyses of the National Institute of Neurological Disorders and Stroke rtPA Stroke Study and third International Stroke Trial (IST-3), focusing on IVT, found no interaction between WML and IVT treatment effect.[22,23] We demonstrate that patients with severe WML have similar treatment benefit from EVT as those with absent to moderate WML. Hence, WML do not modify the effect of EVT on functional outcome.

To gain a better understanding of how WML contribute to poor functional outcome, additional analyses were performed. We found that EVT had a larger effect on follow-up infarct volumes in patients with absent to moderate WML compared to patients with severe WML. This is a relevant finding, because follow-up infarct volume is considered a predictor of functional outcome and infarct volume after EVT partly explains treatment benefit.[24] Correspondingly, prior studies have shown that severe WML is associated with susceptibility to infarct growth[8] and larger cortical infarct volumes.[9] This finding may be explained by the poorer collateral status in patients with severe WML demonstrated here, important for tissue survival but also functional outcome.[2,25] Previous studies investigating the association between WML and collateral status present contradicting findings, reporting similar results[26] while others describe no association.[27] However, different methods were used to assess WML severity (volumetric or Fazekas scale) and collaterals (5-point scale on CTA or angiography) as opposed to the current study, making direct comparisons unreliable. Nevertheless, it is plausible that patients with severe WML have worse collateral status due to underlying cerebrovascular changes related to cerebral small vessel disease

Table 5 *p* Values of Interaction Terms Between Treatment Allocation and White Matter Lesion Severity

	Functional outcome	NIHSS at 24 hours	Recanalization	Follow-up infarct volume
Model 1	0.79	0.34	0.97	0.10
Model 2	0.81	0.29	0.92	0.05
Model 3	0.85	0.29	0.97	0.05

Abbreviations: NIHSS = NIH Stroke Scale.
Model 1 = adjusted for age and sex; model 2 = model 1 plus adjustments for smoking, diabetes mellitus, atrial fibrillation, myocardial infarction, and history of hypertension; model 3 = model 2 plus adjustments for prestroke modified Rankin Scale score, NIHSS at baseline, occlusion of the internal carotid terminus, Alberta Stroke Program Early CT Score on baseline noncontrast CT, collateral status on baseline CT angiography, and time to randomization.

(cSVD), a disease of which WML are a major radiologic hallmark.[28] Furthermore, it is known that cSVD affects cerebral arterioles and capillaries causing decreased microvascular reactivity, narrowing of the vessel lumen, or even occlusion.[28] It could be that in patients with severe WML, due to loss of patency of vascular anastomoses required for adequate collateral circulation, recruitment of leptomeningeal collaterals is limited. Another factor possibly influencing infarct growth in patients with severe WML is cerebral hypoperfusion related to cSVD. A recent study using MRI to assess WML and to measure cerebral blood flow demonstrated that there is a close relationship between decreased cerebral blood flow values in WML and the surrounding normal-appearing white matter.[29] Patients with severe WML may therefore be less resilient to ischemia, thereby facilitating early infarct progression in the event of an AIS. Our findings support this hypothesis, showing that effect of EVT on follow-up infarct volume diminished in patients with severe WML despite similar time to treatment and successful recanalization rates as patients with absent to moderate WML.

In patients treated with EVT, recanalization rates on DSA were similar for patients with absent to moderate and severe WML. In line with previous findings, patients with severe WML were less likely to achieve good functional outcome despite successful recanalization on posttreatment DSA (mTICI 2B-3).[6,30] Previous studies have demonstrated that WML is associated with increased platelet activation[31] and hypercoagulability.[32] These mechanisms could, next to microvascular dysfunction related to cSVD, contribute to impaired restoration of microvascular reperfusion after successful recanalization and possibly help to explain worse outcomes in patients with severe WML. More importantly, several studies have shown that successful microvascular reperfusion is an even stronger predictor of tissue survival and functional outcome compared to reopening of an occluded large intracranial vessel.[33,34] On the other hand, worse outcomes in patients with severe WML may also be explained by increased comorbidity and increased risk of adverse events in these patients. We found that cardiovascular and prognostic risk factors were more prevalent in patients with severe WML, yet equally distributed between treatment groups (data not shown). Furthermore, we found that patients with severe WML more often had recurrent strokes and pneumonias, likely attributing to poorer functional outcome.[35]

In a larger cohort and in the setting of IVT, severe WML was associated with increased risk of sICH.[36] We observed similar rates of sICH irrespective of treatment allocation and WML severity, corresponding to previous results.[5–7] Current and previous studies, however, were not designed to investigate the association between WML and risk of sICH and thus not adequately powered. Future research in larger cohorts is needed to establish whether this association exists for EVT-eligible patients.

