Intracranial carotid artery calcification subtype and collaterals in patients undergoing endovascular thrombectomy

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ABSTRACT

Background and aims: Distinct subtypes of intracranial carotid artery calcification (ICAC) have been found (i.e., medial and intimal), which may differentially be associated with the formation of collaterals. We investigated the association of ICAC subtype with collateral status in patients undergoing endovascular thrombectomy (EVT) for ischemic stroke. We further investigated whether ICAC subtype modified the association between collateral status and functional outcome.
Methods: We used data from 2701 patients with ischemic stroke undergoing EVT. Presence and subtype of ICAC were assessed on baseline non-contrast CT. Collateral status was assessed on baseline CT angiography using a visual scale from 0 (absent) to 3 (good). We investigated the association of ICAC subtype with collateral status using ordinal and binary logistic regression. Next, we assessed whether ICAC subtype modified the association between collateral status and functional outcome (modified Rankin Scale, 0–6).
Results: Compared to patients without ICAC, we found no association of intimal or medial ICAC with collateral status (ordinal variable). When collateral grades were dichotomized (3 *versus* 0–2), we found that intimal ICAC was significantly associated with good collaterals in comparison to patients without ICAC (aOR, 1.41 [95% CI:1.06–1.89]) or with medial ICAC (aOR, 1.50 [95%CI:1.14–1.97]). The association between higher collateral grade and better functional outcome was significantly modified by ICAC subtype (*p* for interaction = 0.01).
Conclusions: Patients with intimal ICAC are more likely to have good collaterals and benefit more from an extensive collateral circulation in terms of functional outcome after EVT.

1. Introduction

Distinct subtypes of intracranial carotid artery calcification (ICAC) have recently been found to exist, namely ICAC located predominantly in the medial layer of the artery and ICAC located predominantly in the intimal layer of the artery [1,2]. The influence of ICAC subtype on the collateral circulation of the brain remains poorly understood, but may have important clinical consequences for patients with ischemic stroke due to large vessel occlusion (LVO).

Adequate collateral circulation is essential for preservation of blood flow to brain tissue at risk of infarction during LVO and is associated with better functional outcome and response to endovascular thrombectomy

(EVT) [3–5]. Formation and development of collaterals is generally thought to be stimulated by chronic cerebral hypoperfusion due to obstruction of antegrade blood flow [6]. Accordingly, previous studies found that patients with stenotic cervical [7–9] or intracranial [10] atherosclerosis have more extensive collaterals. Histopathological analyses of ICAC specimens revealed that the intimal calcification subtype is reflective of atherosclerotic disease, which is characterized by formation of plaques and narrowing of the vessel lumen. On the other hand, a medial calcification subtype was found to particularly affect the internal elastic lamina, without atherosclerotic changes to the artery [1,2]. Against this background, it is conceivable that these different ICAC subtypes exert a differential effect on the formation and development of collateral vessels.

Hence, we investigated whether ICAC subtype is associated with collateral status in patients with ischemic stroke due to LVO undergoing EVT. Given the known association between collateral status and functional outcome, we further sought to investigate whether this association is modified by ICAC subtype.

2. Patients and methods

2.1. Study population and design

We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute ischemic Stroke (MR CLEAN) Registry, a multicenter prospective registry including patients (n = 3,637) with acute ischemic stroke undergoing EVT from March 18, 2014 until November 17, 2017 in the Netherlands. Further details on the methods and definition of variables of the MR CLEAN Registry have been described previously [11]. For the current study, we included patients adhering to the following criteria: 18 years or older; treatment in an MR CLEAN trial center; presence of a proximal intracranial occlusion in either the intracranial carotid artery (ICA), ICA terminus (ICA-T), or middle cerebral artery (M1/M2) confirmed on computed tomography angiography (CTA); groin puncture within 6.5 h after symptom onset; and availability of baseline non-contrast CT (NCCT). We excluded patients for whom the imaging was of too low quality (e.g., due to image artefacts or >5 mm slice thickness) to assess ICAC, or with missing collateral status, resulting in 2,701 patients for the current analysis (Supplementary Figure 1). The Institutional Review Board of the Erasmus MC University Medical Center evaluated the MR CLEAN Registry study protocol, granted permission to carry out the study as a registry, and waived requirement for informed consent.

