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Presence of calcified carotid plaque predicts vascular events: the Northern Manhattan Study

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Abstract

OBJECTIVE: The prognostic implications of carotid plaque calcification (CPC) relative to subsequent vascular events are unclear. Our aim was to determine the association between CPC and risk of vascular events in a prospective multi-ethnic cohort.

METHODS: CPC was assessed among 1,118 stroke-free subjects (mean age 68±8years; 59% women; 59% Hispanic, 22% black, 19% white) from the Northern Manhattan Study using high-resolution B-mode ultrasound. CPC was defined by presence of any acoustic shadowing associated with carotid plaque, producing a reduction in echo amplitude due to intervening structures with high attenuation. Using Cox proportional hazards models, hazard ratios (HR) were estimated for the combined vascular outcome, defined as ischemic stroke (IS), myocardial infarction (MI) or vascular death (VD).

RESULTS: Carotid plaque was present in 637 (57%) subjects. CPC was present in 225 subjects (20% of total cohort; 35% of those with plaque). During a mean follow-up time of 2.7 years, the combined vascular outcome occurred among 52 subjects (20 IS, 22 MI, and 24 VD). Adjusting for demographics, major vascular risk factors, and carotid intima media thickness, those with CPC (in comparison to those without plaque) had a significantly increased risk of the combined vascular outcome (HR 2.5, 95% CI 1.0-5.8).

CONCLUSIONS: In this population-based cohort, the presence of calcified carotid plaque, as assessed by high-resolution B-mode ultrasound, was an independent predictor of vascular events.

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It may serve as a simple and non-invasive marker of increased atherosclerotic risk and further aid in vascular risk stratification.

Keywords

acoustic shadowing; ultrasound; plaque morphology

INTRODUCTION

The association between cardiovascular disease and vascular calcium deposition has been known since the 19th century. More recent studies have confirmed that coronary artery calcification, as detected by electron beam computed tomography (EBCT), is a marker of CAD severity and a predictor of coronary events¹⁻⁴ and stroke.⁵ However, studies assessing the association between carotid plaque calcification (CPC) and vascular events have produced more conflicting results.⁶⁻⁹ Hence, we undertook this study to prospectively determine the association between CPC, as assessed by ultrasonography, and the incidence of vascular events in a multiethnic stroke-free cohort. We hypothesized that presence of CPC increases the risk of vascular events.

METHODS

Subjects and baseline evaluation

As previously described,¹⁰ The Northern Manhattan Study (NOMAS) is an ongoing prospective cohort study of stroke risk factors and outcomes. Between 1993 and 1997, 3,298 subjects were enrolled who were stroke-free, > 40 years of age, and residing in northern Manhattan. A carotid plaque calcification and intima-media thickness (IMT) sub-study of NOMAS began in 2000. Ultrasound data with at least one annual follow-up visit were available for 1,118 NOMAS subjects.

Baseline data collection was standardized, as described elsewhere.¹⁰ Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg based on the mean of 2 blood pressure measurements, self-report of a diagnosis of hypertension, or treatment with anti-hypertensive medications. Diabetes was defined as fasting blood glucose >127 mg/dL, self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Cardiac disease was defined as a history of coronary artery disease, valvular disease, or congestive heart failure. Hypercholesterolemia was defined as fasting total cholesterol > 200 mg/dl, prior history, or lipid-lowering medication use.

Carotid ultrasonography

Carotid ultrasound was performed using high-resolution B-mode ultrasound system GE LogIQ 700 with a multi-frequency 9/13 MHz linear-array probe and previously described scanning protocols.^{11, 12} Both common (CCA) and internal (ICA) carotid arteries were examined for the presence of atherosclerotic plaque, defined as an area of a focal protrusion 50% greater than the neighboring wall. Carotid IMT was measured using a standardized protocol.¹² In the presence of carotid plaque in any of the carotid segments, IMT was

measured outside the portion of plaque. Mean IMT was calculated as the average of the maximal IMT at 12 sites: the near and far walls of CCA, bifurcation, and ICA bilaterally.

