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Carotid Plaque Lipid Content and Fibrous Cap Status Predict Systemic CV Outcomes

The MRI Substudy in AIM-HIGH

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ABSTRACT

OBJECTIVES The aim of this study was to investigate whether and what carotid plaque characteristics predict *systemic* cardiovascular outcomes in patients with clinically established atherosclerotic disease.

BACKGROUND Advancements in atherosclerosis imaging have allowed assessment of various plaque characteristics, some of which are more directly linked to the pathogenesis of acute cardiovascular events compared to plaque burden.

METHODS As part of the event-driven clinical trial AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes), subjects with clinically established atherosclerotic disease underwent multicontrast carotid magnetic resonance imaging (MRI) to detect plaque tissue composition and high-risk features. Prospective associations between MRI measurements and the AIM-HIGH primary endpoint (fatal and nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, and symptom-driven revascularization) were analyzed using Cox proportional hazards survival models.

RESULTS Of the 232 subjects recruited, 214 (92.2%) with diagnostic image quality constituted the study population (82% male, mean age 61 ± 9 years, 94% statin use). During median follow-up of 35.1 months, 18 subjects (8.4%) reached the AIM-HIGH endpoint. High lipid content (hazard ratio [HR] per 1 SD increase in percent lipid core volume: 1.57; $p = 0.002$) and thin/ruptured fibrous cap (HR: 4.31; $p = 0.003$) in carotid plaques were strongly associated with the AIM-HIGH endpoint. Intraplaque hemorrhage had a low prevalence (8%) and was marginally associated with the AIM-HIGH endpoint (HR: 3.00; $p = 0.053$). High calcification content (HR per 1 SD increase in percent calcification volume: 0.66; $p = 0.20$), plaque burden metrics, and clinical risk factors were not significantly associated with the AIM-HIGH endpoint. The associations between carotid plaque characteristics and the AIM-HIGH endpoint changed little after adjusting for clinical risk factors, plaque burden, or AIM-HIGH randomized treatment assignment.

CONCLUSIONS Among patients with clinically established atherosclerotic disease, carotid plaque lipid content and fibrous cap status were strongly associated with *systemic* cardiovascular outcomes. Markers of carotid plaque vulnerability may serve as novel surrogate markers for systemic atherothrombotic risk. (J Am Coll Cardiol Img 2017;10:241–9)

Imaging markers of atherosclerosis, which are traditionally focused on measuring plaque burden, have proven clinical utility in refining cardiovascular risk assessment for individual patients (1,2). Nonetheless, improved understanding of the pathophysiology of myocardial infarction and ischemic stroke directs our attention to high-risk plaques featuring typically thin fibrous cap and large

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ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CAS = Carotid Atherosclerosis Score

CI = confidence interval

HDL = high-density lipoprotein

HR = hazard ratio

IPH = intraplaque hemorrhage

LDL = low-density lipoprotein

LRNC = lipid-rich necrotic core

MRI = magnetic resonance imaging

underlying lipid cores, which are considered the true pathological substrate for acute cardiovascular events (3). As such, imaging measurements on high-risk plaque characteristics, compared to those on plaque burden, may potentially serve as more effective biomarkers for atherothrombotic risk in research and clinical practice.

Advancements in cardiovascular imaging have enabled identification of high-risk plaque characteristics in the carotid artery. Echolucency of carotid plaques on B-mode ultrasound indicates high lipid content and is used as a feature of high-risk lesions (4). Multidetector computed tomography angiography has good performance in detecting vascular calcification but may also identify large lipid cores as low-attenuation regions (5,6). Magnetic resonance imaging (MRI) offers high soft tissue contrast and is increasingly used to evaluate plaque tissue composition and high-risk features (7–12). Although some carotid plaque characteristics have been shown to pose increased risk for ipsilateral stroke (13–15) and are being used for evaluating drug efficacy and defining plaque progression (16–19), data that directly address the association between high-risk carotid plaque characteristics and *systemic* cardiovascular outcomes remain scarce.

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In a prospective cohort study incorporated within AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) (20,21), we investigated whether and what carotid plaque characteristics predict *systemic* cardiovascular outcomes. The use of multicontrast MRI enabled us to examine a wide spectrum of carotid plaque characteristics. Cardiovascular outcomes as determined in an event-driven clinical trial provided a unique opportunity to test novel imaging markers against rigorously adjudicated clinical events among subjects undergoing contemporary intensive medical therapy.

