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Stroke

CLINICAL AND POPULATION SCIENCES

Morphological Subtypes of Intracranial Internal Carotid Artery Arteriosclerosis and the Risk of Stroke

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BACKGROUND: Accumulating evidence highlights the existence of distinct morphological subtypes of intracranial carotid arteriosclerosis. So far, little is known on the prevalence of these subtypes and subsequent stroke risk in the general population. We determined the prevalence of morphological subtypes of intracranial arteriosclerosis and assessed the risk of stroke associated with these subtypes.

METHODS: Between 2003 and 2006, 2391 stroke-free participants (mean age 69.6, 51.7% women) from the population-based Rotterdam Study underwent noncontrast computed tomography to visualize calcification in the intracranial carotid arteries as a proxy for intracranial arteriosclerosis. Calcification morphology was evaluated according to a validated grading scale and categorized into intimal, internal elastic lamina (IEL), or mixed subtype. Follow-up for stroke was complete until January 1, 2016. We used multivariable Cox regression to assess associations of each subtype with incident stroke.

RESULTS: The prevalence of calcification was 82% of which 39% had the intimal subtype, 48% IEL subtype, and 13% a mixed subtype. During a median follow-up of 10.4 years, 155 participants had a stroke. All 3 subtypes were associated with a higher risk of stroke (adjusted hazard ratio [95% CI] for intimal: 2.11 [1.07–4.13], IEL: 2.66 [1.39–5.11], and mixed subtype 2.57 [1.18–5.61]). The association of the IEL subtype with stroke was strongest among older participants. The association of the intimal subtype with stroke was noticeably stronger in women than in men.

CONCLUSIONS: Calcification of the IEL was the most prevalent subtype of intracranial arteriosclerosis. All 3 subtypes were associated with an increased risk of stroke, with noticeable age and sex-specific differences.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: carotid arteries ■ follow-up studies ■ intracranial arteriosclerosis ■ multidetector computed tomography ■ vascular calcification

Within the multifactorial etiology of stroke, intracranial arteriosclerosis is increasingly recognized as the most important risk factor, possibly contributing to up to 75% of all strokes.[1,2]

An important, novel insight into the cause of intracranial arteriosclerosis pertains to the occurrence and coexistence of distinct morphological disease subtypes. Apart from the most well-known subtype of intracranial arteriosclerosis; intimal atherosclerosis (ie, formation of plaques through the accumulation of lipids and calcium in the intimal layer of the artery), specific circular calcification of the internal elastic lamina (IEL) is also commonly

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Nonstandard Abbreviations and Acronyms

HDL	high-density lipoprotein
HR	hazard ratio
ICAC	intracranial carotid artery calcification
ICTRP	International Clinical Trials Registry Platform
IEL	internal elastic lamina
MDCT	multidetector computed tomography
NTR	National Trial Register

observed.[3,4] From a clinical perspective, it is conceivable that these 2 morphological subtypes may harbor a differential influence on the risk of stroke given their potentially divergent effects on the arterial wall structure and the accompanying hemodynamics within the artery.

Until now, population-based studies on the prevalence of morphological subtypes of intracranial arteriosclerosis, and the risk of stroke associated with these subtypes are lacking. Such data could greatly contribute to advancing insights into the cause of stroke.[5] Against this background, we investigated the prevalence of morphological subtypes of intracranial internal carotid arteriosclerosis, as proxy for intracranial arteriosclerosis, and the association of these subtypes with the risk of stroke in a large sample of community-dwelling elderly.

METHODS

Data Availability

Requests to access the data may be sent to the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Setting

The current study was embedded in the Rotterdam Study, a prospective, population-based cohort study ongoing since 1990, which aims at investigating the prevalence and determinants of commonly observed age-related diseases.[6] At study entry, all participants were interviewed at home by a trained research assistant and underwent clinical examinations and blood sampling at the research center. Follow-up examinations take place every 3 to 5 years. The current study includes participants who underwent a noncontrast multidetector computed tomography (MDCT) scan of the intracranial carotid arteries, as part of a larger project on visualization of arterial calcification, during a visit to the research center between 2003 and 2006.[1] We scanned 2524 participants (response rate, 78%). Follow-up for incident stroke took place continuously and was completed for the current study on January 1, 2016.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands NTR (National Trial Register; www.trialregister.nl) and into the WHO ICTRP (International Clinical Trials Registry Platform; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their follow-up information obtained from treating physicians.

Morphological Subtypes of Intracranial Arteriosclerosis

We visualized intracranial carotid artery calcification (ICAC), as proxy for intracranial arteriosclerosis,[7] using a 16-slice (n=775) or 64-slice (n=1720) MDCT scanner (Somatom Sensation, Siemens, Forchheim). Detailed information on the scanning protocol is provided elsewhere.[8] We investigated the presence and morphology of calcifications (Figure 1) in the left and right intracranial internal carotid artery, from the horizontal part of the petrous segment until the confluence with the other arteries of the Circle of Willis. To distinguish between the calcification subtypes, we used a method previously validated against histology.[9] With this method, morphological subtypes were determined using a composite score comprised of specific weighting for calcification circularity, thickness, and continuity. Based upon this score, both the left and right arteries were categorized as having predominantly atherosclerotic intimal calcifications (<7 points; ie, thick, small, and irregular), predominantly IEL calcifications (≥7 points; ie, elongated, circular, and thin), or no calcifications. Then, based upon the following combinations, we classified participants into different morphological subtype groups. Participants with bilateral predominant intimal calcifications or intimal calcifications combined with absent contralateral calcifications were classified as intimal subtype. Similarly, participants with bilateral predominant IEL calcifications or IEL calcifications combined with absent contralateral calcifications were classified as IEL subtype. Participants with predominant intimal or IEL calcifications on one side and a contrasting contralateral subtype were classified as the mixed subtype. Participants without calcifications were classified as absent. The calcification subtypes were classified by 2 observers. A consensus evaluation was performed in case of a discrepancy between the observers. The level of interobserver agreement was expressed in the proportion of agreement and Cohen kappa value (κ) and previously reported to be good (total agreement 93.9%; κ=0.88).[10]