Acoustic shadowing (AS) was defined as a reduction in amplitude of echoes caused by intervening structures with high attenuation.¹³⁻¹⁷ The presence of carotid plaque and any AS was recorded (Figure 1). The inter-rater agreement for repeat detection of AS in our laboratory was good (kappa 0.77-0.86). Subjects were stratified into 3 groups with: a) no carotid plaque; b) carotid plaque without AS (non-calcified plaque); and c) any carotid plaque with AS (calcified plaque). AS alone (without presence of plaque) was considered artefactual and, therefore, not recorded.

Annual prospective follow-up

As previously described,¹⁰ follow-up was done by hospital surveillance and annual telephone interviews, with in-person visits for those who screened positive. Stroke was defined as the first symptomatic occurrence of ischemic stroke (IS) and myocardial infarction (MI) was defined as previously described.¹⁰ Deaths were classified as vascular or nonvascular. Causes of vascular death (VD) included IS, MI, heart failure, pulmonary embolus, and cardiac arrhythmia. Time to the combined vascular outcome was defined as time to first IS, MI, or VD.

Statistical analysis

Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for the combined vascular outcome. In the separate models, the following comparisons were performed: a) subjects with any calcified plaque versus those without plaque; b) subjects with only non-calcified plaque versus those without plaque; and c) subjects with any calcified plaque versus those with only non-calcified plaque. Adjustments were performed for age, gender, race, education, diabetes mellitus, hypertension, hypercholesterolemia, any cardiac disease, current smoking, and mean carotid IMT. SAS was used for data management and analysis, with statistical significance defined at the standard $\alpha = 0.05$ level.

RESULTS

Among 1,118 subjects (mean age 68 ± 8 years; 59% women; 59% Hispanic, 22% black, 19% white), 481 (43.0%) had no plaque, 412 (36.9%) had only non-calcified plaque, and 225 (20.1%) had calcified plaque. Baseline characteristics of the cohort are shown in Table 1. Those who had calcified plaque were older, more frequently white, more likely to have completed high school, more commonly had concurrent vascular risk factors such as diabetes, hypercholesterolemia, and cardiac disease. Mean IMT was higher in those with plaque, with or without AS, compared to those without plaque. All the subjects in our study were asymptomatic at baseline and, by chance, none had internal carotid artery stenosis > 60%.

Over a mean follow-up time of 2.7 years, the combined vascular outcome occurred among 52 (4.7%) subjects (20 IS, 22 MI, and 24 VD). The estimated annual incidence for each outcome was highest among subjects with calcified carotid plaque compared to the other 2

groups (Figure 2). For the combined vascular outcome, the average annual incidence per 100,000 persons was greatest for calcified plaque (1,606) compared to non-calcified plaque (1,151) or no plaque (491).

Table 2 summarizes the different models developed to predict the combined vascular outcome. Using no plaque as the reference, the unadjusted HR for non-calcified plaque was 2.6 (95% CI 1.3-5.3) while for calcified plaque, it was 3.6 (95% CI 1.7-7.5). Adjusting for age, sex, race-ethnicity decreased the estimates for both: non-calcified plaque (HR 1.7, 95% CI 0.8-3.5) and calcified plaque (HR 2.1, 95% CI 1.0-4.6). In the final model adjusting for demographics, mean carotid IMT, education, and vascular risk factors, calcified plaque remained a significant predictor of combined vascular outcomes (HR 2.4, 95% CI 1.0-5.8), while the effect of non-calcified was significantly attenuated (HR 1.5, 95% CI 0.7-3.4). Comparing calcified versus non-calcified plaque, there was no significant difference in event risk (adj. HR 1.6, 95% CI 0.8-3.2).

