

Risk Factor Associations With the Presence of a Lipid Core in Carotid Plaque of Asymptomatic Individuals Using High-Resolution MRI

The Multi-Ethnic Study of Atherosclerosis (MESA)

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Background and Purpose—Atheroma vulnerability to rupture is increased in the presence of a large lipid core. Factors associated with a lipid core in the general population have not been studied.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter cohort study of individuals free of clinical cardiovascular disease designed to include a high proportion of ethnic minorities. We selected MESA participants from the top 15th percentile of maximum carotid intima media thickness by ultrasound and acquired high-resolution black blood MRI images through their carotid plaque before and after the intravenous administration of gadodiamide (0.1 mmol/kg). Lumen and outer wall contours were defined using semiautomated analysis software. We analyzed only plaques with a maximum thickness ≥ 1.5 mm by MRI ($n=214$) and assessed cross-sectional risk factor associations with lipid core presence by multivariable logistic regression.

Results—A lipid core was present in 151 (71%) of the plaques. After controlling for age, ethnicity, sex, maximum arterial wall thickness, hypertension, cigarette smoking, diabetes, and C-reactive protein, compared with participants in the lowest tertile of total plasma cholesterol, the ORs of having a lipid core for participants in the middle and highest tertiles were 2.76 (95% CI: 1.01 to 7.51) and 4.63 (95% CI: 1.56 to 13.75), respectively. None of the other risk factors was associated with lipid core.

Conclusions—In persons with thickened carotid walls, plasma total cholesterol, but not other established coronary heart disease risk factors, is strongly associated with lipid core presence by MRI. High total cholesterol may be associated with rupture proneness of atherosclerotic lesions in the general population. (*Stroke*. 2008;39:329-335.)

Key Words: atherosclerosis ■ carotid artery ■ cholesterol ■ lipid core ■ magnetic resonance ■ MRI ■ risk factors ■ stroke

Atherosclerotic plaque vulnerability to rupture is related to its composition. Studies of ruptured coronary lesions show that rupture of the fibrous cap overlying the lipid core occurs typically where it is thinnest and most heavily infiltrated by inflammatory cells.^{1,2} Cap rupture leads to thrombus, formed as the flowing blood is exposed to tissue factor within the atheromatous core, which underlies 75% of acute coronary syndromes.¹ Larger lipid cores are considered more vulnerable to disruption, leading to the clinical event.³

Cerebral events can be precipitated by plaque rupture resulting from fibrous cap foam-cell infiltration and cap thinning, similar to the mechanism of coronary plaque rupture leading to myocardial events.⁴ Clinical implications of carotid plaque morphology extend beyond the risk of stroke for that lesion. Carotid atherosclerosis reflects generalized atherosclerosis.^{5,6} Moreover, the composition of a carotid plaque might reveal the vulnerability of atherosclerotic disease elsewhere.^{7,8}

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MRI can noninvasively characterize human carotid atheroma composition.^{9–12} It detects a variety of lipid mixtures commonly found in human atherosclerotic plaque, allowing for its delineation *in vivo*.¹¹ MRI has enabled demonstration of a marked reduction in lipid content in carotid atheroma during administration of lipid-lowering therapy.¹³ After the administration of a gadolinium-based contrast agent, the fibrous tissue shows preferential uptake, which allows for greater conspicuity of the lipid core.^{12,14–16}

Using this technique, we explored the associations of cardiovascular risk factors with lipid-rich plaque in a free-living population without a history of cardiovascular disease events.

Methods

The Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated to investigate prevalence, correlates, and progression of subclinical cardiovascular disease. Details about the study design have been published elsewhere.¹⁷ Between July 2000 and August 2002, 6814 men and women who were 45 to 84 years old and free of clinically apparent cardiovascular disease were recruited from 6 US communities: Baltimore City and Baltimore County, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; Northern Manhattan and the Bronx, NY; and St. Paul, Minn. Approval was received from Institutional Review Boards at each participating university before the start of the study and protocol modifications were reviewed and approved each year.

