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Relation of Cholesterol and Lipoprotein Parameters with Carotid Artery Plaque Characteristics: the Atherosclerosis Risk in Communities (ARIC) Carotid MRI Study

Salim S. Virani, MD[a,b,c], **Diane J. Catellier, DrPH**[d], **Lisa A. Pompeii, PhD**[e], **Vijay Nambi, MD, FACC**[b,c], **Ron C. Hoogeveen, PhD**[b,c], **Bruce A. Wasserman, MD**[f], **Josef Coresh, MD, PhD**[g], **Thomas H. Mosley, PhD**[h], **James D. Otvos, PhD**[i], **A. Richey Sharrett, MD, DrPH**[g], **Eric Boerwinkle, PhD**[e], and **Christie M. Ballantyne, MD, FACC**[b,c]

[a]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

[b]Department of Medicine, Baylor College of Medicine, Houston, TX

[c]Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart and Vascular Center, Houston, TX

[d]University of North Carolina at Chapel Hill, Chapel Hill, NC

[e]The University of Texas Health Science Center at Houston, Houston, TX

[f]The Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Medical Institutions, Baltimore, MD

[g]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

[h]University of Mississippi Medical Center, Jackson, MS

[i]LipoScience Inc, Raleigh, NC

Abstract

Objective—There is a paucity of data regarding relations of apolipoproteins (apolipoprotein B [ApoB] and apolipoprotein A-1 [Apo A-1]), lipoprotein particle measures (low-density lipoprotein particle concentration [LDLp] and high-density lipoprotein particle concentration [HDLp]), and lipoprotein cholesterol measures (low-density lipoprotein cholesterol [LDL-C], non–high-density lipoprotein cholesterol [non– HDL-C], and high-density lipoprotein cholesterol [HDL-C]) with atherosclerotic plaque burden, plaque eccentricity, and lipid-rich core presence as a marker of high-risk plaques.

Methods—Carotid artery magnetic resonance imaging was performed in 1,670 Atherosclerosis Risk in Communities study participants. Vessel wall and lipid cores were measured; normalized wall index (NWI), standard deviation (SD) of wall thickness (measure of plaque eccentricity) were calculated; and lipid cores were detected in vessels with ≥1.5 mm thickness. Fasting concentrations of cholesterol, ApoB and Apo A-1, and LDLp and HDLp were measured.

Corresponding Author: Christie M. Ballantyne, MD, Center for Cardiovascular Disease Prevention and Section of Atherosclerosis and Vascular Medicine, Methodist DeBakey Heart and Vascular Center, 6565 Fannin, M.S. A656, Houston, TX 77030, Telephone: 713-798-5034, Fax: 713-798-3057, cmb@bcm.tmc.edu.

Results—Measures of plaque burden (carotid wall volume, wall thickness, and NWI) were positively associated with atherogenic cholesterol and lipoproteins ($p<0.05$ for total cholesterol, LDL-C, non–HDL-C, ApoB, and LDLp), but not with HDL-C, Apo A-1, or HDLp. SD of wall thickness was associated with total cholesterol (p 0.01) and non-HDL-C (p 0.02). Although measures of atherogenic or anti-atherogenic cholesterol or lipoprotein were not individually associated with detection of a lipid-rich core, their ratios (total cholesterol/HDL-C, non–HDL-C/HDL-C, and LDLp/HDLp) were associated with lipid-rich core presence ($p\leq0.05$).

Conclusion—Extent of carotid atherosclerosis is associated with atherogenic cholesterol and lipoproteins. Atherogenic/anti-atherogenic cholesterol or particle ratios were associated with presence of a detectable lipid-rich core.

Keywords

atherogenic lipoproteins; anti-atherogenic lipoproteins; plaque burden; lipid-rich necrotic core

Introduction

It has been suggested that measures of low-density lipoprotein (LDL) particles (Apolipoprotein B [ApoB] or LDL particle number [LDLp] measured by nuclear magnetic resonance [NMR] spectroscopy) perform better in cardiovascular risk prediction than the traditional cholesterol measures, LDL cholesterol (LDL-C) and non– high-density lipoprotein cholesterol (non–HDL-C).[1, 2]. Though this remains debatable in terms of clinical outcomes, there is a paucity of data regarding how these measures of particle number or cholesterol content of the particles relate to measures of either atherosclerotic plaque burden or presence of lipid-rich necrotic core, one of the features of high risk plaques.[3]

Atherosclerosis is a dynamic process with a balance between the cholesterol brought into the intima of the large arteries via atherogenic particles and reverse cholesterol transport mediated by high-density lipoprotein (HDL) particles.[4, 5] Based upon this lipoprotein model of atherogenesis,[4, 5] the use of ratios of atherogenic/anti-atherogenic cholesterol or lipoprotein measures should provide more information regarding assessment of plaque burden or lipid-rich core presence compared with the use of these measures individually.