COMMENT

We found that the presence of calcified carotid plaque was a strong and independent predictor of the combined vascular events. The association was independent of traditional cardiovascular risk factors. The effect was also independent of carotid IMT, an established strong predictor of vascular events.¹⁸ Our results are consistent with some prior studies and support the hypothesis that arterial calcification signifies in-situ plaque vulnerability and serves as a marker for generalized atherosclerosis.

A study using EBCT to measure degree of CPC reported significant correlation with advancing stenosis and neurologic symptoms.⁷ In the Atherosclerosis Risk In Communities (ARIC) study, carotid plaque with acoustic shadowing was an independent predictor of both IS and MI⁶ and recurrent cardiovascular disease.¹⁹ Another study among acute coronary patients found that CPC independently predicted subsequent MI and cardiac death.²⁰ Thus, although CPC may produce cerebrovascular symptoms directly via embolization or flow limitation, it may be a better marker of the extent and vulnerability of plaques in other vascular beds. However, other studies have found either an inverse or no relationship between CPC and vascular risk.^{8,9,21,22}

Arterial calcification involves a complex, regulated process of bio-mineralization resembling osteogenesis.²³ In general, soft tissue calcification arises in areas of chronic inflammation, possibly functioning as a barrier limiting the spread of the inflammatory stimulus. As a corollary, arterial calcification may be an example of this process in which oxidized lipids are the inflammatory stimulus and calcification is a protective response to the development of atherosclerosis.^{24, 25}

Physiological mechanisms may explain the bivalent property of CPC observed in longitudinal studies. Early in the atherosclerotic process, the mechanical instability introduced by areas of plaque calcification at the interface with softer non-calcified plaque may promote plaque rupture and symptomatology.^{26, 27} An increase in arterial stiffness and loss of distensibility compounds the problem.²⁸ As arterial calcification proceeds, this

interface area between rigid and distensible (softer) plaque initially increases, perhaps accounting for increased symptoms in heterogeneous plaques. Eventually, this interface area decreases as calcified regions coalesce. It follows, then, that the risk of rupture of plaques increases initially until the point at which the calcified plaques coalesce. Calcification beyond this point may be associated with plaque stabilization. Ultimately, the most valuable prognostic parameter may be total surface area of calcification rather than calcium score or mass. This hypothesis may be difficult, however, to test in large epidemiological studies because the interface area and total calcified area cannot be measured by ultrasonography.

Our study is one of few large population-based studies to show a significant association between presence of CPC and increased risk of vascular events. However, there are also some potential limitations. First, despite increased unadjusted incidence rates for IS, MI, and VD among those with CPC, we were unable to make further adjustments for specific vascular outcomes due to insufficient statistical power. Second, B-mode ultrasound detects the presence or absence of AS and does not quantify CPC. Although studies have not validated that AS only occurs in the presence of mineralization, the only reported non-artefactual cause of AS is mineralization.^{13, 17} In addition, studies comparing histology with ultrasound findings have reported a strong positive correlation between mineralization and the echogenicity of the lesion.¹⁴⁻¹⁶ Compared with EBCT, ultrasound is operator-dependent and provides primarily qualitative data. EBCT has been shown to quantify carotid calcification more precisely than ultrasound using gray-scale.²⁹ However, novel and more objective computer-assisted methods of assessment of plaque echogenicity using gray-scale medians have been recently introduced and their validation is ongoing.³⁰ Ultrasonography remains a readily available, reproducible, and non-invasive modality to detect CPC as a marker of global vascular risk.

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Abbreviations:

CI	confidence intervals
AS	acoustic shadowing
IMT	intima-media thickness
IS	ischemic stroke
MI	myocardial infarction
VD	vascular death

REFERENCES

1. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36(4):1253–1260. [PubMed: 11028480]

