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Plaque Composition in the Proximal Superficial Femoral Artery and Peripheral Artery Disease Events

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Abstract

OBJECTIVES—The aim of this study was to describe associations of the presence of lipid-rich necrotic core (LRNC) in the proximal superficial femoral artery (SFA) with lower extremity peripheral artery disease (PAD) event rates and systemic cardiovascular event rates.

BACKGROUND—LRNC in the coronary and carotid arteries is associated with adverse outcomes but has not been studied previously in lower extremity arteries.

METHODS—Participants with ankle-brachial index (ABI) values <1.00 were identified from Chicago medical centers and followed annually. Magnetic resonance imaging was used to characterize SFA atherosclerotic plaque at baseline. Medical records for hospitalizations and procedures after baseline were adjudicated for lower extremity revascularization, amputation, and critical limb ischemia and also for new coronary events, ischemic stroke, and mortality.

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RESULTS—Of 254 participants with PAD, 62 (24%) had LRNC and 149 (59%) had calcium in the SFA at baseline. Cox regression analyses were adjusted for age, sex, race, comorbidities, baseline ABI, and other confounders. SFA LRNC was associated with an increased incidence of the combined outcome of lower extremity amputation, critical limb ischemia, ABI decline >0.15, and revascularization at 47-month follow-up (hazard ratio: 2.18; 95% confidence interval: 1.27 to 3.75; p = 0.005). The association of SFA LRNC with PAD events was maintained even when this combined outcome excluded lower extremity revascularization (hazard ratio: 2.58; 95% confidence interval: 1.25 to 5.33; p = 0.01). LRNC in the SFA was not associated with all-cause mortality, acute coronary events, or stroke.

CONCLUSIONS—Among patients with PAD, LRNC in the SFA was associated with higher rates of clinical PAD events, and this association was independent of ABI. Further study is needed to determine whether interventions that reduce SFA LRNC prevent PAD events.

Keywords

femoral artery; lipid rich necrotic core; MRI; vascular medicine

Coronary artery atherosclerotic plaque with a lipid-rich necrotic core (LRNC) and thin fibrous cap is associated with plaque rupture, thrombus formation, and an acute coronary event or progression of coronary artery atherosclerosis (1–4). Similar associations have been reported for the presence of LRNC in the carotid arteries and subsequent cerebrovascular events (5–8). However, the significance of LRNC in the lower extremity arteries is unknown.

We studied whether the presence of magnetic resonance imaging (MRI)–measured LRNC in superficial femoral artery (SFA) plaque is associated with higher rates of lower extremity peripheral artery disease (PAD) events, including amputation, hospitalization for critical limb ischemia, significant ankle-brachial index (ABI) decline, and lower extremity revascularization. We hypothesized that compared with the absence of LRNC, the presence of LRNC in the SFA would be associated with a higher rate of PAD events. We also studied whether MRI-detected calcium in SFA plaque and whether greater SFA plaque volume and smaller SFA luminal area were associated with higher PAD event rates.

Preliminary evidence suggests that local plaque characteristics may also provide information about risk for cardiovascular events in distant artery beds (9–14). Therefore, we studied whether LRNC and calcium in the SFA were associated with higher rates of acute coronary events, ischemic stroke, and all-cause mortality compared with the absence of LRNC or calcium in the SFA. We also studied whether greater MRI-measured plaque volume in the SFA and smaller luminal area in the SFA were associated with higher rates of acute coronary events, ischemic stroke, and mortality.

METHODS

SUBJECTS

Participants were part of the WALCS (Walking and Leg Circulation Study) III cohort, a longitudinal observational study designed to examine the association of MRI-measured atherosclerotic plaque characteristic in the SFA with functional impairment and decline in

men and women with PAD (15). Enrollment occurred between October 26, 2007, and April 2010 (15,16). Participants were identified from among all patients diagnosed with PAD in the noninvasive vascular laboratories or in vascular surgery, cardiology, and/or general medical practices at 4 Chicago-area hospitals according to our Institutional Review Board approved methods. We also invited patients in a general medicine practice age 70 years and older who did not have histories of PAD to be screened with the ABI. Those with ABI values <1.00 were invited to participate. The Institutional Review Boards at all participating sites approved the protocol. Participants gave written informed consent. MRI was performed between January 2008 and April 2010. Because MRI data collection initially required more time than anticipated, between January 2008 and May 2008, a randomly selected 50% subset of participants underwent plaque composition imaging. Once MRI data collection had become more efficient, all participants underwent MRI for plaque composition (between June 2008 and April 2010) (16).

INCLUSION AND EXCLUSION CRITERIA

The inclusion criterion for WALCS III was an ABI <1.00 (17–19).

WALCS III exclusion criteria have been described (15,16) and are summarized here. Potential participants with dementia and those with Mini-Mental Status Examination scores <23 were excluded because it was unclear whether they could answer questions accurately (20). Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because of their impaired functioning. Non-English-speaking patients were excluded. Patients with recent major surgery or contraindications to MRI were excluded. Potential participants requiring oxygen, those who stopped a 6-min walk test because of dyspnea, and those with severe knee osteoarthritis were excluded (21).

ABI MEASUREMENT

The ABI was used to document the presence and severity of PAD. After participants rested supine for 5 min, a handheld Doppler probe (Nicolet Vascular Pocket-Dop II, Natus Medical, Golden, Colorado) was used to measure systolic pressure in the right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Pressure measurements were repeated in reverse order. The ABI was calculated in each leg by dividing average pressures in that leg by the average of the 4 brachial pressures (22). The ABI in the leg in which MRI was measured was used for analyses.