Assessment of Stroke

Stroke was defined based on the World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting ≥24 hours or leading to death, with no apparent cause other than of vascular origin.[11,12] History of stroke was assessed at baseline and verified by reviewing medical records. After enrollment, participants were continuously monitored for incident stroke through linkage of the study databases with medical records from general practitioners. All potential strokes were

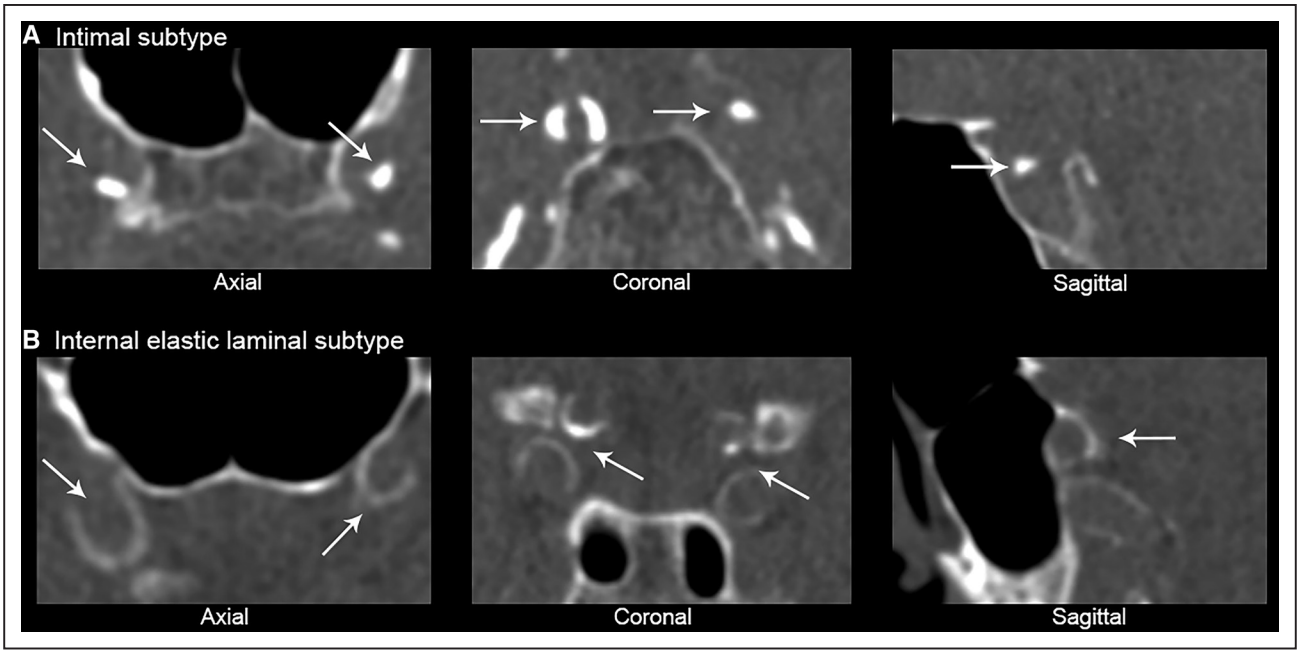

Figure 1. Example of morphological subtypes of intracranial arteriosclerosis.
The mixed subtype is not depicted as the mixed subtype is based on having predominant intimal or internal elastic lamina (IEL) calcifications on one side of the brain and a contrasting subtype on the contralateral side of the brain. The computed tomography images are obtained from the axial plane (**left**), coronal plane (**middle**), and sagittal plane (**right**).

reviewed by research physicians, and verified by an experienced stroke neurologist. Stroke subtype (hemorrhagic or ischemic) were based on neuroimaging reports or hospital discharge letters. In addition, information all-cause mortality was obtained through continuous linkage with data from general practitioners as well as from municipal records.[13] Data on cause-specific mortality were available until January 1, 2015. Cause of death was recoded according to *International Classification of Diseases, Tenth Revision* codes. We categorized the events as deaths due to cancer, dementia, cardiovascular disease, and other causes.

Assessment of Cardiovascular Risk Factors

Cardiovascular risk factors were assessed by means of interview, clinical examination, and blood sampling.[8,13] Body mass index was calculated as weight divided by height squared (kg/m^2). Obesity was defined as a body mass index of ≥30 kg/m^2. Smoking status was dichotomized into current smoking (including recurrent smokers) or noncurrent smoking (ie, former and never smokers). Blood pressure was measured twice at the right arm using a random zero-sphygmomanometer. The average of the 2 measurements was used. Hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg and/or the use of blood pressure-lowering medication. Serum total cholesterol and HDL (high-density lipoprotein) cholesterol were assessed using an automatic enzymatic procedure (Hitachi Analyzer, Roche Diagnostics). Hypercholesterolemia was defined as a serum total cholesterol of ≥6.2 mmol/L (≥240.0 mg/dL) and/or the use of lipid-lowering medication.[14] Low HDL cholesterol was defined as <1.0 mmol/L (<40.0 mg/dL).[14] Fasting plasma glucose was determined enzymatically by the Hexokinase method. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L (126.0 mg/dL) and/or the use of antidiabetic medication.[15] History of coronary heart disease was defined as previous myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft of which definitions have been previously described.[13] By use of ultrasound, we evaluated the common carotid artery, carotid bifurcation, and internal carotid artery bilaterally for the presence of atherosclerotic plaques. Using previously described methodology, a weighted atherosclerotic plaque score was derived. In short, a composite score ranging from 0 to 6 was computed by adding the number of sites at which a plaque was detected, divided by the total number of sites for which an ultrasonographic image was available, multiplied by 6 (the maximum number of sites). The interrater reproducibility coefficient for this score on either side was κ=0.67, indicating moderate agreement.[16]

Population for Analysis

Out of the 2524 participants from the Rotterdam Study that underwent a MDCT scan, 29 were excluded due to image artifacts. Participants with a history of stroke at the time of MDCT (n=99) and those that did not participate in stroke follow-up (n=5) were excluded (details on monitoring for stroke is described in the assessment of stroke). This resulted in 2391 participants available for analysis. A flowchart is provided in the Supplemental Material (Figure S1).

