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ORIGINAL RESEARCH

Impact of single phase CT angiography collateral status on functional outcome over time: results from the MR CLEAN Registry

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ABSTRACT

Background Collateral status modified the effect of endovascular treatment (EVT) for stroke in several randomized trials. We assessed the association between collaterals and functional outcome in EVT treated patients and investigated if this association is time dependent.

Methods We included consecutive patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN) Registry (March 2014–June 2016) with an anterior circulation large vessel occlusion undergoing EVT. Functional outcome was measured on the modified Rankin Scale (mRS) at 90 days. We investigated the association between collaterals and mRS in the MR CLEAN Registry with ordinal logistic regression and if this association was time dependent with an interaction term. Additionally, we determined modification of EVT effect by collaterals compared with MR CLEAN controls, and also investigated if this was time dependent with multiplicative interaction terms.

Results 1412 patients were analyzed. Functional independence (mRS score of 0–2) was achieved in 13% of patients with grade 0 collaterals, in 27% with grade 1, in 46% with grade 2, and in 53% with grade 3. Collaterals were significantly associated with mRS (adjusted common OR 1.5 (95% CI 1.4 to 1.7)) and significantly modified EVT benefit (P=0.04). None of the effects were time dependent. Better collaterals corresponded to lower mortality (P<0.001), but not to lower rates of symptomatic intracranial hemorrhage (P=0.14).

Conclusion In routine clinical practice, better collateral status is associated with better functional outcome and greater treatment benefit in EVT treated acute ischemic stroke patients, independent of time to treatment. Within the 6 hour time window, a substantial proportion of patients with absent and poor collaterals can still achieve functional independence.

INTRODUCTION

Good collateral status is associated with better functional outcome of patients with acute ischemic stroke due to intracranial large vessel occlusion of the anterior circulation.[1–8] Therefore, collateral status was implemented as a patient selection tool in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial.[9] Collateral status has also been shown to modify the effect of endovascular treatment (EVT) in some studies.[10–12] In the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration, this modification was not found.[13] Thus the value of collateral status for prediction of the benefit of EVT benefit, and consequently its role in patient selection for EVT, remains unclear. More specifically, a defined patient group without benefit of EVT has not yet been identified, and the way in which time to treatment and collateral status interact with functional outcome and EVT effect is still a subject of debate.

In this post hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN) Registry,[14] a large dataset representative of clinical practice, we assessed the association between collateral status and functional outcome in patients with acute ischemic stroke and large vessel occlusion treated with EVT, and investigated if this association is time dependent.

METHODS
Patient inclusion

The MR CLEAN Registry is a prospective, multicenter registry, collecting data from all stroke intervention centers that perform EVT in The Netherlands. The study protocol was evaluated by a central medical ethics committee, and permission to

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carry out the study as a registry was granted. All patients treated with EVT for acute ischemic stroke after the final MR CLEAN trial randomization on 16 March 2014 were registered. Data for patients undergoing EVT up to 15 June 2016 are reported here.

Patients adhering to the following criteria, comparable with the MR CLEAN trial, were included in the current analysis: age 18 years or older; treatment in a MR CLEAN intervention center; treated within 6.5 hours of stroke onset; intracranial large vessel occlusion in the anterior circulation (internal carotid artery (intracranial segment (ICA) or internal carotid artery terminus (ICA-T), middle (M1/M2), or anterior (A1/A2) cerebral artery), demonstrated by CT angiography (CTA), and availability of baseline CTA for collateral grade assessment. Upper age limit, minimal Albert Stroke Program Early CT Score (ASPECTS), and collateral grade were not used as predefined selection criteria. An extracranial carotid occlusion by atherosclerosis or dissection was not an exclusion criterion.