Study Groups

In each of the 6 MESA centers, 100 participants with carotid atherosclerosis were randomly selected from the top 15th percentile of maximum intima media thickness of either the right or left internal carotid artery measured by B-mode ultrasound at the baseline MESA examination 2 years prior. Participants with contraindications to MRI were excluded. A total of 577 participants was studied.

MRI Examinations

MRI examinations were performed on a 1.5-T MRI scanner (3 sites used CV/i scanners; GE Medical Systems; one site used a Quantum version Mobile scanner or an Avanto platform and 2 sites used a Sonata platform; Siemens Medical Systems). Bilateral carotid receive-only coils were fixed over each side of the neck. A bilateral 4-channel phased-array coil (Machnet) was used with the Siemens scanners and dual 3-inch surface coils (GE Medical Systems) were used with the GE scanners.

A 3-dimensional time-of-flight MR angiogram was acquired to localize the carotid bifurcations. Three proton-density-weighted black blood images were oriented through the long axis of the bifurcation on the side selected based on thickness. These images were used to position 5 T1- and T2-weighted fat-suppressed black blood images perpendicular to the area of greatest wall thickness with the middle slice traversing the most stenotic point (Figure 1). Black blood images were acquired using a double inversion recovery fast spin echo sequence using peripheral pulse gating. Parameters are shown in Table 1. The acquired resolution was 2 mm×0.54 mm×0.54 mm.

Participants who agreed to the administration of gadolinium received an intravenous injection of 0.1 mmol/kg gadodiamide (Omniscan; GE Healthcare) at a rate of 2 mL/s through a power injector. The 5 T1-weighted transverse black blood images were repeated 5 minutes after gadolinium administration.

MRI Analysis

The postcontrast transverse image showing the largest lipid core area (Figure 2), or the thickest wall if no core was present, was analyzed using Vesselmass software (VesselMass, Division of Image Process-

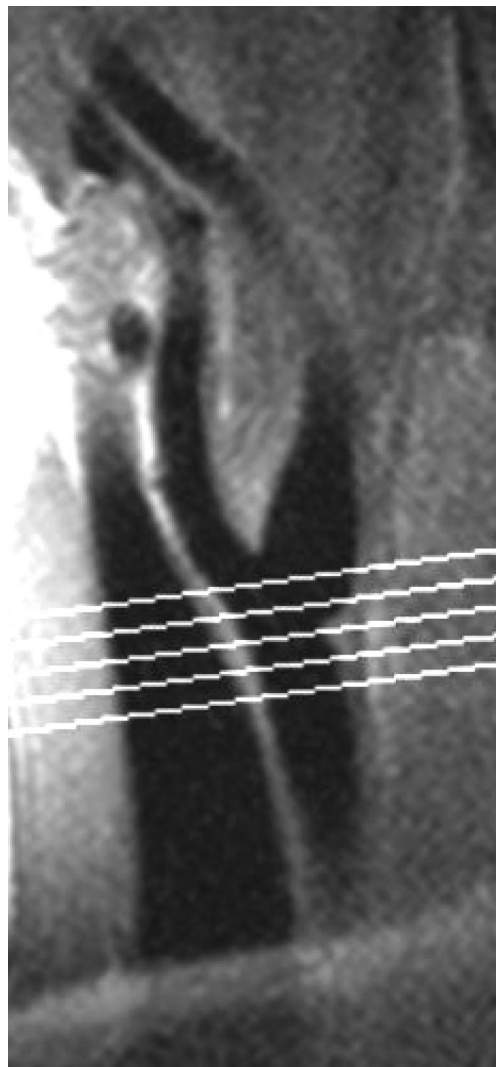


Figure 1. Localization of plaque in the carotid bifurcation of a 57-year-old white female MESA participant with a history of smoking and elevated total cholesterol. A proton density-weighted black blood image is acquired through the long axis of the carotid bifurcation and used as a scout image to orient 5 black blood slices (lines) transversely through the plaque.

