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High-Risk Plaque in the Superficial Femoral Artery of People with Peripheral Artery Disease: Prevalence and Associated Clinical Characteristics

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Disclosures

There are no disclosures from other authors.

Abstract

Objective—We used magnetic resonance imaging (MRI) to study the prevalence and associated clinical characteristics of high-risk plaque (defined as presence of lipid-rich necrotic core [LRNC] and intraplaque hemorrhage) in the superficial femoral arteries (SFA) among people with peripheral artery disease (PAD).

Background—The prevalence and clinical characteristics associated with high-risk plaque in the SFA are unknown.

Methods—Three-hundred-three participants with PAD underwent MRI of the proximal SFA using a 1.5 Tesla Siemens platform. Twelve contiguous 2.5 millimeter cross-sectional images were obtained.

Results—LRNC was present in 68 (22.4%) participants. Only one had intra-plaque hemorrhage. After adjusting for age and sex, smoking prevalence was higher among adults with LRNC than among those without LRNC (35.9% vs. 21.4%, p=0.02). Among participants with vs. without LRNC there were no differences in mean percent lumen area (31% vs. 33%, p=0.42), normalized mean wall area (0.71 vs. 0.70, p=0.67) or maximum wall area (0.96 vs. 0.92, p=0.54) in the SFA. Among participants with LRNC, cross-sectional images containing LRNC had a smaller percent lumen area (33% ± 1% vs. 39% ± 1%, p<0.001), greater normalized mean wall thickness (0.25±0.01 vs. 0.22±0.01, p<0.001), and greater normalized maximum wall thickness (0.41±0.01 vs. 0.31±0.01, p<0.001), compared to cross-sectional images without LRNC.

Conclusions—Fewer than 25% of adults with PAD had high-risk plaque in the proximal SFA using MRI. Smoking was the only clinical characteristic associated with presence of LRNC. Further study is needed to determine the prognostic significance of LRNC in the SFA.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00520312

Keywords

atherosclerosis; magnetic resonance imaging; peripheral vascular disease; plaque

INTRODUCTION

Data from autopsies and direct atherosclerotic plaque visualization demonstrate that presence of high risk plaque, defined as the presence of lipid rich necrotic core (LRNC) with a thin fibrous cap or intra-plaque hemorrhage in the carotid and coronary arteries is associated with an increased rate of local plaque rupture resulting in stroke or myocardial infarction, respectively.[1–10] However, given regional variations in factors such as patterns of inflammation, artery size and sheer stress the plaque composition and its clinical correlates may differ across vascular beds.[11–13]

High resolution magnetic resonance imaging (MRI) identifies characteristics of high-risk plaque in the carotid arteries non-invasively.[14, 15] Studies of individuals with established atherosclerosis in the carotid arteries document a LRNC prevalence of at least 70% in the carotid arteries, with even higher rates among individuals who also experienced symptoms

of stroke or transient ischemic attack.[16, 17] Prevalence rates of intra-plaque hemorrhage in the carotid arteries range from approximately 10% to 64%.[7, 16]

Prior studies regarding MRI of atherosclerotic plaque in the femoral arteries have focused on plaque burden and lumen area, and have shown associations of MRI measures with the ankle-brachial index (ABI), functional performance and lower extremity symptoms.[18, 19] However, to our knowledge, a more detailed assessment of plaque composition to describe the prevalence and associated clinical characteristics of MRI-measured LRNC and intra-plaque hemorrhage in the femoral arteries has not been reported previously. We used MRI of plaque in the superficial femoral artery (SFA) to determine the prevalence of LRNC and intra-plaque hemorrhage among adults with peripheral arterial disease (PAD). We identified clinical characteristics associated with LRNC and intra-plaque hemorrhage in the SFA, and determined the association of LRNC with arterial wall dimensions. Finally, because of the association with plaque eccentricity and future events in the carotid and coronary arteries, we evaluated whether presence of LRNC was associated with eccentric vs concentric plaque.[20, 21] We hypothesized that the presence of LRNC would be associated with more severe local atherosclerosis.