METHODS

STUDY POPULATION. AIM-HIGH is a multicenter event-driven clinical trial that assessed the effect of extended-release niacin in patients with atherosclerotic cardiovascular disease and dyslipidemia (20,21). Participants were male and female (age 45 years or older) who had: 1) established vascular disease, defined as documented coronary artery, cerebrovascular, or peripheral artery disease; and 2) well-controlled low-density lipoprotein (LDL) cholesterol but low high-density lipoprotein (HDL) cholesterol (20). An MRI ancillary study (Carotid Plaque Characteristics by MRI in AIM-HIGH; NCT01178320) was integrated into the main study, which recruited AIM-HIGH subjects who had no contraindications for MRI or administration of gadolinium contrast (e.g., metal implants, claustrophobia, glomerular filtration rate <60 ml/min/1.73 m^2) and were willing to participate. Of 447 available AIM-HIGH subjects at 21 clinical sites, 232 met inclusion criteria of the MRI substudy and underwent MRI at 10 imaging sites (22). Institutional review board approval was obtained at all participating sites. Enrolled subjects provided written informed consent.

CAROTID MRI. Carotid MRI was performed at 3-T using commercially available carotid phased-array surface coils (GE: 6-channel, Neocoil LLC, Pewaukee, Wisconsin; Philips: 8-channel, Shanghai Chenguang Medical Technologies, Shanghai, China). To comprehensively characterize carotid plaques, a multicontrast protocol was standardized and implemented on both GE and Philips platforms, including 3-dimensional time of flight, T_1, T_2, proton density, and magnetization-prepared rapid acquisition gradient echo. Detailed parameters and reproducibility of the MRI protocol have been previously reported (22,23). Each sequence acquired a contiguous stack of cross-sectional images centered on the common carotid bifurcation (acquired in-plane resolution: 0.625 × 0.625 mm^2; slice thickness: 2 mm). Post-contrast T_1-weighted images were acquired at about 5 min after contrast injection (Magnevist, Bayer Healthcare, Wayne, New Jersey). Total acquisition time was approximately 45 min.

Blinded image review was performed in a core laboratory using a custom-designed image analysis software package (CASCADE, University of Washington, Seattle, Washington) (24). Image analysis was limited to the index side, defined as the carotid artery with patent lumen, or, if both were patent, the one with

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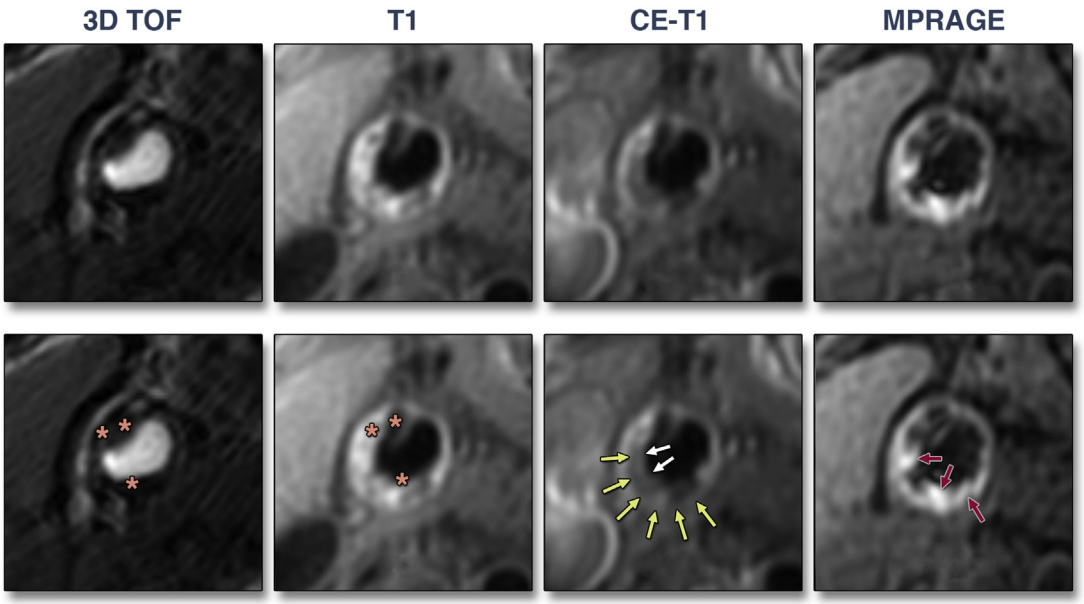
FIGURE 1 Identification of Carotid Plaque Characteristics on Multicontrast Magnetic Resonance Imaging