Collateral assessment
All CT scan protocols applied in the MR CLEAN Registry are provided in the online supplementary table S1. Collateral assessment was performed by 10 observers (each assessed 100–200 different CTAs) from the MR CLEAN Registry imaging core lab, who were blinded to the clinical findings. All observers were provided with a training set including relevant definitions. Collateral status was graded on single phase CTA source images on a 4 point scale, with grade 0 for absent collaterals (0% filling of the occluded vascular territory), grade 1 for poor collaterals (>0% and ≤50% filling of the occluded vascular territory), grade 2 for moderate (>50% and <100% filling of the occluded vascular territory), and grade 3 for good collaterals (100% filling of the occluded vascular territory).[15] Interobserver variability for this method has previously been reported to be moderate ($k=0.60$).[10]

Outcomes
The primary outcome was the modified Rankin Scale (mRS) score at 90 days.[16] The mRS is a 7 point disability scale ranging from 0 (no symptoms) to 6 (dead). Secondary outcomes were dichotomized mRS (mRS 0–1 vs 2–6, 0–2 vs 3–6, and 0–3 vs 4–6), National Institutes of Health Stroke Scale (NIHSS) score 24–48 hours after intervention, and the expanded Thrombolysis in Cerebral Infarction (eTICI) score at the end of the EVT procedure. The eTICI ranges from 0 (no antegrade reperfusion of the occluded vascular territory) to 3 (complete antegrade reperfusion of the occluded vascular territory).[17] An eTICI of 2B or higher was considered successful reperfusion. For this score to be reached, complete DSA runs, including anteroposterior and lateral views, after EVT were mandatory. If a lateral view was missing, eTICI 2A was the highest possible score. Complications during the intervention, during hospital admittance, or in the 3 month follow-up period were registered.

Acquisition phase
Due to the possibility of underestimation of collaterals when assessed on single phase CTA, we evaluated CTA acquisition phase by comparing peak arterial opacification with peak venous opacification according to a predefined method.[18] Opacification of two regions of interest—namely, the contralateral ICA and the transverse sinus—were measured in all patients by one observer (IGHJ). Based on these measurements, CTA studies were classified into one of five acquisition phases: 'early arterial' (artery Hounsfield units (HU) greater than venous structure, and venous

structure ≤200 HU), 'peak arterial' (artery HU ≥100 greater than venous structure and venous structure >200 HU), 'equilibrium' (artery HU <100 greater or equal to venous structure and venous structure >200 HU), 'peak venous' (artery HU >200 and venous structure greater than artery), or 'late venous' (artery HU ≤200 and venous structure greater than artery). Additionally, a subset of 200 patients was graded by a second observer (KMT) to assess interobserver variability for this method.

Safety measurements and complications
Safety measurements included mortality within 7, 30, and 90 days, symptomatic intracranial hemorrhage (sICH), hemicraniectomy, progression of ischemic stroke (resulting in a decline of at least 4 points on the NIHSS), pneumonia, other infections, cardiac ischemia, extracranial hemorrhage, allergic reactions, and other complications. Intracranial hemorrhage was deemed symptomatic if the patient died or deteriorated neurologically (a decline of at least 4 points on the NIHSS) and the hemorrhage was related to the clinical deterioration (according to the Heidelberg criteria).[19] Progression of ischemic stroke and development of new ischemic stroke were evaluated based on medical reports of admission.

Statistical analysis
Baseline characteristics were compared with the χ^2 test, one-way ANOVA, or Kruskal–Wallis test, as appropriate. Differences in acquisition phase were described with the χ^2 test. Interobserver variability for the five CTA acquisition phases was assessed with quadratic weighted kappa statistics. The association of collateral status with functional outcome at 90 days in the MR CLEAN Registry was assessed with univariable and multivariable ordinal logistic regression, expressed as a common odds ratio (OR). In regression analyses, we adjusted for: age, baseline NIHSS score, history of diabetes mellitus or previous stroke, and occlusion location. The effect of time to treatment on this relationship was investigated by adding an interaction term to the model (collateral status × time to treatment). The same analysis was performed for time to reperfusion (TICI 2b–3 achieved or last contrast bolus given). Additionally, the effect of time to reperfusion was investigated on a subset of patients with successful reperfusion only (TICI 2b–3). We assessed the modification of EVT benefit by collateral status by comparing the MR CLEAN Registry patients with the control group of the MR CLEAN trial and adding an interaction term to the model (collateral status × treatment allocation). Additionally, we used a triple interaction term to determine if this modification was dependent on time to treatment (collateral status × treatment allocation × time to treatment). We performed the same analysis for time to reperfusion. Statistical analyses were performed in Stata/SE 14.1 (StataCorp, Texas, USA).