MRI

We imaged the SFA of the leg with the lowest ABI. MRI data were obtained with a 1.5-T platform (Espree, Siemens Medical Solutions, Malvern, Pennsylvania) using a 4-element phased-array surface coil (Nova Medical, Wilmington, Massachusetts). We imaged the proximal SFA because its superficial location was more amenable to high-quality images than the distal SFA. The bifurcation of the common femoral artery was the reference point. Images were collected with a standard, proton density–weighted turbo spin echo acquisition (repetition time [TR] 2,160 ms; echo time [TE] 8 ms; bandwidth 230 Hz/pixel; turbo factor 15). The field of view was 120 × 120 mm^2, and images were acquired on a 192 × 192 matrix

to yield an in-plane spatial resolution of 0.625 × 0.625 mm^2. Three signal averages were acquired.

Twelve contiguous 2.5-mm cross-sectional images in the short-axis plane were obtained, beginning at the common femoral artery bifurcation into the SFA and moving distally using 2-dimensional bright-blood time-of-flight and proton density–weighted images. Bright-blood 2-dimensional time-of-flight images (TR 31.0 ms; TE 7.2 ms) were registered to the proton density–weighted images and acquired using an identical field of view, slice thickness, and imaging matrix. This method has excellent test-retest reliability (15,23). Additional turbo spin echo images were acquired with TR and TE adjusted to provide T1-weighted (TR 800 ms; TE 8 ms) and T2-weighted (TR 2,160 ms; TE 50 ms) images, respectively. These images were prescribed with identical thickness, location, number of slices, and signal saturation (fat saturation and regional blood saturation) as the proton density–weighted images. The additional contrast weighting was used for plaque characterization.

For analysis of plaque area, wall thickness, and luminal area, 2 physician readers with cardiovascular imaging training used CASCADE software (University of Washington, Seattle, Washington). Poor-quality images were excluded, using established criteria (24). Readers traced the outer boundary and the lumen of each cross-sectional image to quantify wall thickness, wall area, and luminal area. Images for each participant were assigned to 1 primary reviewer, and tracings of arterial boundaries were reviewed by the second reviewer to ensure accuracy. Disagreements were resolved via discussion and consensus. Plaque area measurements were normalized for artery size by dividing each measure by the median of the total vessel area (15,25). Luminal area was normalized per slice using total vessel area because of variation in vessel dimensions due to patient size. An assessment of test-retest reliability among a 6% subsample showed coefficient of variation percentage values of 5.8 and 8.9 for mean and maximum plaque area, respectively; the values were 7.9 for mean and 12.9 for minimum percentage luminal area, respectively (15).

The presence of LRNC and calcium was determined at each artery cross section using validated methods (26–28). Images were evaluated at the University of Washington Core Reading Center in the Vascular Imaging Laboratory by 2 readers. Tissue types were identified on the basis of signal intensities relative to the sartorius muscle. LRNC is hypointense on T2-weighted images, isointense or slightly hyperintense on T1-weighted images, and isointense on proton density–weighted and time-of-flight images. Calcium is hypointense on T1-weighted, T2-weighted, and time-of-flight images.

BASELINE COMORBIDITIES

Comorbidities assessed at baseline were diabetes mellitus, hypertension, myocardial infarction (MI), and angina. Comorbidities were identified and confirmed using algorithms developed for the Women's Health and Aging Study (29). The algorithms combine data from patient report, medical record review, medications, laboratory values, and a primary care physician questionnaire. Hypertension was defined as patient report of physician-diagnosed hypertension or physician designation of hypertension on the primary care physician questionnaire.

OTHER BASELINE MEASURES

Height and weight were measured at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Low-density lipoprotein cholesterol was determined using a homogenous direct method from Roche Diagnostics (Indianapolis, Indiana). High-density lipoprotein cholesterol was measured using a direct enzymatic colorimetric assay. Cigarette smoking history was determined by self-report. Participants brought medication bottles or medication lists to their study visit. A study investigator (M.M.M.) identified which participants were taking statin and antiplatelet medications. The presence of exertional leg symptoms and classic symptoms of intermittent claudication were defined using the San Diego Claudication Questionnaire (30,31).

ADJUDICATION OF LOWER EXTREMITY AND CARDIOVASCULAR EVENTS

Participants returned to the medical center for follow-up 1, 2, and 4 years after baseline. At follow-up, participants were interviewed to identify new hospitalizations and underwent repeat ABI measurement. At 3-year follow-up, participants were interviewed by telephone to identify new hospitalizations. Medical records for all hospitalizations after baseline were retrieved and reviewed independently by 2 investigators (M.M.M. and J.W.) using an abstraction form. Differences between reviewers were resolved by discussion. Reviewers were blinded to MRI measures.

Lower extremity PAD events—Lower extremity events indicating PAD progression were defined as medical record–documented hospitalization for critical limb ischemia, amputation, or lower extremity revascularization. Decline in the ABI by >0.15 in the leg with the MRI measurement was defined as PAD progression (31).

