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In-Depth Carotid Calcification Morphometrics and Their Temporal Changes Are Associated with Cardiovascular Risk Factors in Patients with Recent Ischemic Event: The Plaque At Risk Study

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Keywords

Atherosclerosis · Carotid artery · Calcification · Computed tomography angiography · Cardiovascular risk factors

Abstract

Introduction: Ischemic stroke incidence varies significantly with respect to sex and cardiovascular risk factors (CVRFs), a relationship that it is not well understood. Calcification in carotid atherosclerosis is known to impact plaque stability, potentially linked to ischemic stroke. The objective was to assess the in-depth calcification morphometrics within extracranial carotid atherosclerosis, their temporal changes, and associations with sex and CVRFs. ***Methods:*** Carotid arteries ($n = 144$) with confirmed atherosclerosis and mild-to-moderate stenosis from 72 symptomatic patients (Plaque-At-Risk study) with recent ischemic event due to ischemia in the territory of a carotid artery were imaged using multidetector computed tomography angiography (MDCTA) at baseline and after 2 years. The lumen, vessel wall, and calcifications were segmented semiautomatically, and the carotid geometries were 3D reconstructed. A comprehensive morphometric assessment of carotid calcifications was performed on the baseline and follow-up scans. We investigated distributions of these metrics and their associations with sex and CVRFs using generalized linear mixed models. ***Results:*** Our findings suggest that women have larger (4.5 mm^2 [95% CI: 3.2–6.2] vs. 3.2 mm^2 [95% CI: 2.4–4.2]) calcifications, located closer to the lumen (0.6 mm [95% CI: 0.4–0.8] vs. 0.9 mm [95% CI: 0.7–1.2]) in

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contrast to men at baseline and follow-up, adjusted for baseline measurements. At the baseline, nonsmokers had larger (5.3 mm^2 [95% CI: 3.7–7.5] vs. 3.2 mm^2 [95% CI: 2.3–4.4]) and longer (5.7 mm [95% CI: 4.1–7.3] vs. 2.4 mm [95% CI: 1.6–3.6]) calcifications than the current smokers. Diabetic patients had thicker (1.1 mm [95% CI: 0.8–1.3] vs. 0.8 mm [95% CI: 0.7–0.9]) carotid calcifications at baseline. ***Conclusion:*** Our in-depth analyses exposed several geometric features of carotid calcifications associated with sex and CVRFs and provided further insight into the pathophysiology of carotid atherosclerosis.

Plain Language Summary

Calcification is highly prevalent in extracranial atherosclerotic carotid arteries. Carotid calcifications have been so far only analyzed for their prevalence, volume, or calcium score. Comprehensive morphometric analyses of carotid calcifications are still missing although this knowledge may be critical for a better understanding of carotid plaque stability and the role of carotid calcifications in cerebrovascular events. In this study, we performed an in-depth calcification morphometric analysis, including length, shape, size, proximity to the lumen, and number of calcifications, in 144 carotid arteries from 72 symptomatic patients with mild-to-moderate carotid stenosis, using multidetector computed tomography angiography (MDCTA) data collected at baseline and 2-year follow-up. Our study not only provided a detailed report of carotid calcification morphology and its change over time and also demonstrated that some morphometrics of carotid calcifications were significantly associated with sex and cardiovascular risk factors at baseline and follow-up. Our study results may provide additional insight into the underlying mechanisms of carotid atherosclerosis, the (de)stabilizing effect of carotid calcifications, influenced by their location, shape, and size, and their role in ischemic events.

Introduction

Ischemic stroke is one of the leading causes of long-term disability and is the second leading cause of death worldwide [1]. Regarding the incidence of ischemic stroke, there are significant differences related to sex and cardiovascular risk factors (CVRFs), which are not yet fully understood [2].

Within the etiological framework of ischemic stroke, carotid atherosclerosis plays a pivotal role [3]. A highly prevalent structural component in atherosclerotic carotid arteries is calcification [4]. Previous research [5] suggested higher calcification volume in carotid arteries as a stabilizing factor. On the contrary, some other cross-sectional studies found no significant association of total calcification volume or calcification presence with ischemic stroke [6, 7].

The complexity of calcification's potential stabilizing role, and its association with sex and CVRFs, suggests that more advanced and detailed calcification morphometric analyses are required. It is only recently that a few studies described the size and location of carotid calcifications [8, 9]. A thorough characterization and understanding of carotid calcification morphology, its temporal changes, and its associations with sex and CVRFs, which could provide further insights into the variations in stroke incidences associated with sex and CVRFs, remain insufficient.

