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Published in:
Journal of Neurointerventional Surgery

DOI:
[10.1136/neurintsurg-2021-018545](https://doi.org/10.1136/neurintsurg-2021-018545)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

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

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

MR CLEAN Registry Investigators, Uniken Venema, S. M., Dankbaar, J. W., Wolff, L., van Es, A. C. G. M., Sprengers, M., van der Lugt, A., Dippel, D. W. J., & van der Worp, H. B. (2023). Collateral status and recanalization after endovascular treatment for acute ischemic stroke. *Journal of Neurointerventional Surgery*, 15(6), 531-538. Advance online publication. <https://doi.org/10.1136/neurintsurg-2021-018545>

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Original research

Collateral status and recanalization after endovascular treatment for acute ischemic stroke

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/neurintsurg-2021-018545>).

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Received 14 December 2021

Accepted 2 May 2022

Published Online First

18 May 2022



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To cite: Uniken Venema SM, Dankbaar JW, Wolff L, et al. *J NeuroIntervent Surg* 2023;**15**:531–538.

ABSTRACT

Background Successful recanalization and good collateral status are associated with good clinical outcomes after endovascular treatment (EVT) for acute ischemic stroke, but the relationships among them are unclear.

Objective To assess if collateral status is associated with recanalization after EVT and if collateral status modifies the association between successful recanalization and functional outcome.

Methods We retrospectively analyzed data from the MR CLEAN Registry, a multicenter prospective cohort study of patients with a proximal anterior occlusion who underwent EVT in the Netherlands. We determined collateral status with a previously validated four-point visual grading scale and defined successful recanalization as an extended Thrombolysis in Cerebral Infarction score $\geq 2B$. Functional outcome was determined using the modified Rankin Scale score at 90 days. We assessed, with multivariable logistic regression models, the associations between (1) collateral status and successful recanalization, (2) successful recanalization and functional outcome, (3) collateral status and functional outcome. An interaction of collateral status and successful recanalization was assessed. Subgroup analyses were performed for patients treated with intravenous thrombolysis.

Results We included 2717 patients, of whom 1898 (70%) had successful recanalization. There was no relationship between collateral status and successful recanalization (adjusted common OR (95% CI) of grades 1, 2, and 3 vs 0: 1.19 (0.82 to 1.72), 1.20 (0.83 to 1.75), and 1.10 (0.74 to 1.63), respectively). Successful recanalization (acOR (95% CI): 2.15 (1.84 to 2.52)) and better collateral grades (acOR (95% CI) of grades 1, 2, and 3 vs 0: 2.12 (1.47 to 3.05), 3.46 (2.43 to 4.92), and 4.16 (2.89 to 5.99), respectively) were both associated with a shift towards better functional outcome, without an interaction between collateral status and successful recanalization. Results were similar for the subgroup of thrombolysed patients.

Conclusions Collateral status is not associated with the probability of successful recanalization after EVT and does not modify the association between successful recanalization and functional outcome.

INTRODUCTION

Successful recanalization^{1 2} and good collateral status^{3 4} are strongly associated with favorable clinical outcomes after endovascular treatment (EVT) for acute ischemic stroke. Some studies have suggested that good collateral status at baseline is associated with a higher probability of vessel recanalization and tissue reperfusion of the downstream territory after intravenous thrombolysis^{5 6} or EVT,^{7–9} including two recent studies with successful recanalization rates between 85% and 90%.^{10 11} Sufficient flow into collateral vessels may enhance the delivery of thrombolytics to the distal end of the clot⁷ and may prevent detached thrombus segments from occluding more distal vessels.¹⁰ Moreover, it has been suggested that collateral status modifies the relationship between successful reperfusion and functional outcome, in such a way that collateral status and successful reperfusion synergistically contribute to a better outcome.^{12–14} A more recent study did however not confirm this.¹¹

It therefore remains uncertain if, and to what extent, collateral status facilitates recanalization in current practice and if collateral status modifies the association between successful recanalization and functional outcome. We addressed these questions by analyzing data from the MR CLEAN Registry, a multicenter prospective cohort study of patients treated with EVT in routine clinical practice in the Netherlands.

METHODS

Study protocol and patients

The Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) Registry is a prospective, multicenter, observational study of patients with acute ischemic stroke treated with EVT in the Netherlands. The present retrospective study is based on data from patients with acute ischemic stroke included in the MR CLEAN Registry between March 16, 2014 and November 1, 2017 who fulfilled the following criteria: (1) age 18 years or older, (2) EVT initiated within 6.5 hours of symptom onset or last seen well, (3) availability of an extended Thrombolysis in Cerebral Infarction (eTICI) score at the end of EVT, as assessed on two-dimensional (anteroposterior and lateral) digital subtraction angiography (DSA) runs, (4) presence of a proximal arterial

occlusion in the anterior circulation at baseline (internal carotid artery (ICA, ICA-terminus), middle (M1, M2) cerebral artery), confirmed with CT angiography (CTA). EVT was performed as part of routine clinical care and the exact procedure following groin puncture and catheterization to the level of occlusion (ie, mechanical thrombectomy, thrombus aspiration, or both, with or without the use of a thrombolytic agent) was left at the discretion of the treating interventionalist.

