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Risk factors for atherosclerotic and medial arterial calcification of the intracranial internal carotid artery

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ABSTRACT

Background and aims: Calcifications of the intracranial internal carotid artery (iICA) are an important risk factor for stroke. The calcifications can occur both in the intimal and medial layer of the vascular wall. The aim of this study is to assess whether medial calcification in the iICA is differently related to risk factors for cardiovascular disease, compared to intimal calcification.

Methods: Unenhanced thin slice computed tomography (CT) scans from 1132 patients from the Dutch acute stroke study cohort were assessed for dominant localization of calcification (medial or intimal) by one of three observers based on established methodology. Associations between known cardiovascular risk factors (age, gender, body mass index, pulse pressure, eGFR, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous vascular disease, and family history) and the dominant localization of calcifications were assessed via logistic regression analysis.

Results: In the 1132 patients (57% males, mean age 67.4 years [SD 13.8]), dominant intimal calcification was present in 30.9% and dominant medial calcification in 46.9%. In 10.5%, no calcification was seen. Age, pulse pressure and family history were risk factors for both types of calcification. Multivariably adjusted risk factors for dominant intimal calcification only were smoking (OR 2.09 [CI 1.27–3.44]) and hypertension (OR 2.09 [CI 1.29–3.40]) and for dominant medial calcification diabetes mellitus (OR 2.39 [CI 1.11–5.14]) and previous vascular disease (OR 2.20 [CI 1.30–3.75]).

Conclusions: Risk factors are differently related to the dominant localizations of calcifications, a finding that supports the hypothesis that the intimal and medial calcification represents a distinct etiology.

1. Introduction

Calcifications of the intracranial internal carotid artery (iICA) are an important independent risk factor for stroke in the general population [1]. These calcifications are often interpreted as a proxy for atherosclerosis. However, already in 1965, it was described that calcifications in the siphon of the carotid artery are not only found in the intimal layer of the vascular wall, but also in the medial layer and around the internal elastic lamina [2]. Recently, it was shown that calcification in the iICA is predominantly located around the internal elastic lamina [3]. Calcifications in this area are considered to be medial arterial calcifications [4].

Medial calcifications have been described in multiple arteries, including femoral and breast arteries [5,6]. Breast arterial calcifications (BAC), as visualized on mammography, are thought to be exclusively medial [5]. BAC has a similar incidence in patients with angiographically normal arteries and patients with coronary heart disease [7]. However, the incidence of BAC was found to be higher in patients with an indication for coronary angiography than in the general population [7]. Therefore, is has been hypothesized that BAC shares some, but not all risk factors for atherosclerosis [7].

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Combining previous literature, we know that there is a strong association between iICA calcifications and stroke, and that iICA calcifications are predominantly medial. Furthermore, it is hypothesized that risk factors for medial arterial calcifications can be partly different from risk factors for atherosclerotic vascular disease. Therefore, it is important to determine what risk factors influence the different types of iICA calcifications. If medial arterial calcifications are indeed an important factor in the development of stroke, differences in risk factors could influence current clinical practice regarding risk reduction.

Previous reports described associations between iICA calcifications and age, diabetes, hypercholesterolemia, hypertension, smoking, history of cardiovascular disease and high white blood cell count [8–12]. However, these studies did not take the different localizations of calcification in the vascular wall into account. Based on a comparison with histopathology, we recently described a computed tomography (CT) scoring system that can determine the dominant calcification type in the iICA [13]. This scoring system allows us to evaluate the effect of risk factors on the different dominant calcification types. The aim the current study is to assess whether medial calcification in the iICA is differently related to risk factors for cardiovascular disease, compared to intimal calcification.