Although carotid intima-media thickness (CIMT) can reliably assess presence or absence of plaque and provides useful prognostic information,[6] magnetic resonance imaging (MRI) of the carotid arteries extends CIMT measurements to provide useful information regarding plaque burden, vascular remodeling, and the presence of a detectable lipid-rich necrotic core.[7-10] Similarly, normalized wall index [NWI] (carotid wall area divided by total vessel area including lumen area) has been used as a measure of plaque burden, and takes into account inherent differences in wall areas among vessels of different diameters.[11-13] In addition, standard deviation of the wall thickness measurement has been shown to be a marker of plaque eccentricity.[11] Both NWI and standard deviation of the wall thickness have also been shown to be associated with a prior history of coronary heart disease in a recent publication.[11]

Thus the aim of our analysis was to identify which atherogenic or anti-atherogenic cholesterol or particle parameters can predict the burden of atherosclerosis in the carotid arteries, plaque eccentricity, and the presence of a detectable lipid-rich core. We also aimed to identify whether the use of atherogenic/anti-atherogenic cholesterol (or lipoprotein) ratios can provide information regarding plaque burden and lipid-rich core presence beyond that provided by the use of atherogenic and antiatherogenic cholesterol (or lipoprotein) parameters alone.

Methods

Methods for the ARIC MRI study have been described previously.[10, 14] Relevant details are described here. The study sample consisted of members of the Atherosclerosis Risk in Communities (ARIC) study cohort who participated in the ARIC Carotid MRI substudy in 2004–2005 (Year 18). The ARIC study is a population-based cohort study of cardiovascular disease incidence among African American and Caucasian adults (n=15,792)[15].

The ARIC MRI sampling strategy included approximately 1,200 participants with carotid artery wall thickness (maximum over 6 sites: left and right of the common, bifurcation, internal) that was at least >68th percentile as measured by carotid B-mode ultrasound on ARIC study visits 3 (1993–1995) and 4 (1996–1998). Intima-media thickness (IMT) cut-offs were 1.35, 1.00, 1.28, and 1.22 mm in Forsyth County, Jackson, Minneapolis, and Washington County, respectively, representing the 73rd, 69th, 73rd, and 68th percentiles of maximal IMT. A cohort random sample of approximately 800 participants whose carotid intima-media thickness was <68th percentile was also included. Ineligibility criteria for the carotid MRI substudy included standard contra-indications to the MRI exam or to the contrast agent, carotid revascularization on either side for the low CIMT group or on the selected side for imaging for the high CIMT group, and difficulties in understanding questions or in completing the informed consent.

Participant Examination

Protocols for fasting glucose, blood pressure, height and weight measurements were identical at the baseline ARIC cohort examination and 18 years later at the Carotid MRI substudy examination. The study was approved by the institutional review committees of all participating centers, and all participants provided written informed consent.

Traditional cholesterol measurements

Twelve-hour fasting plasma lipid assays were performed on participants of the ARIC MRI substudy. Plasma samples were collected on ice using EDTA as the anticoagulant at the time of the MRI visit. Total cholesterol, triglycerides, and HDL-C were measured enzymatically and expressed in mg/dL units. LDL-C levels were calculated using the Friedewald equation.[16] Non-HDL-C levels were calculated as total cholesterol minus HDL-C. Blind duplicate coefficient of variation for total cholesterol, HDL-C, and triglycerides were 2.0%, 3.0%, and 2.7%, respectively.

Apolipoprotein measurements

Apolipoproteins (ApoB and Apo A-1) were measured in frozen plasma using a commercially available immunoturbidimetric assay (OLYMPUS®, Olympus America Inc). The inter-assay coefficient of variation for Apo A-I and ApoB were 3.9% and 7.2%, respectively. Intra-assay coefficient of variation for Apo A-1 and ApoB were 1.5% and 1.7%, respectively. Reliability coefficients based on 120 blinded split QC samples were 0.93 and 0.95 for ApoA-I and ApoB, respectively.

Lipoprotein particle analysis

Frozen EDTA plasma samples were thawed, and a 200 μL aliquot withdrawn, refrozen, and shipped on dry ice to Liposcience, Inc. (Raleigh, NC) for NMR lipoprotein particle analysis. Using this technique, particle concentrations of lipoproteins of different sizes were calculated from the measured amplitudes of their spectroscopically distinct lipid-methyl group.[17] The NMR variables examined in this manuscript were total LDL particle concentration (LDLp) expressed in nmol/L units and total HDL particle concentration (HDLp) expressed in μmol/L units.

MRI Protocol

The methods for acquisition and interpretation of the MRI images collected in the Carotid MRI substudy have been described previously.[10, 14] Briefly, a contrast-enhanced MRI exam of the thickest 1.6-cm segment of the thicker carotid artery was performed according to a standard protocol on a 1.5T whole-body scanner as follows: A 3-dimensional time-of-flight magnetic resonance angiogram (MRA) was acquired through both carotid bifurcations. Detailed black blood MRI (BBMRI) images were then acquired through the extracranial carotid bifurcation, known to have a thicker maximum wall by the most recent ultrasound study, unless the contralateral carotid bifurcation wall appeared to the technologist to be thicker on the MRA. These BBMRI images consisted of 16 axial T1-weighted, fat-suppressed slices (thickness=2 mm; acquired in-plane resolution=0.51 × 0.58 mm^2; total longitudinal coverage=3.2 cm) oriented perpendicular to the vessel and centered at the thickest part of the internal or common carotid artery wall. These 16 slices were acquired 5 minutes after the intravenous injection of gadodiamide (Omniscan, GE Amersham), 0.1 mmol/kg body weight, with a power injector.