The study protocol of the MR CLEAN Registry was approved by the Erasmus University Medical Center ethics committee and permission was granted to carry out the study as a registry (MEC-2014–235). The requirement for written informed consent was waived, but patients were provided with information on the study and were given the opportunity to refuse participation. Source data from patients cannot be distributed, but syntax and output files from statistical analyses can be made available on reasonable request to the corresponding author.

Assessment of clinical and imaging data

Clinical data were collected from electronic patient records at the recruiting centers by local study investigators. The score on the modified Rankin Scale (mRS), an ordinal disability scale ranging from 0 (no symptoms) to 6 (death), was assessed at 90 days (± 14 days) after stroke through a telephone interview. Neuroimaging data were centrally analyzed by an imaging core laboratory consisting of trained neuroradiologists and interventionalists, blinded to all clinical findings except the symptom side. Collateral status on baseline CTA was determined using a previously validated scoring method.¹⁵ This is a four-point visual grading scale, with 0 for absent collaterals (0% filling of the vascular territory downstream of the occlusion), 1 for poor collaterals ($>0\%$ and $\leq 50\%$ filling), 2 for moderate collaterals ($>50\%$ and $<100\%$ filling), and 3 for excellent collaterals (100% filling). Interobserver agreement for this method has previously been determined and was moderate ($k=0.60$).³ The extent of antegrade recanalization of the previously occluded vascular territory at the end of EVT was assessed on DSA using the eTICI score.¹⁶ A score of 2B or higher, indicating antegrade recanalization of more than half of the previously occluded target artery ischemic territory (eg, in two major divisions of the middle cerebral artery (and their territories), was considered successful recanalization. Time from symptom onset to the end of EVT was defined as the moment at which successful recanalization was achieved or, if not applicable, the moment the last contrast bolus was given.

Outcomes

The primary outcome was successful recanalization (eTICI $\geq 2B$). Secondary outcomes were complete recanalization (eTICI of 3), post-EVT eTICI score (as an ordinal outcome variable), spontaneous recanalization (eTICI $\geq 2B$ prior to EVT on diagnostic DSA), first pass effect (defined as the achievement of near-complete or complete (eTICI 2C–3) recanalization after a single pass of the device, without rescue by intra-arterial thrombolysis) and the score on the mRS at 90 days post-stroke.

Statistical analysis

Baseline characteristics were compared between patients in whom successful recanalization was achieved (eTICI $\geq 2B$) versus those without successful recanalization (eTICI $\leq 2A$). We assessed the relationship between collateral status and recanalization outcomes (successful recanalization, complete recanalization, ordinal eTICI score, spontaneous recanalization, and first pass effect) using multivariable binary or ordinal logistic regression

adjusted for potential confounders. For ordinal outcome variables, we tested the proportional odds assumption and, if not violated, we used ordinal logistic regression. To assess the possibility of a differential effect of collateral status on recanalization by occlusion location, we added an interaction term (collateral status \times occlusion location). If the interaction test was significant, we performed subgroup analyses by occlusion location.

We then assessed the relationship between successful recanalization and functional outcome, as assessed with the mRS score at 90 days, in a multivariable ordinal logistic regression model. We added an interaction term for collateral status (successful recanalization \times collateral status). If the model containing the interaction terms performed significantly better than the model without, as assessed with a likelihood ratio test, we then repeated the analysis in subgroups of patients according to recanalization status. All multivariable models were adjusted for age, systolic blood pressure on admission, Alberta Stroke Program Early CT Score at baseline, extracranial carotid artery disease, occluded segment, and time from symptom onset to recanalization.

Subgroup analyses were performed for patients treated with intravenous alteplase prior to EVT. Sensitivity analyses were performed for the subgroup of patients undergoing intra-arterial thrombectomy. In all models, collateral status was analyzed as an ordinal independent variable, with absent collaterals (grade 0) as a reference category and effect estimates—adjusted common ORs (acOR) and 95% confidence intervals (CIs)—were calculated for collateral grades 1, 2, and 3 compared with grade 0. In sensitivity analyses, collateral status was analyzed as a numeric independent variable, and effect estimates were calculated for each one-point increase in collateral grade. All analyses were done using R software (version 1.3.1093). In order to obtain unbiased effect estimates, missing data (assumed to be missing at random) were imputed with multiple imputations ($n=5$) using the *AregImpute* function. All multivariable analyses were done using imputed data.

RESULTS

Patient characteristics

Of 3279 patients included in the MR CLEAN Registry, 2717 patients were included in the present study (online supplemental figure 1). Successful recanalization at the end of EVT was achieved in 1898 patients (70%). Those with successful recanalization were younger, had a lower systolic blood pressure on admission, less frequently had a history of atrial fibrillation, and used coumarins or direct oral anticoagulants less frequently (table 1). ICA or ICA-T occlusions were more frequent in those with unsuccessful recanalization, whereas those with successful recanalization more frequently had an M1 occlusion. Time from symptom onset to the end of EVT was shorter in those with successful recanalization. Finally, patients with successful recanalization more often underwent general anesthesia and were less frequently treated during shift hours. A total of 411 patients did not undergo intra-arterial thrombectomy (IAT) due to the inability to obtain intracranial access (164 patients), spontaneous recanalization (244 patients) or for an unknown reason (3 patients). The remaining 2306 patients all underwent IAT, 1704 of whom (74%) had successful recanalization.