Missing data
Missing NIHSS scores were retrospectively scored with a standardized chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy. Any mRS score of 0–5 assessed within 30 days was considered not valid and treated as missing. These values were therefore replaced by mRS scores derived from multiple imputation.[20] Multiple imputation was also applied to create time to treatment and time to reperfusion values for patients in the MR CLEAN control group. Multiple imputation was performed with Stata/SE 14.1 (StataCorp, Texas, USA) with the following

Table 1 Baseline characteristics per collateral grade

	Collateral grade 0 (n=98)	Collateral grade 1 (n=467)	Collateral grade 2 (n=544)	Collateral grade 3 (n=303)	P value
Age (years) (median (IQR))	72 (60–79)	72 (62–81)	70 (59–79)	69 (56–78)	0.04
Men (n (%))	64 (65)	273 (58)	277 (51)	137 (45)	<0.001
NIHSS score* (median (IQR))	19 (15–23)	17 (14–21)	15 (11–19)	14 (9–17)	<0.001
Clinical localization: left hemisphere (n (%))	58 (61)	243 (54)	279 (53)	156 (52)	0.14
Systolic blood pressure (mm Hg) (mean (SD))	151 (140–168)	150 (131–165)	149 (130–166)	150 (132–169)	0.45
Angiographic target occlusion inaccessible or dissolved (n (%))†	14 (14)	62 (13)	58 (11)	44 (15)	0.66
Treatment with intravenous alteplase (n (%))	72 (73)	366 (78)	419 (77)	223 (74)	0.33
General anesthesia (n (%))	31 (33)	119 (28)	151 (30)	53 (19)	0.01
Atrial fibrillation (n (%))	24 (25)	100 (21)	129 (24)	54 (18)	0.18
History of ischemic stroke (n (%))	20 (21)	85 (18)	86 (16)	43 (14)	0.30
History of hypertension (n (%))	48 (49)	244 (52)	266 (49)	143 (48)	0.51
History of diabetes mellitus (n (%))	19 (19)	68 (15)	104 (19)	46 (15)	0.18
History of myocardial infarction (n (%))	14 (15)	76 (17)	82 (15)	39 (13)	0.62
History of peripheral artery disease (n (%))	8 (8)	54 (12)	51 (10)	20 (7)	0.14
History of hyperlipidemia (n (%))	30 (31)	136 (30)	152 (29)	87 (29)	0.97
Current smoker (n (%))	22 (22)	109 (24)	128 (24)	78 (26)	0.75
Current statin use (n (%))	38 (40)	178 (39)	183 (34)	97 (32)	0.21
Current antihypertensive drug use (n (%))	50 (53)	261 (57)	281 (52)	130 (43)	0.01
Current NOAC use (n (%))	3 (3)	14 (3)	13 (2)	4 (1)	0.49
Current coumarin use (n (%))	12 (12)	50 (11)	77 (14)	38 (13)	0.44
Current heparin use (n (%))	4 (4)	19 (4)	22 (4)	9 (3)	0.93
Current antiplatelet use (n (%))	31 (32)	187 (41)	160 (30)	94 (31)	0.01
Pre-stroke mRS score (n (%))					0.85
0	62 (65)	311 (68)	360 (67)	204 (69)	
1	16 (17)	51 (11)	70 (13)	43 (14)	
2	8 (9)	39 (8)	43 (8)	18 (6)	
>2	9 (9)	58 (13)	62 (12)	33 (11)	
ASPECTS (median (IQR))‡	8 (6–10)	8 (7–10)	9 (7–10)	9 (8–10)	<0.001
ASPECTS subgroups					<0.001
0–4	14 (15)	39 (9)	24 (5)	9 (3)	
5–7	19 (20)	120 (26)	125 (24)	60 (20)	
8–10	62 (65)	294 (65)	384 (71)	224 (77)	
Location of occlusion (n (%))					0.01
None	0 (0)	0 (0)	0 (0)	2 (1)	
ICA	2 (2)	21 (5)	31 (6)	25 (9)	
ICA-T	39 (40)	131 (28)	109 (20)	40 (13)	
Proximal M1	25 (25)	109 (24)	150 (28)	74 (24)	
Distal M1	23 (24)	146 (31)	177 (32)	112 (36)	
M2	9 (9)	53 (11)	71 (13)	46 (15)	
Other§	0 (0)	5 (1)	6 (1)	5 (2)	
Clot burden score (median (IQR))	6 (3–8)	6 (3–7)	6 (4–8)	7 (6–8)	<0.001
Transfer from primary stroke center (n (%))	56 (57)	272 (58)	286 (52)	127 (42)	<0.001
Known time of stroke onset (n (%))	69 (70)	340 (72)	410 (75)	220 (72)	0.62
Onset/last seen well to intervention center¶ (min) (median (IQR))	135 (89–179)	147 (72–199)	129 (59–189)	129 (54–195)	0.09
Onset/last seen well to EVT start (min) (median (IQR))	204 (160–270)	215 (163–270)	205 (160–265)	210 (155–283)	0.72