METHODS

Subjects

Participants with PAD were part of the WALCS (Walking and Leg Circulation Study) III cohort, a prospective observational study designed to examine the association of MRI-measured atherosclerotic plaque with functional impairment and decline in men and women with PAD. PAD was defined as an ankle-brachial index (ABI) <1.00. Enrollment occurred between October 26, 2007 and December 22, 2009. During the recruitment period, all patients who were diagnosed with PAD in the non-invasive vascular laboratories and/or all PAD patients seen in defined vascular surgery, cardiology, and/or general medical practices at four Chicago-area hospitals were approached for participation according to our IRB approved methods (see Figure 1). To maximize enrollment, we also invited patients in a general internal medicine practice who were age 70 or older and did not have a history of PAD to be screened for PAD with the ABI to determine eligibility. Those with an ABI <1.00 who met inclusion criteria were invited to participate. The Institutional Review Board at all participating sites approved the protocol. Participants gave written informed consent. MRI was performed between January 2008 and April 2010.

Of 473 individuals with PAD in the WALCS III cohort, 16 participants were excluded because of poor image quality on proton-density or time-of-flight MRI images. Of the remaining 457 participants, 303 underwent additional MRI data collection (T1- and T2-weighted imaging) to obtain data for plaque composition. Between 1/1/08 and 5/31/08 time constraints on the MR machine did not allow us to collect plaque characterization images on all participants and therefore data collection for plaque characterization was only performed on a randomly selected 50% subset of participants. Between 6/1/08 and 4/3/2010, all participants underwent additional image collection for plaque characterization. The full imaging protocol is described below.

Inclusion and Exclusion Criteria

The inclusion criterion for WALCS III was an ABI < 1.00. We chose an ABI cutoff of 1.00 because previous studies show that individuals with an ABI 0.90–1.00 have higher rates of mobility loss, exertional leg pain, cardiovascular events, and total mortality compared to individuals with an ABI 1.10–1.40.[22–24]

WALCS III exclusion criteria have been described previously and are summarized here. Potential participants with dementia and those with a Mini-Mental Status Examination score < 23 were excluded because it was unclear whether they could answer questions accurately.[25] 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 because investigators were not fluent in non-English languages. Patients with major surgery during the past three months or contraindications to MRI testing were excluded. We also excluded potential participants who required oxygen therapy, those who stopped a six-minute walk test due to shortness of breath, and those with severe knee osteoarthritis, defined as pain in or around the knee joint combined with a radiograph-measured osteoarthritis K/L score of four.[26] In addition, PAD participants with a completely occluded SFA were excluded from analyses.

Ankle Brachial Index Measurement

ABI methods in the WALCS III cohort have been reported.(19) After participants rested supine for five minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO) was used to measure systolic pressures in this order: right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Pressures were then repeated in reverse order. The ABI was calculated in each leg by dividing average pressures in that leg by the average of the four brachial pressures.[27] Average brachial pressures in the arm with the highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by 10 or more mm Hg in at least one measurement set, since in such cases subclavian stenosis was possible. The lowest leg ABI was used for analyses.

Magnetic Resonance Imaging

We imaged the SFA of the leg with the lowest ABI. MRI data were obtained with a 1.5 Tesla (Espree, Siemens Medical Solutions, Malvern, PA) platform using a four-element phasedarray surface coil (Nova Medical, Wilmington, MA). We imaged the proximal region of the 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. MRI images were collected with a standard, turbo spin echo (TSE) acquisition proton density weighted (TR/TE= 2160 milliseconds/8 milliseconds, 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 for a total scan time of 5 minutes 41 seconds. Regional signal saturation bands were applied superiorly and inferiorly to suppress signal from inflowing blood, ensuring dark blood contrast. Chemically selective lipid saturation pulses eliminated signal from peri-adventitial fat.

A total of 12 contiguous 2.5 millimeter cross-sectional images in the short-axis plane were obtained, beginning at the bifurcation of the common femoral artery into the SFA and moving distally using 2-dimensional bright blood time-of-flight and proton-density weighted images. Bright-blood 2D time-of-flight images (TR/TE=31.0 ms/7.2 ms) were registered to the proton density images and acquired using an identical field of view, slice thickness and imaging matrix. Previous study showed that this method has excellent test re-test reliability.[28, 29]

Additional TSE images were acquired with TR/TE adjusted to provide T1 (TR/TE = 800 ms/8 ms) and T2 (TR/TE= 2160 ms/50 ms) weighted images. 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 the characterization of the plaque components. T1- and T2-weighted images were obtained on the same day as the proton density and time-of-flight images.