Relationship between collaterals and recanalization

In univariable analysis, there was no statistically significant association between collateral grades and the probability of successful recanalization (online supplemental table 1), and

Table 1 Baseline characteristics according to recanalization status post-EVT

	Unsuccessful recanalization* (n=819)	Successful recanalization† (n=1898)	P value
Age, median (IQR)	74 (63–82)	71 (61–80)	<0.01
Men, n (%)	417 (50.9)	1000 (52.7)	0.42
NIHSS, median (IQR)	16 (12–20)	16 (11–19)	0.31
SBP, mm Hg; mean (SD)	152 (26)	149 (24)	0.01
Glucose, mmol/L; median (IQR)	6.8 (5.9–8.2)	6.8 (5.9–8.0)	0.72
Diabetes mellitus, n (%)	131 (16.0)	306 (16.2)	0.99
Hypertension, n (%)	425 (52.9)	958 (51.6)	0.56
Atrial fibrillation, n (%)	218 (27.0)	423 (22.6)	0.02
Myocardial infarction, n (%)	98 (12.2)	269 (14.5)	0.14
Peripheral artery disease, n (%)	78 (9.8)	164 (8.8)	0.45
Ischemic stroke, n (%)	148 (18.2)	307 (16.3)	0.25
Hypercholesterolemia, n (%)	227 (29.1)	566 (31.1)	0.32
Pre-stroke mRS score ≤ 2 , n (%)	691 (86.5)	1652 (89.1)	0.07
Statin use, n (%)	278 (34.7)	680 (36.7)	0.33
Antiplatelet use, n (%)	250 (30.9)	594 (31.7)	0.70
Coumarin use or DOAC, n (%)	150 (18.5)	283 (15.1)	0.03
Antihypertensive use, n (%)	433 (54.0)	1005 (54.0)	1.00
Current smoking, n (%)	170 (26.3)	413 (28.4)	0.33
Left hemisphere, n (%)	391 (47.8)	881 (46.4)	0.11
Occluded segment, n (%)			0.01
ICA	53 (6.8)	81 (4.4)	
ICA-T	177 (22.8)	366 (20.0)	
M1	430 (55.3)	1118 (61.2)	
M2	118 (15.2)	262 (14.3)	
Symptomatic carotid stenosis, n (%)			0.26
<50% stenosis at carotid bifurcation	564 (78.9)	1367 (81.3)	
$\geq 50\%$ stenosis at carotid bifurcation	66 (9.2)	152 (9.0)	
Occlusion at carotid bifurcation	85 (11.9)	163 (9.7)	
ASPECTS on NCCT, median (IQR)	9 (7–10)	9 (8–10)	0.86
Collaterals, n (%)			0.23
Grade 0	53 (6.9)	101 (5.6)	
Grade 1	272 (35.5)	647 (36.2)	
Grade 2	288 (37.6)	707 (39.5)	
Grade 3	153 (20.0)	334 (18.7)	
Intravenous alteplase, n (%)	618 (77.8)	1461 (77.3)	0.45
Time from onset to ER, min; median (IQR)	55 (40–101)	57 (37–95)	0.47
Time from onset to groin puncture, min; median (IQR)	196 (150–262)	190 (150–245)	0.06
Time from onset to successful recanalization, min; median (IQR)	270 (216–334)	240 (191–300)	<0.01
General anesthesia, n (%)	167 (21.9)	524 (29.1)	<0.01
Treatment during shift hours, n (%)	540 (65.9)	1180 (62.2)	0.06

*Post-EVT eTICI 0, 1, or 2A;

†Post-EVT eTICI 2B, 2C, or 3.

ASPECTS, Alberta Stroke Program Early CT Score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; M1/M2, middle cerebral artery; mRS, modified Rankin Scale; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

this did not change after adjusting for potential confounders (table 2). The analyses for secondary outcomes showed consistent results (online supplemental table 1, table 2). Excellent collaterals (grade 3) were borderline associated with complete recanalization (eTICI 3) after EVT (acOR 1.49, 95% CI 0.99 to 2.25). Results were similar for the

subgroup of 2079 patients treated with intravenous alteplase prior to EVT and in the sensitivity analysis of 2306 patients who underwent IAT (online supplemental table 1, table 3). Results were also similar in sensitivity analyses with collateral grade as a numeric independent variable (online supplemental table 2).

Table 2 Multivariable associations of collateral grade with recanalization in all patients

	Collateral grade	n/N	acOR (95% CI)	P value
Primary outcome				
Successful recanalization*	0	101/154	Reference	-
	1	647/919	1.19 (0.82 to 1.72)	0.37
	2	707/995	1.20 (0.83 to 1.75)	0.33
	3	334/487	1.10 (0.74 to 1.63)	0.64
Secondary outcomes				
Complete recanalization†	0	42/154	Reference	-
	1	292/919	1.21 (0.82 to 1.78)	0.35
	2	323/995	1.25 (0.85 to 1.84)	0.26
	3	174/487	1.49 (0.99 to 2.25)	0.05
eTICI score (ordinal)	0	N/A	Reference	-
	1	N/A	1.14 (0.84 to 1.56)	0.4
	2	N/A	1.19 (0.87 to 1.61)	0.27
	3	N/A	1.22 (0.88 to 1.68)	0.23
Spontaneous recanalization‡	0	12/154	Reference	-
	1	68/919	0.73 (0.37 to 1.41)	0.34
	2	89/995	0.82 (0.43 to 1.57)	0.55
	3	51/487	0.91 (0.46 to 1.82)	0.79
First pass effect	0	26/116	Reference	-
	1	173/692	0.88 (0.55 to 1.41)	0.6
	2	184/751	0.91 (0.58 to 1.43)	0.68
	3	103/357	1.21 (0.69 to 2.11)	0.5