2. Materials and methods

2.1. Cohort

The patients were derived from the DUtch acute Stroke Study (DUST) cohort; a multi-center cohort study of 1393 patients with suspected acute ischemic stroke. Patients were included if the following criteria were met: 1) older than 18 years, 2) National Institutes of Health Stroke Scale ≥2, or 1 if an indication for intravenous thrombolysis with recombinant tissue type plasminogen activator was present, 3) acute neurological deficit of less than 9 h of duration. Patients were excluded from the study if another diagnosis on admission non-contrast Computed Tomography (CT) explained the neurological deficits, and in case of a known contrast allergy or previously known renal failure at the time of admission. At the time of admission, patient characteristics were collected, including blood pressure, height, weight, smoking, and family history of vascular diseases (1 or more first degree relative <60 years). Information about the medical history of the patients was collected, including previously diagnosed hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), hyperlipidemia (cholesterol ≥5–8 mmol/l) or diabetes mellitus (fasting glucose ≥7.0 mmol/l and/or glucose ≥11.1 mmol/l) and previous vascular disease (including previous diagnosis of myocardial infarction, transient ischemic attack, stroke and peripheral vascular disease or previous vascular intervention). Furthermore, laboratory tests, including serum creatinine and glucose, and an non-contrast CT-scan were performed. DUST was approved by the Medical Ethical Committee of the participating hospitals under protocol number 08–373. Informed consent was obtained from all patients for use of the data [14].

2.2. CT imaging

Multiple CT scanners were used in the participating centers. The number of detectors ranged from 40 to 320 (LightSpeed VCT, GE Healthcare, Milwaukee, Wisconsin; Brilliance 40, Brilliance 64, and Brilliance iCT 256, Philips Healthcare, Best, the Netherlands; Sensation 64, Siemens, Erlangen, Germany; Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) at 120 kV and 300–375 mA s. Patients were scanned from the skull base to the vertex and scans were reconstructed with a slice thickness ranging from 0.625 to 1 mm.

2.3. CT scoring

For all patients, the presence, morphologic characteristics and severity of iICA calcifications were scored on the thin slice CT data by one of three readers with at least 2 years of experience reading CT images. (PdJ, JdV, RK) The agreement between the readers was previously found to be good, with kappa's ranging from 0.70 to 0.80 [13]. The readers were blinded to the clinical data. Using the previously developed scoring model points were awarded for different morphologic aspects of the calcifications (0–4 points for circularity, 0–3 points for thickness of calcifications, and 0–4 points for continuity of calcification over a longer arterial segment). Based on the total score (range 0–11 points) the calcifications were defined as dominantly intimal (score <7 points), dominantly medial (score ≥7 points), indistinguishable (continuity of calcification unclassifiable, due to the presence of only very small amounts of calcification), or absent (Fig. 1) [13]. Furthermore the severity of the calcifications was scored in a four-tier system (none, mild, moderate, severe) as previously described by Woodcock and colleagues [15].

2.4. Clinical and laboratory characteristics

Body mass index (BMI) was calculated using the collected weight and height of the patients. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. This formula calculates the eGFR based on gender, age, serum creatinine and race. Since information regarding race was not available in the dataset, we calculated the eGFR as if we only included white patients. Given the localization of the study, we assumed the majority of patients to be white.

2.5. Statistical analysis

Characteristics (age, gender, body mass index, systolic blood pressure, diastolic blood pressure, pulse pressure, serum creatinine, eGFR <60 mL/min/1.73 m^2, glucose, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous vascular disease, and family history) were expressed according to the location of

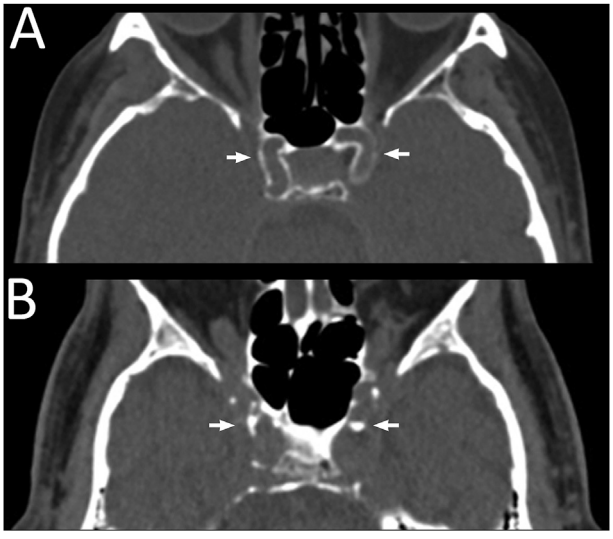

Fig. 1. Examples of predominant intimal and predominant medial calcification on CT. (A) An example of predominant medial calcification: a thin continuous line of calcification (arrows). (B) An example of predominant intima calcification: thick dots of calcification (arrows).

calcifications. Continuous normally distributed variables were presented as mean and standard deviation, skewed continuous variables as median and interquartile range. Categorical variables were presented as percentages. Differences between two groups were assessed using an independent samples T-test (normally distributed continuous variables), a Mann-Whitney test (skewed distributed continuous variables) or a chi-square test (categorical variables).