Continued

Table 1 Continued

	Collateral grade 0 (n=98)	Collateral grade 1 (n=467)	Collateral grade 2 (n=544)	Collateral grade 3 (n=303)	P value
Onset/last seen well to successful reperfusion¶/last contrast bolus (min) (median (IQR))	277 (214–334)	273 (228–335)	265 (215–328)	266 (208–347)	0.43

*NIHSS was measured in survivors only.
†Inaccessible refers to patients in whom the target occlusion was not accessible, mostly because of an elongated carotid artery or aortic arch, or an occlusion or stenosis of the carotid artery that could not be passed.
‡ASPECTS was missing in 38 patients.
§In 9 patients the occlusion location was considered to be M2 at the moment the decision for EVT was made, but the imaging core lab observed an M3 occlusion. 6 patients had an occlusion in the anterior cerebral artery (A1/A2). 12 patients underwent EVT without a definitive occlusion on CT angiography according to the core lab.
¶Successful reperfusion is defined as an expanded Thrombolysis in Cerebral Infarction score of 2B–3.
ASPECTS, Albert Stroke Program Early CT Score; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T; internal carotid artery-terminus; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, novel oral anticoagulants.

variables: age, baseline NIHSS score, glucose level, diabetes mellitus, previous myocardial infarction, previous stroke, hypercholesterolemia, atrial fibrillation, medication use (antiplatelets, statins, anticoagulants, and antihypertensives), pre-stroke mRS, blood pressure, baseline ASPECTS, occlusion segment, time from symptom onset to start of EVT, time from symptom onset to successful reperfusion or last contrast bolus, eTICI score at the end of the intervention, and NIHSS score after 24–48 hours.

RESULTS

In total, 1627 patients were registered in the MR CLEAN Registry between 16 March 2014 and 15 June 2016. For the current study, 215 patients were excluded: in 75 patients no baseline CTA was collected, 2 patients were <18 years old, 79 patients had a posterior circulation occlusion, 39 patients arrived after 6.5 hours of symptom onset, and 20 patients were not treated in a MR CLEAN trial hospital (see online supplementary figure S1). This resulted in 1412 patients available for the final analysis.

Baseline characteristics

Patients with a lower collateral status were older, more often male, had higher baseline NIHSS scores and lower ASPECTS, more often received general anesthesia, and had more proximal occlusion locations (table 1). Also, these patients were more often transferred from a primary stroke center than patients with higher collateral grades, and were more often receiving antihypertensive or antiplatelet therapy. No significant differences between the grades were observed for systolic blood pressure, atrial fibrillation, or a history of diabetes mellitus. The MR CLEAN trial control group with available collateral status consisted of 262 patients. Of these, 17 patients (6%) had grade 0 collaterals, 64 (26%) had grade 1, 110 (41%) had grade 2, and 71 (27%) had grade 3.[10]