For analysis of plaque area, wall thickness, and lumen area, two physician readers with cardiovascular imaging training used CASCADE software (Seattle, WA). Images with poor quality were excluded from the analysis, using previously described criteria.[30] In brief, image quality was determined based on the ability to identify the arterial wall, lumen, composition, and the presence of motion or flow artifacts. Readers traced the outer boundary and the lumen of each cross-sectional image (see the Figure). These tracings were used to quantify wall thickness, wall area and lumen area. Readers were blinded to all clinical data. Images for each participant were assigned to one primary reviewer, and tracings of arterial boundaries were reviewed by the second reviewer to ensure accuracy. Both reviewers analyzed images in 29 participants, to assess inter-reader variability.[31] Vessel measurements were normalized for artery size by dividing each measure by the median of the total vessel area.[15] We normalized measurements because of the variation in vessel dimensions and absolute plaque burden according to patient size.

Measurements are defined in Table 1. Because normalized measurements represent ratios, there are no units. An assessment of test-retest reliability among a 6% subsample showed a coefficient of variation percent value 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 percent lumen area, respectively.[31]

Plaque composition was measured using previously validated methods.[8] Both the presence and area of LRNC and intra-plaque hemorrhage were calculated at each artery cross-section. Images were evaluated at the University of Washington Reading Center by two readers who had completed at least three months of training in reading atherosclerotic plaque composition. All tissue types were identified based on signal intensities relative to the sartorius muscle. LRNC without hemorrhage is hypointense on T2-weighted images, isointense or slight hyperintense on T1-weighted images, and isointense on proton density-weighted and time of flight images. Intra-plaque hemorrhage is hyperintense on time of flight and T1-weighted images and hyperintense/hypointense (depending on the stage of hemorrhage) on T2-weighted and proton density-weighted images. Spatial resolution in the superficial femoral artery was not adequate for measurement of fibrous cap thickness.

Previous studies in the carotid artery showed excellent inter-reader reliability for LRNC area (ICC 0.92) and good reliability for intra-plaque hemorrhage (ICC 0.73).[14]

Comorbidities

Comorbidities assessed were diabetes mellitus, myocardial infarction, stroke, and hypertension. Algorithms developed for the Women's Health and Aging Study and the Cardiovascular Health Study were used for identifying and documenting comorbidities.[32] These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. Hypertension was defined as the presence of one of the following: a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg at the study visit, participant report of physician-diagnosed high blood pressure, or a designation of a history of hypertension on the primary care physician questionnaire.

Other Measures

Resting systolic blood pressure was measured three times with the Omron HEM-907XL automated oscillometric sphygmomanometer (Omron HealthCare, Kyoto, Japan) in the seated position, after waiting five minutes. The average of the final two measurements was used for analysis. Height and weight were measured at the study visit. Body mass index (BMI) was calculated as kg/meters^2. Low and high-density lipoprotein cholesterol were measured from venous blood samples. Low density lipoprotein cholesterol (LDL-C) was determined by a homogenous direct method from Roche Diagnostics (Indianapolis, IN). High density lipoprotein cholesterol (HDL-C) was measured using a direct enzymatic colorimetric assay. Cigarette smoking history was determined by self-report. Participants brought their medication bottles or a list of medications to their study visit. The study principal investigator (MMM) identified which participants were taking statin and anti-platelet medications, blinded to participant characteristics.

Statistical Analyses

Baseline characteristics and atherosclerotic plaque characteristics in the SFA were compared between participants with vs. without LRNC, adjusting for age and sex. A general linear model was used for continuous variables and logistic regression analysis was used for categorical variables. Among participants with LRNC, we performed additional analyses using individual cross-sections to compare the wall thickness and percent lumen area between cross-sections with vs. without LRNC. For the per-slice analysis we used a mixed model and a variance-covariance matrix of compound symmetry.

We also compared the prevalence of eccentric vs concentric plaque in adults with and without LRNC, using the eccentricity index. The eccentricity index was calculated as (maximum wall thickness – minimum wall thickness)/maximum wall thickness. Concentric and eccentric lesions were defined as an index <0.5 and ≥ 0.5, respectively.[21, 33]

Analyses were performed using SAS Statistical Software version 9.4 (SAS Inc, Cary, NC).