The crude and adjusted associations between the risk factors and the dominant localization of calcifications (intimal or medial) were assessed by logistic regression. We first compared patients with calcifications that could be classified as dominant intimal or dominant medial by binomial logistic regression. We repeated this analysis in patients with severe, often more easily classifiable, calcifications. Finally, as comparing only patients with calcifications can mask a protective effect of a determinant and hide a risk factor that is significant for both types of calcification, we also conducted multinomial logistic regression for assessing risk factors for a dominant intimal and a dominant medial pattern of calcifications in all patients suspected for acute stroke (with indistinguishable calcifications as reference category).

Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Adjusted OR were adjusted for all other risk factors listed. Missing values in variables used in multivariable analyses were accounted for via multiple imputation using the fully conditional specification Markov Chain Monte Carlo (MCMC) method. Multivariable analyses were run on 15 imputed datasets and combined using Rubin's rule. Statistical analyses were conducted using SPSS Statistics version 21.0 (IBM Corporation, New York, United States). p-values of <0.05 were considered significant.

3. Results

In all 1393 patients included in the study a CT-scan was performed. However, in 261 of these 1393 patients thin slice unenhanced CT-images were not available. Therefore, calcifications of the iICA were scored in the remaining 1132 patients (57% males; mean age 67.4 years [SD 13.8]; diagnosis at discharge: cerebral infarction in 89.3%, transient ischemic attack in 6.1% and another diagnosis in 4.6%). In 30.9% (350 of 1132) of patients a dominant intimal pattern of calcification was found, in 46.9% (531 of 1132) a dominant media pattern. In 11.7% (132 of 1132) of patients the main localization of calcification could not be determined (indistinguishable category) and in 10.5% (119 of 1132) calcifications were absent (Table 1). Calcifications were severe in 34.5%, moderate in 28.1% and mild in 26.9% (Supplemental Table 1).

3.1. Dominant intima versus dominant media calcifications

In the 881 patients, who were either scored as predominant media or intima calcification, logistic regression analysis showed that patients with predominant media calcification were significantly older (OR 1.49 per 10 years of age [CI 1.29–1.73]), more often female (OR male gender 0.64 [CI 0.47–0.87]), smoked less often (OR 0.57 [CI 0.40–0.80]), and more often had a history of previous vascular diseases (OR 1.49 [CI 1.06–2.09]) than patients with predominant intima calcifications (Table 2). The other risk factors did not differ significantly between the two groups. The results were comparable when only the patients with severe calcifications (often more easily classifiable) were analyzed by binominal regression (Supplemental Table 2).

3.2. Risk factors for intimal and risk factors for medial calcifications

When assessing the risk factors for dominant intimal calcification in all patients, including the patients without or with unclassifiable calcifications, by multinomial regression, intimal calcifications were associated with older age (OR 1.89 per 10 years of age [CI 1.53–2.32]), higher pulse pressure (OR 1.12 per 10 mmHg [CI 1.01–1.24]), smoking (OR 2.09 [CI 1.27–3.44]), hypertension (OR 2.09 [CI 1.29–3.40]) and a positive family history (OR 1.80 [1.08–2.99]). Medial calcifications were associated with older age (OR 2.84 per 10 years of age [CI 2.29–3.51]), higher pulse pressure (OR 1.12 per 10 mmHg [CI 1.01–1.25]), diabetes mellitus (OR 2.39 [CI 1.11–5.14]), previous vascular disease (OR 2.21 [CI 1.30–3.75]) and positive family history (OR 1.75 [1.04–2.95]) (Table 3).

4. Discussion

In this study, we assessed the risk factors for the two types of arterial calcification, intimal and medial, that are known to affect the iICA, and determined whether a difference in risk profile exists between the dominant calcification types. Our study showed that patients with predominant medial calcification of the iICA were older, more often female, smoked less often and more often had a history of previous vascular diseases, compared to patients with predominant intimal calcification. Multinomial regression confirmed the existence of differences in risk factors for predominant intimal and medial calcification. Older age, higher pulse pressure and positive family history were risk factors for both types of calcification. Whereas, smoking and hypertension were only risk factors for predominant intimal calcification, and diabetes mellitus and previous vascular disease were only risk factors for predominant medial calcification (Fig. 2).