Outcomes

Primary outcome

Notably, the proportion of functional independence (mRS 0–2) in the MR CLEAN Registry was 13% in collateral grade 0 and 27% in collateral grade 1 (figure 1). In unadjusted analysis, better collateral status in the MR CLEAN Registry was significantly associated with lower mRS scores at 90 days (adjusted common OR (acOR) 1.8 (95% CI 1.6 to 2.0)) (see online supplementary table S2). After adjustments, this remained the case (acOR 1.5 (95% CI 1.3 to 1.7)) (table 2). In the MR CLEAN Registry, the relationship between collateral status and functional outcome was not time dependent for all three assessed time parameters (stroke onset to start of EVT, P=0.81; onset to end of EVT, P=0.80; and onset to successful reperfusion, P=0.11). The proportion of patients with functional independence (mRS 0–2) increased with higher collateral grade for all three time metrics (figure 2).

Treatment effect modification

In adjusted analysis, collateral status significantly modified the effect of EVT on functional outcome (P=0.04). We observed a significant shift in the distribution on the mRS in favor of the MR CLEAN Registry group for grade 2 (acOR 1.9 (95% CI: 1.3
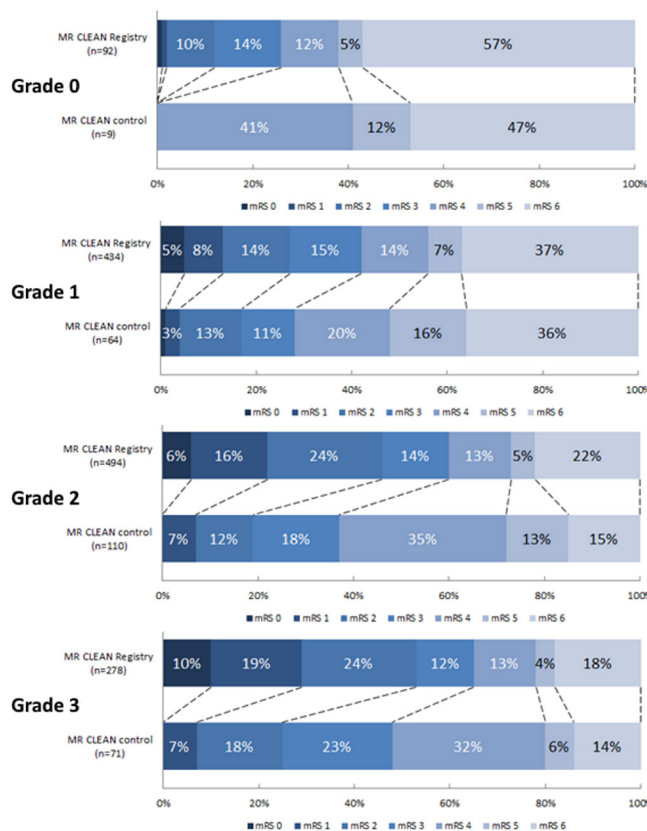

Figure 1 Distribution of scores on the modified Rankin Scale (mRS) per collateral grade in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN) Registry (before imputation) and in the MR CLEAN trial control group. Scores range from 0 to 6, with 0 indicating 'no symptoms' and 6 'dead'.

Table 2 Effect of endovascular treatment on outcome in the MR CLEAN Registry relative to the MR CLEAN control group, in the total population and per collateral grade, adjusted for age, baseline NIHSS score, history of diabetes mellitus or previous stroke, and occlusion location

Outcome	Effect parameter	All patients (n=1412)	Collateral grade 0 EVT effect (n=98)	Collateral grade 1 EVT effect (n=467)	Collateral grade 2 EVT effect (n=544)	Collateral grade 3 EVT effect (n=303)
Primary						
mRS at 90 days	acOR (95% CI)	1.5 (1.3 to 1.7)	1.0 (0.4 to 2.5)	1.2 (0.8 to 2.0)	1.9 (1.3 to 2.7)	2.1 (1.4 to 3.4)
Secondary to clinical						
mRS 0 to 1	aOR (95% CI)	1.5 (1.3 to 1.8)	n/a	2.2 (0.6 to 7.6)	3.1 (1.4 to 6.8)	4.9 (1.9 to 12.9)
mRS 0 to 2	aOR (95% CI)	1.6 (1.3 to 1.8)	n/a	1.6 (0.8 to 3.4)	4.1 (2.4 to 7.1)	3.7 (1.9 to 7.0)
mRS 0 to 3	aOR (95% CI)	1.5 (1.3 to 1.7)	n/a	2.0 (1.0 to 3.8)	2.9 (1.8 to 4.7)	2.3 (1.3 to 4.1)
NIHSS score after 24 to 48 hours*	β (95% CI)	−1.7 (−2.3 to 1.2)	−0.4 (−5.4 to 4.5)	−2.5 (−4.7 to 0.4)	−3.6 (−5.2 to 2.1)	−3.6 (−5.6 to 1.5)