In this study, a comprehensive morphometric examination of calcifications in carotid arteries with mild-to-moderate carotid stenosis was conducted, using multidetector computed tomography angiography (MDCTA) data. The baseline and follow-up MDCTA data also enabled us to analyze the temporal change of carotid calcification morphologies. The associations of the in-depth calcification morphometrics, and their temporal changes, with sex and CVRFs were investigated.

Methods

Study Population

For the present retrospective study, the baseline and the 2-year follow-up MDCTA dataset of the multicenter Plaque At RISK study (PARISK; clinical trials.gov NCT01208025) was utilized [10]. Written informed permission was provided by each patient, and Institutional Ethical Review Board (IRB) authorization (MEC 09-2-082) was acquired. The research centers' ethics committees had previously authorized the study procedure, which complied with the 1975 Declaration of Helsinki's ethical standards. The PARISK cohort consists of patients with recent (<3 months) transient ischemic attack, including amaurosis fugax and minor stroke, due to ischemia in the territory of a carotid artery with nonsevere (<70%) stenosis at baseline. A likely cause of a heart embolism (such as atrial fibrillation), renal clearance less than 30 mL/min, coagulation disorders, severe comorbidities, and known allergies to contrast agents were among the exclusion criteria.

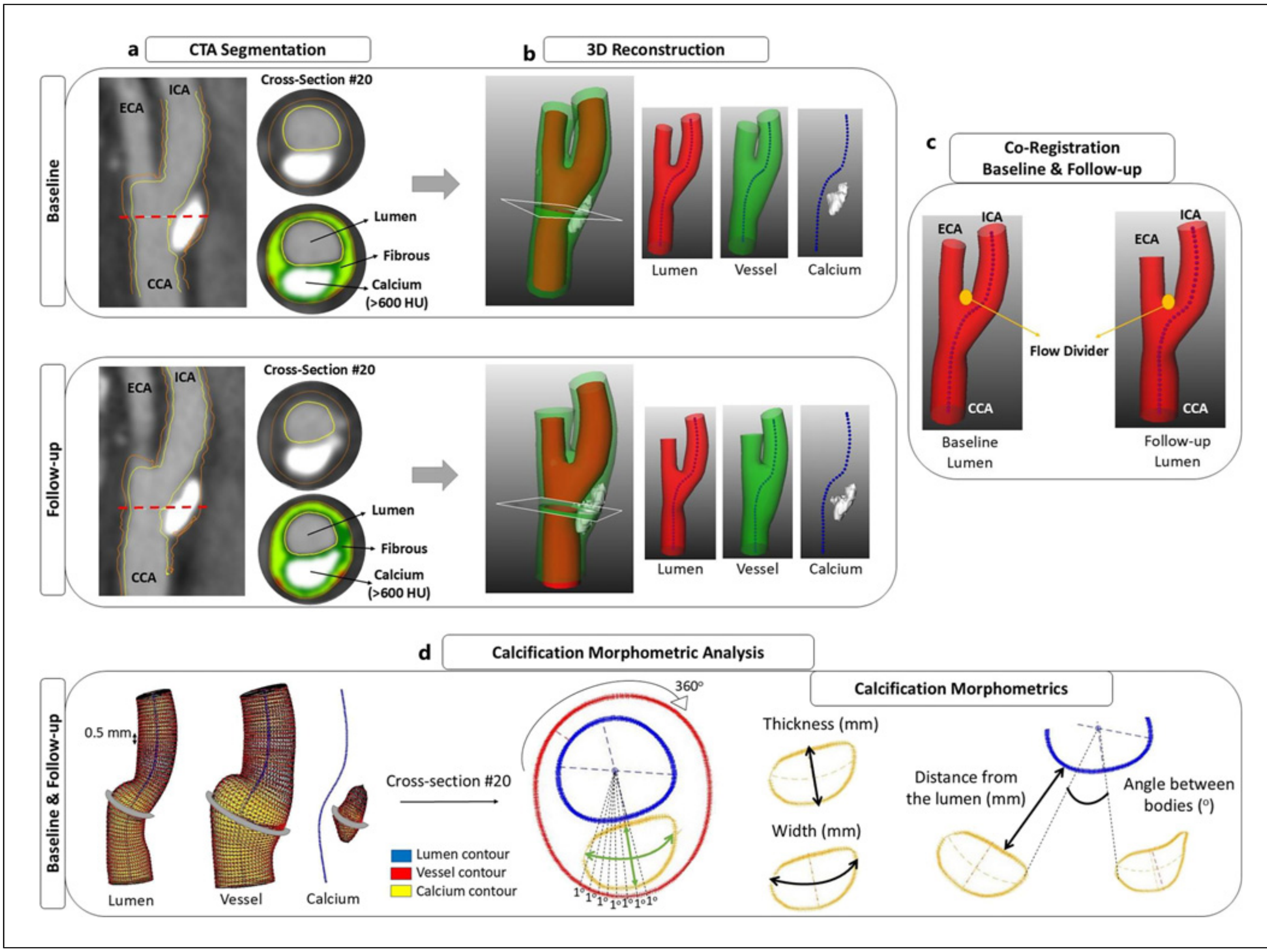


Fig. 1. Pipeline of calcification morphometric analysis. **a** CTA segmentation of CCA, ICA, and external carotid artery (ECA) based on HU. **b** 3D reconstruction of lumen, vessel wall, and calcification. **c** Co-registration of baseline and follow-up geometries. **d** In-depth calcification morphometric analysis.

For this study, we included only patients who underwent MDCTA imaging at both baseline and 2-year follow-up. Specifically, among the 244 patients enrolled in the PARISK study between September 2010 and December 2014, 51 patients did not receive MDCTA imaging due to either an allergic reaction to the iodinated contrast agent (*n* = 6), or logistical problems (*n* = 20), or glomerular filtration rate <60 mL/min with a high risk of contrast-induced nephropathy (*n* = 25). Of the 