2.2. Assessment of ICAC subtype

Presence of ICAC and ICAC subtype was assessed for both the left and right ICA by an observer on baseline NCCT using a previously validated method [12]. This scoring method evaluates circularity, thickness, and morphology of calcifications using a specific weighting to determine whether calcification is predominately intimal (<7 points) or medial (≥7 points). In general, a medial calcification subtype is characterized by thin, continuous, and often almost circular calcifications, whereas an intimal calcification subtype is characterized by thick, irregular, and non-circular calcifications (Fig. 1). The observer was blinded to all clinical information including collateral status and functional outcome during image assessment.

2.3. Assessment of collateral status

Collateral status has been evaluated on baseline single-phase CTA by (interventional) neuroradiologists according to a 4-point visual grading scale where filling of vessels in the occluded middle cerebral artery territory is compared to the unaffected hemisphere: grade 0 for absent collaterals (0% filling of the occluded territory), grade 1 for poor collaterals (1–49% filling of the occluded territory), grade 2 for moderate collaterals (50–99% filling of the occluded territory), grade 3 for good collaterals (100% filling of the occluded territory) [13]. All assessors were blinded to ICAC subtype, functional outcome, and all other clinical information except the side of stroke symptoms.

2.4. Assessment of other patient characteristics and functional outcome

Information on cardiovascular risk factors including smoking, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, and previous stroke was documented based on patient records at hospital admission. Stroke severity was assessed at baseline using the NIH Stroke Scale (NIHSS) and baseline infarct extent on NCCT using the Alberta Stroke Program Early CT Score (ASPECTS) [14]. Cervical carotid atherosclerosis was defined as >50% atherosclerotic stenosis or occlusion at the bifurcation of the carotid artery on the symptomatic side of stroke and was assessed on baseline CTA. Reperfusion status was assessed on post-procedural digital subtraction angiography (DSA) images using the expanded Treatment in Cerebral Infarction (eTICI) score, and eTICI 2B-3 was considered as successful reperfusion. An imaging core laboratory adjudicated all patient imaging. Functional outcome was assessed at 90 days after EVT using the modified Rankin Scale

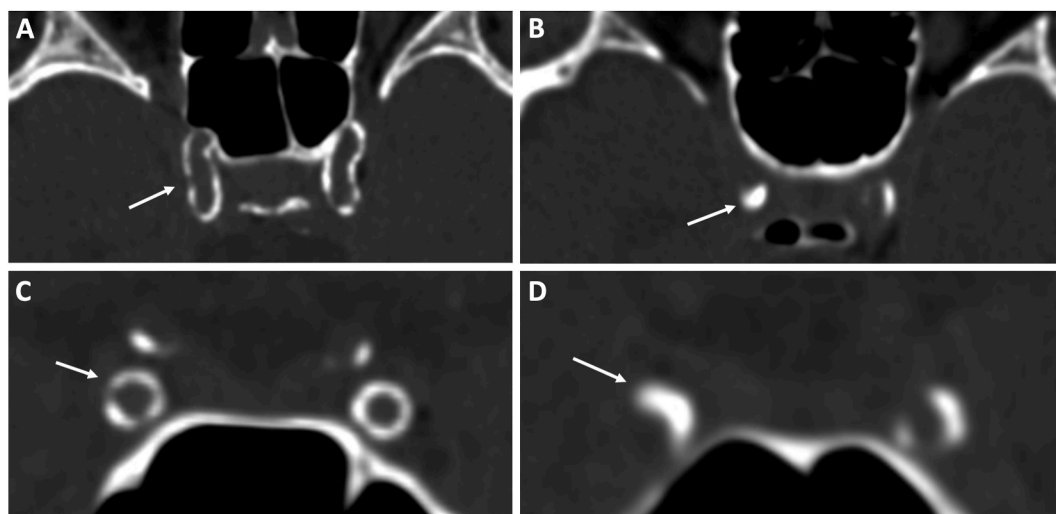**Fig. 1.** Distinct subtypes of intracranial carotid artery calcification (ICAC) on non-contrast CT in two patients.
Medial ICAC is characterized by thin calcifications distributed in a continuous and circular pattern shown in axial (A) and coronal (C) views. Intimal ICAC is characterized by thick calcifications distributed in an irregular and patchy pattern shown in axial (B) and coronal (D) views.