Although the differences are limited; the finding of differences in risk factors for the two calcification patterns support the concept that both types of calcification represent a difference in etiology [17]. Our findings are overall in agreement with previous studies in different vascular beds [18]. However, given the difficulty of separating medial and intimal calcifications in vivo, data on risk factors for the separate types of calcification are very limited. This literature is confined to some studies in breast arterial calcification (BAC) which is thought to be exclusively medial, and studies in which linear ^{18}F-sodium fluoride uptake in the femoral artery and high ankle brachial index are used as surrogate markers for medial arterial calcification.

For medial arterial calcification, previous studies also showed a relation between older age, diabetes mellitus, and previous vascular diseases [18–21].

We did not find a relation between a previous diagnosis of hypertension and medial calcification. However, we did find an association with pulse pressure. The relation between medial calcification and hypertension has been investigated before, with conflicting results [18,19,21,22]. If a relation exists, one could speculate about the cause and effect. It could be that hypertension functions as a risk factor for medial arterial calcification. However, the other way around medial calcification is thought to result in a decreased arterial compliance or stiffening of the arterial wall, which could lead to increased pulse pressure and hypertension [23,24].

The relation between positive family history and medial arterial calcification differs from the sparse findings in literature, where no association was found [21]. The current found association between medial calcification and family history of cardiovascular diseases in this study could suggest that medial calcification does play a role in the development of cardiovascular diseases. However, it could also mean that in case of cardiovascular diseases, due to vascular damage medial calcification develops more easily. A third hypothesis is that due to the presence of some shared risk factors, both intimal and medial calcification develop in the same families.

Table 1
Characteristics in association with dominant localization of calcifications.

	Absent n = 119	Intima n = 350	Media n = 531	Indistinguishable n = 132	*p*-value[a]
Age (years)	48.6 ± 10.9	67.4 ± 10.8	73.8 ± 11.2	58.5 ± 12.3	<0.0005
Gender (male)	66 (55.5%)	228 (65.1%)	269 (50.7%)	80 (60.6%)	<0.0005
Body mass index (kg/m^2)	26.3 (24.7–30.6)	26.5 (23.8–29.3)	26.0 (23.1–28.4)	26.6 (24.4–29.2)	0.058
Pulse pressure (mmHg)	60.7 ± 16.6	72.8 ± 22.2	76.0 ± 25.0	64.5 ± 21.3	0.053
eGFR < 60 mL/min/1.73 m^2	5 (4.2%)	38 (11%)	91 (17.3%)	11 (8.4%)	0.010
Current smoker	40 (34.2%)	124 (37.6%)	102 (21.2%)	38 (30.6%)	<0.0005
Hypertension	33 (28.0%)	205 (58.7%)	313 (59.6%)	44 (33.8%)	0.795
Diabetes mellitus	6 (5%)	53 (15.1%)	102 (19.3%)	10 (7.6%)	0.112
Hyperlipidemia	17 (14.4%)	141 (41.5%)	192 (37.4%)	38 (29.5%)	0.236
Previous vascular disease	26 (22.2%)	150 (44.8%)	264 (51.4%)	36 (27.9%)	0.061
Family history (positive)	37 (36.6%)	83 (33.2%)	92 (27.5%)	24 (22.2%)	0.140
Severity of calcification					<0.0005
Absent	119 (100%)	0 (0%)	0 (0%)	0 (0%)	
Mild	0 (0%)	102 (29.1%)	71 (13.4%)	132 (100%)	
Moderate	0 (0%)	159 (45.4%)	159 (29.9%)	0 (0%)	
Severe	0 (0%)	89 (25.4%)	301 (56.7%)	0 (0%)	

Variables described as mean ± standard deviation for continuous variables, median (interquartile range) for skewed continuous variables, and number (%) for categorical variables.
[a] *p*-values are given for a difference between the groups with dominant intimal and dominant medial calcification.