Statistical Analysis

Baseline characteristics of the total study population, stratified by presence of each morphological subtype and absence of calcification, were presented as means with SD or absolute values with percentages. We calculated the overall, artery and age-specific (5-year age categories) prevalence of the morphological subtypes of intracranial arteriosclerosis.

Next, we examined the association between each morphological subtype and the risk of stroke using the following strategy. First, we estimated the cumulative proportion of participants with a stroke according to the presence of each subtype and absence of calcification using the Kaplan-Meier method and compared the between-group cumulative incidence using the log-rank test. Additionally, we used the Kaplan-Meier method to compare the cumulative incidence of death between the subtypes. We also provided information on the causes of death of the total population. Second, we determined the association of each subtype with the risk of any stroke, and with the risk of ischemic stroke using Cox proportional hazard models. We made 2 comparisons, namely the presence of each subtype versus no calcifications, and the presence of each morphological subtype versus the presence of the other subtypes. Model 1 was adjusted for age, sex, and scanner type. Model 2 was additionally adjusted for hypercholesterolemia, low HDL cholesterol, non-HDL cholesterol, current smoking, hypertension, diabetes, obesity, and history of coronary heart disease. Third, we calculated the population attributable risk for stroke of each calcification subtype using the following formula[17]:

$$\mathrm{PAR} = \mathrm{PD}\left(\frac{\mathrm{RR}-1}{\mathrm{RR}}\right)\times 100\%$$

In this formula, PD is the proportion of cases exposed to the calcification subtypes, and RR represents the relative risk for stroke associated with each subtype, that is, the adjusted hazard ratio (HR) for presence of a subtype compared with absence of calcification.[17] Fourth, based on previous research showing that the presence of IEL calcification is particularly age-related,[18] we investigated the associations of each subtype versus no calcifications with the risk of any stroke while stratifying by median age of the population. Also, considering differences in stroke pathophysiology between women and men,[19] we similarly performed stratified analyses by sex. In addition, we formally tested interaction by adding multiplicative interaction terms of age and sex to the model. For all Cox proportional hazard models, we used follow-up time as timescale starting from date of MDCT scan until date of incident stroke, death, loss to follow-up, or January 1, 2016, whichever came first.

Finally, we performed 3 sensitivity analyses. First, to minimize potential overlap between the intimal and IEL subtypes, we redefined the subtypes by using only the most extreme scores to classify individuals. Accordingly, we defined the intimal subtype as a score of 1 to 4, the IEL subtype as ≥9, and assessed the associations of these redefined subtypes with stroke. Second, to assess whether the associations between the subtypes and stroke were independent of atherosclerosis, we performed a sensitivity analysis for the associations between the subtypes and any stroke in the total population in which model 2 was additionally adjusted for ultrasound-assessed carotid plaque score. Third, similarly, we performed a sensitivity analysis in which model 2 was additionally adjusted for ICAC volume.

We accounted for missing values of covariables (maximum amount of missing values, 6%) using multiple imputation by chained equations (n=5 imputations) along with age, sex, subtypes of arteriosclerosis, and cardiovascular risk factors.[20] Data were analyzed using STATA v.15 (StataCorp), R (R Foundation for Statistical Computing, Vienna, Austria, URL: http://www.R-project.org/), and RStudio 3.4.4 (Boston, MA, URL: http://www.rstudio.org/). We followed the STROBE guidelines for reporting of cohort studies.[21]

RESULTS

Baseline characteristics of the study population according to each subtype are shown in Table 1. A total of 2391 participants were included with a mean age of 69.5 (SD: 6.7), of whom 1245 (52.1%) were women. Participants with the IEL subtype were generally older (71.7 years, SD: 7.4) and more often women (54.6%) than those with presence of other subtypes or absence of calcification.

Prevalence of Morphological Subtypes of Intracranial Arteriosclerosis

Of participants with presence of ICAC (n=1952; 81.6%), 765 (39.2%) participants had a predominantly intimal subtype, 936 (48.0%) a predominantly IEL subtype, and 251 (12.9%) the mixed subtype (Figure 2 and Table S1 for artery-specific prevalence). The intimal subtype was most prevalent up to the age category of 65 to 70 years, after which IEL became and remained the most prevalent subtype over the age range (Figure 3).

Morphological Subtypes of Intracranial Arteriosclerosis and Risk of Stroke

During 21 549 person-years of follow-up (median 10.4 years), 155 strokes occurred, of which 124 (80.0%) were ischemic. Of the ischemic strokes, 26 (21.0%) strokes originated from cardioembolism, 10 (8.1%) from large-artery atherosclerosis, 2 (1.6%) from small-vessel occlusion, 1 (0.8%) from other causes, 81 (65.3%) had an undetermined cause, and 4 (3.2%) were unknown. The location of ischemic strokes involved the anterior circulation in 38 cases (30.7%), posterior location in 12 cases (9.7%), both the anterior and posterior circulation in 1 case (0.8%), and in 73 cases (58.9%) the location was unspecified. The cumulative incidence of stroke was highest among participants with the IEL subtype (Figure 4). In addition, 510 participants died during follow-up. Overall, the cumulative incidence of death was highest among participants with the IEL subtype (Figure S2). Information on cause-specific mortality is provided in Table S2.

Compared with the absence of calcification, intimal (HR [95% CI], 2.11 [1.07–4.13]), IEL (2.66 [1.39–5.11]), and mixed subtypes (2.57 [1.18–5.61]) were all associated with an increased risk of stroke in the total population (Table 2, model 2). When using other subtypes as reference category we found that the IEL subtype was most strongly associated with ischemic stroke (HR, 1.47 [95% CI, 0.99–2.16];Table 2, model 2). Overall, effect estimates for ischemic stroke were of similar magnitudes compared with any stroke (Table 2). The proportion of strokes attributable to the IEL subtype was 33%. The intimal subtype contributed to 14% and the mixed subtype to 7% of all strokes.