193 patients who underwent baseline MDCTA imaging, two had to be excluded due to poor scan quality. Of the remaining 191 patients with good quality baseline MDCTA scans, 118 could be scheduled for follow-up MDCTA scans (after 2 years) and the others (*n* = 73) not due to logistical problems, or informed consent withdrawal and or glomerular filtration rate <60 mL/min. Of 118 patients, the follow-up MDCTA scans could be performed on 82 patients only and not on the others (*n* = 36), because of logistical problems (*n* = 13), contraindications for contrast material (*n* = 11), informed consent withdrawal (*n* = 9), and patient death (*n* = 3). A detailed description of our study design flowchart is available in online supplementary Data: Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000546164), and further details regarding the study design have been previously published [10].

MDCTA Scan Protocol

The baseline and follow-up MDCTA datasets used in the current study had been acquired with a 16-, 64-, or 128-slice multidetector row CT system. The cerebral circulation

Table 1. Baseline characteristics of the study population

	All	Men	Women
n (%)	72	54 (75)	18 (25)
NASCET score, median [IQR]	29.4 [13.5–38.4]	29.4 [14–37.3]	25.1 [8.9–41]
ECST score, median [IQR]	57.5 [49–67.5]	58.4 [49.4–68.5]	52.5 [45.5–66.7]
Age, years, mean±SD	66±7.6	66±8.4	64±9.3
Medication			
Antidiabetic, *n* (%)	13 (18)	10 (13)	3 (5)
Lipid-lowering, *n* (%)	35 (48)	17 (23)	18 (25)
Antihypertensive, *n* (%)	40 (55)	23 (32)	17 (23)
BMI, kg/m^2, mean±SD	26±4.3	26±4.1	26±3.7
Diabetes mellitus, *n* (%)	13 (18)	11 (20.4)	2 (11.1)
Hypertension, *n* (%)	48 (66.6)	38 (70.3)	10 (55.5)
Hypercholesterolemia, *n* (%)	58 (80.5)	43 (79.6)	15 (83.3)
Smoking, *n* (%)			
Current	22 (31)	14 (26)	8 (44)
Former	31 (43)	26 (48)	5 (28)
Never	19 (26)	14 (26)	5 (28)

NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; IQR, interquartile range; SD, standard deviation.

(3 cm above the sella turcica) and the ascending aorta were both included in the scan range. At an injection rate of 4 or 5 mL per second, each patient received 80–85 mL of an iodinated contrast agent (300–320 mg/mL) and a 45-mL saline bolus chaser. A detailed description of the imaging protocol has been previously published [10].