RESULTS

We mailed recruitment letters to 3391 patients with PAD identified through the vascular laboratory and in defined medical practices (Figure 1). Of these, 1161 did not respond, 504 met 1 or more exclusion criteria, 954 were not interested, and 304 did not show for their study visit, leaving 468 participants. We mailed an additional 558 letters to adults without an established diagnosis of PAD who were older than 70 and seen in the general internal medicine clinic. Of the 275 participants who responded to the letter, 58 met one or more exclusion criteria, 125 were not interested in participating, 41 could not be scheduled or did not show for their visit, and underwent a screening ABI >1.00, leaving 4 additional participants, for a total of 472. Compared to the 154 participants with PAD who did not undergo imaging for plaque composition, those who did were slightly older (age 71 vs 65, p=0.006), less likely to smoke (17% vs 28%, p=0.009) and had a lower BMI (28.6 kg/m^2 vs 29.8 kg/m^2, p=0.03).

Overall, 68 (22.4%) of the 303 participants had LRNC (see Table 2). Only one participant with PAD had intra-plaque hemorrhage. The mean age among individuals with LRNC was 67.5 (±11.5), compared to a mean age of 68.5 (±9.6) among those without LRNC (p=0.52). The proportion of men was higher among individuals with vs. without LRNC (82.4% vs. 63.0%, p=0.003). Stratified by ABI, 64 adults with LRNC had an ABI <0.9, and 4 had an ABI 0.9–1.0.

Baseline characteristics according to presence vs. absence of LRNC are shown in Table 2, adjusting for age and sex. Compared to those without LRNC, those with LRNC had a higher prevalence of current smoking (p=0.02). Overall, there were no differences in SFA plaque area or lumen area between participants with vs. without LRNC (Table 3).

Results in Table 4 are restricted to the subset of 68 participants with LRNC. Twenty six percent (202/778) of the cross-sectional SFA images contained LRNC. Among these 68 participants, a median of 3 cross-sections per person contained LRNC (interquartile range: 2 to 4). The cross-sectional images containing LRNC had significantly greater mean and maximum wall thickness and a smaller percent lumen area compared to the cross-sectional images that did not contain LRNC (Table 4).

Most participants had evidence of both eccentric and concentric plaque within the SFA. Twenty one (6.9%) participants had all eccentric, 92 (30.4%) all concentric, and 190 (62.7%) had both concentric and eccentric plaque. Among the 190 adults with both eccentric and concentric plaque, 120 (63.2%) had predominantly concentric vs eccentric plaque. After adjusting for age, sex, tobacco use, systolic blood pressure, antihypertensive medication use, LDL, HDL, and statin use, cross sections with LRNC had a higher eccentricity index than those without LRNC, demonstrating more eccentric plaque in patients with LRNC (see Table 5).

DISCUSSION

Among 303 men and women with PAD who underwent MRI of their proximal SFA, 22.4% had LRNC, and only one had intra-plaque hemorrhage. Prior studies of MRI in the SFA have

focused primarily on plaque burden and lumen area. Prior studies that measured LRNC in the superficial femoral artery using MRI have been limited by small sample size. For example, Li et al. showed that plaque eccentricity was associated with preserved lumen size, presence of LRNC and larger plaque burden in 28 randomly selected PAD participants from the WALCS III cohort.[33] In 16 adults with cardiovascular risk factors, Silvera et al. used MRI and positron emission tomography/computed tomography (PET/CT) to demonstrate that lipid rich plaques in the carotid and femoral arteries are more inflamed than calcified or collagen-rich plaques.[34]

To our knowledge, the present report represents the largest study to report the prevalence of LRNC in people with PAD as well as clinical characteristics associated with LRNC in the SFA among people with PAD. Adjusting for age and sex, participants with LRNC had a higher prevalence of current smoking, compared to those without LRNC. There were no other differences in clinical characteristics, including the ABI, between PAD participants with vs. without LRNC. In addition, there was not a significant difference in the overall wall area or percent lumen stenosis between participants with and without LRNC. However, LRNC was associated with the localized severity of atherosclerosis - among participants with LRNC, the cross-sections with LRNC had significantly greater wall thickness and smaller lumen area compared to cross-sections without LRNC. Finally, cross-sections with LRNC had more eccentric plaque than those without LRNC. It is possible that the presence of LRNC signifies more extensive atherosclerosis. Alternatively, much of the increased wall thickness or eccentricity may simply be explained by the space occupied by the LRNC itself.