After stratifying for median age, we found that the IEL subtype in particular was associated with a higher risk

Table 1. Baseline Characteristics of the Study Population, According to Morphological Subtypes of Intracranial Arteriosclerosis

Characteristics	Morphological subtypes				
	Intimal	Mixed	IEL	Absent*	*P* value†
N	765	251	936	439	
Women, n (%)	370 (48.4)	123 (49.0)	511 (54.6)	241 (54.9)	0.030
Age, mean (SD), y	68.1 (5.7)	69.5 (6.0)	71.7 (7.4)	67.1 (5.3)	<0.001
Body mass index, mean (SD), kg/m^2	27.7 (3.9)	28.2 (4.0)	27.4 (4.2)	27.6 (4.0)	0.049
Obesity, n (%), ≥30 kg/m^2	190 (24.8%)	78 (31.1%)	204 (21.8%)	94 (21.4%)	0.010
Systolic blood pressure, mean (SD), mm Hg	145.8 (19.6)	145.7 (19.6)	149.4 (21.2)	142.8 (17.8)	<0.001
Diastolic blood pressure, mean (SD), mm Hg	81.6 (10.4)	80.5 (10.6)	78.3 (11.3)	81.5 (10.0)	<0.001
Blood pressure-lowering medication use, n (%)	297 (39.3)	115 (46.4)	413 (44.9)	116 (26.7)	<0.001
Hypertension, n (%)	564 (74.1)	196 (78.4)	724 (77.5)	292 (66.7)	<0.001
Serum HDL cholesterol (SD), mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	0.069
Serum total cholesterol, mean (SD), mmol/L	5.7 (1.0)	5.7 (1.0)	5.6 (1.0)	5.7 (1.0)	0.380
Non-HDL cholesterol, mean (SD), mmol/L	4.2 (1.0)	4.3 (1.0)	4.3 (1.0)	4.2 (1.0)	0.370
Lipid-lowering medication use, n (%)	178 (23.6)	79 (31.9)	240 (26.1)	62 (14.3)	<0.001
Hypercholesterolemia, n (%)	318 (41.6)	122 (48.6)	399 (42.6)	152 (34.6)	0.003
HDL<1 mmol/L, n (%)	85 (11.1)	36 (14.3)	93 (9.9)	46 (10.5)	0.250
Current smoking, n (%)	124 (16.2)	44 (17.5)	149 (15.9)	58 (13.2)	0.410
Diabetes, n (%)	83 (11.4)	38 (16.3)	131 (14.9)	35 (8.5)	0.003
History of CHD, n (%)	54 (7.1)	18 (7.2)	123 (13.1)	8 (1.8)	<0.001

Values are based on nonimputed data. CHD indicates coronary heart disease; HDL, high-density lipoprotein; and IEL, internal elastic lamina.

*Absent indicates that intracranial calcifications were not present.

†*P* values for differences in baseline characteristics between the subtypes were estimated using ANOVA for continuous variables and χ^2 tests for categorical variables.

of stroke among older participants (HR, 95% CI for the IEL subtype compared with absence of calcification: 3.20 [1.26–8.13]; Table S3, model 2 in the Supplemental Material). In women, all 3 subtypes were strongly associated with a higher risk of stroke, but the mixed subtype did not reach statistical significance in the adjusted model (HR, 95% CI for the IEL subtype compared with absence of calcification: 3.26 [1.12–9.48], the mixed subtype: 3.20 [0.88–11.64], the intimal subtype: 3.14 [1.05–9.35]). In men, the IEL subtype was most strongly associated with a higher risk of stroke (HR, 95% CI for the IEL subtype: 2.51 [1.10–5.76], the mixed subtype: 2.21 [0.81–6.08], the intimal subtype: 1.58 [0.66–3.78]). Multiplicative interaction tests of age and sex did not reach statistical significance (*P*>0.05). The use of redefined subtypes based on the most extreme scores did not materially change the results (Table S4) nor did adjustment for carotid plaque score or ICAC volume (Tables S5 and S6).

DISCUSSION

In this population-based study, we found that calcification of the IEL was the most common form of intracranial arteriosclerosis, followed by intimal calcification. A mixed subtype was least common. In the total population, all 3 subtypes similarly increased the risk of stroke >2-fold. The presence of an IEL subtype contributed to 33%, the intimal subtype to 14% and the mixed subtype to 7% of all strokes in the total population. The association of the IEL subtype with stroke was especially evident among older participants. The association of the intimal subtype was noticeably stronger in women than in men.

From a historical perspective, the presence of arterial calcification has mostly been directly translated to the presence of atherosclerotic disease. Yet, especially in the intracranial arteries, intimal calcifications—that exist within atherosclerotic plaque—can be distinguished from IEL calcifications, which are not linked to atherosclerotic disease, as was highlighted in a recent study on the correlation of imaging and histopathology.[9] In line with this, within our population-based sample, we identified the presence of IEL, intimal, and mixed subtypes of intracranial arteriosclerosis and found that IEL calcifications were even more prevalent than the intimal subtype in the intracranial internal carotid artery.