Calcification Analysis

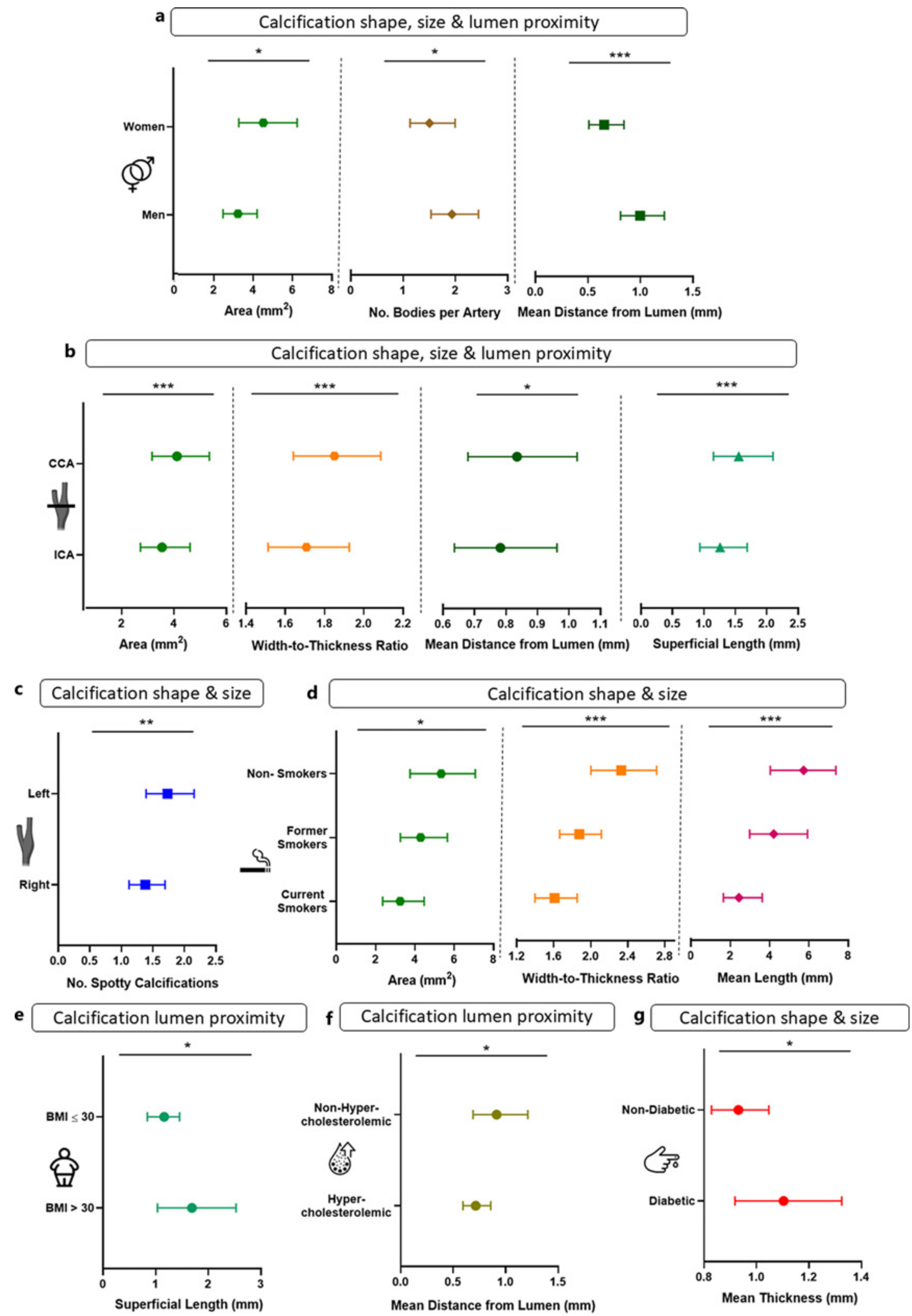
Segmentation, 3D Reconstruction, and Co-Registration

A trained reader (A.T.), blinded to the anonymized clinical data of the patients, performed semiautomatic lumen, vessel, and calcification segmentation of the carotid bifurcations (common carotid artery [CCA], external carotid artery, and internal carotid artery [ICA]) on both sides at baseline and follow-up, using the QAngioCT RE, Medis Suite software package (Research Edition, version 3.2.0.13, Medis Medical Imaging Systems, Leiden, The Netherlands) [11]. A minimum of 30 horizontal computed tomography angiography (CTA) slices upstream and downstream of the carotid bifurcation were chosen in order to identify the region of interest. Then, QAngioCT performed longitudinal contouring, based on Hounsfield units (HU), of the inner lumen (320–500 HU) and outer vessel wall (>90 HU) automatically [12], and manual adjustments were made as needed. The HU for the calcification detection was ≥600 HU [13] to distinguish the calcifications from and the contrast agent (Fig. 1a). The reader and a second trained reader (F.F.) re-segmented and evaluated independently a subset of 30 patients at baseline and follow-up (120 arteries) to assess the intra-observer and interobserver variability, respectively.