Table 1
Patient characteristics according to ICAC subtype.

	No calcification N = 897	Intimal ICAC N = 669	Medial ICAC N = 1135	*p*-value
Age, years (SD)	60 (15)	70 (11)	78 (10)	<0.001
Male sex, n (%)	479 (53.4)	418 (62.5)	509 (44.8)	<0.001
Smoking, n (%)	211 (28.9)	197 (37.7)	183 (21.9)	<0.001
Diabetes mellitus, n (%)	77 (8.6)	119 (17.9)	232 (20.6)	<0.001
Hypercholesterolemia, n (%)	174 (20.1)	206 (32.2)	398 (37.1)	<0.001
Hypertension, n (%)	296 (33.5)	335 (51.0)	727 (65.7)	<0.001
Atrial fibrillation, n (%)	159 (17.9)	133 (20.1)	353 (31.6)	<0.001
Previous stroke, n (%)	95 (10.7)	101 (15.1)	248 (22.1)	<0.001
NIHSS at baseline, median [IQR]	15 [11–19]	16 [11–19]	16 [12–20]	0.003
ASPECTS, median [IQR]	9 [7–10]	9 [8–10]	9 [8–10]	0.009
Cervical carotid atherosclerosis, n (%)	81 (9.8)	148 (24.7)	250 (24.2)	<0.001
Occlusion location, n (%)				0.27
Intracranial ICA	46 (5.2)	39 (5.9)	46 (4.1)	
ICA-T	186 (20.9)	157 (23.7)	226 (20.1)	
M1	523 (58.7)	369 (55.7)	684 (60.7)	
M2	136 (15.3)	97 (14.7)	171 (15.2)	
Successful reperfusion, n (%)	573 (65.2)	408 (62.6)	663 (59.8)	0.05
Collateral status, n (%)				<0.001
Absent (grade 0)	37 (4.1)	43 (6.4)	86 (7.6)	
Poor (grade 1)	301 (33.6)	260 (38.9)	418 (36.8)	
Moderate (grade 2)	378 (42.1)	223 (33.3)	453 (39.9)	
Good (grade 3)	181 (20.2)	143 (21.4)	178 (15.7)	

ICAC = intracranial carotid artery calcification, NIHSS = NIH Stroke Scale, ASPECTS = Alberta Stroke Program Early CT Score.

Table 2
Association of ICAC subtype with collateral status.

	Collateral status acOR (95% CI)	Presence of good collaterals aOR (95% CI)
Intimal ICAC *versus* no calcification		
Model 1	0.99 (0.81–1.21)	1.35 (1.03–1.77)
Model 2	0.99 (0.81–1.22)	1.38 (1.04–1.82)
Model 3	0.99 (0.80–1.22)	1.41 (1.06–1.89)
Medial ICAC *versus* no calcification		
Model 1	0.90 (0.74–1.10)	0.90 (0.67–1.19)
Model 2	0.93 (0.76–1.14)	0.93 (0.69–1.25)
Model 3	0.90 (0.73–1.11)	0.89 (0.66–1.20)
Intimal *versus* medial ICAC		
Model 1	1.12 (0.94–1.35)	1.44 (1.10–1.87)
Model 2	1.11 (0.92–1.34)	1.43 (1.09–1.86)
Model 3	1.16 (0.96–1.41)	1.50 (1.14–1.97)

ICAC = intracranial carotid artery calcification.
Effect parameter for analysis assessing the association of intracranial carotid artery calcification (ICAC) subtype with collateral status is the adjusted common odds ratio (acOR) for a shift towards higher collateral grade (0–3). Effect parameter for analysis assessing the association of ICAC subtype with presence of good collaterals is the adjusted odds ratio (aOR) for good (grade 3) *versus* absent to moderate collaterals (grade 0–2).
Model 1: age, sex. Model 2: model 1 + smoking, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, previous stroke. Model 3: model 2 + NIHSS at baseline, ASPECTS, cervical carotid atherosclerosis, occlusion location.