The strong association of the intimal subtype with the risk of stroke in the total population is in line with our expectations based on atherosclerotic pathophysiology and is further supported by previous literature on intracranial atherosclerotic disease and stroke risk.[22] Interestingly, we found that the IEL subtype, compared with the intimal subtype, yielded a similar effect estimate for the risk of stroke in the total population. The strength of the associations did not change after adjustment for carotid plaques

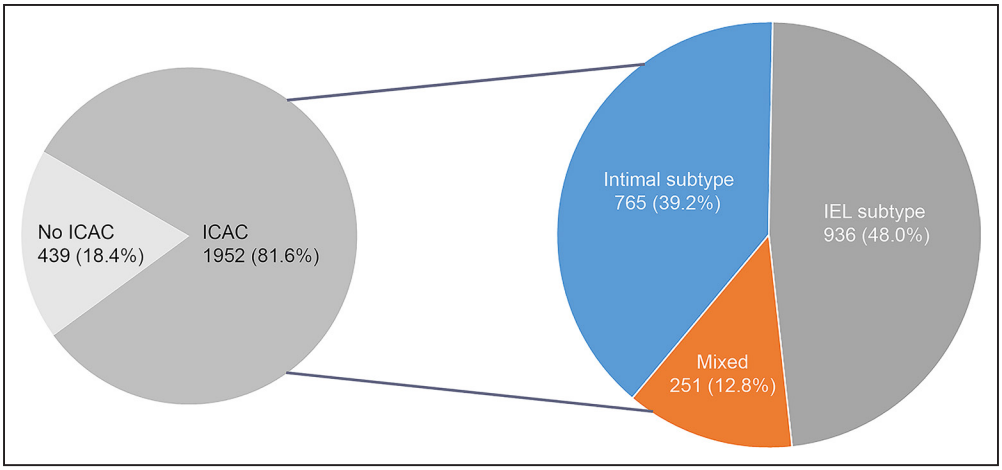

Figure 2. Prevalence of morphological subtypes of intracranial arteriosclerosis.
Values represent the prevalence in absolute numbers (percentages). ICAC indicates intracranial carotid artery calcification; and IEL, internal elastic lamina.

nor after adjustment for ICAC volume, indicating both subtypes of arteriosclerosis independently increase the risk of stroke. Yet, carotid plaques were assessed outside the cranium and may, therefore, not adequately reflect plaque in the intracranial internal carotid arteries.[23] Nonetheless, on histology the IEL subtype was previously found to be unrelated to the occurrence of atherosclerotic lesions within the intracranial internal carotid arteries specifically.[4] This suggests that the IEL subtype itself could play an important role in the cause of stroke, independently of atherosclerotic plaque. We found that the presence of an IEL subtype contributes to 33% of all strokes indicating that the occurrence of stroke may be reduced by this percentage if IEL calcifications could be eliminated. This large population attributable risk illustrates great promise for stroke risk reduction on public health level.

Several mechanisms may be involved in stroke caused by IEL arteriosclerosis. First, although the exact mechanism is not fully understood, we may argue that the IEL subtype is accompanied by structural changes of the vessel

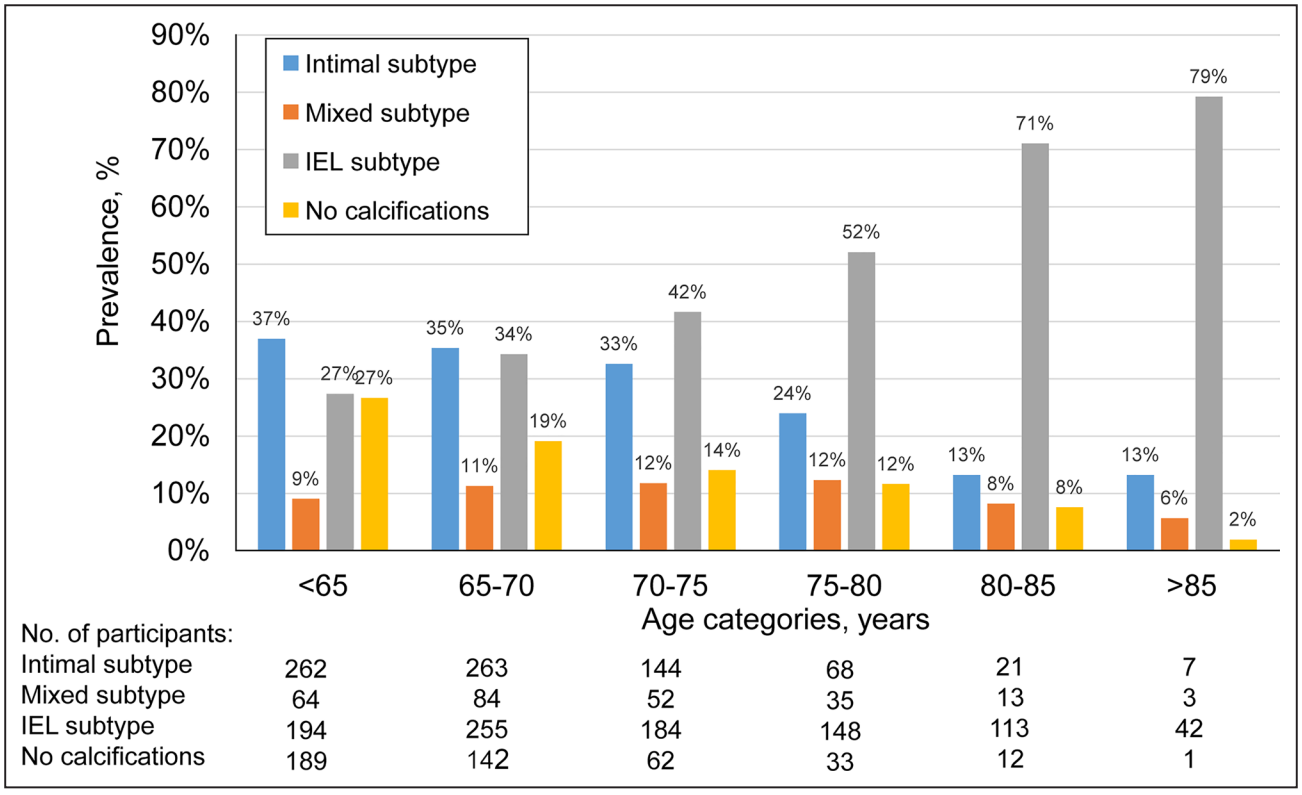

Figure 3. Prevalence of morphological subtypes of arteriosclerosis across 5-y age categories.
IEL indicates internal elastic lamina.