Table 2
Association between risk factors and a predominant medial localized calcification pattern in patients with classifiable iICA calcifications.[a]

Determinant	Crude OR (95% CI) for predominant media calcification	*p*-value	Adjusted OR (95% CI) for predominant media calcification	*p*-value
Gender (male)	0.549 (0.416–0.725)	<0.0005	0.640 (0.472–0.868)	0.004
Age (per 10 years)	1.680 (1.475–1.913)	<0.0005	1.491 (1.287–1.726)	<0.0005
BMI (kg/m^2)	0.968 (0.935–1.003)	0.075	0.979 (0.943–1.016)	0.265
Pulse pressure (per 10 mmHg)	1.058 (0.999–1.120)	0.053	1.007 (0.945–1.073)	0.827
eGFR <60 mL/min/1.73 m^2	1.700 (1.133–2.550)	0.010	1.310 (0.844–2.034)	0.229
Current smoker	0.451 (0.331–0.614)	<0.0005	0.568 (0.402–0.801)	0.001
Hypertension	1.035 (0.786–1.363)	0.807	0.737 (0.531–1.024)	0.069
Diabetes mellitus	1.338 (0.930–1.924)	0.117	1.448 (0.965–2.172)	0.074
Hyperlipidemia	0.869 (0.658–1.149)	0.326	0.724 (0.508–1.032)	0.074
Previous vascular disease	1.329 (1.012–1.746)	0.041	1.489 (1.062–2.086)	0.021
Positive family history	0.849 (0.610–1.180)	0.327	0.984 (0.697–1.387)	0.925

eGFR indicates estimated glomerular filtration rate; BMI, body mass index; OR, odds ratio; and 95%, CI 95% confidence interval. All adjusted OR are adjusted for all other determinants listed.
[a] Classifiable calcifications: all patients with a calcifications that could be scored as predominant intimal or predominant medial; patients without calcifications or indistinguishable calcifications were not included in this analysis.

Table 3
Association between risk factors and a predominant intimal or predominant medial localized calcification pattern in the full cohort.

Determinant	Adjusted OR (95% CI) for predominant intima calcification	*p*-value	Adjusted OR (95% CI) for predominant media calcification	*p*-value
Gender (male)	1.371 (0.878–2.142)	0.166	0.860 (0.553–1.339)	0.505
Age (per 10 years)	1.886 (1.533–2.320)	<0.0005	2.837 (2.294–3.510)	<0.0005
BMI (kg/m^2)	0.983 (0.935–1.033)	0.491	0.965 (0.918–1.015)	0.169
Pulse pressure (per 10 mmHg)	1.118 (1.005–1.242)	0.040	1.122 (1.010–1.246)	0.031
eGFR <60 mL/min/1.73 m^2	0.545 (0.254–1.169)	0.119	0.718 (0.344–1.498)	0.377
Current smoker	2.092 (1.273–3.438)	0.004	1.240 (0.740–2.079)	0.414
Hypertension	2.093 (1.287–3.403)	0.003	1.528 (0.943–2.478)	0.085
Diabetes mellitus	1.674 (0.771–3.634)	0.193	2.393 (1.114–5.142)	0.025
Hyperlipidemia	0.796 (0.452–1.403)	0.431	0.578 (0.329–1.016)	0.057
Previous vascular disease	1.507 (0.881–2.576)	0.134	2.205 (1.295–3.753)	0.004
Positive family history	1.800 (1.084–2.987)	0.023	1.753 (1.041–2.953)	0.035

eGFR indicates estimated glomerular filtration rate; BMI, body mass index; OR, odds ratio; and 95% CI 95% confidence interval. All adjusted OR are adjusted for all other determinants listed.

Different from previous studies, we did not find a direct or inverse relation between medial calcification and smoking. Although previous studies investigating the relationship between medial calcification and smoking have not been able to elucidate their interaction, a protective effect has been suggested in several of these studies [12,19–22]. As well, a recent study found an (unadjusted) inverse relation between overall, thus intimal and medial, iICA calcification severity and smoking [25], which may be explained by the compelling higher prevalence of medial calcification in the iICA [3] in combination with a possible protective effect of smoking on medial calcification.

For intimal calcification, the relation with smoking has extensively been described in literature, and was confirmed in our data [26–28].

Furthermore, we found a clear relation between intimal calcification and hypertension. Hypertension can cause endothelial damage, resulting in impaired vascular contractility and proinflammatory activity, causing atherosclerosis [29].