The baseline and follow-up 2D contours of the lumen, vessel wall, and calcifications were transformed into 3D solid surfaces via in-house developed MATLAB (v.2017B, MathWorks, Inc., USA) code (Fig. 1b). For each patient, the 3D volumetric geometries at baseline and follow-up were co-registered and aligned longitudinally and circumferentially using the information of the lumen flow divider point location at the carotid bifurcation [14], the location of the ICA and the external carotid artery, and the reconstructed lumen centerlines (Fig. 1c). Slice distance was kept the same at baseline and follow-up scans.

Calcification Morphometric Analyses

The following parameters were evaluated using the QAngioCT RE: vessel wall volume (including calcifications), absolute and relative (per vessel) total calcification volume, number of calcifications per vessel, and total volume of each calcification. The reconstructed centerline at the lumen was utilized to provide cross-sections of the arterial lumen, wall, and calcifications that are orthogonal to the centerline, with 0.5 mm separating each cross-section (Fig. 1d).



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At each cross-sectional slice, 2D calcification metrics were calculated based on the radial lines at every 1° originating from the lumen center (Fig. 1d). The 2D calcification metrics included calcification area, thickness, width, distance from the lumen, and the length of the superficial calcifications. The 3D calcification metrics included the number of calcifications and spotty calcifications, calcification volume, length, and the contact area of superficial calcifications with the lumen. A detailed description of the in-depth calcification morphometrics assessment is presented at online supplementary Data.

Cardiovascular Risk Factors at Baseline

CVRFs assessed included hypercholesterolemia, hypertension, diabetes, smoking status, obesity (defined as body mass index [BMI] >30), and use of cardiovascular medication. Hypercholesterolemia was defined as a total cholesterol level of >5 mmol/L or the use of lipid-lowering drugs at baseline. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg on clinical examination or the use of antihypertensive medication. Diabetes was defined as a serum glucose level of >6.9 mmol/L, a 2-h post-load glucose level of >11.0 mmol/L, or the use of antidiabetic medication [14]. Smoking status at baseline was split into current, former and nonsmokers.

Statistical Analysis

The distribution of continuous variables is presented as mean and standard deviation or in case of skewed distribution, as median and interquartile range (Q1–Q3), and the categorical variables are presented as absolute numbers and relative frequencies. The intra- and interobserver reliability of the cross-sectional area measurements (lumen, vessel wall, plaque burden, calcification) was determined by calculating the intraclass correlation coefficient, coefficient of variation, and Bland-Altman plots for each metric. The correlations among the 2D and 3D calcification metrics were assessed using the Spearman correlation test.

To comprehensively address our research objective of investigating the association of the 2D and 3D calcification morphological metrics with sex, artery (right-left), and CVRFs, we applied the following strategy. First, we calculated the distributions of the metrics at baseline and follow-up. Then, we used the mixed-effect model to investigate the associations at baseline and follow-up. Since the residuals of the mixed model were not normally distributed, the generalized linear mixed model was used with gamma regression distribution and log link transformation. The sex, artery (right-left), location (CCA-ICA), hypertension, hypercholesterolemia, obesity, smoking status, and diabetes mellitus were implemented as fixed factors. Repeated p-values evaluation was corrected using the Bonferroni procedure. Statistical analyses were conducted utilizing SPSS (IBM 27), and a two-tailed $p < 0.05$ was deemed significant. The artery and patient information was used as random factors to account for the intra-artery and within-patient correlation when multiple calcifications were segmented within the same patient, while correcting for the patient's age and vessel wall thickness. The follow-up analysis was adjusted for baseline calcification metrics to reflect the change over time.