Adjudication of acute coronary events—Acute coronary events were defined as MI, hospitalization for unstable angina, and cardiac death. Additional outcomes were ischemic stroke and all-cause mortality. Criteria for MI were derived from the ARIC (Atherosclerosis Risk In Communities) and MESA (Multi-Ethnic Study of Atherosclerosis) studies (32,33). An acute MI required 2 of the following criteria: 1) chest pain; 2) abnormal electrocardiographic findings consistent with an MI (ST-segment elevation, new left bundle branch block, new Q waves); and 3) abnormal cardiac enzymes (troponin >2 times the upper limit of normal). Criteria for unstable angina were derived from the MESA and LIFE (Lifestyle Interventions and Independence for Elders) studies (33,34). Unstable angina was defined as nonelective hospital admission with a discharge diagnosis of acute coronary ischemia that was not definite or probable MI. Clinical symptoms were required. In addition, 1 of the following was required: 1) treatment with nitrates, heparin, or beta-blockers; 2) coronary revascularization during the hospitalization; 3) >70% obstruction of a coronary artery by angiography during hospitalization; or 4) an electrocardiogram showing horizontal or down-sloping ST-segment depression or abnormal ST-segment elevation >1 mm, and these findings were present only during chest pain. Acute coronary death consisted of definite fatal MI, definite coronary heart disease death, and possible coronary heart disease death (33,34).

Ischemic stroke and mortality—The outcome of ischemic stroke was based on criteria from the LIFE study (34) and consisted of acute onset of neurological symptoms combined with an imaging study consistent with acute ischemic stroke. Deaths were ascertained from medical records and from proxies if medical records were not available.

STATISTICAL ANALYSES

Baseline characteristics were compared between PAD participants with versus without LRNC and with versus without calcium at baseline. Student *t* tests were used for continuous variables, and chi-square tests were used for categorical variables. Kaplan-Meier analyses compared cumulative rates of PAD events, acute coronary events, stroke, and all-cause mortality between participants with and those without LRNC and with and those without calcium, using the log-rank test for statistical significance. PAD events, acute coronary events, stroke, and all-cause mortality were compared across tertiles of mean luminal area and mean plaque area using Kaplan-Meier curves and log-rank tests.

Associations of plaque LRNC and plaque calcium with PAD events, cardiovascular outcomes, and mortality were evaluated using Cox proportional hazards models, adjusting for age, sex, race, diabetes, hypertension, history of MI, angina, cholesterol values, BMI, smoking, statin use, antiplatelet therapy, and baseline ABI. Similarly, associations of mean plaque area tertiles and mean luminal area tertiles with outcomes were evaluated using Cox proportional hazards models, adjusting for age, sex, race, diabetes, hypertension, history of MI, angina, cholesterol values, BMI, smoking, statins, antiplatelet therapy, and baseline ABI. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

In total, 473 participants with PAD underwent MRI of the SFA. Sixteen were excluded because of poor image quality. Of the remaining 457 participants, 305 underwent additional MRI data collection (T1- and T2-weighted imaging) for plaque composition. Of these, 13 (4.3%) did not return for any follow-up visits and were considered lost to follow-up, 37 (12.0%) were excluded because of missing data on cholesterol, and 1 (0.32%) was excluded because of missing data on smoking, leaving 254 for plaque composition analyses. Median follow-up duration was 47 months. For the analyses of plaque volume and luminal area, of the 457 participants with valid MRI data, 20 (4.0%) did not return for any follow-up visits, 57 (12.0%) were excluded because of missing data on cholesterol, and 1 (0.22%) was excluded because of missing data on smoking, leaving 379 for analyses of plaque and luminal area. Three participants with PAD were identified from ABI screening of general medicine patients age >70 years, and 2 of these participants underwent MRI of plaque composition.

Of 254 participants with plaque composition data, 62 (24.4%) had LRNC and 149 (58.7%) had calcium in the SFA. Seventy (27.6%) had classic symptoms of intermittent claudication, 41 (16.1%) were asymptomatic, and 143 (56.3%) had exertional leg symptoms that were not consistent with classic intermittent claudication. LRNC in the SFA was associated with a lower prevalence of former smokers and higher prevalence rates of current smoking and male sex compared with absence of LRNC (Table 1). LRNC was also associated with lower

high-density lipoprotein cholesterol levels. Calcium was associated with older age, lower BMI, and higher high-density lipoprotein and was more prevalent in men, former smokers, and those using statins at baseline (Table 1).

Among participants with plaque composition data, 66 experienced 1 or more PAD events during followup. Of these, 38 (58%) had lower extremity revascularization, 8 (12%) had amputation or critical limb ischemia, and 31 (47%) experienced ABI declines of >0.15 compared with baseline. Seventy-five participants had acute coronary events, ischemic stroke, or death. Of these, 38 (51%) had acute coronary events, 15 (20%) had ischemic stroke, and 45 (60%) died of any cause during follow-up.

Participants with LRNC in the SFA had higher rates of PAD events, measured by the combined outcome of lower extremity revascularization, amputation, hospitalization for critical limb ischemia, or ABI decline >0.15, compared with those without LRNC in the SFA (Figure 1, Table 2). This association remained after excluding lower extremity revascularization from the composite endpoint (Figure 2, Table 2). There were no significant associations of LRNC with acute coronary events, ischemic stroke, or all-cause mortality (Table 2).

Adjusting for age, sex, race, cholesterol values, smoking, BMI, history of MI, angina, hypertension, diabetes, statin use, antiplatelet therapy, and baseline ABI, LRNC in the SFA was associated with an increased hazard for a PAD event ($p = 0.005$) and for any PAD event other than revascularization ($p = 0.010$) (Table 3). LRNC in the SFA was also associated with an increased hazard for lower extremity revascularization ($p = 0.013$) (Table 3). There were no associations of SFA LRNC with other individual PAD events, acute coronary events, ischemic stroke, or all-cause mortality (Table 3).