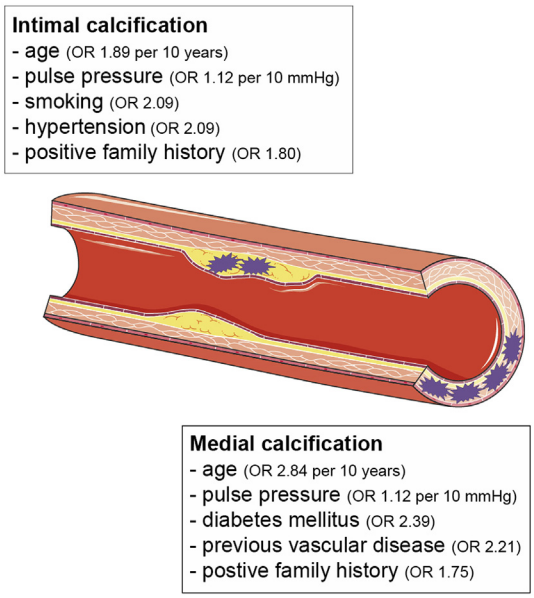

Fig. 2. Risk factors for intimal and medial arterial calcification.
Risk factors for dominant intimal and dominant medial arterial calcification in multinomial regression. Figure prepared using templates from the Servier medical art Website (https://smart.servier.com).

Previous literature does describe positive family history to be a risk factor for atherosclerosis [30]. We could confirm this in our study.

Surprisingly, we did not find a relation between diabetes mellitus and intimal calcification, even though pathways of hyperglycemia leading to development, progression and instability of atherosclerotic lesions have been described in literature [31]. Also, we were not able to show a relation between previous vascular diseases or hyperlipidemia and intimal calcification.

This study has some important limitations, including the cross-sectional design and the inclusion of only patients with acute stroke or stroke-like symptoms (diagnosis at discharge: cerebral infarction in 89.3%, transient ischemic attack in 6.1% and another diagnosis in 4.6%). Repeated analyses in only the patients with final diagnosis infarction gave comparable results (Supplemental Tables 3 and 4). The patients without calcifications were in general younger and suffered more often from acute stroke due to arterial dissection than the patients with calcifications (Supplemental Table 5). It has been suggested that craniocervical artery dissection is triggered by a combination of both an underlying susceptibility (i.e. genetic, vascular anomaly, infection) and a (minor) mechanical trauma [32]. Furthermore, it is known that risk factors such as pregnancy, oral contraceptives and illicit drug use are related to ischaemic stroke in young adults (<50 year) [33]. As we do not know if the differences in risk factors for ischaemic stroke in the young population also propagate to a different cardiovascular risk profile as compared to healthy controls, we decided to exclude this population as a control population in this study. The patients with indistinguishable calcifications were also younger than patients with intimal or medial calcifications and suffered more often from stroke due to dissection. In these patients, the differences from patients with clear calcifications were smaller than in the patients without calcifications. Therefore, we chose to analyse the data in multiple ways and to compare the patients with predominant intimal and medial calcification with the patients with very small amounts of calcification (indistinguishable category).

Another limitation of this study is the lack of larger amounts of patients with decreased renal function, therefore, we cannot draw firm conclusions on renal function.

Furthermore, we used a radiological scoring method to differentiate between the types of calcification. The model previously showed good inter-rater agreement, but only moderate agreement to histology. This means that misclassification can occur using CT. In our experience the misclassification occurs most often due to small amounts of calcification, and the misclassification rate is unrelated to the type of calcification present (non-differential misclassification) [13]. Finally, the used radiological scoring model in our study does not discriminate between intimal and medial calcification, but only distinguishes dominant calcification patterns. This means that patients with a dominant medial calcification pattern can, to variable extents, also suffer from intimal calcification, and vice versa. Nevertheless, this does not invalidate our results but might have diluted the associations.