(mRS), a 7-point disability scale ranging from 0 (no symptoms) to 6 (dead) [15].

2.5. Statistical analysis

Patients were categorized into the following three groups based on presence of ICAC and ICAC subtype: no calcification, intimal ICAC, or medial ICAC. In patients with a mixed subtype (i.e. different ICAC subtype between the left and right ICA), the subtype on the side of stroke symptoms was selected for the current analysis as this was also the hemisphere in which collateral status was assessed. Baseline characteristics between patients with no calcification, intimal ICAC, or medial ICAC were compared using chi-square test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables. We assessed the association of ICAC subtype with collateral status (grades 0 to 3) using ordinal logistic regression analysis. Since formation of more extensive collaterals is suggestive of underlying hemodynamic impairment rather than natural development [16], we also assessed the association of ICAC subtype with good (grade 3) *versus* absent to moderate (grade 0–2) collaterals using binary logistic regression analysis. Both these regression analyses were pre-specified. Comparisons between patients without ICAC and separate ICAC subtypes were made, and also between patients with intimal and medial ICAC. In the next analysis, we investigated the association between collateral status and functional outcome in the total study population and stratified by presence and subtype of ICAC. Additionally, we assessed whether ICAC subtype (intimal *versus* medial) modified the association between collateral status and functional outcome using a multiplicative interaction term. Adjustments for confounders were made in three models by sequentially adjusting for age and sex, cardiovascular risk factors (smoking, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, and previous stroke), and stroke characteristics (baseline NIHSS, ASPECTS, cervical carotid atherosclerosis, and occlusion location). In the analysis investigating the association between collateral status and functional outcome, we additionally adjusted for successful reperfusion (eTICI 2B-3). Missing

Table 3

Association between collateral status and better functional outcome according to ICAC subtype.

	Better functional outcome acOR (95% CI)
Total study population	
Model 1	1.59 (1.46–1.73)
Model 2	1.59 (1.46–1.73)
Model 3	1.33 (1.22–1.46)
No calcification	
Model 1	1.58 (1.36–1.84)
Model 2	1.62 (1.39–1.89)
Model 3	1.33 (1.13–1.56)
Intimal ICAC	
Model 1	1.90 (1.61–2.26)
Model 2	1.94 (1.63–2.30)
Model 3	1.62 (1.36–1.94)
Medial ICAC	
Model 1	1.49 (1.31–1.70)
Model 2	1.47 (1.29–1.68)
Model 3	1.26 (1.10–1.45)

ICAC = intracranial carotid artery calcification.

Patients additionally excluded due to missing mRS score (n = 184).

Model 1: age, sex. Model 2: model 1 + smoking, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation, previous stroke. Model 3: model 2 + NIHSS at baseline, ASPECTS, cervical carotid atherosclerosis, occlusion location, successful reperfusion.

data in the covariables were imputed using multiple imputation (n = 5) with chained equations. Effect estimates are reported as adjusted common odds ratios (acOR) or adjusted odds ratio (aOR) with corresponding 95% confidence intervals (95% CI). Statistical analyses were performed in R (version 3.6.1) with packages rms and mice.

3. Results

We included a total of 2,701 patients in this study (mean age (standard deviation; [SD]), 70 (14) years; male sex 52%). From these, 897 patients had no ICAC (33%), 669 (25%) showed a predominant intimal ICAC subtype, and 1,135 (42%) a medial ICAC subtype. Patients with medial ICAC were older, more often had diabetes, hypercholesterolemia, hypertension, atrial fibrillation, and a history of stroke, but were less often male and current smokers (Table 1).