2. Keelan PC, Bielak LF, Ashai K, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation*. 2001;104(4):412–417. [PubMed: 11468202]
3. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation*. 2000;101(8):850–855. [PubMed: 10694523]
4. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;86(5):495–498. [PubMed: 11009264]
5. Vliegenthart R, Hollander M, Breteler MM, et al. Stroke is associated with coronary calcification as detected by electron-beam CT: the Rotterdam Coronary Calcification Study. *Stroke*. 2002;33(2):462–465. [PubMed: 11823653]
6. Hunt KJ, Evans GW, Folsom AR, et al. Acoustic shadowing on B-mode ultrasound of the carotid artery predicts ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2001;32(5):1120–1126. [PubMed: 11340220]
7. Nandalur KR, Baskurt E, Hagspiel KD, et al. Carotid artery calcification on CT may independently predict stroke risk. *AJR Am J Roentgenol* 2006;186(2):547–552. [PubMed: 16423966]
8. Seeger JM, Barratt E, Lawson GA, Klingman N. The relationship between carotid plaque composition, plaque morphology, and neurologic symptoms. *J Surg Res* 1995;58(3):330–336. [PubMed: 7885031]
9. Shaalan WE, Cheng H, Gewertz B, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg* 2004;40(2):262–269. [PubMed: 15297819]
10. Sacco RL, Anand K, Lee HS, et al. Homocysteine and the risk of ischemic stroke in a triethnic cohort: the Northern Manhattan Study. *Stroke*. 2004;35(10):2263–2269. [PubMed: 15345803]
11. Elkind MS, Cheng J, Boden-Albala B, Paik MC, Sacco RL. Elevated white blood cell count and carotid plaque thickness: the northern manhattan stroke study. *Stroke*. 2001;32(4):842–849. [PubMed: 11283380]
12. Rundek T, Elkind MS, Pittman J, et al. Carotid intima-media thickness is associated with allelic variants of stromelysin-1, interleukin-6, and hepatic lipase genes: the Northern Manhattan Prospective Cohort Study. *Stroke*. 2002;33(5):1420–1423. [PubMed: 11988625]
13. Wolverson MK, Bashiti HM, Peterson GJ. Ultrasonic tissue characterization of atheromatous plaques using a high resolution real time scanner. *Ultrasound Med Biol* 1983;9(6):599–609. [PubMed: 6670145]
14. Ratliff DA, Gallagher PJ, Hames TK, Humphries KN, Webster JH, Chant AD. Characterisation of carotid artery disease: comparison of duplex scanning with histology. *Ultrasound Med Biol* 1985;11(6):835–840. [PubMed: 3913082]
15. Kagawa R, Moritake K, Shima T, Okada Y. Validity of B-mode ultrasonographic findings in patients undergoing carotid endarterectomy in comparison with angiographic and clinicopathologic features. *Stroke*. 1996;27(4):700–705. [PubMed: 8614934]
16. Goes E, Janssens W, Maillet B, Freson M, Steyaert L, Osteaux M. Tissue characterization of atheromatous plaques: correlation between ultrasound image and histological findings. *J Clin Ultrasound* 1990;18(8):611–617. [PubMed: 2172307]
17. Carotid artery plaque composition--relationship to clinical presentation and ultrasound B-mode imaging. European Carotid Plaque Study Group. *Eur J Vasc Endovasc Surg* 1995;10(1):23–30. [PubMed: 7633965]
18. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340(1):14–22. [PubMed: 9878640]
19. Wattanakit K, Folsom AR, Chambless LE, Nieto FJ. Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2005;149(4):606–612. [PubMed: 15990741]