Our study has several strengths. First, we used data from the MR CLEAN trial, which included a well-defined population with broad inclusion criteria, making current results applicable to a large part of the general stroke population. Second, in contrast to prior studies,[5–7] we incorporated both patients treated with EVT and controls who did not receive EVT. This allowed us to evaluate the benefit of EVT in patients with different WML burden and to assess whether the effect of EVT is modified by WML. Third, treatment allocation was randomized, thereby limiting potential selection bias and reducing confounding. Yet, since patients included in the MR

Table 6 Serious Adverse Events (SAEs) According to Treatment Allocation and White Matter Lesion (WML) Severity

	Absent to moderate WML, n (%)		Severe WML, n (%)	
	Intervention (n = 170)	Control (n = 196)	Intervention (n = 52)	Control (n = 55)
Any SAE[a,b]	67 (39.4)	76 (38.8)	35 (67.3)	30 (54.5)
sICH	12 (7.1)	11 (5.6)	4 (7.7)	4 (7.3)
Extracranial hemorrhage	0 (0)	1 (0.5)	1 (1.9)	1 (1.8)
Progression of stroke	30 (17.6)	34 (17.3)	13 (25)	11 (20.0)
Recurrent stroke[a]	6 (3.5)	1 (0.5)	7 (13.5)	0 (0)
Cardiac ischemia	0 (0)	3 (1.5)	1 (1.9)	1 (1.8)
Pneumonia[a]	13 (7.6)	27 (13.8)	12 (23.1)	16 (29.1)
Other infection	10 (5.9)	4 (2.0)	4 (7.7)	5 (9.1)

Abbreviation: sICH = symptomatic intracranial hemorrhage.
[a] Significant difference between patients with absent to moderate and severe WML $p < 0.05$.
[b] Only first event of 1 type was counted.

CLEAN trial were not randomized based on WML severity, there may still be unequal distribution of other unmeasured confounders between treatment groups. Limitations of our study include the visual scoring method used to assess WML and dichotomization of severity. A more quantitative approach could provide more accurate estimations of individual WML burden. Nevertheless, our results remained unchanged after performing a sensitivity analysis and are consistent with those using quantitative measurements of WML.[7] In addition, software for automated WML quantification still needs to be approved for use in routine clinical practice, making the VSS currently more applicable for clinicians. Furthermore, this study is hypothesis-generating but does not provide evidence for the causal relationship between WML and functional outcome. Future research is needed to provide more insight into pathophysiologic mechanisms linked to cSVD and their relationship with poststroke functional outcome.

Our findings confirm that WML severity is an important independent predictor of poor functional outcome but does not modify the effect of EVT. In current clinical practice, WML severity may be helpful for evaluating prognosis in patients with AIS but should not play a role in selecting eligible patients for EVT.

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Disclosure

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Kars C.J. Compagne, BSc	Erasmus MC, Rotterdam, the Netherlands	Study concept and design, acquisition of data, statistical analysis, analysis or interpretation of data, drafting/revising the manuscript
Lennard Wolff, MD	Erasmus MC, Rotterdam, the Netherlands	Study concept and design, revised the manuscript
Charles B.L.M. Majoie, MD, PhD	Academic Medical Center, Amsterdam, the Netherlands	Major role in the acquisition of data, revised the manuscript
Yvo B.W.E.M. Roos, MD, PhD	Academic Medical Center, Amsterdam, the Netherlands	Major role in the acquisition of data, revised the manuscript
Wim H. van Zwam, MD, PhD	Maastricht University Medical Center, the Netherlands	Major role in the acquisition of data, revised the manuscript
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Aad van der Lugt, MD, PhD	Erasmus MC, Rotterdam, the Netherlands	Major role in the acquisition of data, analysis or interpretation of data, drafting/revising the manuscript
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B250

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