Collateral grade is treated as an ordered predictor variable in all analyses. Binary or ordinal logistic regression models were used. Effect estimates are adjusted common ORs for collateral grade 1 compared with 0, 2 compared with 0, and 3 compared with 0 (grade 0 being the reference category). Analyses were adjusted for age, blood pressure on admission, Alberta Stroke Program Early CT Score at baseline, extracranial carotid artery disease, occluded segment, and time from onset to recanalization (or last contrast bolus).
 *eTICI \geq 2B after EVT.
 †eTICI 3 after EVT.
 ‡eTICI 2B–3 on diagnostic DSA.
 eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment.

Relationship between recanalization and functional outcome

In multivariable analysis, both successful recanalization (acOR 2.15, 95% CI 1.84 to 2.52) and better collateral grades (grade 1 vs 0, acOR 2.12, 95% CI 1.47 to 3.05; grade 2 vs 0, acOR 3.46, 95% CI 2.43 to 4.92; grade 3 vs 0, acOR 4.16, 95% CI 2.89 to 5.99) were independently associated with a shift towards good functional outcome. Patients with unsuccessful recanalization and absent (grade 0) collaterals had the poorest outcomes (6% functional independence), whereas the best outcomes were achieved by those with successful recanalization and excellent (grade 3) collaterals (61% functional independence). There was no interaction between collateral grades and successful recanalization (likelihood ratio test $p=0.78$). Figure 1 depicts the distribution of mRS scores according to collateral grades and recanalization status after EVT.

Results for the subgroup analysis of patients treated with intravenous alteplase were similar: successful recanalization (acOR 2.24, 95% CI 1.87 to 2.71) and better collateral grades (grade 1 vs 0, acOR 2.06, 95% CI 1.37 to 3.09; grade 2 vs 0, acOR 3.34, 95% CI 2.23 to 4.99; grade 3 vs 0, acOR 3.92, 95% CI 2.59 to 5.93) were independently associated with a shift towards favorable functional outcome and there was no interaction between those variables. Similar results were also found for patients undergoing IAT (acOR for collateral grade 1 vs 0, 2.46, 95% CI 1.72 to 3.53; grade 2 vs 0, acOR 4.09, 95% CI 2.84 to 5.89; grade 3 vs 0, acOR 4.61, 95% CI 3.10 to 6.85; acOR for

successful recanalization, 1.99, 95% CI 1.67 to 2.37, without a statistical interaction).

Results were similar when collateral status was analyzed as a numeric independent variable in all patients (acOR for a shift towards good functional outcome: 1.51, 95% CI 1.38 to 1.65 per one-point increase in collateral grade; 2.18, 95% CI 1.84 to 2.58 for successful recanalization), in the subgroup of patients treated with intravenous thrombolysis (cOR for a shift towards good functional outcome: 1.48, 95% CI 1.34 to 1.65 per one-point increase in collateral grade; 2.28, 95% CI 1.88 to 2.77 for successful recanalization), and in the subgroup of patients undergoing IAT (cOR for a shift towards good functional outcome: 1.52, 95% CI 1.37 to 1.68 per one-point increase in collateral grade; 2.01, 95% CI 1.66 to 2.43 for successful recanalization), without interactions between collateral status and successful recanalization.

DISCUSSION

In this large cohort of patients with large vessel occlusion treated with EVT, there was no relation between collateral status at baseline and the probability of spontaneous recanalization before EVT or successful recanalization after EVT. Higher collateral grades and successful recanalization were each associated with better functional outcome, but there was no statistical interaction between these variables. This suggests that achieving successful recanalization after EVT is similarly beneficial for patients with

Table 3 Multivariable associations of collateral grade with recanalization in patients who were treated with intravenous thrombolysis (n=2079) and patients who underwent intra-arterial treatment (n=2306)