Top: Multicontrast images of a representative carotid plaque with all the common plaque characteristics. **Bottom:** Markers for specific plaque characteristics are added. Areas that are hypointense on all contrast weightings indicate calcification **(asterisks)**. Noncalcified areas that have no or little enhancement on post-contrast images indicate LRNC **(yellow arrows)**. Hyperintense signals on MPRAGE indicate intraplaque hemorrhage **(red arrows)**. The absence of fibrous cap signals (LRNC is immediately adjacent to lumen) on TOF and CE-T1 indicates the presence of thin/ruptured fibrous cap **(white arrows)**. CE-T1 = contrast-enhanced T_1-weighted; LRNC = lipid-rich necrotic core; MPRAGE = magnetization-prepared rapid acquisition gradient echo; T1 = T_1-weighted; TOF = time of flight.

the larger (based on maximum thickness) plaque. The various contrast weightings were aligned using the common carotid bifurcation as a fiducial marker. Lumen, outer wall, and plaque components were outlined using a semi-automated contouring tool in CASCADE based on multicontrast review criteria (**Figure 1**) that have been validated previously (7-9). Calcification was classified as areas that were hypointense on all contrast weightings. For juxtaluminal calcifications, accurate detection requires matching and comparing bright-blood (time of flight) and black-blood images (**Figure 1**). Lipid-rich necrotic cores (LRNCs) were then classified as noncalcified areas that had no or little enhancement on post-contrast T_1-weighted images using the pre-contrast images as reference. Presence of intraplaque hemorrhage (IPH) was recorded if hyperintense signals were noted on magnetization-prepared rapid acquisition gradient echo images (10). Presence of thin/ruptured fibrous cap was recorded if the integrity of the fibrous cap was compromised (thin cap: partially invisible with smooth surface; ruptured cap: partially invisible with surface irregularity or juxtaluminal hyperintensity on time of flight images) on time of flight, post-contrast T_1-weighted, or T_2-weighted images (11,12). Presence of ulceration was recorded if there was distinct depression below the luminal surface that showed similar signals to flowing blood. Presence of calcified nodule, as described by Virmani et al. (3), was recorded if a piece of calcification protruded into the lumen.

Continuous measurements were calculated based on plaque segmentation, which are thought to be pathophysiologically relevant to cardiovascular outcomes according to experience from previous studies (16,17): 1) plaque burden, including maximum wall thickness, maximum percent wall area (wall area/total vessel area), and percent wall volume (wall volume/total vessel volume); and 2) plaque composition, including absolute and percent volume (component volume/wall volume) of calcification and LRNC, using component-containing slices only and assigned zero if not detected (16,17). Interscan reproducibility of plaque measurements derived from multicontrast MRI review using CASCADE has been previously reported, with intraclass correlation coefficient ranging from 0.87 to 0.99 for all morphological and compositional measurements (23,25). Furthermore, the previously proposed definitions of high-risk plaques that include

heterogeneous plaque types were also studied (7,22,26): American Heart Association (AHA) type VI lesions include plaques with surface disruption (i.e., cap rupture, ulceration, and calcified nodule), IPH, or mural thrombus; and Carotid Atherosclerosis Score type 4 lesions (CAS-4) include AHA type VI lesions as well as those with maximum percent LRNC area (LRNC area/wall area) >40%. Individual plaque types included in type VI lesions were not examined alone because of low prevalence (<10%) except IPH, which was shown previously to predict systemic cardiovascular outcome (27,28).