In conclusion, we showed that the effect of risk factors on vascular calcification in the iICA depends on the location of these calcifications in the vascular wall, with age, pulse pressure, diabetes mellitus, previous vascular disease and positive family history being risk factors for medial arterial calcification and age, pulse pressure, smoking, hypertension and positive family history for intimal calcification. Our data support the hypothesis that these two types of calcifications represent different entities, and support the hypothesis that a non-atherosclerotic pathway may also lead to stroke. This concept may evolve into novel strategies to prevent stroke in the future beyond atherosclerotic cardiovascular risk reduction.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Concept and design of the study: AV, RK, JV, YTS, ICS, BV, WM, PJ; Analysis and interpretation: AV, RK, JV, YTS, PJ; drafting of the work or revising it critically: AV, RK, JV, YTS, ICS, BV, WM, PJ.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.008.

References

[1] D. Bos, M.L.P. Portegies, A. Van Der Lugt, M.J. Bos, P.J. Koudstaal, A. Hofman, et al., Intracranial carotid artery atherosclerosis and the risk of stroke in whites: the Rotterdam study, JAMA Neurol. 71 (2014) 405–411.

[2] C.M. Fisher, I. Gore, N. Okabe, P.D. White, Calcification of the carotid siphon, Circulation 32 (1965) 538–548.

[3] A. Vos, W. Van Hecke, W.G.M. Spliet, R. Goldschmeding, I. Isgum, R. Kockelkoren, et al., Predominance of nonatherosclerotic internal elastic lamina calcification in the intracranial internal carotid artery, Stroke 47 (2016) 221–223.

[4] R.G. Micheletti, G.A. Fishbein, J.S. Currier, M.C. Fishbein, Mönckeberg sclerosis revisited - a clarification of the histologic definition of Mönckeberg sclerosis, Arch. Pathol. Lab Med. 132 (2008) 43–47.

[5] V. Duhn, E.T. D'Orsi, S. Johnson, C.J. D'Orsi, A.L. Adams, W.C. O'Neill, Breast arterial calcification: a marker of medial vascular calcification in chronic kidney disease, Clin. J. Am. Soc. Nephrol. 6 (2011) 377–382.

[6] F. Vasuri, S. Fittipaldi, A. Pacilli, M. Buzzi, G. Pasquinelli, The incidence and morphology of Monckeberg's medial calcificaiton in banked vascular segments from a monocentric donor population, Cell Tissue Bank. 17 (2016) 219–223.

[7] Y. Henkin, A. Abu-Ful, I. Shai, P. Crystal, Lack of association between breast artery calcification seen on mammography and coronary artery disease on angiography, J. Med. Screen 10 (2003) 139–142.

[8] T. Ptak, G.H. Hunter, R. Avakian, R.A. Novelline, Clinical significance of cavernous carotid calcifications encountered on head computed tomography scans performed on patients seen in the emergency department, J. Comput. Assisted Tomogr. 27 (2003) 505–509.

[9] X.Y. Chen, W.W.M. Lam, K.N. Ho, Y.H. Fan, K.S. Wong, The frequency and determinants of calcification in intracranial arteries in Chinese patients who underwent computed tomography examinations, Cerebrovasc. Dis. 21 (2006) 91–97.

[10] T.T. De Weert, H. Cakir, S. Rozie, S. Cretier, E. Meijering, D.W.J. Dippel, et al., Intracranial internal carotid artery calcifications: association with vascular risk factors and ischemic cerebrovascular disease, Am. J. Neuroradiol. 30 (2009) 177–184.

[11] D. Bos, M.J.M. Van Der Rijk, T.E.A. Geeraedts, A. Hofman, G.P. Krestin, J.C.M. Witteman, et al., Intracranial carotid artery atherosclerosis: prevalence and risk factors in the general population, Stroke 43 (2012) 1878–1884.

[12] A. Yilmaz, E. Akpinar, M.A. Topcuoglu, E.M. Arsava, Clinical and imaging features associated with intracranial internal carotid artery calcifications in patients with ischemic stroke, Neuroradiology 57 (2015) 501–506.

[13] R. Kockelkoren, A. Vos, W. Van Hecke, A. Vink, R.L.A.W. Bleys, D. Verdoorn, et al., Computed tomographic distinction of intimal and medial calcification in the intracranial internal carotid artery, PLoS One 12 (2017), e0168360.

[14] T. van Seeters, G.J. Biessels, I.C. van der Schaaf, J.W. Dankbaar, A.D. Horsch, M.J. Luitse, et al., Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial (DUST) study protocol, BMC Neurol. 14 (2014) 37.