In unadjusted analyses, SFA calcium was not associated with PAD events (Table 2). However, calcium in the SFA was associated with a lower rate of acute coronary events (Table 2). Adjusting for age, sex, race, cholesterol values, smoking, BMI, MI, angina, hypertension, diabetes, statin use, antiplatelet therapy, and baseline ABI, there was no association of SFA calcium with subsequent PAD events or acute coronary events, ischemic stroke, or all-cause mortality (Table 4). There was no association of SFA plaque area or luminal area with any outcome (Table 5).

DISCUSSION

Our results indicate that the presence of LRNC in the SFA is associated with a higher rate of clinically important PAD events, measured by a composite outcome of lower extremity amputation, hospitalization for critical limb ischemia, significant ABI decline, and lower extremity revascularization. This association was observed even after excluding lower extremity revascularizations from the composite PAD outcome. Associations were independent of potential confounders, including PAD severity, measured by the ABI. After adjusting for confounders, none of the plaque measures (LRNC, calcium, or plaque burden) was associated with events that occurred remotely from the lower extremities such as acute coronary events or ischemic stroke.

Histopathologic studies from the coronary arteries demonstrate that coronary artery atherosclerotic plaque with an LRNC and a thin fibrous cap is associated with increased risk for plaque rupture and thrombus formation, resulting in an acute coronary event or progression of coronary artery atherosclerosis (1–3). Similar associations have been reported for the carotid arteries (4–8). Takaya et al. (7) reported that a larger LRNC, measured by MRI, was associated with a higher rate of ipsilateral cerebrovascular events over a mean follow-up of 38.2 months. However, to our knowledge, the clinical significance of LRNC in the SFA has not been reported previously.

Guzman et al. (35) reported that computed tomography–measured calcium in the tibial artery was associated with amputation risk in 229 patients with PAD. The finding reported here, that calcium in the SFA is not related to subsequent lower extremity events, is likely related to several factors. First, computed tomography is more sensitive for detecting calcium than MRI. Second, only a short proximal segment of the SFA was imaged in the present study, whereas the prior study shows that calcification is more prevalent in distal segments of lower extremity arteries. Our finding that plaque burden was not associated with lower extremity events is consistent with a previous study showing that plaque burden in the SFA is not associated with decline in 6-min walk (36).

Preliminary evidence supported the hypothesis that local plaque characteristics convey risk for atherosclerotic events in distant vascular beds. For example, plaque morphology and the presence of arterial LRNC is typically consistent throughout the vascular tree (11–13). In a case-control study, Underhill et al. (14) compared MRI-measured carotid artery characteristics between 97 participants with >50% coronary artery stenosis and 94 participants with no angiographic evidence of coronary artery disease. Participants with coronary artery disease had a higher prevalence of carotid artery LRNC than those without coronary artery disease. A separate study of community-dwelling men and women in MESA without clinically evident cardiovascular disease reported that MRI-measured carotid intima-media thickness and the presence of MRI-detected carotid artery LRNC or calcium were each associated with increased rates of cardiovascular events (37). However, a recent histopathologic study of 176 arterial segments from 60 amputated limbs in patients with PAD reported intimal thickening without atheromatous changes in 68% of lower extremity arteries. In some arteries, intimal thickening was so severe that it occluded the artery, but intimal thickening was not accompanied by atheromatous change (38). This study suggests that the arterial histopathology in the lower extremity arteries of PAD patients differs from arterial histopathology in the coronary or cerebrovascular arteries.

STUDY LIMITATIONS

First, although the sensitivity and specificity of MRI for plaque composition in the carotid artery, including calcium and LRNC, range from 84% to 100% (26), MRI is not optimally sensitive for detecting arterial calcium.

Second, we imaged a proximal segment of the SFA in the leg with the lowest ABI. Although a previous study showed that the presence of LRNC in 1 lower extremity artery is highly correlated with LRNC in the opposite leg (13), it is conceivable that the composition of

plaque in the short proximal segment of the SFA that we imaged does not reflect plaque composition in the rest of the lower extremity artery bed.

Third, the outcome of lower extremity revascularization is determined in part by clinician determinations about patient disability from PAD and ability to safely undergo revascularization. However, LRNC predicted lower extremity events even after revascularizations were excluded.

Fourth, we did not collect data on whether calcium was eccentric or concentric within the artery.

Fifth, we did not collect data on Rutherford classification.

CONCLUSIONS

Among patients with PAD, LRNC in the SFA was associated with higher rates of lower extremity PAD events, independent of PAD severity, measured by the ABI. Further study is needed to determine whether interventions that reduce LRNC in the SFA can prevent lower extremity outcomes in PAD.

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ABBREVIATIONS AND ACRONYMS

ABI	ankle-brachial index
BMI	body mass index
LRNC	lipid-rich necrotic core
MI	myocardial infarction
MRI	magnetic resonance imaging
PAD	peripheral artery disease
SFA	superficial femoral artery
TE	echo time
TR	repetition time

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE

Among patients with lower extremity PAD who underwent MRI of the proximal segment of the SFA, 24% had LRNC in the SFA. The presence of LRNC in the SFA was associated with a higher incidence of the combined outcome of lower extremity amputation, critical limb ischemia, significant ABI decline, and lower extremity revascularization over 47-month follow-up.