3.1. ICAC subtype and collateral status

Compared to patients without ICAC, we found no association of intimal nor medial ICAC with collateral status (ordinal variable) (Table 2). Among patients with ICAC, there was a statistically non-significant tendency towards better collateral status in patients with intimal ICAC compared to those with a medial ICAC (acOR, 1.16 [95% CI: 0.96–1.41]; Table 2). When dichotomizing collaterals into good (grade 3) *versus* absent to moderate (grade 0–2) collaterals, 20.2% (181/897) of patients without ICAC had good collaterals, 21.4% (143/669) with intimal ICAC, and 15.7% (178/1135) with medial ICAC. We found that intimal ICAC was significantly associated with good collaterals in comparison to patients with medial ICAC (aOR, 1.50 [95% CI: 1.14–1.97]), and also in comparison to patients without ICAC (aOR, 1.41 [95% CI: 1.06–1.89]; Table 2).

We found a shift towards better functional outcome per higher collateral grade in the total study population and among all patient subgroups (Table 3). However, when comparing patients with ICAC, this shift was stronger in patients with intimal ICAC (acOR, 1.62 [95% CI: 1.36–1.94]) than in patients with medial ICAC (acOR, 1.26 [95% CI: 1.10–1.45]; *p* for interaction = 0.01; Fig. 2). In patients with good collaterals stratified by ICAC subtype, 62% (106/172) without ICAC was functionally independent (mRS 0–2) at 90 days, 63% (81/129) with intimal ICAC, and 36% (61/169) with medial ICAC.

4. Discussion

In this nationwide cohort of consecutive patients undergoing EVT for ischemic stroke due to LVO, we found that patients with intimal ICAC were more likely to have good collaterals in comparison to patients without ICAC or medial ICAC. We further found that the association between higher collateral grade and better functional outcome was modified by ICAC subtype. In particular, patients with intimal ICAC benefit more from an extensive collateral circulation in terms of functional outcome after ischemic stroke than patients with medial ICAC.

In line with our findings, an earlier *post-hoc* analysis of the MR CLEAN trial found that patients with intimal ICAC more often had better collaterals compared to patients with medial ICAC [17]. In the current study, we explored this association further in an independent large consecutive series of patients undergoing EVT in routine clinical practice and found similar results. However, another study reported an opposite association and found that medial ICAC was associated with good collaterals in comparison to intimal ICAC [18]. Contradictory findings may be explained by different patient selection criteria. In the latter study, only a small number of patients with LVO were included and only those with an M1 occlusion were selected for the analysis. Nevertheless, considering recent findings in other studies [7–10], the association we describe here seems more plausible. Furthermore, intimal ICAC is related to atherosclerotic changes with the presence of plaques and arterial stenosis whereas medial ICAC is considered non-atherosclerotic without compromising the vessel lumen [1,2]. Impaired cerebral blood flow to more downstream arterial territories, generally thought to stimulate the formation and development of collaterals [6], is therefore more likely to occur in patients with intimal ICAC and less so in patients without ICAC or medial ICAC. Other studies supporting this notion have repeatedly shown that patients with stenotic cervical or intracranial atherosclerotic lesions have better collaterals in comparison to patients without such lesions [7–10].

Interestingly, we found that patients with intimal ICAC had more benefit from an extensive collateral circulation in terms of functional recovery after EVT. The relationship between higher collateral grade and better functional outcome is considered to be determined by the capacity to preserve blood flow to ischemic brain tissue during LVO, thereby reducing infarct growth and final infarct volume [19–21]. Our findings thus imply that in patients with intimal ICAC collaterals are more effective in fulfilling this task compared to patients with medial ICAC. This finding may be related to the adverse effects of medial ICAC on vessel wall and blood flow mechanics. Furthermore, medial ICAC predominately affects the internal elastic lamina adjacent to smooth muscle cells of the medial vascular layer leading to loss of arterial elasticity and compliance [1,2,22]. Such stiffening of the arterial wall is associated with an increase in pulse wave velocity and pulse pressure [23,24]. Consequently, this may impair regulation of collateral blood flow [25,26] thereby reducing the beneficial effect of collaterals predominately in patients with medial ICAC.