	IVT subgroup				IAT subgroup		
	Collateral grade	n/N	acOR (95% CI)	P value	n/N	acOR (95% CI)	P value
Successful recanalization*	0	72/109	Reference	–	89/131	Reference	–
	1	515/712	1.26 (0.80 to 1.98)	0.32	596/796	1.36 (0.90 to 2.05)	0.14
	2	537/758	1.17 (0.74 to 1.83)	0.5	636/847	1.38 (0.91 to 2.10)	0.13
	3	250/317	0.99 (0.62 to 1.59)	0.97	295/411	1.23 (0.78 to 1.92)	0.37
Complete recanalization†	0	29/109	Reference	–	41/131	Reference	–
	1	241/712	1.36 (0.86 to 2.17)	0.19	280/796	1.12 (0.75 to 1.67)	0.58
	2	240/758	1.26 (0.79 to 1.99)	0.33	315/847	1.23 (0.83 to 1.83)	0.31
	3	128/371	1.43 (0.89 to 2.32)	0.14	165/411	1.45 (0.94 to 2.22)	0.09
eTICI score (ordinal)	0	N/A	Reference	–	N/A	Reference	–
	1		1.24 (0.86 to 1.79)	0.25		1.16 (0.84 to 1.62)	0.36
	2		1.14 (0.80 to 1.64)	0.46		1.26 (0.90 to 1.76)	0.17
	3		1.11 (0.76 to 1.63)	0.58		1.27 (0.89 to 1.82)	0.19
Spontaneous recanalization‡	0	12/109	Reference	–	N/A	N/A	N/A
	1	60/712	0.61 (0.31 to 1.19)	0.14			
	2	79/758	0.73 (0.37 to 1.41)	0.35			
	3	44/371	0.78 (0.39 to 1.57)	0.49			
First pass effect	0	20/79	Reference	–	26/116	Reference	–
	1	144/533	0.81 (0.47 to 1.41)	0.46	173/692	0.99 (0.58 to 1.69)	0.96
	2	142/551	0.78 (0.46 to 1.32)	0.36	184/751	1.00 (0.59 to 1.69)	0.99
	3	82/263	1.09 (0.57 to 2.10)	0.78	103/357	1.29 (0.70 to 2.37)	0.42

Collateral grade is treated as an ordered predictor variable in all analyses. Binary or ordinal logistic regression models were used. Effect estimates are adjusted common ORs for collateral grade 1 compared with 0, 2 compared with 0, and 3 compared with 0 (grade 0 being the reference category). Analyses were adjusted for age, blood pressure on admission, Alberta Stroke Program Early CT Score at baseline, extracranial carotid artery disease, occluded segment, and time from onset to recanalization (or last contrast bolus)

*eTICI \geq 2B after EVT.
†eTICI 3 after EVT.
‡eTICI 2B–3 on diagnostic DSA.
eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; IAT, intra-arterial treatment; IVT, intravenous thrombolysis.

different collateral grades at baseline. As expected, the best outcomes were achieved by those with the highest collateral grade who were successfully recanalized during EVT (61% functional independence).

Our findings contradict several previous studies, including two studies with recruitment periods similar to ours,^{10 11} that found an association between good collateral status and better tissue reperfusion or vessel recanalization after IV thrombolysis (IVT) alone^{5 6 17} or EVT with or without prior IVT.^{7–11 18} We tested the hypothesis that the collateral circulation may facilitate the delivery of thrombolytics to the distal end of the clot, thereby enhancing recanalization, but we also found no association in the subgroup of patients treated with IVT. The absence of an association between collateral status and recanalization appeared to be independent of occlusion location. Most previous studies differed from ours in their dichotomization of collateral status into good versus poor, whereas we analyzed collateral status with the full ordinal scale in order to be able to detect a trend. Moreover, some studies used different imaging modalities and a local, rather than central, assessment of imaging variables. Nonetheless, we cannot fully explain the absence of a previously established relationship between collateral status and the probability of achieving successful recanalization during EVT.

Sufficient flow into collateral vessels can preserve viability of the downstream territory until recanalization occurs, so it has been hypothesized that the effect of collateral status on outcome

is greater for recanalized patients than for non-recanalized patients. Vice versa, achieving successful recanalization may be more beneficial for those with a good collateral status than for those with a poor collateral status. This hypothesis was confirmed in the Interventional Management of Stroke III trial, where better collateral grades were strongly associated with a good functional outcome only in patients with recanalization (modified TICI \geq 2), but not in those without recanalization.⁷ Several additional studies suggested a similar effect modification.^{9 12–14 19} By contrast, we found no interaction between collateral grades and successful recanalization in the analysis for functional outcome. This suggests that the effect of successful recanalization on functional outcome is similar for all collateral grades and there is no synergistic effect of the two. Our finding is in line with several previous studies,^{11 20 21} including a recent analysis from 2020 patients in the multicenter Endovascular Treatment in Ischemic Stroke (ETIS) Registry, the previously mentioned ETIS study.¹¹ The comparability of the studies is limited because of the use of various different grading scales for collateral status.

Of note, our rate of successful recanalization after EVT of 70% was lower than that in most previous studies, with recent studies reporting rates as high as 85% to 90%.^{10 11 22 23} In contrast to most registries, patients eligible for EVT were included consecutively in our registry so our cohort represents an unselected group of EVT-eligible patients, which could explain the difference.