TRANSLATIONAL OUTLOOK

Further study is needed to confirm that LRNC in the SFA is an important predictor of adverse lower extremity events, independent of the ABI. Further study is also needed to determine whether interventions that reduce SFA LRNC prevent lower extremity events in people with PAD.

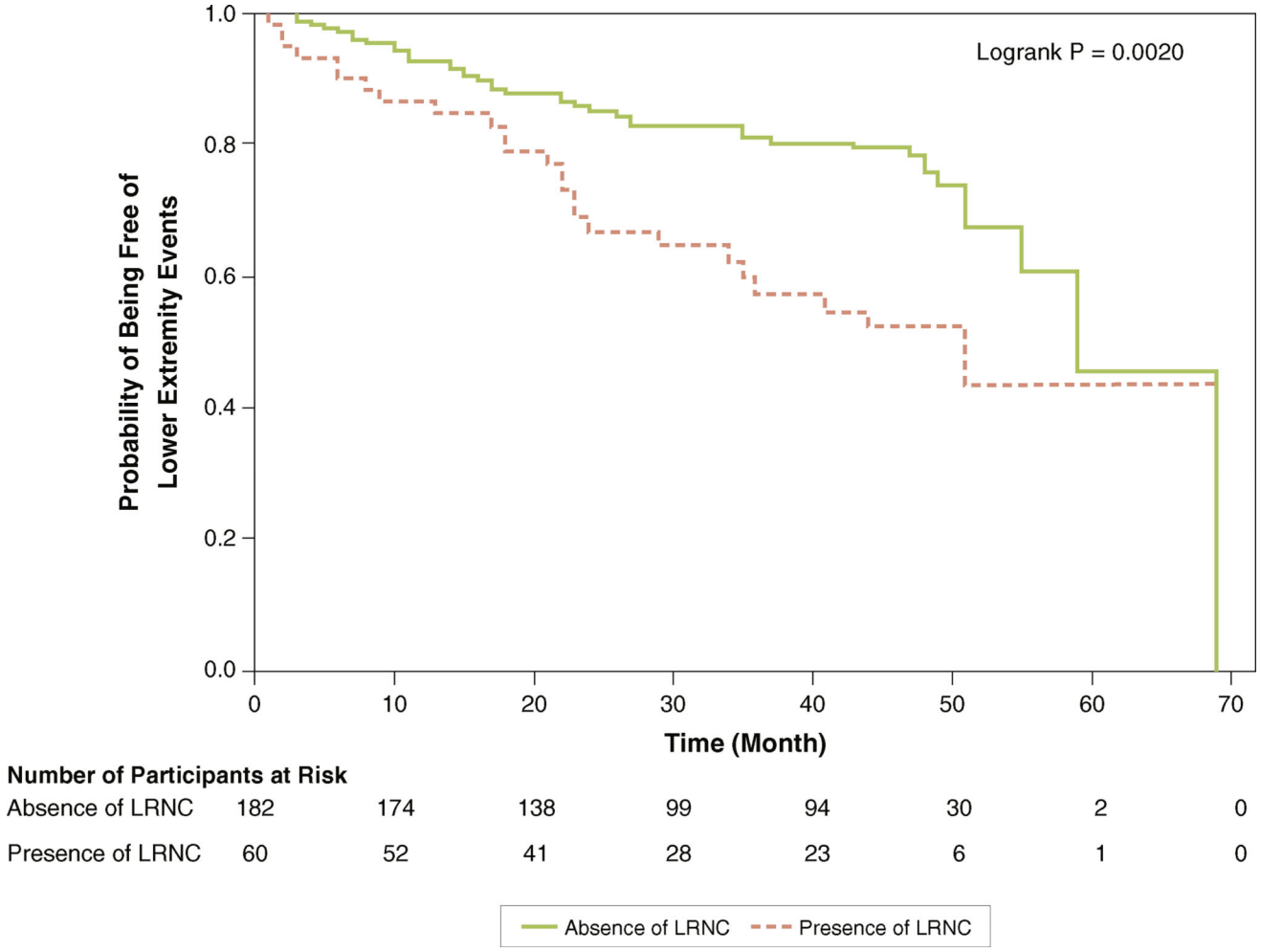

FIGURE 1. Association of Presence Versus Absence of Lipid-Rich Necrotic Core and Subsequent Rates of Lower Extremity Events

Lower extremity events are defined as the first occurrence of 1 of the following: lower extremity amputation, critical limb ischemia, ankle-brachial index decline of >0.15, or lower extremity revascularization. LRNC = lipid-rich necrotic core.