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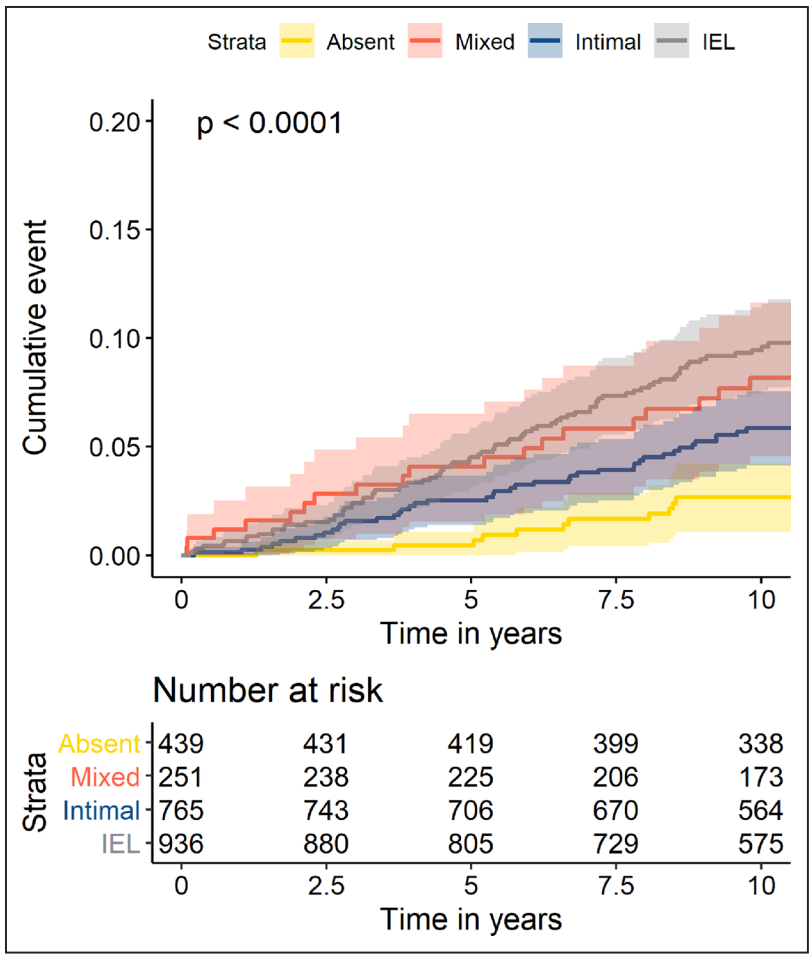

Figure 4. Cumulative incidence of stroke by each morphological subtype of intracranial arteriosclerosis.
Among participants with the intimal subtype, 42 stroke cases were identified, among mixed 19, among IEL 83, and among those without calcification 11 stroke cases were identified. IEL indicates internal elastic lamina.

wall and subsequent loss of functional vessel capacity. In turn, this could result in increased blood flow pulsatility.[24,25] Increased hemodynamic pulsatility into the distal microcirculation might mechanically insult the endothelium of downstream arterioles, leading to lacunar infarcts. Indeed, it has been shown that calcification of the intracranial internal carotid artery is associated with increased transmission of pulsatility into the middle cerebral artery,[26] and pulsatility in cerebral perforators seems to be greater in patients with lacunar infarcts than in healthy controls.[27] Second, elaborating on the former, chronic hypertensive stress due to increased blood flow pulsation could lead to hemorrhagic stroke.[27] Third, intracranial IEL arteriosclerosis might be a reflection of a systemic process also affecting other arteries. If so, aortic arteriosclerosis might cause aortic stiffening, which is associated with increased

Table 2. Morphological Subtypes of Intracranial Arteriosclerosis and Risk of Stroke

	Stroke, HR (95% CI)			
	Any		Ischemic	
ICAC subtype	N/n: 155/2391		N/n: 124/2391	
Reference: no calcification	Model 1	Model 2	Model 1	Model 2
Intimal subtype	2.12 (1.08–4.13)	2.11 (1.07–4.13)	1.83 (0.87–3.88)	1.85 (0.87–3.94)
Mixed subtype	2.63 (1.23–5.64)	2.57 (1.18–5.61)	2.61 (1.13–6.02)	2.63 (1.12–6.16)
IEL subtype	2.95 (1.55–5.63)	2.66 (1.39–5.11)	3.13 (1.54–6.39)	2.79 (1.36–5.74)
Reference: other calcification subtypes	Model 1	Model 2	Model 1	Model 2
Intimal subtype	0.68 (0.47–0.98)	0.73 (0.50–1.05)	0.57 (0.37–0.87)	0.61 (0.40–0.94)
Mixed subtype	1.03 (0.64–1.67)	1.06 (0.65–1.73)	1.09 (0.64–1.85)	1.12 (0.66–1.91)
IEL subtype	1.40 (0.99–1.97)	1.30 (0.92–1.83)	1.58 (1.08–2.32)	1.47 (0.99–2.16)

HRs for stroke are presented for intimal, IEL, and mixed subtypes compared with absence of calcifications or any other subtype. Model 1 is adjusted for age, sex, and scanner type. Model 2 is additionally adjusted for hypercholesterolemia, low HDL cholesterol, non-HDL cholesterol, current smoking, hypertension, diabetes, obesity, and history of coronary heart disease. HDL indicates high-density lipoprotein; HR, hazard ratio; ICAC, intracranial carotid artery calcification; IEL, internal elastic lamina; N, number of strokes; and n, total number of individuals.

left ventricular hypertrophy[28,29] and atrial fibrillation[30] which in turn could increase the risk for cardiogenic stroke.[31] To further elucidate the role of the each subtype in the cause of stroke, future studies should investigate how the morphological subtypes are related to central and intracranial hemodynamic changes, how they impact other important stroke risk factors, such as arterial stenosis, and how they relate to specific stroke subtypes, such as cardioembolism and small-vessel occlusion.[32]

We showed, in accordance with previous research,[18] that individuals with a predominantly IEL subtype were generally older. We hypothesize that calcium accumulation along the IEL of the intracranial artery is an almost inevitable result of advancing age and the parallel co-occurrence of other cardiovascular risk factors. This hypothesis is strengthened by prior studies that demonstrated progressive lipid depositions and calcium accumulation with advancing age across the medial layer of the aortic wall.[33,34] Also, the association between the IEL subtype and stroke was most evident in older participants. The different effect estimates for the risk of stroke according to age could partly be explained by the dichotomization of the subtypes. It is plausible that while the IEL subtype becomes predominant with increasing age, the intimal subtype is still present. Regarding sex-differences, we observed a particularly striking contrast between men and women for the intimal subtype and the risk of stroke. Sex-specific differences in atherosclerosis and the risk of stroke have previously been reported.[35] However, the sex-specific mechanisms underlying the association of intracranial atherosclerosis in particular with the risk of stroke are largely unknown. This should be further evaluated.