Seven readers were trained to interpret the MRI images and contour the wall components using specialized software (VesselMass, Leiden University Medical Center). Readers were blinded to the characteristics of the study population. Each reader drew contours to delineate the lumen, outer wall, lipid core, and calcification. Eight slices centered at the slice with the thickest wall were analyzed. All exams were assigned quality scores by the reader based on image quality and protocol adherence; exams that failed were not analyzed.

Using semi-automated software, vessel walls were divided into 12 radial segments, and mean thickness values were generated for each segment (Figure 1). Standard deviation of the wall thickness measurement was also computed and provides a measure of the plaque eccentricity. Area measurements were calculated for the lipid core and calcification contours. Volumetric data were computed by integrating area measurements over all 8 slices examined.

Maximum segmental wall thickness (in mm) was defined as the maximum wall thickness of 12 segments at the slice with the largest lipid contour area. Vessel wall area and lumen area (in cm^2) were computed at the slice with the largest mean segmental wall thickness. Volume measurements for total wall volume (in mm^3) was computed by integrating area measurements over 8 slices. Normalized wall index (NWI) was then calculated. NWI was derived as carotid wall area divided by the total vessel area. The total vessel area in these measurements includes the lumen area. Lipid-rich core was represented as a binary variable (present or absent).

Statistical Methods

All analyses were weighted and appropriately accounted for the stratified random sampling design of the ARIC Carotid MRI substudy. Analyses were conducted using SAS version 9.1 for descriptive statistics or SUDAAN for domain analysis. Wall thickness and wall volume were analyzed in the full data set. Due to the resolution constraints of the MRI scan, we restricted consideration of lipid core to those 1,131 participants whose maximum wall thickness was ≥1.5 mm. Only 4 lipid cores were excluded using this cut point. Among the 1,131 participants who were included in the analyses, a total of 542 participants had an identifiable lipid-rich core.

For continuous MRI variables, standardized regression coefficients (β) are presented for linear regression models, standardizing by one standard deviation (SD) of exposure and outcome with adjustment for covariates. These β coefficients can be interpreted as number of SD difference in the dependent variable (e.g., total wall volume) associated with a single

SD difference in plasma cholesterol or lipoprotein level or their ratio. For the dichotomous lipid-rich core variable (presence or absence), standardized odds ratio (OR) are presented for logistic regression models adjusting for covariates. These ORs can be interpreted as the odds for the presence of lipid-rich core associated with a single SD difference in plasma cholesterol or lipoprotein level or their ratio. Covariates included for adjustment were age, race, gender, smoking status, body mass index, blood glucose, hypertensive medication use, cholesterol-lowering medication use, aspirin use, diabetic medication use, hs-CRP, and plasma triglyceride concentration. Similarly, the coefficients of determination (R^2) were described for each model including the above-mentioned covariates as well as lipid or lipoprotein particle measure of interest. R^2 can be interpreted as proportion of the variance in the dependent variable (e.g., total wall volume) as explained by the set of independent variables in the model including the cholesterol or lipoprotein particle concentration parameter of interest.

Because the presence of lipid-rich core on carotid MRI has been shown to highly correlate with carotid wall thickness,[10] we conducted additional analyses to examine the presence of lipid-rich core, while controlling for carotid wall thickness in addition to the covariates mentioned above.

Results

Final analyses, after excluding those with insufficient quality or missing MRI variables (n=336) and those missing lipid measurement (n=60) data, included 1,670 participants. Baseline characteristics and baseline lipid and lipoprotein levels for the current study participants are shown in Table 1. The mean age of this cohort was 71 years with 49% men and a predominance of Caucasians (78%). The proportion of participants with history of diabetes, hypertension, current smoking, or statin medication use was 24%, 68%, 9%, and 39%, respectively. More than half of the patients fulfilled the National Heart, Lung and Blood Institute/American Heart Association criteria for metabolic syndrome.[18] Mean levels of total cholesterol, LDL-C, non-HDL-C, ApoB and LDLp were 193 mg/dL, 113 mg/dL, 144 mg/dL, 98 mg/dL and 1148 nmol/L, respectively. Mean levels of HDL-C, ApoA-1 and HDLp were 49 mg/dL, 131 mg/dL, and 35 μmol/L, respectively.

As expected, LDL-C was correlated with ApoB (r=0.74), and LDLp (r=0.66), and non-HDL-C was even more strongly correlated (r=0.85 for ApoB; r=0.77 for LDLp). HDL-C levels had a high correlation with Apo A-1 levels (r=0.80), and a more modest correlation with HDLp (r = 0.63).

Associations between cholesterol or lipoprotein parameters and measures of plaque burden and plaque eccentricity (Table 2)

Among the atherogenic lipid measures, total cholesterol, LDL-C, non-HDL-C, ApoB, and LDLp were all associated with maximum wall thickness as well as carotid wall volumes in fully adjusted models. It can also be noted from Table 2 that the standardized beta coefficients (β) were numerically higher for total cholesterol (β=0.13), and non-HDL-C (β=0.13) compared with LDL-C (β=0.09) for total wall volume. The β for total cholesterol and non–HDL-C were also higher than those obtained for ApoB 0=0.06) and LDLp (β=0.08).