CLINICAL RISK FACTORS AND FOLLOW-UP OF CARDIOVASCULAR EVENTS. In AIM-HIGH, all subjects were taking simvastatin with or without ezetimibe to achieve the LDL cholesterol target of 40 to 80 mg/dl (1.0 to 2.1 mmol/l). Regular clinical follow-up visits were arranged to monitor safety and adjust dosage as needed, which was previously reported in detail (20). Depending on study assignment, subjects were on extended-release niacin 1,500 to 2,000 mg/day or its active placebo. Clinical management beyond lipid-modifying treatment was consistent with current standard of care and at the discretion of local physicians. Demographics and information on traditional risk factors were collected at study entry and updated during follow-up visits. A clinical risk score was calculated on the basis of a previously published Framingham risk model for predicting risk of recurrent events in patients with a history of coronary heart disease or stroke (29).

In order to leverage the high-quality outcome data available from the main study, the MRI substudy was designed a priori to use the AIM-HIGH primary endpoint, which was the composite of the first occurrence of fatal or nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization. All recorded events were adjudicated by the AIM-HIGH Clinical Events Committee. After the databases were locked, individual participant data on clinical profile, carotid plaque measurements, and incident events were linked. Time to event (or end of follow-up) was modified to start from MRI scan instead of study enrollment as in the main study.

STATISTICAL ANALYSIS. Patient characteristics are given as mean ± SD for continuous variables and as n (%) for categorical variables. Associations between MRI characteristics and incident clinical events were quantified using hazard ratios (HRs) by Cox proportional hazards survival models. Kaplan-Meier curves of event-free survival grouped by individual carotid features were used to visualize associations and estimate absolute event-free survival rates at 3 years. As a sensitivity analysis, leave-one-out regression diagnostics (dfbetas) were performed to detect influential observations that changed the regression coefficients by more than 0.5 SEs. Models without influential observations were run to test the robustness of statistically significant findings. For carotid plaque characteristics, exploratory multivariate analysis was performed to evaluate their associations with incident clinical events after adjusting separately for the Framingham risk score, maximum wall thickness, or AIM-HIGH randomized treatment assignment. Data analyses were performed using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$, and all tests were 2-tailed.

RESULTS

DEMOGRAPHICS, RISK PROFILE, AND CLINICAL OUTCOMES. Of the 232 subjects recruited, 214 (92.2%) with acceptable diagnostic image quality constituted the study cohort (**Table 1**). Mean age was 61.2 ± 8.6 years, and 82% were males. Detailed clinical characteristics of the MRI cohort and their association with carotid plaque characteristics have been reported in a previous publication (22).

During median follow-up of 35.1 months (range 1.2 to 57.7 months), 18 subjects (8.4%) reached the AIM-HIGH primary endpoint, including myocardial infarction (n = 6), ischemic stroke (n = 2), hospitalization for acute coronary syndrome (n = 2), symptom-driven coronary revascularization (n = 7), and symptom-driven cerebrovascular revascularization (n = 1). None of the traditional risk factors or AIM-HIGH randomized treatment assignment (i.e., on extended-release niacin) were significantly associated with the AIM-HIGH primary endpoint (**Table 1**), nor was the Framingham risk score, which aggregates multiple risk factors including age, sex, smoking, blood pressures, lipid levels, and diabetes status.

CAROTID PLAQUE CHARACTERISTICS AND SYSTEMIC CARDIOVASCULAR OUTCOMES. Despite a high rate of long-term statin use (<1 year: 22%, 1 to 5 years: 36%, >5 years: 36%), calcification, LRNC, IPH, and thin/ruptured fibrous cap were detected by carotid MRI in 48%, 52%, 8%, and 14% of the subjects, respectively. Twenty-three subjects (11%) had AHA type VI lesions, the majority of which were the result of IPH alone (n = 6), cap rupture alone (n = 2), or both (n = 12). The remaining 3 were caused by the presence of ulceration in the absence of remnant LRNC

TABLE 1 Patient Characteristics and Associations With Systemic Cardiovascular Outcomes