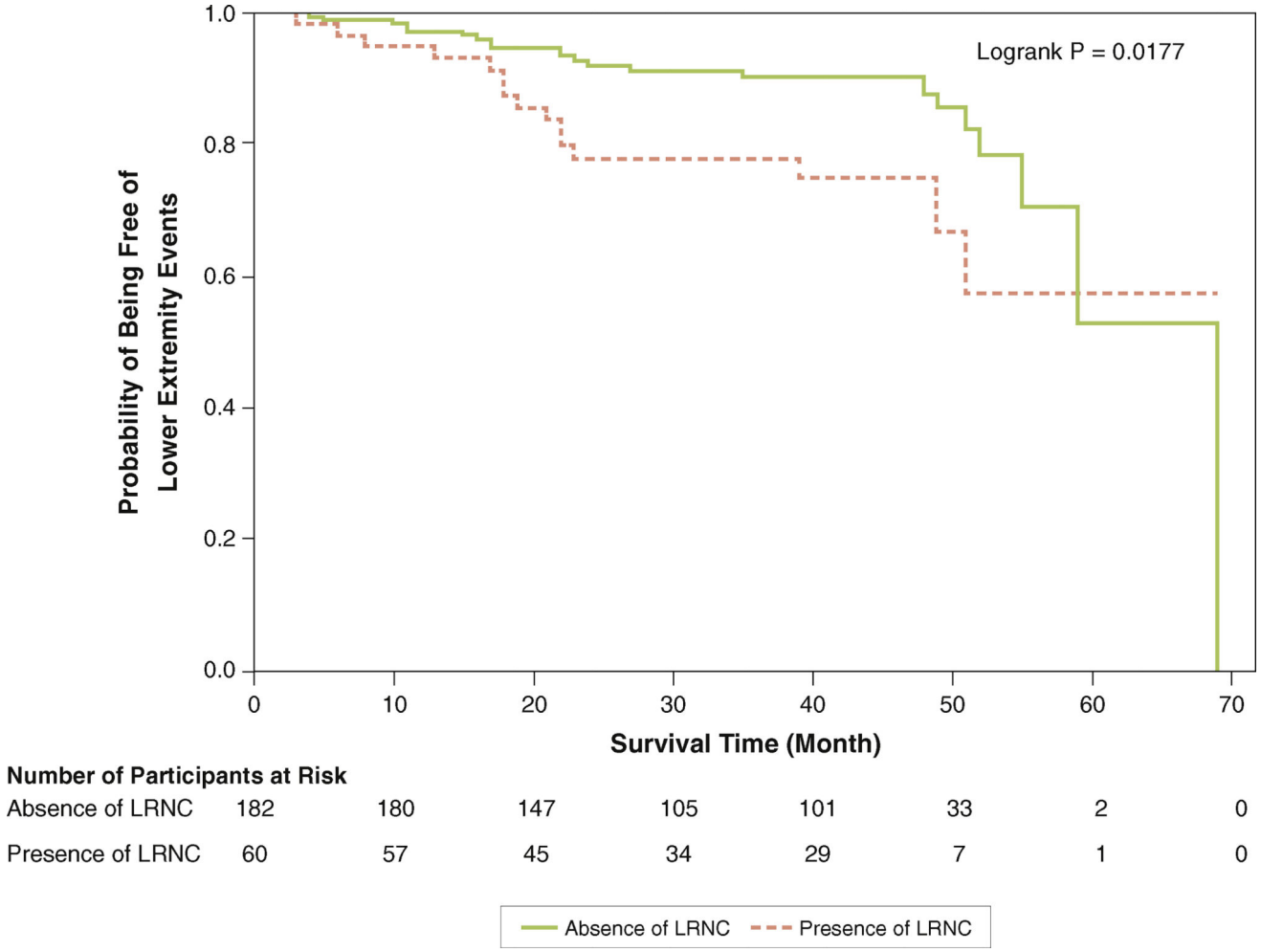

FIGURE 2. Association of Presence Versus Absence of Lipid-Rich Necrotic Core and Subsequent Rates of Lower Extremity Events Other Than Lower Extremity Revascularization

Lower extremity events are defined as the first occurrence of 1 of the following: lower extremity amputation, critical limb ischemia, or ankle-brachial index decline of >0.15. LRNC = lipid-rich necrotic core.

TABLE 1

Associations of Superficial Femoral Artery Plaque Composition With Baseline Characteristics in Participants With Peripheral Artery Disease

	Total (n = 254)	Absence of LRNC (n = 192)	Presence of LRNC (n = 62)	p Value	Absence of Calcium (n = 105)	Presence of Calcium (n = 149)	p Value
Age, yrs	68.53 ± 9.96	68.72 ± 9.33	67.94 ± 11.76	0.591	66.15 ± 11.69	70.20 ± 8.17	0.001
ABI	0.67 ± 0.17	0.68 ± 0.18	0.66 ± 0.16	0.308	0.70 ± 0.18	0.66 ± 0.17	0.054
Male	181 (71.3)	130 (67.7)	51 (82.3)	0.028	67 (63.8)	114 (76.5)	0.028
African American	83 (32.7)	60 (31.3)	23 (37.1)	0.393	37 (35.2)	46 (30.9)	0.465
Never smoker	27 (10.6)	18 (9.4)	9 (14.5)	0.253	19 (18.1)	8 (5.4)	0.001
Former smoker	163 (64.2)	133 (69.3)	30 (48.4)	0.003	58 (55.2)	105 (70.5)	0.013
Current smoker	64 (25.2)	41 (21.4)	23 (37.1)	0.013	28 (26.7)	36 (24.2)	0.651
Diabetes	108 (42.5)	78 (40.6)	30 (48.4)	0.282	44 (41.9)	64 (43.0)	0.868
BMI, kg/m^2	29.89 ± 6.54	30.14 ± 6.72	29.10 ± 5.92	0.277	31.09 ± 7.29	29.04 ± 5.82	0.013
HDL-C, mg/dl	49.01 ± 17.40	50.37 ± 18.36	44.80 ± 13.27	0.028	46.43 ± 14.08	50.83 ± 19.24	0.047
LDL-C, mg/dl	92.08 ± 31.97	93.43 ± 33.16	87.90 ± 27.83	0.237	95.56 ± 32.54	89.63 ± 31.45	0.146
Pulmonary disease	95 (37.4)	70 (36.5)	25 (40.3)	0.585	40 (38.1)	55 (36.9)	0.848
Cancer	40 (15.7)	32 (16.7)	8 (12.9)	0.479	16 (15.2)	24 (16.1)	0.851
Angina	54 (21.3)	41 (21.4)	13 (21.0)	0.948	17 (16.2)	37 (24.8)	0.097
MI	44 (17.3)	30 (15.6)	14 (22.6)	0.208	15 (14.3)	29 (19.5)	0.283
Stroke	42 (16.5)	31 (16.1)	11 (17.7)	0.769	18 (17.1)	24 (16.1)	0.827
Heart failure	37 (14.6)	31 (16.1)	6 (9.7)	0.209	16 (15.2)	21 (14.1)	0.799
Hypertension	237 (93.3)	182 (94.8)	55 (88.7)	0.139	98 (93.3)	139 (93.3)	0.989
On statin medication at baseline	196 (77.2)	152 (79.2)	44 (71.0)	0.181	74 (70.5)	122 (81.9)	0.033