ing, Radiology Department, Leiden University Medical Center). Window and level settings were set to constant levels to standardize signal intensities for each analyzed image. Two analysts drew lumen, lipid core, and outer wall contours on this image using the software. Contours were reviewed by an experienced MRI physician. All observers were blinded to characteristics of the study population. The postcontrast image was used based on reports that gadolinium enhancement improves delineation of the lipid core and outer wall.^{12,16,18} The corresponding T2-weighted image was used to confirm lipid core delineation when questionable on the postcontrast series, and the corresponding precontrast T1-weighted image was used to confirm the lumen contour when flow artifact from gadolinium was present.

The vessel wall was divided into 12 radial segments by a semiautomated feature of Vesselmass software (Figure 3). Arteries with a maximum segmental wall thickness less than 1.5 mm were excluded because of the resolution limitation of this technique. No lipid cores were excluded by this criterion.

Risk Factor Measurements

Blood was drawn after an overnight fast for inflammatory marker measurements (a high-sensitivity assay for C reactive protein [CRP]

Table 1. MRI Parameters for the Black Blood Sequences

	Long Axis View PD-Weighted	Transverse View	
		T1-Weighted	T2-Weighted
TR,* ms	2RR	1RR	2RR
TE, ms	5	5	68
TI,† ms	600	350‡	600
Slice thickness, mm	2	2	2
Gap	0	0	0
Matrix	256×256	256×256	256×256
Field of view, cm	14	14	14
ETL	10	10	10
NEX	1	1	1
BW, kHz	62.5	62.5	62.5
Scan time per slice,§ sec	44	22	44

*The sequences were cardiac gated with the TR based on an RR interval of the cardiac cycle.

†TI was automatically set (~600 or 350 ms) based on the heart rate to minimize the blood pool signal on the basis of estimated T1 values of blood.

‡TI was set to 200 ms after contrast administration to account for the reduction in T1 relaxation of the blood pool.

§Reported scan times are based on a heart rate of 70 beats/min. Times shorten with faster rates.

PD indicates proton density; TR, repetition time; TE, echo time; TI, inversion time; ETL, echo train length; NEX, No. of excitations; BW, band width.

and interleukin 6 [IL-6]) at the baseline clinic visit (18 to 26 months before the MRI) and then again within 30 days of the MRI examination for plasma total and high-density lipoprotein (HDL) cholesterol and plasma triglyceride measurements. All blood samples were sent to a central laboratory. Plasma total and HDL cholesterol was measured using a cholesterol oxidase method and

triglyceride using the Triglyceride GB reagent on a Roche COBAS FARA centrifugal analyzer (Roche Diagnostics). Analytical coefficients of variation were 1.6%, 2.9%, and 4.0%, respectively. Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula.¹⁹ We restricted our analysis of LDL to participants with plasma triglyceride ≤ 400 mg/dL because LDL is not estimated accurately for those with higher values using this equation. CRP and IL-6 were measured in batches. CRP was measured by particle-enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc) with interassay analytical coefficients of variation ranging from 2.1% to 5.7%. IL-6 was measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems) with an analytical coefficient of variation of 6.3%.

Resting blood pressure was measured 3 times in the right arm after 5 minutes in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last 2 measurements was used for analysis. Hypertension was defined as either an average systolic blood pressure of 140 mm Hg or above, an average diastolic blood pressure of 90 mm Hg or above, or taking antihypertensive medication.

Body mass index was determined using the following formula: weight(kg)/height(m)². Cigarette smoking status was categorized as never, former, or current. Ever was defined as ≥ 100 cigarettes in one's lifetime; current was defined as smoking cigarettes within the past 30 days.

Impaired fasting glucose and diabetes mellitus were defined by 1997 American Diabetes Association fasting criteria as a fasting glucose of 110 to 125 mg/dL and of ≥ 126 mg/dL, respectively. Use of insulin or oral diabetes medication was also considered diagnostic for diabetes.