Strengths of the current study include the unique population-based setting and the image-based assessment of intracranial arteriosclerosis. As a result of the solid infrastructure of the Rotterdam Study in terms of follow-up of stroke events, the follow-up in the current sample was virtually complete. Yet, there are also several limitations. First, the current visual assessment scale for intracranial arteriosclerosis classifies calcification into either a predominantly intimal or IEL subtype, whereas co-occurrence is regularly seen.[4] A quantitative method to assess the subtypes of calcification and their coexistence in the same artery would provide important additional information and should be sought for in the near future. Yet, a stricter redefinition of the subtypes—to capture only those individuals with the most prominent IEL or intimal subtype—resulted in similar effect estimates. Second, we lacked statistical power to further assess the association between subtypes of intracranial arteriosclerosis and stroke subtypes. Third, we evaluated the intracranial internal carotid arteries as proxy for arteriosclerosis of the anterior circulation, but posterior arteriosclerosis is also often observed.[36,37] The prevalence and distribution of intracranial carotid arteriosclerosis differs from that of posterior intracranial arteries.[4,38] However, as the CT classification method that we used is not histologically validated to determine posterior arteriosclerotic subtypes on CT, posterior arteries were not addressed in our study. Fourth, while calcification of other arteries of the Circle of Willis might also contribute to stroke risk, with the current generation CT scanners we were unable to detect calcification in small arteries of the Circle of Willis and adjacent branches. In addition, a histologically validated method to determine arteriosclerotic subtypes in these arteries remains to be developed. Lastly, no information on the degree of intracranial stenosis was available as our sample was derived from the general population, and thus CT scans without contrast were used. However, we adjusted for the severity of carotid plaque on ultrasound, as a proxy for intracranial atherosclerosis, which did not change the results. To improve knowledge on stroke etiology, we encourage future studies to further the associations of subtypes of anterior and posterior intracranial arteriosclerosis with hemodynamic changes, with different stroke subtypes, with stroke location.

CONCLUSIONS

Calcification of the IEL was the most prevalent subtype of intracranial arteriosclerosis among middle-aged and elderly persons from a general population. All subtypes increased the risk of stroke in the total population, with important differences observed according to age and sex. To enable development of personalized preventive strategies for stroke, it is important to further determine the age and sex-specific values of these subtypes for stroke risk prediction.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S6
Figures S1–S2
STROBE checklist