	Total (n = 254)	Absence of LRNC (n = 192)	Presence of LRNC (n = 62)	p Value	Absence of Calcium (n = 105)	Presence of Calcium (n = 149)	p Value
Antiplatelet therapy	205 (80.7)	156 (81.3)	49 (79.0)	0.700	79 (75.2)	126 (84.6)	0.064
Leg symptoms							
Intermittent claudication	70 (27.6)	60 (31.3)	10 (16.1)		24 (22.9)	46 (30.9)	
Exertional leg symptoms other than intermittent claudication	143 (56.3)	104 (54.2)	39 (62.9)	0.058	59 (56.2)	84 (56.4)	0.135
Asymptomatic	41 (16.1)	28 (14.6)	13 (21.0)		22 (21.0)	19 (12.8)	

Values are mean ± SD for continuous variables and n (%) for categorical variables. ABI values are from the leg in which MRI measures were obtained.

ABI = ankle-brachial index; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LRNC = lipid-rich necrotic core; MI = myocardial infarction; MRI = magnetic resonance imaging.

TABLE 2

Associations of Lipid-Rich Necrotic Core and Calcium in the Superficial Femoral Artery With Subsequent Lower Extremity Peripheral Artery Disease Events, Acute Coronary Events, Ischemic Stroke, and All-Cause Mortality

	LRNC Present in SFA (n = 62)	LRNC Absent in SFA (n = 192)	p Value	Calcium in SFA (n = 149)	No Calcium in SFA (n = 105)	p Value
Lower extremity PAD events						
≥1 PAD event*	25 (41.7)	41 (22.5)	0.004	33 (23.4)	33 (32.7)	0.110
≥1 PAD event other than revascularization†	15 (25.0)	23 (12.6)	0.022	17 (12.1)	21 (20.8)	0.065
Any lower extremity revascularization	16 (25.8)	22 (11.5)	0.006	19 (12.8)	19 (18.1)	0.240
Amputation or critical limb ischemia	4 (6.5)	4 (2.1)	0.102	4 (2.7)	4 (3.8)	0.721
ABI decline >0.15	11 (18.6)	20 (11.1)	0.131	13 (9.4)	18 (17.8)	0.053
Acute coronary events, ischemic stroke, all-cause mortality						
Coronary events, stroke, or all-cause mortality‡	18 (29.0)	57 (29.7)	0.922	44 (29.5)	31 (29.5)	0.999
Acute coronary events	10 (16.1)	28 (14.6)	0.767	16 (10.7)	22 (21.0)	0.025
Ischemic stroke	3 (4.8)	12 (6.3)	1.000	8 (5.4)	7 (6.7)	0.666
All-cause mortality	12 (19.4)	33 (17.2)	0.698	29 (19.5)	16 (15.2)	0.385

Values are n (%).

*Patients who experienced 1 or more lower extremity PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, ABI decline of >0.15, or lower extremity revascularization.

†Patients with 1 or more PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, or ABI decline of >0.15.

‡Participants who experienced 1 or more events. Participants may have had more than one type of event.

PAD = peripheral artery disease; SFA = superficial femoral artery; other abbreviations as in Table 1.

TABLE 3

Adjusted and Unadjusted Associations of Lipid-Rich Necrotic Core in the Superficial Femoral Artery With Subsequent Lower Extremity Peripheral Artery Disease Events, Acute Coronary Events, Ischemic Stroke, and All-Cause Mortality

	Model 1, Unadjusted		Model 2, Fully Adjusted	
	Hazard Ratio (95% CI)	**p Value**	**Hazard Ratio (95% CI)**	**p Value**
Lower extremity PAD events				
Any PAD event *	2.15 (1.30–3.54)	0.003	2.18 (1.27–3.75)	0.005
Any PAD event excluding revascularization †	2.16 (1.12–4.16)	0.021	2.58 (1.25–5.33)	0.010
Lower extremity revascularization	2.47 (1.30–4.70)	0.006	2.42 (1.20–4.86)	0.013
Amputation or hospitalization for critical limb ischemia.	3.12 (0.78–12.49)	0.107	2.75 (0.56–13.61)	0.215
ABI decline >0.15	1.68 (0.80–3.53)	0.169	2.20 (0.97–5.01)	0.06
Coronary and cerebrovascular events and all-cause mortality				
Acute coronary event, ischemic stroke, or all-cause mortality	0.97 (0.57–1.65)	0.911	0.86 (0.49–1.51)	0.608
Acute coronary events	1.11 (0.54–2.29)	0.771	0.86 (0.38–1.94)	0.711
Ischemic stroke	0.76 (0.21–2.69)	0.671	0.80 (0.21–3.10)	0.752
All-cause mortality	1.12 (0.58–2.18)	0.728	0.93 (0.45–1.89)	0.831

Model 2 adjusted for age, sex, race, diabetes, hypertension, history of MI, angina, LDL-C, HDL-C, BMI, cigarette smoking, statin use, antiplatelet therapy, and baseline ABI.