Statistical Analysis

Intraobserver and interobserver variability of lipid core detection by MRI were estimated by rereading 10% of cases 3 months after the initial reading. SAS software (version 9.1) was used for all analyses. Multivariable logistic regression was used to predict lipid core

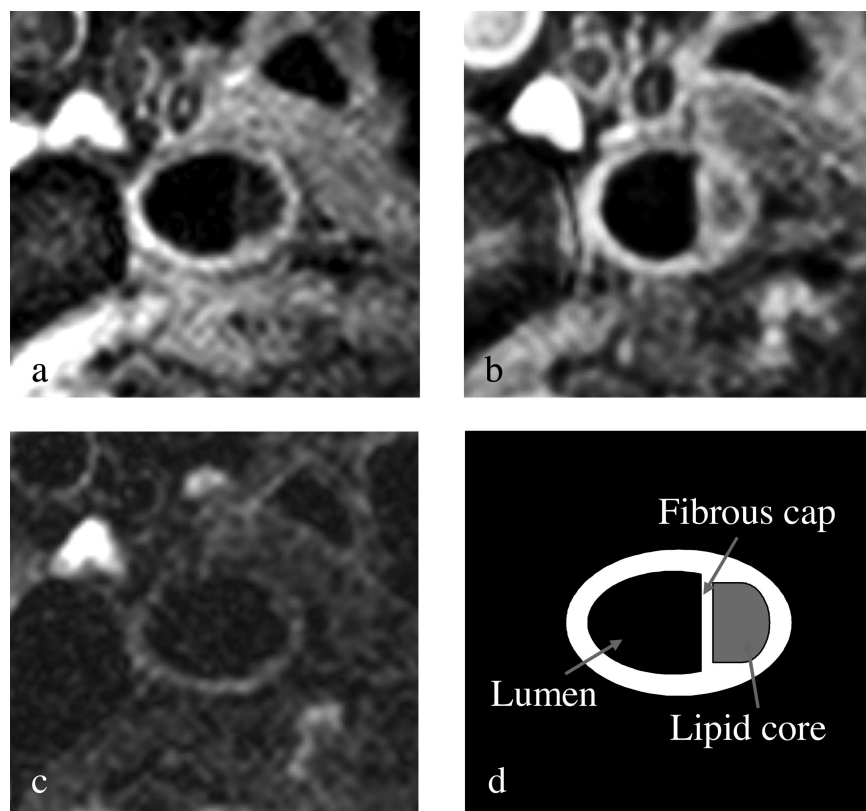


Figure 2. Black blood images taken through thickest part of the plaque (middle line, Figure 1). Flow suppression was achieved using a double inversion recovery turbo spin echo sequence with cardiac gating. Chemical suppression of fat signal was applied. T1-weighted pre- and postcontrast (a and b, respectively) and T2-weighted (c) images were acquired (acquired resolution, 2 mm×0.54 mm×0.54 mm). The conspicuity of the lipid core (schematic, d) was improved after administration of the gadolinium-based contrast agent (A–B).

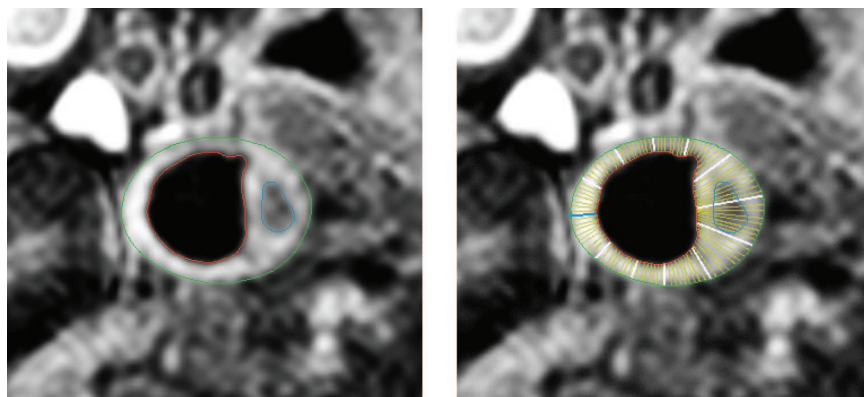


Figure 3. Analysis images for the plaque shown in Figure 1 and 2. a, Contours were drawn to delineate the lumen (red), lipid core (blue), and outer wall (green). b, The wall was then divided into 12 radial segments (white lines) using semi-automated software, and the mean thickness was determined for each segment based on the length of the individual cords (yellow lines) distributed through the segment.