The prevalence of LRNC in the femoral arteries that we observed among PAD participants is substantially lower than the prevalence of LRNC previously reported in MRI studies of the carotid arteries among individuals with carotid atherosclerosis. For example, Takaya et al. studied 152 asymptomatic patients with carotid artery stenosis of 50–79%.[3] The prevalence of LRNC on MRI was 72% and intra-plaque hemorrhage was 28%. Mean age in the cohort described by Takaya et al. was 71±9.3 years and the prevalence of smoking was 38%. Similarly, the prevalence of LRNC in the carotid arteries was 71% among 214 individuals from the Multi-Ethnic Study of Atherosclerosis (MESA). The MESA participants had no clinically evident cardiovascular disease, but their carotid intima media thickness (CIMT) was above the 85th percentile compared to other MESA participants.[35] Finally, the prevalence of LRNC ranged from 37% to 52% among 1,769 participants in the Atherosclerosis Risk in Communities (ARIC) Study who had moderately elevated CIMT values compared to other ARIC participants.[36]

Our findings suggest the possibility of fundamental differences in the pathophysiology of atherosclerosis between the femoral arteries and other vascular beds. It is conceivable that geometric variables that determine sheer stress, such as vessel tortuosity or velocity of blood flow and vessel size, may be related to plaque accumulation and remodeling. While we found an association of the LRNC with a smaller vessel lumen area, studies in the coronary arteries have demonstrated that the LRNC was associated with positive remodeling and preservation of the lumen area.[37] In pathologic studies, Pasterkamp et al. showed that positive remodeling was substantially more common in the coronary and carotid arteries, compared to the femoral arteries, and that with higher plaque burden the femoral arteries are

more likely to undergo constrictive remodeling than the carotid arteries.[12] The variation between vascular beds in the patterns of remodeling and LRNC prevalence may be related to the degree of inflammation in different vessels. Using fluorodeoxyglucose positron-emission tomography (FDG-PET) imaging of the carotid and iliac arteries and the aorta Rudd et al found the lowest degree of FDG-PET activity (signifying less inflammation) in the femoral arteries.[11] Further, we found that smoking was the only clinical characteristic associated with LRNC in the SFA, whereas total or LDL cholesterol have been associated with LRNC in the carotid arteries.[30,31] Future study in which different vascular beds are imaged in the same individual will help determine whether the prevalence of LRNC and intra-plaque hemorrhage varies by vascular bed or by individual participants.

An important consideration is that we acquired images in the proximal SFA to maximize image quality. Some participants may have had a greater plaque burden more distally. Had we acquired images at the level of the greatest stenoses we may have found a higher prevalence of LRNC and intra-plaque hemorrhage. However, results from recent histologic studies of the femoral arteries in patients with PAD reported prevalence rates of LRNC that are consistent with findings reported here; in contrast, histologic studies showed higher rates of intra-plaque hemorrhage than reported here.[38] For example, Derksen et al. analyzed femoral endarterectomy specimens using histopathology from 274 patients undergoing lower extremity revascularization.[38] Approximately 30% of patients had LRNC, and 63% had intra-plaque hemorrhage. A previous investigation by Yuan et al. reported that MRI was 85% sensitive for intra-plaque hemorrhage within LRNC in the carotid arteries, compared to histologic examination.[15] However, when regions of hemorrhage smaller than 2.81 mm^2 were included, the sensitivity decreased to 66%.[39] It is important to point out that histopathology enables identification of individual red blood cells, whereas MRI only detects larger collections of hemorrhage. For these reasons, it is not surprising that histopathology and MRI have different sensitivities for detecting intra-plaque hemorrhage.