Anti-atherogenic cholesterol (HDL-C) or lipoprotein parameters (Apo A-1, HDLp) were not associated with carotid wall volume or maximum wall thickness. Although total cholesterol/ HDL-C ratio and non-HDL-C/ HDL-C ratio were associated with carotid wall volume, they were not associated with an improvement in model prediction (R^2 values) compared with the use of atherogenic cholesterol or lipoprotein parameters alone.

Normalized wall index was associated with atherogenic cholesterol (or lipoproteins) and the ratio of atherogenic/anti-atherogenic cholesterol or lipoproteins, but not when anti-atherogenic cholesterol or lipoproteins parameters were used alone. Similarly, plaque eccentricity was positively associated with total cholesterol and non-HDL-C in the fully adjusted models.

Associations between cholesterol or lipoprotein parameters and presence of lipid-rich core on carotid MRI (Tables 3 and 4)

Among persons with arteries ≥1.5 mm in thickness, the associations between the presence of detectable lipid-rich core and various atherogenic or anti-atherogenic lipoprotein cholesterol/ particle measures as well as their ratios on carotid MRI are shown in Table 3. Although neither atherogenic nor anti-atherogenic lipoprotein measures could individually predict the presence of lipid-rich core in the plaques, ratios of total cholesterol/ HDL-C, non-HDL-C/ HDL-C, and LDLp/HDLp were associated with the presence of lipid-rich core. Apo B/Apo A-1 ratio was not significantly associated with presence of lipid-rich core in fully adjusted models.

Because detection of lipid-rich core is highly dependent on wall thickness,[10] we subsequently added maximum wall thickness to the adjustment model (Table 4). The overall model prediction (R^2) was substantially improved by adding maximum wall thickness to the model, but the associations between the presence of lipid-rich core and atherogenic/anti-atherogenic cholesterol as well as lipoprotein ratios were attenuated. On the other hand, the inverse associations between the presence of lipid-rich core and Apo A-1 (OR=0.84, p=0.08) or HDLp (OR=0.84, p=0.06) became borderline significant.

Discussion

Our findings indicate that measures of carotid artery plaque burden and plaque eccentricity were positively associated with atherogenic particle number or atherogenic cholesterol content (especially total cholesterol and non–HDL-C). Although the various measures of anti-atherogenic lipids were not associated with measures of plaque burden when examined individually, the ratio of atherogenic/anti-atherogenic lipids was associated with lipid-rich core presence in arteries of >1.5 mm thickness. This association between the presence of lipid-rich core and atherogenic/anti-atherogenic ratios was attenuated once maximum wall thickness was included in the adjustment model, but the association between anti-atherogenic lipoprotein measures and the presence of lipid-rich core approached significance after including maximum wall thickness in the adjustment model. The strengths of association for carotid plaque burden assessed using total cholesterol and non–HDL-C were numerically higher compared with LDL-C, ApoB, and LDLp.

Several cholesterol and particle measures of atherogenic lipoproteins have been associated with measures of plaque burden. In a prior manuscript,[19] both small and large LDLp subclasses were associated with carotid intima media thickness (a marker of carotid plaque burden). Similarly, LDL-C has been shown to be associated with carotid IMT.[20, 21] Our findings confirm these earlier observations when carotid MRI is used to measure atherosclerosis burden. We show that all the measures of atherogenic cholesterol or particle number are indeed associated with measures of plaque burden using carotid MRI.

In addition, two other observations could be made. First, the β coefficients were higher for total cholesterol and non–HDL-C compared with LDL-C. This is not surprising because non–HDL-C measures cholesterol content within all the atherogenic particles (very-low-density lipoproteins, intermediate-density lipoproteins, and lipoprotein(a) in addition to LDL).[22-24] Therefore, non–HDL-C use may provide a more comprehensive assessment of

the plaque burden. Second, we show that the strength of association (β coefficient) as well as the overall model prediction (R^2) is at least as strong or stronger with measures of cholesterol content (total cholesterol and non–HDL-C) compared with measures of atherogenic particle number (ApoB or LDLp).

Presence of lipid-rich core identified by carotid MRI has been shown to have a very strong association with wall thickness,[10] and our models for core which included wall thickness had substantially larger R^2 compared with those without wall thickness. This could be due to the fact that carotid MRI is not sensitive for detecting very small lipid-rich cores. Individuals with a higher burden of atherosclerosis (as evidenced by having thicker carotid walls) are expected to have larger lipid-rich cores. We also showed that after adjusting for maximum wall thickness which is a measure of the size of the atherosclerotic lesion, the atherogenic parameters or the ratios of atherogenic/anti-atherogenic parameters were not associated with lipid-rich core presence. Interestingly, the negative association between HDLp (or Apo A-1) and presence of lipid-rich core increased after adjustment was made for maximum wall thickness, and the association became borderline significant. These results indicate that although atherogenic lipoproteins are the primary determinants of plaque burden, the development of detectable lipid rich cores in large plaques may be influenced by low levels of HDL.