		AIM-HIGH Primary Endpoint*				
	All Subjects (N = 214)	Yes (N = 18)	No (N = 196)	HR†	95% CI	p Value
Clinical characteristics						
Age, yrs	61.2 ± 8.6	63.5 ± 9.8	61.0 ± 8.5	1.26	0.79–2.00	0.3
Male	82	94	81	3.98	0.53–29.89	0.2
Caucasian	88	100	87	NA	NA	NA
Body mass index, kg/m^2	30.1 ± 4.5	29.0 ± 6.0	30.2 ± 4.4	0.75	0.45–1.24	0.3
Smoker						
Never	29	33	29	1.00 (ref.)		
Former	53	56	53	0.92	0.33–2.52	0.9
Current	17	11	18	0.57	0.12–2.85	0.5
Hypertension	83	89	83	1.65	0.38–7.19	0.5
Diabetes mellitus	25	17	26	0.59	0.17–2.04	0.4
Coronary artery disease	95	94	95	1.00	0.13–7.52	1.0
Cerebrovascular disease	16	17	16	0.99	0.29–3.42	1.0
Total cholesterol, mg/dl	146 ± 31	144 ± 21	146 ± 32	0.94	0.58–1.52	0.8
LDL cholesterol, mg/dl	77 ± 27	79 ± 16	76 ± 28	1.08	0.70–1.68	0.7
HDL cholesterol, mg/dl	35 ± 6	34 ± 5	35 ± 6	0.90	0.57–1.42	0.6
Triglycerides, mg/dl	174 ± 66	158 ± 52	176 ± 67	0.70	0.39–1.27	0.2
Systolic blood pressure, mm Hg	128 ± 17	132 ± 16	127 ± 17	1.27	0.82–1.99	0.3
Diastolic blood pressure, mm Hg	75 ± 10	76 ± 10	75 ± 10	1.05	0.67–1.66	0.8
Framingham risk score, %	8.3 ± 2.7	8.8 ± 2.0	8.2 ± 2.7	1.19	0.76–1.86	0.4
On extended-release niacin	44	33	45	0.65	0.24–1.73	0.4
Carotid plaque burden						
Maximum wall thickness, mm	2.7 ± 1.4	3.3 ± 2.1	2.7 ± 1.3	1.43	0.96–2.11	0.08
Maximum percent wall area	48 ± 15	54 ± 27	48 ± 14	1.34	0.92–1.94	0.12
Percent wall volume	41.8 ± 7.1	42.5 ± 7.5	41.7 ± 7.1	1.12	0.72–1.74	0.60
Carotid plaque characteristics						
LRNC volume, mm^3	40 ± 99	130 ± 206	31 ± 78	1.43	1.16–1.75	<0.001
LRNC volume, %	6.6 ± 9.6	14 ± 15	5.9 ± 8.7	1.57	1.22–2.01	0.002
Calcification volume, mm^3	12 ± 24	6 ± 11	13 ± 25	0.60	0.26–1.41	0.2
Calcification volume, %	2.8 ± 4.2	1.7 ± 2.4	2.9 ± 4.3	0.66	0.35–1.27	0.2
Intraplaque hemorrhage	8	22	7	3.00	0.99–9.13	0.053
Thin/ruptured fibrous cap	14	39	11	4.31	1.67–11.1	0.003
High-risk plaque classifications						
AHA type VI‡	11	22	10	2.36	0.77–7.17	0.13
CAS-4§	12	28	11	2.79	0.99–7.85	0.051

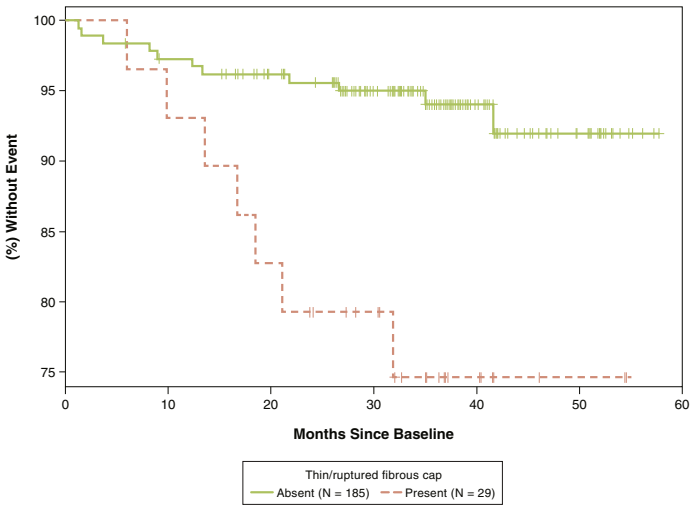
Values are mean ± SD or %. *The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial primary endpoint was the composite of the first occurrence of fatal or nonfatal myocardial infarction or ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization. †For continuous variables, HRs are presented per 1 SD increase. ‡AHA type VI lesions include plaques with surface disruption (i.e., cap rupture, ulceration, and calcified nodule), intraplaque hemorrhage, or mural thrombus. §CAS-4 lesions include AHA type VI lesions as well as those with maximum percent LRNC area (LRNC area/wall area) >40%.