In the MR CLEAN trial, the effect of EVT on reduction of infarct volume seemed negligible in patients with intimal ICAC, but was clearly directed towards a reduction of infarct volume in patients with medial ICAC [17]. These findings taken together with ours might suggest that patients with intimal ICAC experience less infarct growth even in the absence of EVT possibly due to persistent preservation of collateral blood flow. Knowing that smaller infarct volumes lead to better functional outcome [27], this could to some extent provide an explanation as to why clear benefit of recanalization therapies including IVT and EVT can be seen in patients with medial ICAC but not intimal ICAC [17,18].

The main strength of the current study is that we included a large sample size of consecutive patients undergoing EVT as part of routine clinical care, making the current results generalizable to the population encountered in daily clinical practice. Our study also has several limitations. First, collateral status was assessed on single-phase CTA, which could have led to underestimation of collateral flow especially in patients
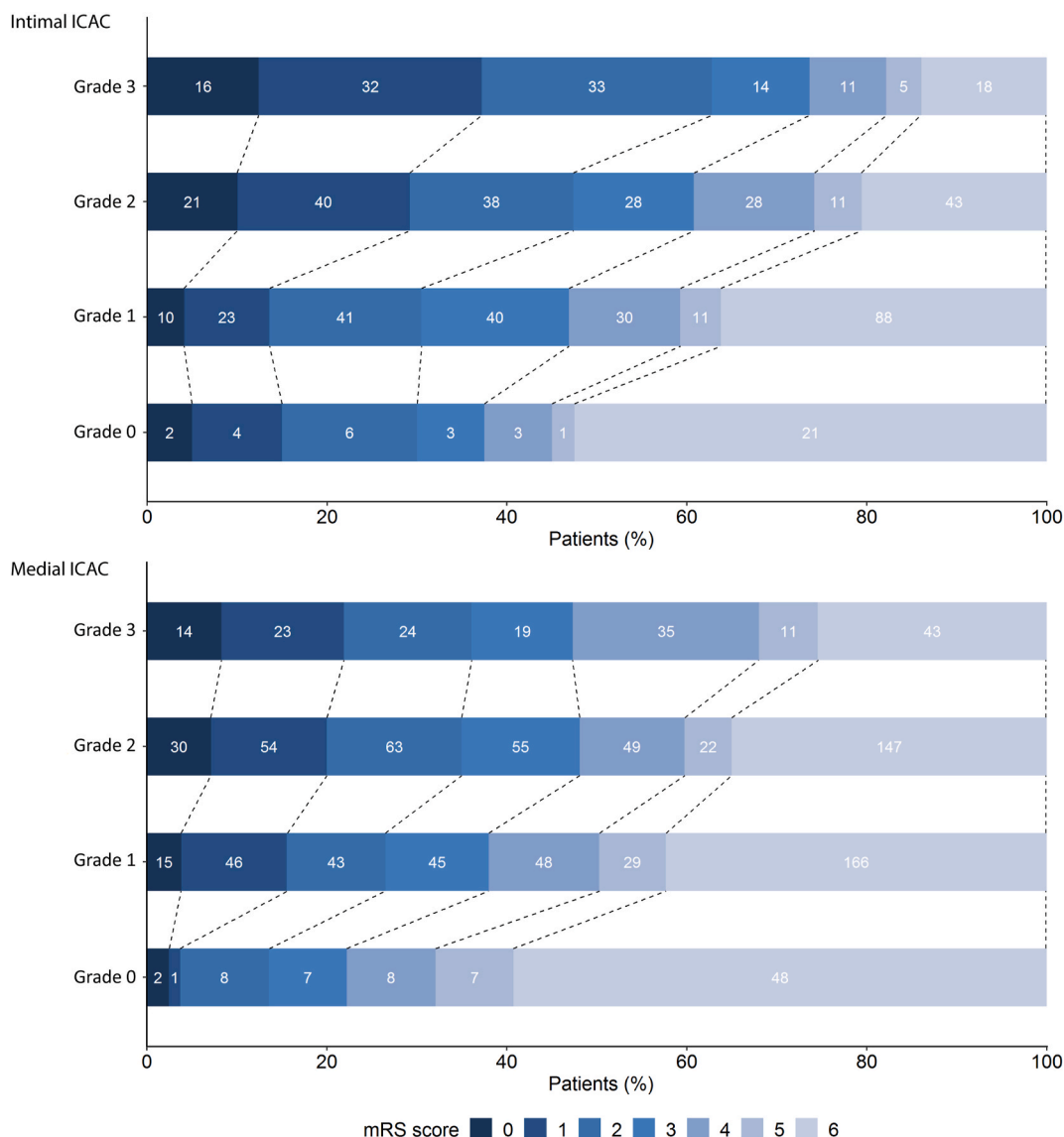
Fig. 2. Distribution of scores on the modified Rankin Scale at 90 days (mRS, 0–6) per collateral grade in patients with intimal and medial intracranial carotid artery calcification (ICAC).
Shifts towards better functional outcome per collateral grade increase were stronger in patients with intimal ICAC (acOR, 1.62 [95% CI: 1.36–1.94]) than with medial ICAC (acOR, 1.26 [95% CI: 1.10–1.45]; *p* for interaction = 0.01). White numbers in bars indicate absolute numbers of patients.