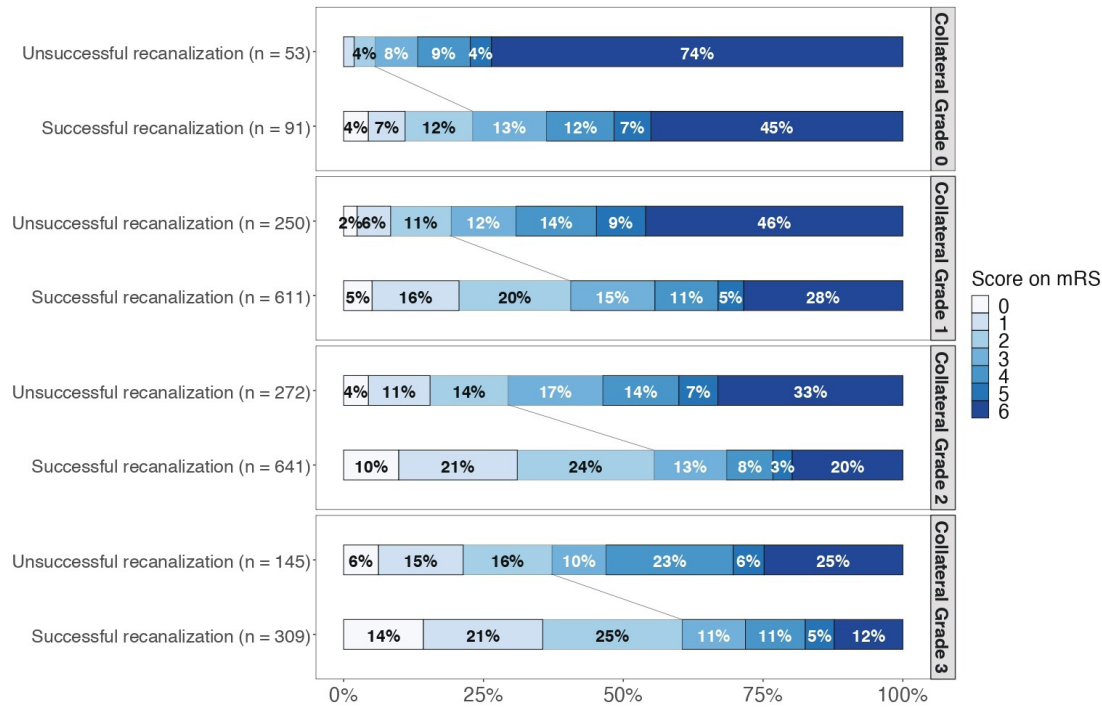


Figure 1 Distribution of modified Rankin Scale scores at 90 days according to collateral grades and recanalization status post-EVT. Lines indicate the difference between functional independence (mRS score ≤ 2) and no functional independence (mRS score ≥ 3). The benefit of successful recanalization on the mRS score is approximately equal in all collateral grade groups (as indicated by the parallel lines), suggesting that no effect modification is present. mRS, modified Rankin Scale.

The main strengths of this study are the large sample size and the fact that imaging data were prospectively collected and analyzed centrally by a core laboratory of trained neuroradiologists. Limitations include the use of single-phase CTA to assess collateral status, which could have led to misclassification of collateral status in cases of early or late imaging acquisition.²⁴ However, differential misclassification is unlikely and therefore it is doubtful that it influenced our results. Second, we measured only vessel recanalization—the reinstatement of antegrade flow in the affected vascular territory—using angiography. Since vessel recanalization does not always result in subsequent tissue reperfusion, the latter being assessed with perfusion imaging, we cannot exclude the possibility that the results of this study might have been different if we had measured reperfusion. Nonetheless, in a previous study, the association between recanalization and reperfusion was similar regardless of collateral status.²⁵ Third, the primary analyses also included patients in whom no IAT attempt was made due to the inability to obtain intracranial access or spontaneous recanalization. However, sensitivity analyses of patients who did undergo IAT showed similar results, mitigating the concern that this could explain the neutral findings. Fourth, collateral status was analyzed both as an ordinal and as a numeric variable in our study, which differs from most previous studies that dichotomized collateral status and therefore direct comparisons cannot be made. However, our approach prevented the loss of information that results from merging collateral grade categories.

CONCLUSIONS

We found no evidence that better collateral status at baseline facilitates vessel recanalization after EVT. Successful recanalization and better collateral grades were independently associated with improved functional outcome, but there

was no statistical interaction between them. Therefore, the effect of successful recanalization on outcome appears to be independent of baseline collateral grade.

Acknowledgements We would like to thank the MR CLEAN Registry investigators; a complete list of the MR CLEAN Registry investigators is provided in the Appendix.

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Funding The MR CLEAN Registry was partly funded by TWIN (Toegepast Wetenschappelijk Instituut voor Neuromodulatie) Foundation, Erasmus MC Medical Center, Maastricht University Medical Center, and Academic Medical Center Amsterdam. Simone M. Uniken Venema performed this work as coordinator of the trial MR ASAP, which is funded by Netherlands Cardiovascular Research Initiative, an initiative from the Dutch Heart Foundation.

Competing interests Simone M. Uniken Venema, Jan Willem Dankbaar, Lennard Wolff, Adriaan C. G. M. van Es, Marieke Sprengers report no disclosures; Diederik W. J. Dippel: reports funding from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences and Health, and unrestricted grants from Penumbra Inc., Stryker, Medtronic, Cerenovus and Thrombolytic Science, LLC for research, all paid to his institution; Aad van der Lugt: reports funding from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences and Health, and unrestricted grants from Penumbra Inc., Stryker, Medtronic, Cerenovus, and Thrombolytic Science, LLC for research, all paid to his institution; H. Bart van

der Worp: received fees for consultation for Bayer and LivaNova, all paid to his institution.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Source data from patients cannot be distributed, but syntax and output files from statistical analyses can be made available upon reasonable request to the corresponding author.