presence from the following variables: age, sex, ethnicity, and coronary risk factors (cholesterol, smoking, diabetes and impaired fasting glucose, hypertension, CRP or IL-6, and carotid wall thickness by MRI). Inclusion of the wall thickness variable in the model assures that the results for other variables pertain to their relationship to core presence, not just their size.

Results

Of the 427 participants who accepted gadolinium and had an adequate MRI examination, 213 were excluded because their maximum segmental thickness by MRI was <1.5 mm. They did not differ significantly from those with thicker walls with respect to any risk factors, although somewhat fewer were women, black or Chinese, current smokers, or diabetic. The remaining participants included 121 men and 93 women with thick walls (mean age, 66.7 years; range, 46 to 84 years). Of the 214 remaining participants, one was missing cholesterol data, one CRP, and one smoking status. Of the remaining participants, 151 (71%) had a lipid core on the postcontrast MRI image. Four of the 214 participants in our sample had cardiovascular events by the time of their MRI study, which included congestive heart failure, peripheral vascular disease, and probable angina. Exclusion of data from these 4 participants had no substantive effect on the analyses.

Interobserver agreement for the presence of a lipid core was present for 19 of 22 cases studied (86%, kappa: 0.70). Intraobserver agreement was present for 19 of 21 cases (90%, kappa: 0.81). Age, ethnicity, and distributions of key variables are shown in Table 2 together with the prevalence of a lipid core based on risk factor levels.

The independent associations of demographic and risk factors with lipid core presence are shown in Table 3. Compared with participants in the lowest tertile of total cholesterol, adjusted ORs of having a lipid core for participants in the middle and highest tertiles were 2.76 (95% CI: 1.01 to 7.51) and 4.63 (95% CI: 1.56 to 13.75), respectively. The presence of a lipid core was associated significantly with carotid wall thickness but not with any other cardiovascular risk factor (ie, hypertension, smoking, diabetes, CRP concentration). The cholesterol associations were not substantially altered by further adjustment for use of lipid lowering medication (Table 3). When IL-6 tertiles replaced CRP in the model, IL-6 was not significantly associated with lipid core

Table 2. Characteristics of the Study Population and Percentage With Lipid Core by the Presence of Characteristic

	N	Percent (no.) With Lipid Core
Total sample	214	71 (151)
Women	93	73 (68)
Men	121	69 (83)
White	113	75 (85)
Black	35	57 (20)
Hispanic	47	70 (33)
Chinese	19	68 (13)
Age, years		
45–54	30	47 (14)
55–64	55	71 (39)
65–74	75	75 (56)
≥ 75	54	78 (42)
Carotid wall thickness		
1.5–2.7 mm	113	50 (57)
≥ 2.7 mm	101	93 (94)
Cholesterol tertiles		
<181 mg/dL	75	55 (41)
181–210 mg/dL	71	77 (55)
>210 mg/dL	67	82 (55)
Smoking		
Current	26	62 (16)
Former	102	72 (73)
Never	85	72 (61)
Diabetes or IFG	52	73 (38)
No diabetes or IFG	162	70 (113)
Hypertension	118	73 (86)
No hypertension	96	68 (65)
CRP tertiles		
<1.14 mg/L	64	77 (49)
1.14–2.92 mg/L	76	64 (49)
>2.92 mg/L	73	73 (53)
Lipid-lowering medication	60	67 (40)
No lipid-lowering medication	154	72 (111)

IFG indicates impaired fasting glucose.