Similar to our findings in the SFA, previous studies in the coronary arteries suggest that LRNC may not be an adequate surrogate for overall atherosclerotic disease burden. For example, in a post-mortem study of 31 adults who died suddenly of ischemic heart disease, there was no association between the size of the LRNC and the degree of coronary stenosis or plaque size.[40] While Qian et al. demonstrated a linear association between LRNC and plaque area in a study of patients undergoing percutaneous coronary intervention and intravascular ultrasound, there was no association between lumen and LRNC area.[41] In addition, the correlation between LRNC and plaque areas was substantially weaker than the correlations between fibrous and fibrofatty tissues and plaque areas.

Our study has limitations. First, we imaged only the proximal SFA. Whether our results are representative of the entire length of the SFA is unknown. However, previous data from the WALCS III cohort shows strong correlations of plaque measures from the same proximal SFA segment with the ABI and functional performance.[29, 31] Our imaging did not include gadolinium, which may have reduced the sensitivity of our images for LRNC.[42] However, the absence of gadolinium does not reduce sensitivity of MRI for intra-plaque hemorrhage.[14] We only imaged the leg with the lower ABI for each patient. MRI of the SFA does not have the spatial resolution to measure fibrous cap thickness which is an important measure of

plaque vulnerability in the carotid and coronary arteries. We excluded non-English speakers, which may limit the generalizability of our results. We normalized plaque measures to the median of the total vessel area, because SFA dimensions (and as a result, the absolute plaque area) vary greatly based on patient size. If participants had significant expansive or constrictive remodeling then this may have led to errors in our plaque measures. However, any potential for error is likely far outweighed by the need to account for artery size. Finally, our data are cross-sectional and observational. Associations reported here should not be construed as causal.

In conclusion, the prevalence of high-risk plaque was relatively low in 303 participants with PAD, only 22.4% had MRI-identified LRNC and one had intra-plaque hemorrhage in the proximal SFA. Further study is needed to determine the prognostic significance of LRNC in the SFA among men and women with PAD.

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HIGHLIGHTS

- We used magnetic resonance imaging (MRI) to study superficial femoral artery plaque
- Study participants were 302 adults with peripheral arterial disease
- Lipid rich necrotic core was seen in 68 (22.5%); only 1 had intraplaque hemorrhage
- Smoking was the only clinical characteristic associated with necrotic core