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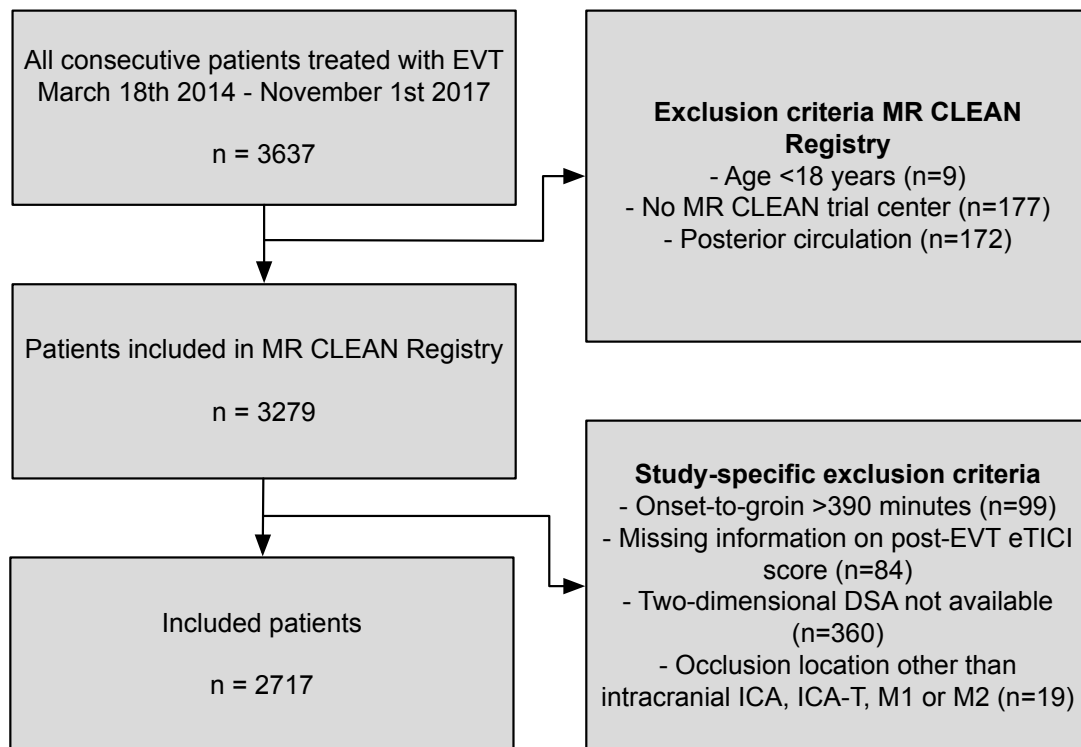
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Supplementary materials

**Collateral status and recanalization after endovascular treatment for acute
ischemic stroke.**



Supplementary Figure 1: Flowchart of patients through selection process.

EVT, endovascular treatment; MR CLEAN, Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke; eTICI, extended thrombolysis in cerebral infarction; DSA, digital subtraction angiography; ICA(-T), internal carotid artery (terminus).

Supplementary Table 1: Univariable associations of collateral grade with recanalization in all patients, patients treated with intravenous thrombolysis and patients treated with intra-arterial treatment.

	All patients			IVT subgroup			IAT subgroup		
	Collateral grade	(c)OR	P value	Collateral grade	(c)OR	P value	Collateral grade	(c)OR	P value
Primary outcome									
Successful recanalization*	0	Reference	-	0	Reference	-	0	Reference	-
	1	1.25 [0.87-1.81]	0.23	1	1.31 [0.84-2.06]	0.24	1	1.42 (0.95-2.11)	0.09
	2	1.29 [0.90-1.86]	0.17	2	1.23 [0.79-1.92]	0.35	2	1.43 (0.96-2.14)	0.08
	3	1.17 [0.79-1.71]	0.43	3	1.05 [0.66-1.68]	0.82	3	1.22 (0.79-1.87)	0.37
Secondary outcomes									
Complete recanalization†	0	Reference	-	0	Reference	-	0	Reference	-
	1	1.24 [0.85-1.83]	0.27	1	1.39 [0.88-2.21]	0.16	1	1.20 (0.81-1.77)	0.36
	2	1.28 [0.88-1.88]	0.20	2	1.28 [0.81-2.01]	0.30	2	1.31 (0.89-1.93)	0.17
	3	1.49 [1.01-2.22]	0.05	3	1.45 [0.91-2.32]	0.12	3	1.48 (0.98-2.25)	0.06
eTICI score (ordinal)	0	Reference	-	0	Reference	-	0	Reference	-
	1	1.17 [0.86-1.60]	0.31	1	1.26 [0.87-1.82]	0.22	1	1.22 (0.88-1.68)	0.23
	2	1.22 [0.90-1.66]	0.19	2	1.17 [0.81-1.68]	0.40	2	1.31 (0.95-1.81)	0.10
	3	1.25 [0.91-1.72]	0.17	3	1.16 [0.79-1.69]	0.45	3	1.30 (0.91-1.84)	0.15
Spontaneous recanalization‡	0	Reference	-	0	Reference	-	N/A	N/A	N/A
	1	0.75 [0.42-1.35]	0.34	1	0.74 [0.38-1.41]	0.36			
	2	0.98 [0.56-1.72]	0.95	2	0.97 [0.52-1.83]	0.94			
	3	1.16 [0.65-2.10]	0.61	3	1.07 [0.56-2.11]	0.81			
First pass effect	0	Reference	-	0	Reference	-	0	Reference	-
	1	0.98 (0.62-1.56)	0.95	1	0.89 [0.53-1.49]	0.65	1	1.10 (0.66-1.85)	0.72
	2	1.06 (0.69-1.64)	0.80	2	0.88 [0.54-1.44]	0.62	2	1.14 (0.69-1.88)	0.60
	3	1.38 (0.81-2.34)	0.24	3	1.23 [0.67-2.24]	0.32	3	1.42 (0.80-2.55)	0.23