Table 3. OR (95% CIs) for Lipid Core Presence With Cardiovascular Risk Factors (N=214)

	Adjusted* OR	95% CI
Women vs men	1.35	0.56–3.25
Black vs white	0.52	0.16–1.76
Hispanic vs white	0.77	0.27–2.24
Chinese vs white	2.07	0.49–8.78
Age 45–54 vs >74	0.25	0.06–1.05
55–64 vs >74	0.93	0.28–3.12
65–74 vs >74	0.65	0.20–2.08
Maximum wall thickness per 100 μ m	1.28	1.18–1.40
Total cholesterol	2.76†	1.01–7.51
181–210 mg/dL vs \leq 180 mg/dL		
>210 mg/dL vs \leq 180 mg/dL	4.63‡	1.56–13.75
Smoking: current vs never smoked	0.63	0.16–2.49
Former vs never smoked	0.83	0.33–2.10
Diabetes or IFG vs no diabetes or IFG	0.79	0.28–2.18
Hypertension vs nonhypertensives	1.07	0.43–2.67
CRP: 1.14–2.92 mg/L vs <1.14 mg/L	0.53	0.18–1.53
>2.92 mg/L vs <1.14 mg/L	0.97	0.33–2.90

*Adjusted for all listed variables.

†Reduced to 2.43 (95% CI: 0.87 to 6.75) after adjusting for lipid-lowering medication.

‡Reduced to 4.23 (95% CI: 1.40 to 12.78) after adjusting for lipid-lowering medication.

IFG indicates impaired fasting glucose.

presence, but the association between lipid core presence and cholesterol remained strong (data not shown). We also considered total cholesterol divided into quintiles and found a stepwise increase with the strongest association in the highest quintile (>226 mg/dL) compared with the lowest quintile with an OR of 6.35 (95% CI: 1.60 to 25.2). Cholesterol associations remained significant after adjusting for use of lipid-lowering medications with only slight changes in ORs.

Although none of the standard risk factors appeared to be associated with lipid core presence, we in fact were adequately powered to detect effect sizes of moderate strength or greater. For example, we had 80% power to detect ORs of 1.38 or greater for smoking, 1.31 or greater for diabetes or impaired fasting glucose, 1.31 or greater for hypertension, and 1.29 or greater for upper tertile of CRP.

In a model in which total cholesterol was replaced by LDL cholesterol and HDL cholesterol, ORs for the second and third tertiles of LDL cholesterol were 2.22 (0.84 to 5.87) and 3.08 (1.01 to 9.34), respectively, and for HDL cholesterol were 1.26 (0.44 to 3.64) and 1.45 (0.44 to 4.77), respectively. In a similar model with non-HDL cholesterol and HDL cholesterol, ORs for non-HDL cholesterol tertiles, 3.41 (1.26 to 9.21) and 3.92 (1.31 to 11.7), respectively, were stronger than for LDL cholesterol tertiles as shown in the previously mentioned model. HDL cholesterol associations remained nonsignificant. Triglyceride levels were not independently associated with lipid core presence.

Discussion

This is the first study of associations between plaque lipid core detected by MRI and the major cardiovascular risk

factors measured in a largely asymptomatic population. It shows core presence strongly associated with plasma cholesterol but not with hypertension, smoking, diabetes, or inflammatory factors. Previous studies have established that cholesterol is associated with carotid thickness, but our thickness-adjusted association is a new finding relating specifically to plaque characteristics. The cholesterol association remained strong even after adjusting for carotid thickness, medication use, and other cardiovascular risk factors, including hypertension, diabetes, smoking, and CRP. Because no other cardiovascular risk factors appeared to be associated with the presence of a lipid core, our findings can be considered evidence that blood cholesterol levels, and in particular non-HDL cholesterol, which includes LDL and the atherogenic triglyceride-rich lipoproteins, may be of prime importance for development of the clinically important lipid-rich atherosclerotic plaque. The weakly positive HDL cholesterol association with lipid core was unexpected and not statistically significant.