with delayed vessel filling in combination with the early acquisition phase. This may have affected patients with intimal ICAC more due to flow-limiting stenotic lesions than patients with medial ICAC. Because of this, it is possible that the association between intimal calcification and good collaterals may even be more pronounced. Second, the visual scoring method used in our study was developed to determine ICAC subtype on NCCT without specifically rating the degree of stenosis [12]. While stenotic lesions are expected to be more prevalent in patients with intimal calcifications [1], the degree of stenosis caused by these lesions may also correlate with the degree of collateral flow [10]. Third, our findings could have been biased by possible underlying differences in stroke etiology and thrombus characteristics according to ICAC subtype. In patients with intimal ICAC for instance, it is plausible that LVO is more likely to occur due to rupture of a carotid plaque. This may have important implications for the current results as previous studies have shown that thrombus characteristics relate to collateral status and functional outcome [28,29]. More work is therefore needed aimed at investigating whether ICAC subtype is associated with differences in stroke etiology and thrombus characteristics.

4.1. Conclusions

Patients with intimal ICAC are more likely to have good collaterals and benefit more from an extensive collateral circulation in terms of functional outcome after EVT. These findings show that making a distinction between different ICAC subtypes can have important implications for clinical outcomes in patients undergoig EVT for ischemic stroke.

Author contributions

SPRL, BR, and DB were responsible for the study concept and design. SPRL, SvdD, KCJC, LSFY, MESS, CBLMM, YBWEMR, WHvZ, RvO, DWJD,

AvdL, BR, and DB were responsible for or contributed to data acquisition. SPRL, SvdD, BR, and DB were responsible for the analysis and interpretation of the data. SPRL and DB were responsible for drafting the manuscript. SvdD, KCJC, LSFY, MESS, CBLMM, YBWEMR, WHvZ, RvO, DWJD, AvdL, and BR were responsible for critical revision of the manuscript.

Declaration of competing interest

Dr Majoie reports that he is a shareholder of NICO.LAB and grants from CVON/Dutch Heart Foundation, European Commission, TWIN Foundation, and Stryker, all paid to institution. Dr Roos reports that he is a shareholder of NICO.LAB. Dr van Zwam reports grants from Stryker and Cerenovus, all paid to institution. Dr Dippel reports grants from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Researce and Development, Health Holland Top Sector Life Sciences and Health, and grants from Penumbra, Stryker, Medtronic, Thrombolytic Science, LLC, and Cerenovus, all paid to institution. Dr van der Lugt reports grants from Penumbra, Stryker, Cerenovus, and Medtronic, all paid to institution. The other authors report no disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.10.005.

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