*NIHSS was measured in survivors only.

acOR, adjusted common OR; aOR, adjusted OR; β, beta coefficient; EVT, endovascular treatment; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

to 2.7)) and grade 3 (acOR 2.1 (95% CI 1.4 to 3.4)) but not for grade 0 (acOR 1.0 (95% CI 0.4 to 2.5)) or grade 1 (acOR 1.2 (95% CI: 0.8 to 2.1)) (figure 1, table 2). The modification of EVT benefit by collateral status was not dependent on time to treatment (P=0.76) or time to reperfusion (P=0.63).

Secondary outcomes

Rate of successful reperfusion in the MR CLEAN Registry has been reported previously.[14] In the MR CLEAN Registry, collateral status was significantly associated with functional independence (mRS 0–2) (OR 1.6 (95% CI 1.3 to 1.8)) and mRS 0–3 (OR 1.5 (95% CI 1.3 to 1.7)). When compared with the MR CLEAN trial controls with functional independence or mRS 0–3 as the endpoint, collateral status did significantly modify EVT benefit (P=0.21; P=0.19). Results of all secondary regression analyses are shown in table 2.

Acquisition phase

Interobserver variability for the assessment of the five CTA acquisition phases expressed by the quadratic weighted κ was 0.87 (95% CI 0.82 to 0.93). Although early CTA acquisition phase scans corresponded to lower collateral grades (P<0.001; online supplementary table S3), the effect of this difference on functional outcome was, surprisingly, absent. Collateral grade 0 patients with a CTA acquired in the early arterial phase (online supplementary table S3; row 1, column 1), the group theoretically most susceptible to underestimation of collaterals, achieved precisely the same proportion of functional independence as the overall collateral grade 0 group (13%). Moreover, for patients with an early arterial phase CTA and grade 1 collaterals, the proportion of achieved functional independence was even higher than the overall grade 1 group (35% vs 27%). After correcting for scan timing in our regression model, the association of collateral status with mRS at 90 days in the MR CLEAN Registry was practically unchanged (acOR 1.6 (95% CI 1.4 to 1.8)).

Safety outcomes

We observed significant differences in the MR CLEAN Registry across collateral grades for mortality and progression of ischemic stroke, but not for sICH (see online supplementary table S4). In the MR CLEAN Registry, sICH occurred in 6 (6%) patients with grade 0 collaterals, compared with none in the associated MR CLEAN trial control group (P=0.30). For patients with grade 1, we found 33 (7%) had suffered from sICH in the MR

CLEAN Registry, compared with 9 (14%) in the MR CLEAN trial controls (P=0.05). For grades 2 and 3, rates of sICH were similar between the MR CLEAN Registry and MR CLEAN trial controls.

DISCUSSION

In the MR CLEAN Registry, better collateral status on baseline CTA was significantly associated with better functional outcome in patients treated with EVT for acute ischemic stroke due to an intracranial large vessel occlusion in the anterior circulation. Also, better collateral status corresponded to larger EVT benefit. This relationship was not time dependent, and a substantial proportion of patients with absent and poor collateral status treated at the end of the 6 hour time window still achieved functional independence after 90 days.