Results

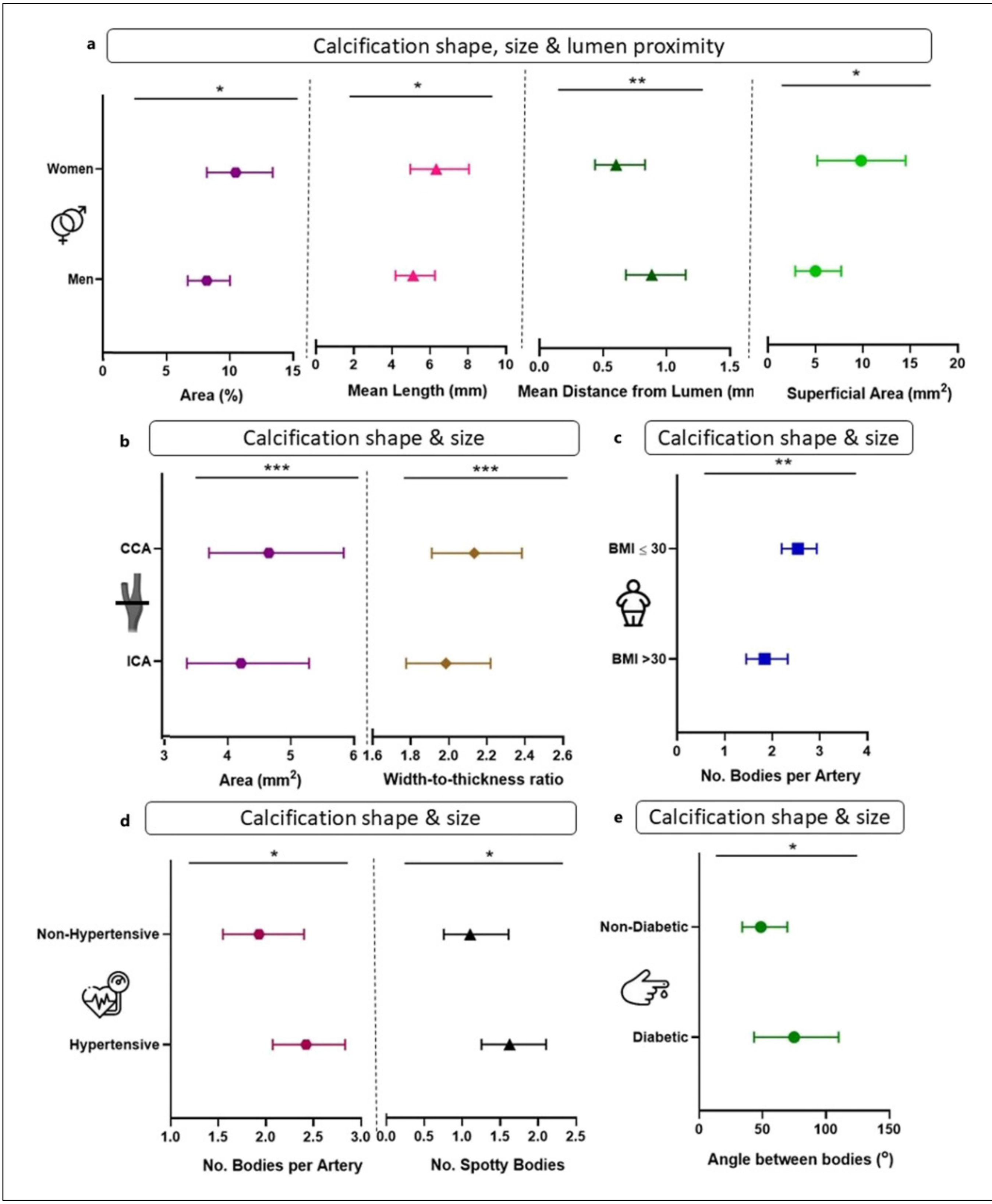
Patient Characteristics

Of the 82 patients of the PARISK cohort who underwent MDCTA imaging at baseline and 2-year follow-up, 10 patients were excluded from any prospective analysis, due to either low-quality CTA scans ($n = 2$) or lack of calcifications in both carotids at baseline and follow-up ($n = 8$). The present study examined the remaining individuals ($n = 72$). Of these patients, 64 had bilateral calcifications and 4 had one-sided (right side) calcifications both at baseline and follow-up. The remaining 4 patients had one-sided (right side) calcifications at baseline and bilateral calcifications at follow-up (online suppl. Data: Fig. S1). In Table 1, the population's characteristics at the time of inclusion are listed and there were no significant differences in CVRFs between men and women. Regarding the CVRFs at the follow-up, 6 patients quit smoking, and similar patient distribution in the other CVRFs was observed.

Calcification Morphometrics at Baseline and Follow-Up

The intra- and interobserver variability assessment demonstrated excellent agreement with intraclass correlation coefficient >0.92 and coefficient of variation

Fig. 2. Baseline associations of calcification metrics with sex, artery, and CVRFs based on the generalized linear mixed model. Associations of carotid calcification: shape, size, and lumen proximity with sex (**a**); shape, size, and lumen proximity with ICA and CCA (**b**); shape and size with left and right artery (**c**); shape and size with smoking (**d**); lumen proximity with patients with BMI >30 (**e**); lumen proximity with hypercholesterolemia (**f**); and shape and size with diabetes (**g**). Data are presented as mean with 95% CI. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.