AHA = American Heart Association; CAS = Carotid Atherosclerosis Score; CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; LRNC = lipid-rich necrotic core.

(ulceration overlying a remnant LRNC was considered as cap rupture) or calcified nodule. CAS-4 lesions had a slightly higher prevalence of 12%, with the addition of 3 cases due to maximum percent LRNC area >40%.

Notably, subjects with thin/ruptured fibrous cap had a 4.31-fold (95% confidence interval [CI]: 1.67 to 11.12; p = 0.003) increased risk for the AIM-HIGH primary endpoint (Table 1). The estimated 3-year primary event-free survival rate was 74.6% for subjects with thin/ruptured fibrous cap versus 94.0% for those without (Figure 2). Plaque lipid content was also significantly associated with the AIM-HIGH primary endpoint (HR per 1 SD increase in percent LRNC volume: 1.57; 95% CI: 1.22 to 2.01; p = 0.002), whereas the association of plaque calcification content was not statistically significant and in the other direction (HR per 1 SD increase in percent calcification volume: 0.66; 95% CI: 0.35 to 1.27; p = 0.2) (Table 1). The association of IPH with the AIM-HIGH primary endpoint was positive but did not reach statistical significance (HR: 3.00; 95% CI: 0.99 to 9.13; p = 0.053). There was no significant association between the AIM-HIGH primary endpoint and AHA type VI (HR: 2.36; 95% CI: 0.77 to 7.17; p = 0.13) or

FIGURE 2 Kaplan-Meier Estimates of Event-Free Survival



Kaplan-Meier curves show event-free survival in the group with **(pink line)** and without **(green line)** thin/ruptured fibrous cap. The corresponding hazard ratio is 4.31 (95% confidence interval: 1.67 to 11.12; p = 0.003) for the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial primary endpoint (fatal or nonfatal myocardial infarction or ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebrovascular revascularization). The estimated 3-year primary event-free survival rate was 74.6% for subjects with thin/ruptured fibrous cap versus 94.0% for those without.

CAS-4 (HR: 2.79; 95% CI: 0.99 to 7.85; p = 0.051) lesions, which include heterogeneous plaque types (Table 1). The 3 subjects who were included in the category of type VI lesions because of complications other than IPH or cap rupture remained event-free during follow-up. None of the plaque burden measurements were significantly associated with the primary endpoint, although there was a trend for maximum wall thickness (HR per 1 SD increase: 1.43; 95% CI: 0.96 to 2.11; p = 0.08).

EXPLORATORY MULTIVARIATE ANALYSIS. The associations between carotid plaque characteristics and the AIM-HIGH primary endpoint changed little in multivariate analyses adjusting separately for Framingham risk score, maximum wall thickness, or AIM-HIGH randomized treatment assignment (Table 2). Thin/ruptured fibrous cap remained significantly associated with the AIM-HIGH primary endpoint after each adjustment, with HRs ranging from 4.04 to 4.61 (p < 0.02 for each). Similarly, percent LRNC volume also remained significantly associated with the primary endpoint after each adjustment, with HRs ranging from 1.56 to 1.99 per 1 SD increase (p < 0.03 for each).

DISCUSSION

By leveraging the rigorously adjudicated outcome data of a contemporary clinical trial, we evaluated MRI measurements of carotid plaque characteristics as surrogate markers for *systemic* cardiovascular outcomes. Among subjects with clinically established atherosclerotic disease receiving intensive medical therapy, high plaque lipid content and thin/ruptured fibrous cap were shown to identify those with substantially worse short- to intermediate-term prognosis. IPH had a low prevalence and was marginally associated with poor prognosis. In contrast, although calcium deposition is traditionally pursued as a marker for atherosclerosis, high plaque calcification content was not associated with poor prognosis. The observed associations between carotid plaque characteristics and *systemic* cardiovascular outcomes were not driven by traditional risk factors, plaque burden, or AIM-HIGH treatment assignment, which did not significantly predict the primary endpoint by themselves and had little influence on the associations of plaque characteristics with outcomes in multivariate analyses.