The recent literature emphasizes the strong association between collateral status and functional outcome, which is in line with our results.[1–7 10] However, most of these studies were not able to adequately investigate EVT benefit due to lack of a treatment control group or because by design patients with absent and poor collateral status were excluded altogether. Our results suggest that collateral status alone might not be sufficient to discriminate between patients who will and will not benefit from EVT within the 6 hour time window, and that a multivariable approach to this important question is necessary, as has previously been proposed.[21]

The potential impact of multiphase CTA in assessment of collateral status has been previously suggested, noting the added value of time based parameters such as rate of wash out and degree of delay on this assessment.[22] However, in this study, single phase CTA was still significantly associated with functional independence at 90 days, and the predictive value of assessment on multiphase CTA was only slightly increased. This is in line with our study, as the effect of acquisition phase on the relationship between collateral status and functional outcome was minimal. Three recent studies reported a faster decrease over time in the chance of functional independence after EVT for patients with poor collaterals, with possible loss of benefit in these patients before expiration of the 6 hour time window.[23–25] In our study we did not observe such a relationship. A strong relationship between collateral status on single phase CTA and conventional angiography has also been reported, still generally considered the gold standard for collateral
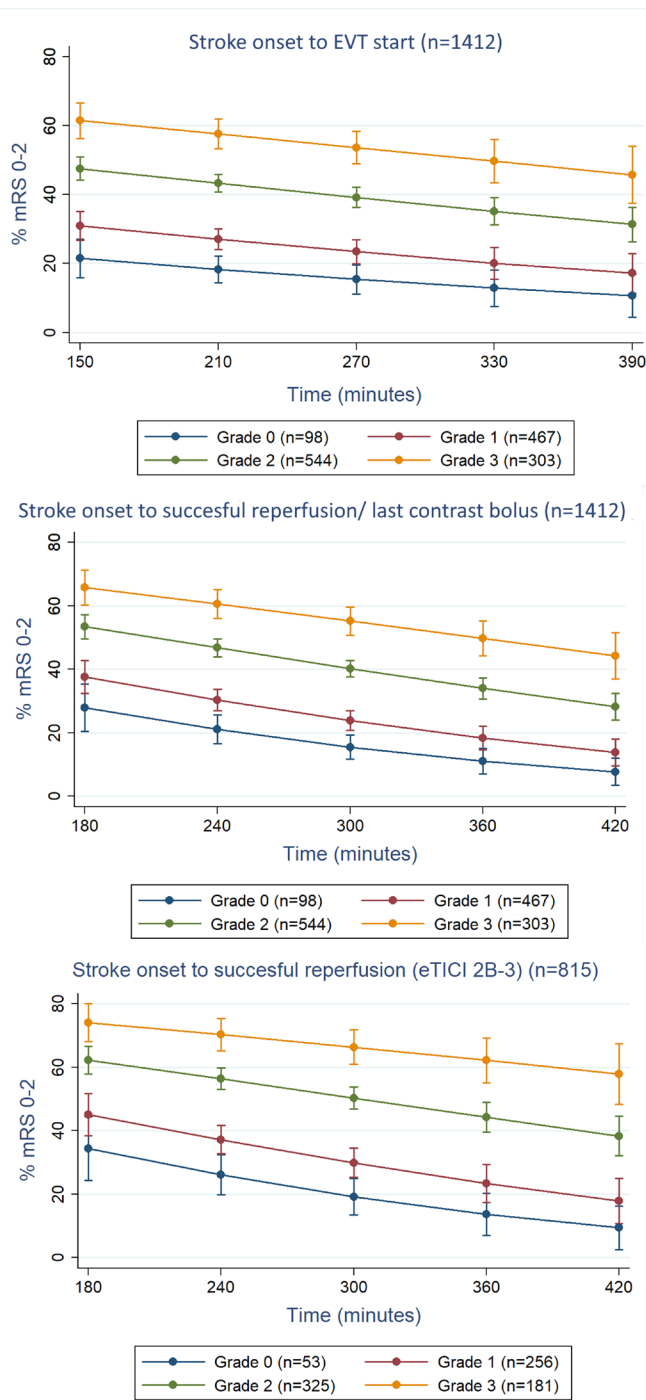
Figure 2 Proportion of patients achieving functional independence (a modified Rankin Scale (mRS) score of 0–2) per collateral grade relative to: time from onset to endovascular treatment (EVT) start (top); time from onset to end of EVT (middle); and time from onset to successful reperfusion (expanded Thrombolysis in Cerebral Infarction (eTICI) score of 2B–3) (bottom).