Our findings have potentially important research implications in terms of which MRI parameters to follow when therapies that lower atherogenic lipids or raise anti-atherogenic lipids are used. Our results indicate that measures of plaque burden could be monitored for disease progression when evaluating the impact of therapies that lower atherogenic lipids, whereas lipid-rich necrotic core presence might be an important imaging parameter to follow with therapies that markedly improve the ratio of atherogenic/anti-atherogenic lipids by both reducing the atherogenic cholesterol (or lipoproteins) and raising anti-atherogenic cholesterol (or lipoproteins). Our results showed that although atherogenic lipids can explain the variance in measures of plaque burden in the artery wall to a greater extent, the development of plaques with large lipid-rich necrotic cores is more likely to occur when anti-atherogenic lipid levels are low.

Limitations

The cross-sectional nature of this study does not allow us to imply causal relationships; however, the findings are valuable for generating hypotheses. We only evaluated the associations between cholesterol and lipoprotein parameters, and measures of plaque burden and presence of lipid-rich core. Though there are studies suggesting that wall thickness, wall area, NWI, and measures of plaque eccentricity can predict cardiovascular outcomes,[11] we did not evaluate cardiovascular outcomes in this cohort given limited statistical power. Our associations for the presence of lipid-rich core were attenuated once wall thickness was entered as a covariate in the adjusted models. This observation is not surprising as a prior study from the ARIC MRI cohort has shown that wall thickness itself is very highly correlated with the presence of a lipid-rich core.[10] Similarly, the resolution constraints of the MRI limit the ability to fully characterize the presence of lipid-rich core in small plaques.

The strengths of this study include relatively large number of patients in the ARIC MRI cohort and extensive quality control measures for the carotid MRI as well as lipid and lipoprotein measurements in the ARIC study. Moreover, representation from both African American and Caucasian participants makes our results generalizable to a broader population. To our knowledge, this is the largest study evaluating the associations between measures of cholesterol content and particle number and carotid plaque characteristics using carotid MRI as the imaging modality.

We conclude the measures of plaque burden in the carotid arteries are positively associated with both cholesterol and particle measures of lipoproteins. Measures of plaque eccentricity are also positively associated with total cholesterol and non-HDL-C. Although anti-atherogenic cholesterol or lipoproteins are not directly associated with carotid plaque burden, the development of detectable lipid rich cores in large plaques could be influenced by low levels of anti-atherogenic lipoproteins.

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References

1. Cromwell WC, Otvos JD. Heterogeneity of low-density lipoprotein particle number in patients with type 2 diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. Am J Cardiol. 2006; 98:1599–602. [PubMed: 17145217]
2. Sniderman A, Williams K, Cobbaert C. ApoB versus non-HDL-C: what to do when they disagree. Curr Atheroscler Rep. 2009; 11:358–63. [PubMed: 19664379]
3. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J. 1993; 69:377–81. [PubMed: 8518056]
4. Classics in arteriosclerosis research: On experimental cholesterin steatosis and its significance in the origin of some pathological processes byAnitschkow N, Chalatow S. Pelias, Mary Z.Arteriosclerosis. 1983; 3:178–82.
5. Carew TE, Koschinsky T, Hayes SB, Steinberg D. A mechanism by which high-density lipoproteins may slow the atherogenic process. Lancet. 1976; 1:1315–7. [PubMed: 58308]
6. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010; 55:1600–7. [PubMed: 20378078]
7. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation. 2000; 102:959–64. [PubMed: 10961958]

8. Trivedi RA, JM UKI, Graves MJ, Horsley J, Goddard M, Kirkpatrick PJ, Gillard JH. MRI-derived measurements of fibrous-cap and lipid-core thickness: the potential for identifying vulnerable carotid plaques in vivo. Neuroradiology. 2004; 46:738–43. [PubMed: 15309350]
9. Yuan C, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, Small R, Davies JW, Kerwin WS, Hatsukami TS. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation. 2001; 104:2051–6. [PubMed: 11673345]
10. Wagenknecht L, Wasserman B, Chambless L, Coresh J, Folsom A, Mosley T, Ballantyne C, Sharrett R, Boerwinkle E. Correlates of carotid plaque presence and composition as measured by MRI: the Atherosclerosis Risk in Communities Study. Circ Cardiovasc Imaging. 2009; 2:314–22. [PubMed: 19808612]
11. Mani V, Muntner P, Gidding SS, Aguiar SH, El Aidi H, Weinshelbaum KB, Taniguchi H, van der Geest R, Reiber JH, Bansilal S, Farkouh M, Fuster V, Postley JE, Woodward M, Fayad ZA. Cardiovascular magnetic resonance parameters of atherosclerotic plaque burden improve discrimination of prior major adverse cardiovascular events. J Cardiovasc Magn Reson. 2009; 11:10. [PubMed: 19393089]
12. Kerwin W, Xu D, Liu F, Saam T, Underhill H, Takaya N, Chu B, Hatsukami T, Yuan C. Magnetic resonance imaging of carotid atherosclerosis: plaque analysis. Top Magn Reson Imaging. 2007; 18:371–8. [PubMed: 18025991]
13. Gaubatz JW, Ballantyne CM, Wasserman BA, He M, Chambless LE, Boerwinkle E, Hoogeveen RC. Association of circulating matrix metalloproteinases with carotid artery characteristics: the Atherosclerosis Risk in Communities Carotid MRI Study. Arterioscler Thromb Vasc Biol. 2010; 30:1034–42. [PubMed: 20167662]
14. Wasserman BA, Astor BC, Sharrett AR, Swingen C, Catellier D. MRI measurements of carotid plaque in the atherosclerosis risk in communities (ARIC) study: methods, reliability and descriptive statistics. J Magn Reson Imaging. 2010; 31:406–15. [PubMed: 20099354]
15. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989; 129:687–702. [PubMed: 2646917]
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
17. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med. 2006; 26:847–70. [PubMed: 17110242]
18. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109:433–8. [PubMed: 14744958]
19. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2007; 192:211–7. [PubMed: 16765964]
20. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Risk factors and segment-specific carotid arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1996; 27:69–75. [PubMed: 8553406]
21. Paramsothy P, Knopp RH, Bertoni AG, Blumenthal RS, Wasserman BA, Tsai MY, Rue T, Wong ND, Heckbert SR. Association of combinations of lipid parameters with carotid intima-media thickness and coronary artery calcium in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010; 56:1034–41. [PubMed: 20846602]
22. Blaha M, Blumenthal R, Brinton E, Jacobson T. The importance of non– HDL cholesterol reporting in lipid management. J Clin Lipidol. 2008; 2:267–73. [PubMed: 21291742]
23. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2008; 51:1512–24. [PubMed: 18402913]