We studied a large diverse population of asymptomatic individuals. Compared with small studies of patients whose plaques have ruptured and caused symptoms, use of an asymptomatic population has the advantage of reduced potential for selection bias and greater assurance that the risk factor associations observed relate to the causes of lipid-rich plaques rather than reflecting the effects of medical intervention or other lifestyle modifications consequent to manifest carotid disease.

Burke et al²⁰ reported that lipids and white race but not smoking or hypertension were associated with the presence of a thin fibrous cap overlying a lipid-rich core in coronary atheromas of autopsied men with coronary disease who died suddenly. Our findings, on a sample of both men and women, substantially extend those of Burke from fatal disease to the types of lipid-filled plaques found in living populations and reduce the likelihood that they are the result of the potential biases seen with populations selected for autopsy.

It might be argued that risk factors established for coronary plaque features are less applicable to carotid disease. However, atherosclerosis is a systemic process and there is evidence that the composition and clinical consequences of plaques at different locations within an individual are similar.⁸ Honda et al²¹ showed that carotid plaque echolucency, which suggests lipid or intraplaque hemorrhage,²² in stable patients with coronary artery disease predicted future coronary events independent of other risk factors. Hence, our cholesterol associations have implications beyond stroke risk assessment.

Ultrasound studies of the echolucency of carotid plaques have generally shown associations with plasma lipids.^{23–25} Although these associations are implicitly related to core lipid content, ultrasound is unable to discriminate lipid from intraplaque hemorrhage, which might be a destabilizing factor that could influence the associations with clinical outcomes.²⁶

Surprisingly, we found that lipid cores tended to be much less prevalent in carotid walls of blacks than whites. Although the finding was not statistically significant, it is consistent with the findings of Burke et al,²⁰ who reported substantially

and significantly fewer lipid-rich vulnerable plaques in black compared with white men with coronary disease who died suddenly.

The lack of an association in our study between CRP and core presence is noteworthy because CRP has been strongly associated with plaque rupture^{27,28} and predicts stroke risk.²⁹ Along with our findings, this suggests that CRP may be a marker of plaque instability independent of presence of a lipid core.

It should be noted that the thin cap/large core atheroma is not the only lesion at risk for thrombosis. The “erosive plaque,” lacking an endothelium, exposes the underlying intima with consequent thrombosis.³⁰ A core, if present, is usually small. If plaques prone to erosion are not associated with elevated cholesterol, as suggested,³¹ they could account for the lower cholesterol levels in our noncore group.

Study limitations include: (1) the acquired in-plane resolution of the MRI images was 0.54 mm×0.54 mm. We excluded individuals with wall thicknesses <1.5 mm because no cores were apparent in thinner walls and small cores could be missed; (2) the sample sizes were too small to identify race–ethnic-specific risk factor associations; (3) we studied only one carotid artery per participant, targeting the thickest wall, but this does not fully characterize his or her lipid core burden. Because we expect this error to be nondifferential with respect to risk factors, the association we observed between lipid core and plasma cholesterol is likely to be underestimated; and (4) rheological factors may have some influence on the development of a lipid core. This was not assessed in this study due to the complexity of geometrically characterizing atheromatous plaque location.

Summary

This study of the MESA population offers unique insight into a population not subject to the selection and cause–effect biases encountered with symptomatic cohorts. Plasma cholesterol was clearly the most important determinant of the putatively thrombogenic lipid core, which portends risk for rupture. It is increasingly recognized that clinically silent, vulnerable plaques can carry a significant risk for rupture, but risk stratification is both difficult and important given the high prevalence of these lesions. We found a lipid core in 71% of the thickest carotid walls selected from this asymptomatic population. Smaller vulnerable plaques, not detectable by MRI, would add to overall population prevalence. If the evaluation of patients with carotid plaques included scanning for a lipid core, this knowledge might provide the basis for more aggressive cholesterol-reducing therapy.

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Disclosures

None.

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