assessment. This improves the validity of single phase CTA as the imaging modality for ascertaining collateral status in acute stroke situations, particularly considering the practical advantages and wide availability of CTA.[25] Finally, we graded collaterals on a scale that is very common and easily applicable.[15] However, it is relatively coarse. More refined grading methods could further improve prediction of patient outcome after stroke.[26]

The MR CLEAN Registry is a large, consecutive, nationwide registry with core lab evaluation of all imaging and complications. Furthermore, this was one of the few studies in which a relatively large number of patients with absent or poor collaterals was treated. However, there were limitations. First, all patients underwent single phase CTA, which could have led to underestimation of collateral status in the case of delayed filling in combination with an early acquisition phase. However, in our study, the relation between collateral status and functional independence in these patients was similar to those with later acquisition phases, suggesting that the effect on collateral assessment was limited, improving the reliability of our results. Also, as single phase CTA is still widely used, we think our data are representative of current clinical practice and our results are widely applicable. Second, due to the large number of centers in our study, CTA was acquired with varying scan protocols. However, we think this heterogeneity further adds to the generalizability of our results. Third, there was no second reader available for collateral assessment in the MR CLEAN Registry, which could have led to inconsistencies in interpretation between observers. However, because interventionists were offered training sets and instructed to assess images according to relevant definitions, we expect this effect to be limited. Finally, no consideration of stroke etiology was made in this study, and thus the potential influence of this on collateral status cannot be fully appreciated. However, because stroke etiology is in general often unknown for a large proportion of patients, it might be difficult to draw meaningful conclusions from such an analysis.

Our study underlines the beneficial effect of collaterals for patients with acute ischemic stroke. As expected, patients with moderate and good collaterals did relatively well, the latter achieving functional independence in more than half of the cases. Still, a substantial proportion of patients with absent and poor collateral status achieved functional independence. Moreover, for patients with poor collaterals, more than one in four patients achieved functional independence after 3 months. For mRS 0–3, which can also be considered an acceptable outcome for patients with poor imaging profiles, this even increased to two in five patients. This cannot be explained by underestimation of collaterals because of scan timing issues alone. A possible explanation could be that median time from stroke onset to the start of EVT in the MR CLEAN Registry was almost an hour shorter than in the MR CLEAN trial, greatly improving the chance of functional independence irrespective of collateral status. Also of note in our study is that median ASPECTS was relatively high for all collateral grades. Despite our broad inclusion criteria, we think that a combination of very low ASPECTS and poor collaterals might be underrepresented in our registry due to some patient selection for EVT by local physicians. Additionally, it is possible that depending on the time of imaging of the patient, ASPECTS and collateral status are not aligned. In our dataset the majority of patients were imaged and treated relatively early and we believe that the relatively high median ASPECTS of poor collateral grades in our dataset is partly caused by the fact that ischemic changes were not yet visible and so the ASPECTS underrepresented the infarcted territory.

The chance of achieving functional independence after EVT is known to decrease over time, as is also seen in our study. However, we found this association with time to treatment was not significantly modified by collateral status. Despite a relative decrease over time of more than 50% in functional independence in the absent collateral group, some patients still achieved this outcome, even at the end of the 6 hour time window. Patients with moderate and good collaterals were highly likely to achieve

functional independence up to 6 hours. We can speculate that the EVT benefit in these patients ranges well beyond this time point, but this is beyond the scope of our current study.

Some advocate that collateral status can be considered when selecting patients for EVT in acute stroke.[27] However, our analysis indicates that selection of patients for EVT based on collateral status alone should be approached with caution, both in clinical practice and in future clinical trials. Despite this, our study shows that collateral status is predictive of functional outcome and could therefore be useful for prognosis in patients treated with EVT for acute ischemic stroke.

CONCLUSION

In routine clinical practice, better collateral status is associated with better functional outcome and larger treatment benefit in EVT-treated acute ischemic stroke patients, independent of time to treatment. Within the 6-hour time window a substantial proportion of patients with absent and poor collaterals can still achieve functional independence.

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