24. Robinson JG. Are you targeting non-high-density lipoprotein cholesterol? J Am Coll Cardiol. 2009; 55:42–4. [PubMed: 20117362]

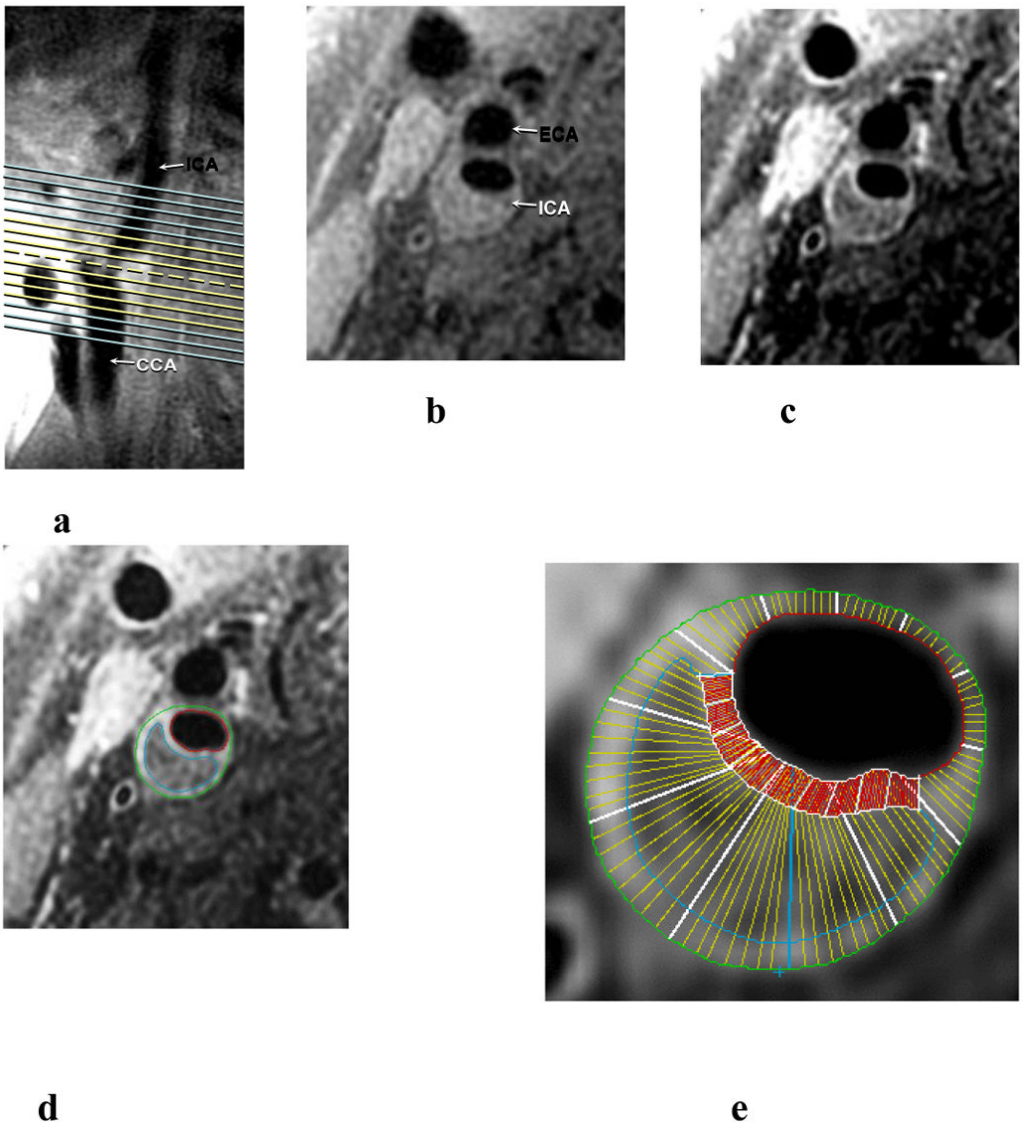

Figure 1.