The field of cardiovascular medicine has seen a longstanding quest to use imaging measures of carotid atherosclerosis as surrogate markers in clinical management of atherosclerotic disease. However, whether the emerging imaging measures of carotid plaque characteristics, some of which were shown to predict ipsilateral cerebrovascular events and thought to reflect plaque vulnerability (13–15), can be used as novel surrogate markers remains elusive because of the limited data currently available. The concept is supported by a histopathologic study in which Hellings et al. (27) reported that carotid plaque features including IPH and neovasculature identified in endarterectomy specimens were associated with future cardiovascular events in 818 patients who underwent carotid endarterectomy. Compared to the previous observation in highly selected patients undergoing carotid surgery, our findings provide prospective evidence in a broader group of patients with clinically established atherosclerotic disease that carotid plaque characteristics were strongly associated with *systemic* cardiovascular outcomes, whereas traditional risk factors and plaque burden were not. Further evidence can be seen from 2 focused studies that respectively reported that echolucent carotid plaques on ultrasound (indicating high lipid content) and hyperintense signals on MRI (indicating IPH) predicted coronary events in patients with existing coronary artery disease (28,30). Therefore, it has

TABLE 2 Exploratory Multivariate Analysis of Associations Between Carotid Plaque Characteristics and AIM-HIGH Primary Endpoint

	Adjusted for Framingham Risk Score*			Adjusted for Maximum Wall Thickness*			Adjusted for AIM-HIGH Treatment Arm*		
	HR†	95% CI	p Value	HR†	95% CI	p Value	HR†	95% CI	p Value
LRNC volume, mm^3	1.42	1.15–1.74	0.001	1.58	1.06–2.35	0.02	1.44	1.17–1.77	<0.001
LRNC volume, %	1.56	1.14–2.13	0.005	1.99	1.06–3.73	0.03	1.62	1.21–2.16	0.001
Calcification volume, mm^3	0.58	0.24–1.40	0.20	0.45	0.18–1.15	0.10	0.60	0.26–1.39	0.20
Calcification volume, %	0.65	0.33–1.26	0.20	0.53	0.27–1.06	0.07	0.67	0.35–1.27	0.20
Intraplaque hemorrhage	2.80	0.89–8.82	0.08	2.07	0.50–8.60	0.30	3.53	1.13–11.05	0.03
Thin/ruptured fibrous cap	4.18	1.57–11.14	0.004	4.04	1.23–13.22	0.02	4.61	1.77–11.98	0.002
AHA type VI‡	2.33	0.74–7.31	0.15	1.47	0.35–6.12	0.60	2.51	0.82–7.68	0.11
CAS-4§	2.79	0.97–8.06	0.06	2.01	0.52–7.73	0.30	3.04	1.07–8.63	0.04

*All models are bivariate, with 1 plaque characteristic variable and a single adjustment variable. Adjustment was made individually for the Framingham risk score for recurrent events in patients with coronary heart disease or stroke (29), maximum wall thickness, and treatment assignment in AIM-HIGH. †For continuous variables, hazard ratios are presented per 1 SD increase. ‡AHA type VI lesions include plaques with surface disruption (i.e., cap rupture, ulceration, and calcified nodule), intraplaque hemorrhage, or mural thrombus. §CAS-4 lesions include AHA type VI lesions as well as those with maximum percent LRNC area (LRNC area/wall area) >40%.

Abbreviations as in Table 1.

become increasing clear that imaging measurements of carotid plaque characteristics can serve as novel surrogate markers and provide useful information for understanding systemic atherothrombotic risk in individual patients, particularly in patients with established atherosclerotic cardiovascular disease in whom the predictive value of traditional risk factors and carotid plaque burden could be more limited than in low-risk populations.