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16.5% in lumen, 8.2% in vessel wall, 3.1% in plaque burden, and 5.6% in calcification area cross-sectional measurements (online suppl. Data: Table S1; Fig. S2).

At baseline, no correlation was found between the calcification morphometrics other than the expected ones, i.e., the correlation of area with thickness and width (r = 0.89), the correlation of volume with length (r = 0.74), and the number of calcifications with the number of spotty calcifications (r = 0.8) (online suppl. Data: Table S2). At the follow-up, the correlation analysis (online suppl. Data: Table S4) showed that besides the correlations present for the baseline measurements, the number of calcifications correlated with the arc-angle between them (r = 0.78) and the calcification width with the calcification width-to-thickness ratio (r = 0.72).

For the calcification morphometric analysis at baseline, only the cross-sections with at least one calcification body were selected (29%, n = 2,037 out of 6,910). At baseline, the vessel wall thickness was (median [IQR]) 3.2 mm [2.6–4.0], and in online supplementary Data (Table S3), a detailed analysis of the absolute and relative 2D and 3D calcification morphometrics at baseline is presented. For the 2-year follow-up analysis, cross-sections with at least one calcification body at baseline and/or follow-up were selected to study the calcification change over time (40%, n = 2,745 out of 6,910). At follow-up, the vessel wall thickness was a median of 3.6 mm (IQR: 2.9–4.4), with detailed analyses of absolute and relative calcification morphometrics available in online supplementary Table S5 and S6.

Sex, CVRFs, and Calcification Morphometrics

Women vs. Men

Generalized linear mixed model analyses at baseline demonstrated that women's carotid arteries presented larger calcifications, regarding calcification area, thickness, and width, than those of the men. Moreover, women had fewer calcification bodies and their calcifications were closer to the lumen (shorter absolute and relative calcification-lumen distances) (Fig. 2a). At the follow-up, after adjusting for baseline values to reflect the change over time, calcifications in women were still larger (in area, thickness and width) and longer than men. They were also closer to the lumen and had a larger superficial area (Fig. 3a).

Common vs. Internal and Left vs. Right Carotids

The flow divider was used to separate the CCA and ICA. Compared to the ICA cross-sections at baseline, the CCA cross-sections had larger calcifications (in area, thickness, and width) and greater width-to-thickness ratios, presenting circumferentially longer shapes. They were also further away from the lumen than their ICA counterparts (Fig. 2b). Left carotids presented more spotty calcifications than right carotids (Fig. 2c). At the follow-up, CCAs had larger calcifications with greater width-to-thickness ratio at follow-up, after adjusting for baseline values (Fig. 3b). The right and left carotids did not significantly differ in calcification parameters at follow-up.

Cardiovascular Risk Factors

Current smokers at the baseline presented smaller and shorter calcifications, with a smaller width-to-thickness ratio (Fig. 2d) compared to former and nonsmokers. The data showed a positive trend in calcification area, length, and width-to-thickness ratio, progressing from current smokers to former smokers and then to nonsmokers (Fig. 2d). Patients with BMI >30 had longer superficial calcifications (Fig. 2e). Patients with hypercholesterolemia had their carotid calcifications closer to the lumen (Fig. 2f) and diabetic patients had thicker calcifications (Fig. 2g). Patients with a BMI under 30 had more calcifications at follow-up than those with a BMI over 30 (Fig. 3c), and in hypertensive patients compared to normotensive patients, after adjusting for baseline values (Fig. 3d). Hypertensive patients had also more spotty calcifications at follow-up (Fig. 3d). Diabetic patients had more spread calcifications, derived from the angle measurements between calcifications (Fig. 3e).

Discussion

A comprehensive evaluation of calcification morphology in carotid arteries was performed in this study, extracted from MDCTA data. To the best of our knowledge, this is the first in-depth evaluation of the carotid calcification morphology, which goes beyond the state-of-the-art calcification prevalence, score, and volume assessment. Our study has revealed important differences in calcification morphometrics associated with

Fig. 3. Follow-up associations of calcification metrics with sex and CVRFs based on the generalized linear mixed model. Associations of carotid calcification: shape, size, and lumen proximity with sex (**a**); shape and size with ICA and CCA (**b**); shape and size with patients with BMI >30 (**c**); shape and size with hypertension (**d**); and shape and size with diabetes (**e**). Data are presented as mean with 95% CI. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

sex, smoking, obesity, hypercholesterolemia, hypertension, and diabetes at baseline and 2-year follow-up.