[15] R.J. Woodcock Jr., J.H. Goldstein, F.G. Kallmes, H.J. Cloft, C.D. Phillips, Angiographic correlation of CT calcification of the carotid siphon, AJNR AM J Neuroradiol 20 (1999) 495–499.

[16] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro, H.I. Feldman, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.

[17] K. Amann, Media calcification and intima calcification are distinct entities in chronic kidney disease, Clin. J. Am. Soc. Nephrol. 3 (2008) 1599–1605.

[18] A.H.E.M. Maas, Y.T. van der Schouw, D. Beijerinck, J.J.M. Deurenberg, W.P.T.M. Mali, Y. Van Der Graaf, Arterial calcifications seen on mammograms: cardiovascular risk factors, pregnancy, and lactation, Radiology 240 (2006) 33–38.

[19] T. Janssen, P. Bannas, J. Herrmann, S. Veldhoen, J.D. Busch, A. Treszl, et al., Association of linear 18F-sodium fluoride accumulation in femoral arteries as a measure of diffuse calcification with cardiovascular risk factors: a PET/CT study, J. Nucl. Cardiol. 20 (2013) 569–577.

[20] E.J. Hendriks, J. Westerink, P.A. De Jong, G.J. de Borst, H.M. Nathoe, W.P.T.M. Mali, et al., Association of high ankle brachial index with incident cardiovascular disease and mortality in a high-risk population, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 412–417.

[21] C. Iribarren, A.S. Go, I. Tolstykh, S. Sidney, S.C. Johnston, D.B. Spring, Breast vascular calcification and risk of coronary heart disease, stroke and heart failure, J. Wom. Health 13 (2004) 381–389.

[22] E.J. Hendriks, P.A. De Jong, Y. Van Der Graaf, W.P.T.M. Mali, Y.T. van der Schouw, J.W. Beulens, Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events, Atherosclerosis 239 (2015) 11–20.

[23] P. Lanzer, M. Boehm, V. Sorribas, M. Thiriet, J. Janzen, T. Zeller, et al., Medial vascular calcification revisited: review and perspectives, Eur. Heart J. 35 (2014) 1515–1525.

[24] N.M. van Popele, F.E. Grobbee, M.L. Bots, R. Asmar, J. Topouchian, R.S. Reneman, et al., Association between arterial stiffness and atherosclerois, Stroke 32 (2001) 454–460.

[25] A. Yilmaz, et al., Clinical and imaging features associated with intracranial internal carotid artery calcifications in patients with ischemic stroke, Neuroradiology 57 (2015) 201–206.

[26] W. Herrington, B. Lacey, P. Sherliker, J. Armitage, S. Lewington, Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease, Circ. Res. 118 (2016) 535–546.

[27] H. Ueno, S. Pradhan, D. Schlessel, H. Hirasawa, B.E. Sumpio, Nicotine enhances human vascular endothelial cell expression of ICAM-1 and VAM-1 via protein kinase C, p38 mitogen-activated protein kinase, NF-kappaB, and AP-1, Cardiovasc. Toxicol. 6 (2006) 39–50.

[28] T. Nakahara, J. Narula, H.W. Strauss, Calcification and inflammation in atherosclerosis: which is the chicken, and which is the egg? J. Am. Coll. Cardiol. 67 (2016) 79–80.

[29] J. Hurtubise, K. McLellan, K. Durr, O. Onasanya, F. Nwabuko, J.F. Ndisang, The different facets of dyslipidemia and hypertension in atherosclerosis, Curr. Atherosclerosis Rep. 18 (2016) 82.

[30] National cholesterol education program (NCEP) expert panel on detection, Evaluation and treatment of high blood cholesterol in adults (adult treatment panel III) final report, Circulation 106 (2002), 3143–3421.

[31] S. Del Turco, G. Basta, An update on advanced glycation endproducts and atherosclerosis, Biofactors 38 (2012) 266–274.

[32] L.C. Thomas, D.A. Rivett, J.R. Attia, C.R. Levi, Risk factors and clinical presentation of craniocervical arterial dissection: a prospective study, BMC Muscoskel. Disord. 13 (2012) 164.

[33] J.M. Ferro, A.R. Massaro, J.L. Mas, Aetiological diagnosis of ischaemic stroke in young adults, Lancet Neurol. 9 (2010) 1085–1096.