REFERENCES

1. Bos D, Portegies ML, van der Lugt A, Bos MJ, Koudstaal PJ, Hofman A, Krestin GP, Franco OH, Vernooij MW, Ikram MA. Intracranial carotid artery atherosclerosis and the risk of stroke in whites: the Rotterdam study. *JAMA Neurol*. 2014;71:405–411. doi: 10.1001/jamaneurol.2013.6223
2. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke*. 2008;39:2396–2399. doi: 10.1161/STROKEAHA.107.505776
3. Fisher CM, Gore I, Okabe N, White PD. Calcification of the carotid siphon. *Circulation*. 1965;32:538–548. doi: 10.1161/01.cir.32.4.538
4. Vos A, Van Hecke W, Spliet WG, Goldschmeding R, Isgum I, Kockelkoren R, Bleys RL, Mali WP, de Jong PA, Vink A. Predominance of nonatherosclerotic internal elastic lamina calcification in the intracranial internal carotid artery. *Stroke*. 2016;47:221–223. doi: 10.1161/STROKEAHA.115.011196
5. Kockelkoren R, De Vis JB, de Jong PA, Vernooij MW, Mali WPTM, Hendrikse J, Schiestl T, Pellikaan K, van der Lugt A, Bos D. Intracranial carotid artery calcification from infancy to old age. *J Am Coll Cardiol*. 2018;72:582–584. doi: 10.1016/j.jacc.2018.05.021
6. Ikram MA, Brusselle G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, Kieboom BCT, Klaver CCW, de Knegt RJ, Luik AI, et al. Objectives, design and main findings until 2020 from the Rotterdam study. *Eur J Epidemiol*. 2020;35:483–517. doi: 10.1007/s10654-020-00640-5
7. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol*. 1998;31:126–133. doi: 10.1016/s0735-1097(97)00443-9
8. Odink AE, van der Lugt A, Hofman A, Hunink MG, Breteler MM, Krestin GP, Witteman JC. Risk factors for coronary, aortic arch and carotid calcification; the Rotterdam study. *J Hum Hypertens*. 2010;24:86–92. doi: 10.1038/jhh.2009.42
9. Kockelkoren R, Vos A, Van Hecke W, Vink A, Bleys RL, Verdoorn D, Mali WP, Hendrikse J, Koek HL, de Jong PA, et al. Computed tomographic distinction of intimal and medial calcification in the intracranial internal carotid artery. *PLoS One*. 2017;12:e0168360. doi: 10.1371/journal.pone.0168360
10. Compagne KCJ, Clephas PRD, Majoie CBLM, Roos YBWEM, Berkhemer OA, van Oostenbrugge RJ, van Zwam WH, van Es ACGM, Dippel DWJ, van der Lugt A, et al; MR CLEAN Investigators. Intracranial carotid artery calcification and effect of endovascular stroke treatment. *Stroke*. 2018;49:2961–2968. doi: 10.1161/STROKEAHA.118.022400
11. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1976;54:541–553.
12. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. *Eur J Epidemiol*. 2012;27:287–295. doi: 10.1007/s10654-012-9673-y
13. Leening MJ, Kavousi M, Heeringa J, van Rooij FJ, Verkroost-van Heemst J, Deckers JW, Mattace-Raso FU, Ziere G, Hofman A, Stricker BH, et al. Methods of data collection and definitions of cardiac outcomes in the Rotterdam study. *Eur J Epidemiol*. 2012;27:173–185. doi: 10.1007/s10654-012-9668-8
14. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii). *Jama*. 2001;285:2486–2497. doi: 10.1001/jama.285.19.2486
15. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:S14–S31. doi: 10.2337/dc20-S002
16. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam study. *Circulation*. 2004;109:1089–1094. doi: 10.1161/01.CIR.0000120708.59903.1B
17. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88:15–19. doi: 10.2105/ajph.88.1.15
18. Vos A, Kockelkoren R, de Vis JB, van der Schouw YT, van der Schaaf IC, Velthuis BK, Mali WPTM, de Jong PA; DUST study group. Risk factors for atherosclerotic and medial arterial calcification of the intracranial internal carotid artery. *Atherosclerosis*. 2018;276:44–49. doi: 10.1016/j.atherosclerosis.2018.07.008
19. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. *J Cereb Blood Flow Metab*. 2012;32:2100–2107. doi: 10.1038/jcbfm.2012.141
20. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res*. 2011;20:40–49. doi: 10.1002/mpr.329
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349. doi: 10.1016/j.jclinepi.2007.11.008
22. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, Woimant F. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology*. 2006;66:1187–1191. doi: 10.1212/01.wnl.0000208404.94585.b2
23. van der Toorn JE, Rueda-Ochoa OL, van der Schaft N, Vernooij MW, Ikram MA, Bos D, Kavousi M. Arterial calcification at multiple sites: sex-specific cardiovascular risk profiles and mortality risk-the Rotterdam Study. *BMC Med*. 2020;18:263. doi: 10.1186/s12916-020-01722-7
24. Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Tseng BM, Parker R, Riley J, Tinajero C, Zhang R. Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. *J Cereb Blood Flow Metab*. 2014;34:971–978. doi: 10.1038/jcbfm.2014.44
25. Heffernan KS, Augustine JA, Lefferts WK, Spartano NL, Hughes WE, Jorgensen RS, Gump BB. Arterial stiffness and cerebral hemodynamic pulsatility during cognitive engagement in younger and older adults. *Exp Gerontol*. 2018;101:54–62. doi: 10.1016/j.exger.2017.11.004
26. Park KY, Chung PW, Kim YB, Moon HS, Suh BC, Yoon WT. Increased pulsatility index is associated with intracranial arterial calcification. *Eur Neurol*. 2013;69:83–88. doi: 10.1159/000342889
27. Lennart JG, Jaco JMZ, Catharina JMK, Peter RL, Geert Jan B. Higher pulsatility in cerebral perforating arteries in patients with small vessel disease related stroke, a 7t MRI study. *Stroke*. 2019;50:62–68.
28. Pääkkö TJW, Perkiömäki JS, Kesäniemi YA, Ylitalo AS, Lumme JA, Huikuri HV, Ukkola OH. Increasing ambulatory pulse pressure predicts the development of left ventricular hypertrophy during long-term follow-up. *J Hum Hypertens*. 2018;32:180–189. doi: 10.1038/s41371-018-0034-5
29. Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens*. 1995;13:943–952. doi: 10.1097/00004872-199509000-00002
30. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D'Agostino RB Sr, Kannel WB, Levy D, Benjamin EJ. Pulse pressure and risk of new-onset atrial fibrillation. *JAMA*. 2007;297:709–715. doi: 10.1001/jama.297.7.709
31. Acampa M, Camarri S, Lazzerini PE, Guideri F, Tassi R, Valenti R, Cartocci A, Martini G. Increased arterial stiffness is an independent risk factor for hemorrhagic transformation in ischemic stroke undergoing thrombolysis. *Int J Cardiol*. 2017;243:466–470. doi: 10.1016/j.ijcard.2017.03.129
32. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41. doi: 10.1161/01.str.24.1.35
33. Elliott RJ, McGrath LT. Calcification of the human thoracic aorta during aging. *Calcif Tissue Int*. 1994;54:268–273. doi: 10.1007/BF00295949
34. McGrath LT, Elliott RJ. Formation of a lipid gradient across the human aortic wall during ageing and the development of atherosclerosis. *Atherosclerosis*. 1991;87:211–220. doi: 10.1016/0021-9150(91)90023-v
35. Ellisiv BM, Stein Harald J, Tom W, Kaare HB, Maja-Lisa L, Inger N. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke. *Stroke*. 2011;42:972–978.
36. van der Toorn JE, Engelkes SR, Ikram MK, Ikram MA, Vernooij MW, Kavousi M, Bos D. Vertebrobasilar artery calcification: prevalence and risk factors in the general population. *Atherosclerosis*. 2019;286:46–52. doi: 10.1016/j.atherosclerosis.2019.05.001
37. van den Beukel TC, Lucci C, Hendrikse J, Spiering W, Koek HL, Geerlings MI, de Jong PA; UCC-SMART-Studygroup. Risk factors for calcification of the vertebrobasilar arteries in cardiovascular patients referred for a head CT, the SMART study. *J Neuroradiol*. 2021;48:248–253. doi: 10.1016/j.neurad.2020.02.004
38. Yang WJ, Zheng L, Wu XH, Huang ZQ, Niu CB, Zhao HL, Leung TW, Wong LK, Chen XY. Postmortem study exploring distribution and patterns of intracranial artery calcification. *Stroke*. 2018;49:2767–2769. doi: 10.1161/STROKEAHA.118.022591