A recent meta-analysis [15] on traditional carotid calcification volume measurements reported no significant difference between men and women, relative to the plaque volume. This finding was also confirmed by our current analysis. However, our detailed morphometric analysis revealed numerous, statistically significant sex-related differences in calcification shape and size, which can be possibly attributed to different levels of estrogen [16]. Compared to women, men presented more and smaller calcification bodies both at baseline and follow-up. Moreover, men and women had significant differences in calcification proximity to the lumen and superficial area. Previous research [9] highlighted the association of superficial calcifications with the presence of intraplaque hemorrhage, a plaque vulnerability marker, influencing atherosclerotic carotid plaque instability. From a biomechanical standpoint, superficial calcifications may generate stress concentration points around the lumen, due to their greater stiffness compared to the plaque tissue, causing a potential carotid plaque rupture [17].

The presence of multiple spotty calcifications was shown to be associated with intraplaque hemorrhage [18]. Selwaness et al. [19] reported more intraplaque hemorrhage in left carotid arteries. Our finding of a higher number of spotty calcifications in left carotids at baseline might point to a higher vulnerability in the left carotids.

The current smokers in our study group had smaller calcifications (in terms of all size-related metrics, i.e., width, thickness, and length) compared to former and nonsmokers at baseline. This finding indicates a higher prevalence of less calcified, "softer" plaques in the carotids of current smokers, which are considered to be more likely to undergo plaque rupture [20]. Moreover, previous research demonstrated an association of diabetes mellitus with a higher prevalence of calcifications in carotid arteries [21]. Our detailed morphometric analysis not only supports this finding but also shows that diabetic people have thicker calcifications, with increased arc angle between calcifications over time.

Earlier research reported a significant association of calcification prevalence with hypercholesterolemia [22], and of calcification presence and score with obesity [23]. Our current study showed furthermore that the calcifications in patients with hypercholesterolemia were closer to the lumen, and that the patients with BMI >30 presented longer superficial calcifications and less calcification bodies over time.

There are some limitations in this analysis that should be taken into account. We segmented calcifications >600 HU [13] with potential underestimation of the total calcification amount and missing the low-density calcifications. One must note the potential reverse effect of medication on plaque calcification growth [24]. Therefore, our results, especially the follow-up results, must be interpreted cautiously. To investigate the association of calcification metrics with CVRFs, independent of possible drug effects, a randomized clinical trial should be performed. Our study focused on carotid calcifications; hence, standard clinical CTA scans were sufficient. However, new advancements in CT imaging, such as photon-counting computed tomography, can also provide some information on soft plaque components and their relation to calcifications [25]. Furthermore, our study focused on calcification morphometric analysis at the cross-sectional level at both baseline and follow-up, which limited our ability to calculate associations between the individual morphometric changes and individual CVRF changes, as well as to conduct a longitudinal study.

Conclusion

In this study, we conducted a comprehensive morphometric assessment of extracranial carotid calcifications, evaluating parameters such as length, width, thickness, area, and proximity to the lumen. Besides reporting the calcification morphometrics, and their temporal changes, we demonstrated associations of calcification shape, size, and proximity to the lumen with sex and CVRFs. These findings suggest that the detailed carotid calcification morphometrics may help further elucidate the variations in stroke incidence associated with sex and CVRFs.

Acknowledgments

We thank the study participants and the clinical staff for their dedication and involvement to the Plaque At Risk (PARISK) Study.

Statement of Ethics

The study was approved by the Institutional Medical Ethics Committee of all participating centers and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each participant before enrollment (MEC 09-2-082).

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Aikaterini Tziotziou: data analysis, software development, and writing – original draft. Federica Fontana: data analysis and writing – review and editing. Suze-Anne Korteland: software development and writing – review and editing. Kelly Nies, Paul Nederkoorn, Pim A de Jong, and M. Eline Kooi: data collection and writing – review and editing. Aad van der Lugt and Anton F.W. van der Steen: supervision and writing – review and editing. Jolanda J. Wentzel: conceptualization, and writing – review and editing. Daniel Bos and C. Akyildiz: supervision, conceptualization, writing – review and editing.

Data Availability Statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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