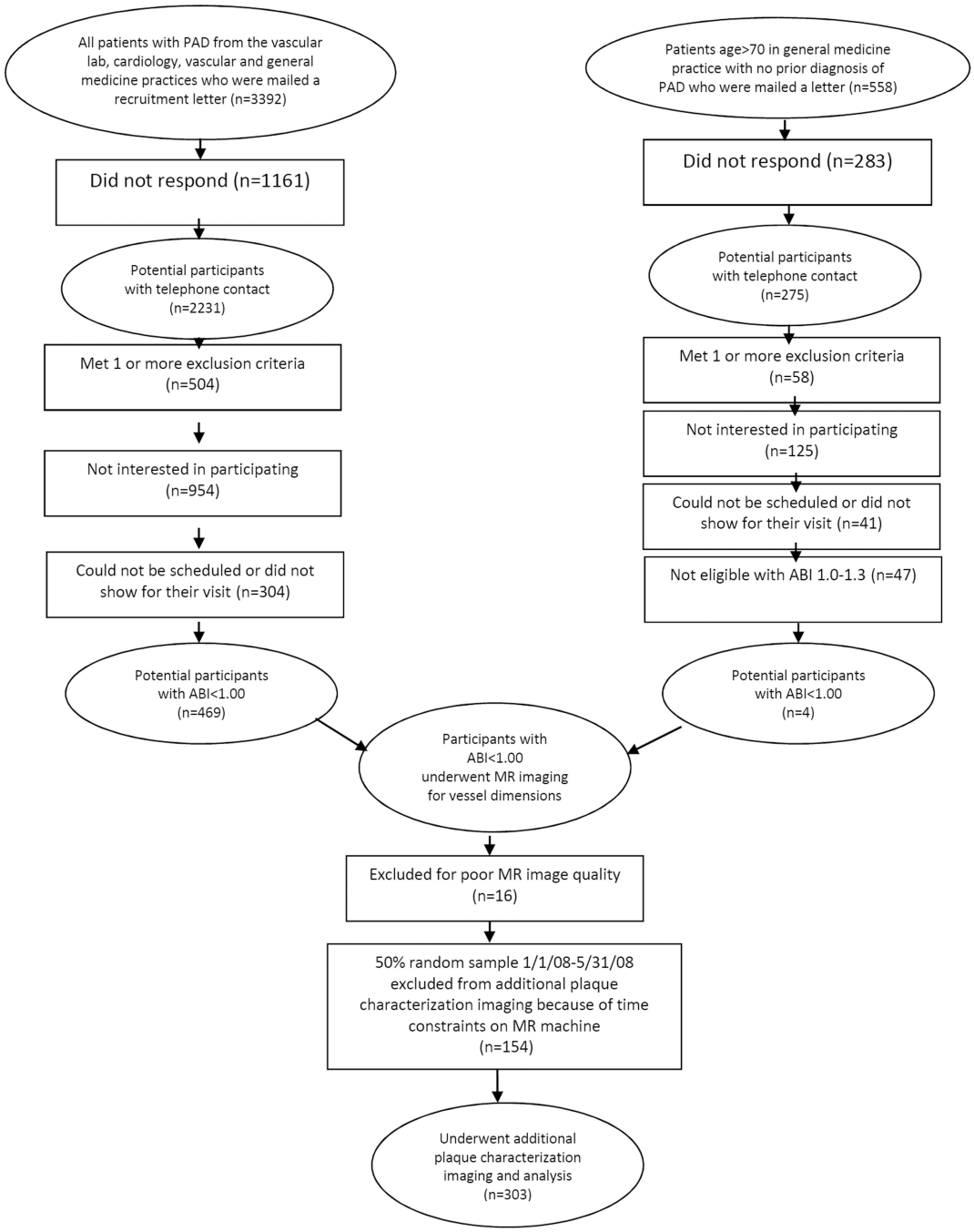
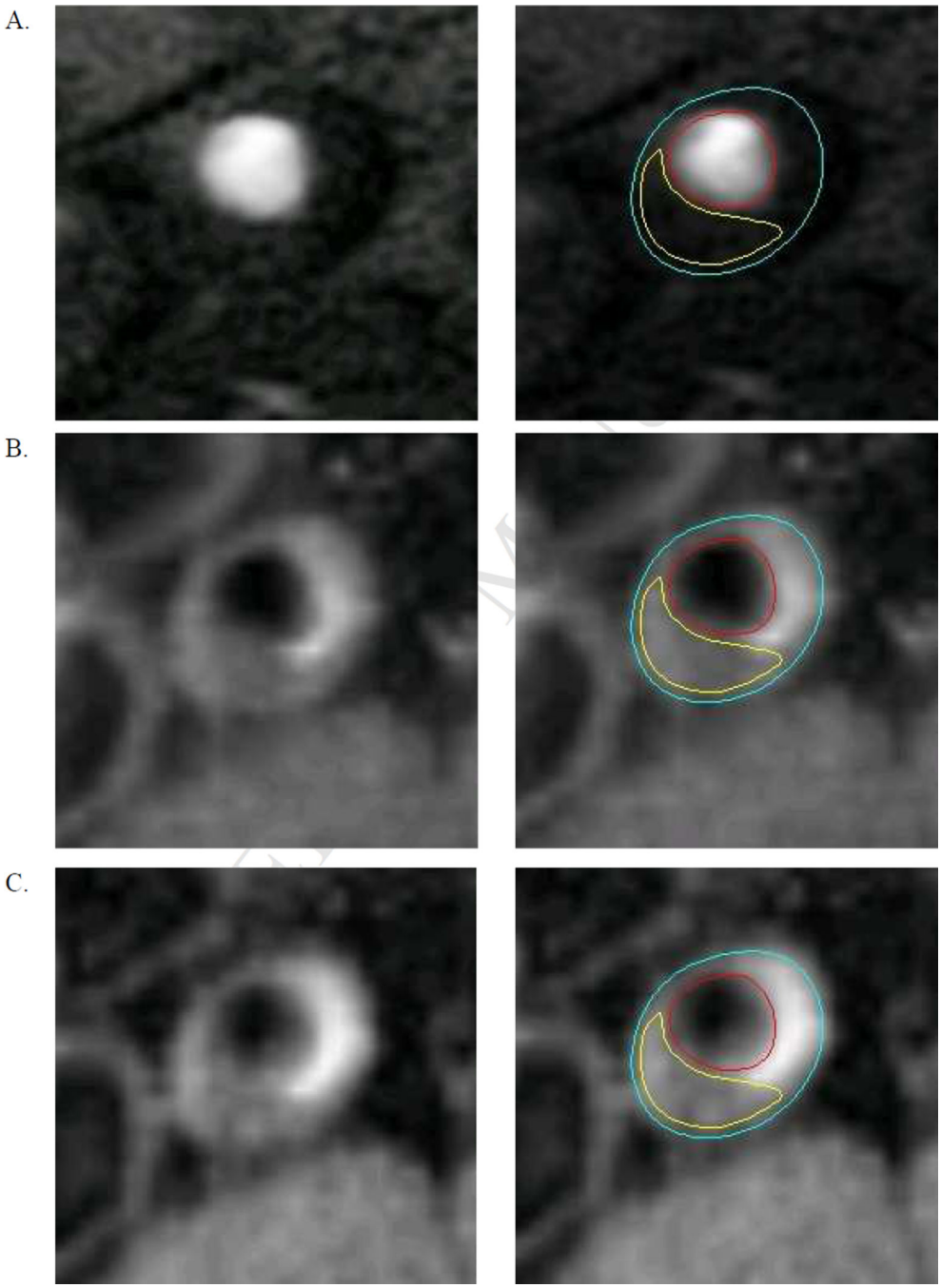