* eTICI ≥2B after EVT. † eTICI 3 after EVT. ‡ eTICI 2B-3 on diagnostic DSA

Collateral grade is treated as an ordered predictor variable in all analyses. Binary or ordinal logistic regression models were used. Effect estimates are adjusted (common) odds ratio's for collateral grade 1 compared to 0, 2 compared to 0 and 3 compared to 0 (grade 0 being the reference category).

eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; IVT, intravenous thrombolysis; IAT, intra-arterial treatment; (c)OR, (common) odds ratio; CI, confidence interval

Supplementary table 2: Univariable and multivariable associations of collateral grade as a numeric variable with recanalization in all patients, patients treated with intravenous thrombolysis and patients treated with intra-arterial treatment.

	n/N	Univariable (c)OR (95% CI)	P	Multivariable a(c)OR (95% CI)	P
All patients					
Successful recanalization*	1898/2717	1.00 (0.90-1.11)	0.99	0.99 (0.89-1.10)	0.89
Complete recanalization†	878/2717	1.10 (0.99-1.21)	0.07	1.11 (1.00-1.23)	0.05
eTICI score (ordinal)	N/A	1.05 (0.96-1.13)	0.28	1.04 (0.96-1.14)	0.32
Spontaneous recanalization‡	244/2717	1.19 (1.00-1.41)	0.05	1.06 (0.88-1.30)	0.51
First pass effect	510/2016	1.13 (0.99-1.27)	0.06	1.09 (0.96-1.24)	0.18
IVT subgroup					
Successful recanalization*	1461/2079	0.94 (0.84-1.05)	0.29	0.93 (0.82-1.05)	0.25
Complete recanalization†	676/2079	1.04 (0.93-1.17)	0.48	1.05 (0.93-1.18)	0.45
eTICI score (ordinal)	N/A	0.98 (0.89-1.08)	0.72	0.98 (0.89-1.08)	0.63
Spontaneous recanalization‡	216/2079	1.15 (0.95-1.38)	0.14	1.05 (0.86-1.29)	0.63
First pass effect	406/1504	1.10 (0.97-1.25)	0.15	1.06 (0.91-1.23)	0.48
IAT subgroup					
Successful recanalization*	1704/2306	0.99 (0.86-1.11)	0.90	1.01 (0.89-1.14)	0.91
Complete recanalization†	843/2306	1.12 (1.01-1.24)	0.04	1.13 (1.02-1.26)	0.03
eTICI score (ordinal)	N/A	1.06 (0.97-1.16)	0.19	1.07 (0.97-1.17)	0.16
First pass effect	510/2016	1.09 (0.96-1.24)	0.16	1.08 (0.94-1.23)	0.29

* eTICI ≥2B after EVT

† eTICI 3 after EVT

‡ eTICI 2B-3 on diagnostic DSA

Collateral grade is treated as a numeric predictor variable in all analyses. Binary or ordinal logistic regression models were used. Effect estimates are adjusted (common) odds ratio's for collateral grade 1 compared to 0, 2 compared to 0 and 3 compared to 0 (grade 0 being the reference category). Multivariable analyses were adjusted for age, blood pressure on admission, Alberta Stroke Program Early CT Score at baseline, extracranial carotid artery disease and occluded segment and time from onset to recanalization (or last contrast bolus).

eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; IVT, intravenous thrombolysis; IAT, intra-arterial treatment; (c)OR, (common) odds ratio; a(c)OR, adjusted (common) odds ratio; CI, confidence interval.

ICMJE DISCLOSURE FORM

Date: 4/22/2022

Your Name: Aad van der Lugt

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input type="checkbox"/> None	
		Reports funding from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences & Health, and unrestricted grants from Penumbra Inc., Stryker, Medtronic, Cerenovus and Thrombolytic Science, LLC for research.	All funding was paid to his institution.

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4/20/2022

Your Name: Adriaan C. G. M. van Es

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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ICMJE DISCLOSURE FORM

Date: 4/22/2022

Your Name: H. Bart van der Worp

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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		Received fees for consultation for Bayer and LivaNova.	All fees were paid to his institution.
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
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ICMJE DISCLOSURE FORM

Date: 4/22/2022

Your Name: Diederik W. J. Dippel

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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ICMJE DISCLOSURE FORM

Date: 4/20/2022

Your Name: Simone M. Uniken Venema

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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ICMJE DISCLOSURE FORM

Date: 4/20/2022

Your Name: Jan Willem Dankbaar

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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ICMJE DISCLOSURE FORM

Date: 4/20/2022

Your Name: Lennard Wolff

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr><td style="width: 60%; height: 20px;"></td><td style="width: 40%;"></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> </table>						
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6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
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8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

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Date: 4/20/2022

Your Name: Marieke Sprengers

Manuscript Title: Collateral status and recanalization after endovascular treatment for acute ischemic stroke.

Manuscript Number (if known): neurintsurg-2021-018545.R2

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