20. Komorovsky R, Desideri A, Coscarelli S, et al. Prognostic implications of sonographic characteristics of carotid plaques in patients with acute coronary syndromes. *Heart*. 2005;91(6): 819–820. [PubMed: 15894789]
21. O'Holleran LW, Kennelly MM, McClurken M, Johnson JM. Natural history of asymptomatic carotid plaque. Five year follow-up study. *Am J Surg* 1987;154(6):659–662. [PubMed: 3322073]
22. Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke*. 2004;35(12):2788–2794. [PubMed: 15528460]
23. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol* 2004;24(7):1161–1170. [PubMed: 15155384]
24. Hunt JL, Fairman R, Mitchell ME, et al. Bone formation in carotid plaques: a clinicopathological study. *Stroke*. 2002;33(5):1214–1219. [PubMed: 11988593]
25. Demer LL, Tintut Y. Mineral exploration: search for the mechanism of vascular calcification and beyond: the 2003 Jeffrey M. Hoeg Award lecture. *Arterioscler Thromb Vasc Biol* 2003;23(10): 1739–1743. [PubMed: 12958041]
26. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on Assuring of coronary atherosclerotic plaques. *Lancet*. 1989;2(8669):941–944. [PubMed: 2571862]
27. Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ. Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. *Circulation*. 1991;83(5): 1764–1770. [PubMed: 2022029]
28. Zureik M, Bureau JM, Temmar M, et al. Echogenic carotid plaques are associated with aortic arterial stiffness in subjects with subclinical carotid atherosclerosis. *Hypertension*. 2003;41(3): 519–527. [PubMed: 12623953]
29. Denzel C, Lell M, Maak M, et al. Carotid artery calcium: accuracy of a calcium score by computed tomography-an in vitro study with comparison to sonography and histology. *Eur J Vasc Endovasc Surg* 2004;28(2):214–220. [PubMed: 15234704]
30. Sztajzel R, Momjian S, Momjian-Mayor I, et al. Stratified gray-scale median analysis and color mapping of the carotid plaque: correlation with endarterectomy specimen histology of 28 patients. *Stroke*. 2005;36(4):741–745. [PubMed: 15705933]

Figure 1.
Ultrasonographic examples of carotid artery plaques a) with AS and b) without AS

Figure 2.
Average annual incidence per 100,000 for vascular outcomes by carotid artery lesion

Table 1.

Baseline characteristics of the cohort (n=1,118)

	No plaque (n=481)	Plaque without AS (n=412)	Plaque with AS (n=225)
*Age in years, mean (SD)	63.8 (7.7)	67.1 (8.2)	70.3 (8.5)
Male, n (%)	178 (37.0)	178 (43.2)	94 (41.3)
**Race, n (%)			
White	55 (11.8)	82 (20.7)	70 (31.4)
Black	91 (19.4)	84 (21.2)	59 (26.5)
Hispanic	322 (68.8)	231 (58.2)	94 (42.2)
**Completed high school	200 (41.6)	204 (49.5)	135 (60.0)
Current smoker, n (%)	49 (10.2)	49 (11.9)	34 (15.1)
Hypertension, n (%)	338 (70.3)	306 (74.3)	175 (77.8)
**Hypercholesterolemia, n (%)	253 (52.6)	261 (63.4)	162 (72.0)
**Diabetes, n (%)	82 (17.1)	106 (25.7)	47 (20.9)
***Cardiac disease, n (%)	74 (15.4)	81 (19.7)	52 (23.1)
*IMT in mm, mean (SD)	0.65 (0.15)	0.70 (0.17)	0.71 (0.18)

* ANOVA, $p < 0.01$ ** chi-square, $p < 0.01$ *** chi-square, $p < 0.05$

Table 2.

Hazard ratios and 95% CI for combined vascular outcome (stroke, MI, or vascular death)

	Unadjusted	Model 1*	Model 2 [#]	Model 3 [‡]
Plaque with AS vs. no plaque	3.6 (1.7-7.5)	2.1 (1.0-4.6)	2.4 (1.1-5.6)	2.4 (1.0-5.8)
Plaque without AS vs. no plaque	2.6 (1.3-5.3)	1.7 (0.8-3.5)	2.0 (0.9-4.4)	1.5 (0.7-3.4)
Plaque with AS vs. plaque without AS	1.4 (0.7-2.6)	1.3 (0.7-2.4)	1.2 (0.6-2.3)	1.6 (0.8-3.2)

* adjusted for age, sex, and race-ethnicity

[#] adjusted for above and mean IMT[‡] adjusted for above, education, and vascular risk factors (hypertension, diabetes, hypercholesterolemia, current smoking, and cardiac disease)