* Patients who experienced 1 or more lower extremity PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, ABI decline of >0.15, or lower extremity revascularization.

† Patients with 1 or more PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, or ABI decline of >0.15.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

TABLE 4

Adjusted and Unadjusted Associations of Calcium in the Superficial Femoral Artery With Subsequent Lower Extremity Peripheral Artery Disease Events, Acute Coronary Events, Ischemic Stroke, and All-Cause Mortality

	Model 1, Unadjusted		Model 2, Fully Adjusted	
	Hazard Ratio (95% CI)	**p Value**	**Hazard Ratio (95% CI)**	**p Value**
Lower extremity PAD events				
Any PAD event *	0.68 (0.42–1.10)	0.12	0.70 (0.40–1.21)	0.203
Any PAD event excluding revascularization †	0.60 (0.31–1.13)	0.115	0.73 (0.34–1.59)	0.432
Lower extremity revascularization	0.70 (0.37–1.32)	0.265	0.71 (0.35–1.48)	0.365
Amputation or hospitalization for critical limb ischemia	0.73 (0.18–2.93)	0.66	2.00 (0.35–11.32)	0.433
ABI decline >0.15	0.56 (0.28–1.16)	0.118	0.53 (0.22–1.32)	0.175
Coronary events, ischemic stroke, and all-cause mortality				
Acute coronary event, ischemic stroke, or all-cause mortality	1.05 (0.66–1.66)	0.839	1.11 (0.66–1.87)	0.69
Acute coronary events	0.54 (0.28–1.02)	0.058	0.59 (0.28–1.25)	0.169
Ischemic stroke	0.85 (0.31–2.33)	0.747	0.72 (0.21–2.47)	0.596
All-cause mortality	1.41 (0.77–2.60)	0.267	1.66 (0.82–3.38)	0.159

Model 2 adjusted for age, sex, race, diabetes, hypertension, history of MI, angina, LDL-C, HDL-C, BMI, cigarette smoking, statin use, antiplatelet therapy, and baseline ABI.

* Patients who experienced 1 or more lower extremity PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, ABI decline of >0.15, or lower extremity revascularization.

† Patients with 1 or more PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, or ABI decline of >0.15.

Abbreviations as in Tables 1, 2, and 3.

TABLE 5

Unadjusted Associations of Plaque Quantity and Luminal Area With Cardiovascular Outcomes

	Plaque Area				Luminal Area			
	Tertile 1 (Lowest Plaque Quantity)	**Tertile 2**	**Tertile 3 (Highest Plaque Quantity)**	**Trend p Value**	**Tertile 1 (Largest Luminal Area)**	**Tertile 2**	**Tertile 3 (Smallest Luminal Area)**	**p Value**
Lower extremity PAD events								
≥1 PAD event *	37/119 (31.09)	38/120 (31.67)	33/120 (27.50)	0.748	39/120 (32.50)	37/120 (30.83)	32/119 (26.89)	0.624
≥1 PAD event other than revascularization †	27/119 (22.69)	24/120 (20.00)	20/120 (16.67)	0.504	28/120 (23.33)	24/120 (20.00)	19/119 (15.97)	0.360
Any lower extremity revascularization	20/126 (15.87)	18/127 (14.17)	17/126 (13.49)	0.858	20/126 (15.87)	17/127 (13.39)	18/126 (14.29)	0.851
Amputation or critical limb ischemia	5/126 (3.97)	3/127 (2.36)	4/126 (3.17)	0.718	5/126 (3.97)	3/127 (2.36)	4/126 (3.17)	0.718
ABI decline >0.15	23/118 (19.49)	21/119 (17.65)	16/118 (13.56)	0.461	24/118 (20.34)	20/119 (16.81)	16/118 (13.56)	0.381
Coronary events, ischemic stroke, and all-cause mortality								
Coronary events, stroke, or all-cause mortality ‡	29/126 (23.02)	42/127 (33.07)	39/126 (30.95)	0.179	31/126 (24.60)	39/127 (30.71)	40/126 (31.75)	0.402
Acute coronary events	17/126 (13.50)	24/127 (18.90)	12/126 (9.50)	0.097	16/126 (12.70)	23/127 (18.10)	14/126 (11.10)	0.242
Ischemic stroke	9/126 (7.14)	7/127 (5.51)	7/126 (5.56)	0.826	9/126 (7.14)	7/127 (5.51)	7/126 (5.56)	0.826
All-cause mortality	17/126 (13.49)	26/127 (20.47)	25/126 (19.84)	0.279	21/126 (16.67)	22/127 (17.32)	25/126 (19.84)	0.786

Values are n/N (%).

* Patients who experienced 1 or more lower extremity PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, ABI decline of >0.15, or lower extremity revascularization.

† Patients with 1 or more PAD events, consisting of lower extremity amputation, hospitalization for critical limb ischemia, or ABI decline of >0.15.

‡ Participants who experienced 1 or more events. Participants may have had more than one type of event.

Abbreviations as in Tables 1 and 2.