Compared to previous studies, the use of a standardized multicontrast MRI protocol allowed us to examine a spectrum of carotid plaque characteristics in the same cohort and perform quantitative assessment on plaque tissue composition. Notably, this is one of the first studies to highlight the prognostic value of thin-cap fibroatheroma in terms of *systemic* cardiovascular outcomes. Approximately 25% of those with thin/ruptured fibrous cap on carotid MRI experienced the AIM-HIGH primary endpoint in 3 years by Kaplan-Meier analysis, whereas the event-free survival at 3 years was 94% among those without. This finding supports the pathophysiological concept that high-risk individuals harbor multiple vulnerable plaques and that intensive medical treatment should play a primary role in clinical management. Quantification of plaque lipid content provided another promising imaging marker that informs about *systemic* atherothrombotic risk. Recently, there have been studies using imaging measures of plaque lipid content for testing drug efficacy in clinical trials in order to get an early signal of drug efficacy or reveal the underlying mechanisms of clinical treatment (16,17,31). These efforts are supported by findings from the present study. However, plaque calcification content in extracranial carotid artery was not associated with future risk for *systemic* cardiovascular events in this cohort, questioning the value of surrogate artery calcification in identifying high-risk patients. Unlike lipid content, it is possible that calcification is more reflective of plaque burden but not plaque vulnerability. Previous investigations have stressed the importance of distinguishing the patterns of plaque calcification. Macrocalcification has been hypothesized as a feature of stable plaques, whereas microcalcification has been associated with plaque inflammation (32). Alternatively, increasing evidence suggests that statins promote plaque calcification while reducing the risk for clinical events (33). The predictive value of calcification, measured as total volume, could be limited in intensively treated patients.

STUDY LIMITATIONS. Despite the unique strength of merging imaging data on novel plaque measurements and clinical outcome data in the setting of a contemporary clinical trial, there are several notable limitations of the present study. First, because of the small number of clinical events, our findings should be considered hypothesis generating. It primarily tested the hypothesis that imaging measures of carotid plaque vulnerability have potential for understanding *systemic* atherothrombotic risk in individuals. The C statistic and net reclassification index were not performed, so we could not quantify the incremental predictive value of carotid plaque characteristics beyond clinical risk models and established imaging markers (e.g., carotid intima-media thickness and coronary artery calcium score). Accordingly, the implications are mainly pathophysiological and do not immediately translate into changes of clinical practice. Some of the clinical events were revascularizations rather than hard events. However, the inclusion of symptom-driven

revascularization was made a priori to be consistent with the parent AIM-HIGH study. These revascularizations were performed after new-onset symptoms in an effort to prevent more severe clinical complications. Including these events would be consistent with the hypothesis that carotid plaque vulnerability indicates increased *systemic* atherothrombotic risk. Another limitation was that all patients in this study were already considered candidates for intensive medical therapy before imaging. Even though a subgroup with very poor prognosis was identified, how we can utilize this information to improve their clinical outcomes currently is unclear. Nonetheless, in light of the high prevalence of vulnerable plaque characteristics despite contemporary intensive medical therapy, the development of novel agents that are able to stabilize plaques is needed to reduce the residual risk.

CONCLUSIONS

By leveraging the rigorously adjudicated outcome data of the AIM-HIGH trial, we found that among patients with clinically established atherosclerotic disease, high-risk carotid plaque features despite intensive medical therapy, including thin/ruptured fibrous cap, high lipid content, and marginally IPH, were associated with *systemic* cardiovascular outcomes independent of traditional risk factors and plaque burden. In contrast, high calcification content did not indicate poor prognosis. Markers of carotid plaque vulnerability may serve as novel surrogate markers for *systemic* atherothrombotic risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with clinically established atherosclerotic disease, high lipid content and thin/ruptured fibrous cap in carotid plaques identify those with substantially worse short- to intermediate-term prognosis, whereas plaque calcification content, plaque burden, and traditional risk factors did not.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with high-risk carotid plaques represent a unique population that could benefit from more intensive lifestyle intervention and novel medical therapy.

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KEY WORDS atherosclerosis, cardiovascular events, carotid artery, magnetic resonance imaging, surrogate marker, vulnerable plaque

APPENDIX For a list of participating institutions, investigators, and coordinators, please see the online version of this article.