Black blood MRI (BBMRI) slices through the carotid bifurcation and plaque. A long axis BBMRI image adjacent to the slice shown in Figure 1a was used to orient 8 precontrast (yellow lines) and 16 postcontrast (yellow and blue lines) slices through the plaque. Transverse BBMRI image through the thickest part of the plaque (a, broken line) is shown before (b) and after (c) contrast administration. Contours were drawn on the postcontrast image to delineate the core (blue), lumen (red) and outer wall (green) (d). The wall was automatically divided into 12 radial segments and the cap was segmented at 15 ° increments (e). Segmental thickness measurements were determined by averaging the yellow line thicknesses for the wall and red line thicknesses for the cap (e).

Table 1
Baseline characteristics of the study cohort

Characteristics	n = 1,670
Age in years, mean ± standard deviation (SD)	71 ± 5.6
Men, n (%)	823 (49.3)
Caucasian, n (%)	1,305 (78.1)
History of diabetes, n (%)	402 (24.3)
History of hypertension, n (%)	1,119 (67.7)
Presence of metabolic syndrome*, n (%)	970 (58)
Current smoking, n (%)	142 (8.6)
Systolic blood pressure (mm Hg), mean ± SD	127 ± 19
Diastolic blood pressure (mm Hg), mean ± SD	66 ± 10.5
Body mass index (kg/m$^{2)}$, mean ± SD	28.3 ± 4.7
hs-CRP mg/L, median (inter-quartile range)	1.97 (1.02-4.02)
Antihypertensive medication use, n (%)	1,140 (68.5)
Antidiabetes medication use, n (%)	253 (15.2)
Statin use, n (%)	639 (38.8)
Aspirin use, n (%)	1,142 (69.3)
Total cholesterol (mg/dL), mean ± SD	193 ± 41
Low-density lipoprotein cholesterol (mg/dL), mean ± SD	113 ±38
Non–high-density lipoprotein cholesterol (mg/dL), mean ± SD	144 ± 37
High-density lipoprotein cholesterol (mg/dL), mean ± SD	49±5
Apolipoprotein B (mg/dL), mean ± SD	98 ±24
Apolipoprotein A-1 (mg/dL), mean ± SD	131 ±18
Low-density lipoprotein particle concentration (nmol/L), mean ± SD	1,148 ±350
High-density lipoprotein particle concentration (μmol/L), mean ± SD	35 ±6

* Defined by the National Heart, Lung and Blood Institute/American Heart Association criteria[18] as the presence of 3 or more of the following 5 criteria: waist circumference >40 inches in men and >35 inches in women, triglycerides >150 mg/dL, HDL-C concentration <40 mg/dL in men and <50 mg/dL in women, blood pressure >130/>85 mm Hg, and fasting glucose >100 mg/dL

Table 2

Associations of measures of plaque burden and plaque eccentricity with cholesterol content (or lipoprotein) parameters in fully adjusted models*

	Total wall volume (mm^3)			Maximum wall thickness (mm)			Normalized wall index (NWI)‡			Standard deviation of wall thickness (mm)		
	β**	p	$R^{2\dagger}$	β**	p	$R^{2\dagger}$	β**	p	$R^{2\dagger}$	β**	p	$R^{2\dagger}$
Atherogenic cholesterol or lipoproteins												
TC	0.13	**<.0001**	0.14	0.10	**0.001**	0.09	0.10	**0.003**	0.09	0.09	**0.01**	0.08
LDL-C	0.09	**0.004**	0.13	0.09	**0.002**	0.09	0.09	**0.004**	0.09	0.03	0.37	0.07
Non–HDL-C	0.13	**<.0001**	0.14	0.10	**0.001**	0.09	0.12	**<.0001**	0.09	0.08	**0.02**	0.08
ApoB	0.06	**0.04**	0.13	0.05	0.12	0.09	0.07	**0.02**	0.09	0.05	0.11	0.07
LDLp	0.08	**0.006**	0.13	0.08	**0.008**	0.09	0.10	**0.002**	0.09	0.03	0.32	0.07
Anti-atherogenic cholesterol or lipoproteins												
HDL-C	0.03	0.44	0.13	0.02	0.54	0.08	−0.02	0.59	0.09	0.05	0.17	0.07
Apo A-1	0.07	0.07	0.13	0.02	0.57	0.09	<−.001	0.99	0.09	0.06	0.07	0.07
HDLp	0.01	0.74	0.13	0.002	0.94	0.08	−0.02	0.61	0.09	0.04	0.26	0.07
Atherogenic/Anti-atherogenic cholesterol or lipoprotein ratios												
TC/HDL-C	0.09	**0.01**	0.13	0.06	**0.06**	0.09	0.09	**0.01**	0.09	0.02	0.52	0.07
Non–HDL-C/HDL-C	0.09	**0.01**	0.13	0.06	**0.06**	0.09	0.09	**0.01**	0.09	0.02	0.52	0.07
ApoB/Apo A-1	0.02	0.49	0.13	0.03	0.34	0.09	0.06	**0.05**	0.09	0.02	0.60	0.07
LDLp/HDLp	0.05	0.09	0.13	0.05	0.08	0.09	0.08	**0.01**	0.09	0.003	0.91	0.07

TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, Non-HDL-C = non-high-density lipoprotein cholesterol, ApoB = apolipoprotein B, LDLp = low-density lipoprotein particle concentration, HDL-C = high-density lipoprotein cholesterol, Apo A-1 = apolipoprotein A-1, HDLp = high-density lipoprotein particle concentration

*Adjusted for age, race, gender, smoking status, body mass index, blood glucose, hypertensive medication use, cholesterol-lowering medication use, aspirin use, diabetic medication use, hs-CRP, and triglycerides

**β coefficients (β) are standardized regression coefficients and can be interpreted as number of standard deviation (SD) difference in the dependent variable (e.g., total wall volume) associated with a 1-SD difference in plasma cholesterol or lipoprotein levels

†Model R^2 values (coefficient of determination) can be interpreted as proportion of the variance in the dependent variable (e.g., total wall volume) as explained by the set of independent variables in the model including the cholesterol or lipoprotein particle parameter of interest

‡Normalized wall index (NWI) = wall area/total vessel wall area

Table 3

Associations between presence of lipid-rich core on the carotid MRI, and cholesterol content (or lipoprotein) parameters in fully adjusted models*

	Presence of lipid-rich core in fully adjusted model		
	OR**	**p**	**Model $R^{2\dagger}$**
Atherogenic cholesterol or lipoproteins			
Total cholesterol	1.10	0.23	0.12
Low-density lipoprotein cholesterol	1.13	0.14	0.13
Non–high-density lipoprotein cholesterol (non–HDL-C)	1.15	0.08	0.13
Apolipoprotein B (ApoB)	1.08	0.34	0.12
Low-density lipoprotein particle concentration (LDLp)	1.15	0.08	0.13
Anti-atherogenic cholesterol or lipoproteins			
High-density lipoprotein cholesterol (HDL-C)	0.91	0.31	0.12
Apolipoprotein A-1 (Apo A-1)	0.90	0.20	0.13
High-density lipoprotein particle concentration (HDLp)	0.88	0.10	0.13
Atherogenic/Anti-atherogenic cholesterol or lipoprotein ratios			
Total cholesterol/HDL-C	1.17	**0.05**	0.13
Non–HDL-C/HDL-C	1.17	**0.05**	0.13
ApoB/Apo A-1	1.13	0.14	0.13
LDLp/HDLp	1.16	**0.04**	0.13

*Adjusted for age, race, gender, smoking status, body mass index, blood glucose, hypertensive medication use, cholesterol-lowering medication use, aspirin use, diabetic medication use, hs-CRP, and triglycerides

*** Represent the standardized odds ratios (OR) and can be interpreted as the odds for the presence of lipid-rich core associated with a 1 SD difference in plasma cholesterol or lipoprotein levels

$^{\dagger}R^2$ values (coefficient of determination) can be interpreted as proportion of the variance in the dependent variable (e.g. lipid-rich core presence) as explained by the set of independent variables in the model including the cholesterol or lipoprotein particle parameter of interest

Table 4

Associations between presence of lipid-rich core on the carotid MRI, and cholesterol content or lipoprotein parameters in fully adjusted models with additional adjustment for maximum carotid wall thickness*

	Presence of lipid-rich core in fully adjusted model plus adjusted for wall thickness		
	OR**	**p**	**Model $R^{2\dagger}$**
Atherogenic cholesterol or lipoproteins			
Total cholesterol	0.98	0.85	0.56
Low-density lipoprotein cholesterol	1.02	0.80	0.56
Non–high-density lipoprotein cholesterol (non–HDL-C)	1.04	0.69	0.56
Apolipoprotein B (ApoB)	1.04	0.68	0.56
Low-density lipoprotein particle concentration (LDLp)	1.07	0.44	0.56
Anti-atherogenic cholesterol or lipoproteins			
High-density lipoprotein cholesterol (HDL-C)	0.86	0.16	0.56
Apolipoprotein A-1 (Apo A-1)	0.84	0.08	0.56
High-density lipoprotein particle concentration (HDLp)	0.84	0.06	0.56
Atherogenic/Anti-atherogenic cholesterol or lipoprotein ratios			
Total cholesterol/HDL-C	1.13	0.20	0.56
Non–HDL-C/HDL-C	1.13	0.20	0.56
ApoB/Apo A-1	1.13	0.20	0.56
LDLp/HDLp	1.14	0.13	0.56

*Adjusted for covariates as in Table 3 plus maximum carotid wall thickness

**represent the standardized odds ratios and can be interpreted as the odds for the presence of lipid-rich core associated with a 1 SD difference in plasma cholesterol or lipoprotein levels

$^{\dagger}R^2$ values (coefficient of determination) can be interpreted as proportion of the variance in the dependent variable (e.g. lipid-rich core presence) as explained by the set of independent variables in the model including the cholesterol or lipoprotein particle parameter of interest