Figure 1. Recruitment for Walking and Leg Circulation Study (WALCS) III

PAD = peripheral artery disease; ABI = ankle-brachial index, MR = magnetic resonance



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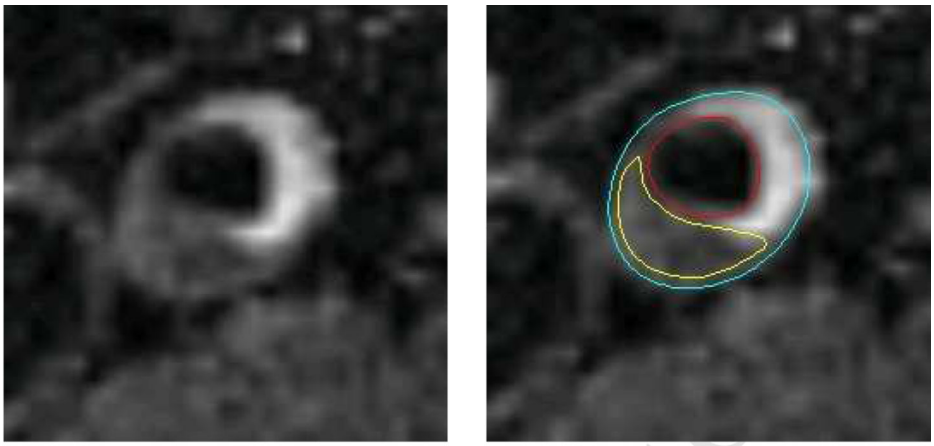

Figure 2. MRI images of the proximal superficial femoral artery (SFA) from a participant in the Walking and Leg Circulation Study III cohort

Imaging sequence is time of flight (a), T1 (b), proton-density (c) and T2 (d). Panels on the left are the original images, and panels on the right include the traced contours for the plaque composition analysis. The blue contour delineates the outer boundary of the SFA, the red contour delineates the lumen, and the yellow contour delineates the lipid rich necrotic core.

Table 1

Definitions of Plaque Measures*

Plaque Measure	Definition
Normalized mean wall area	Average (wall area)/median (total vessel area)
Normalized maximal wall area	Maximum (wall area)/median (total vessel area)
Mean percent lumen area	Average (lumen area/total vessel area)
Minimum percent lumen area	Minimum (lumen area/ total vessel area)
Normalized mean wall thickness	Mean wall thickness/√(median total vessel area)
Normalized maximum wall thickness	Maximum wall thickness/√(median total vessel area)

* Twelve cross-sectional images per participant of the proximal superficial femoral artery were obtained starting at the bifurcation of the common femoral artery. All measurements are normalized for vessel size. Because the plaque measures represent ratios, there are no units for these measures.

Table 2

Associations of Clinical Characteristics with Presence vs. Absence of Lipid Rich Necrotic Core in Participants with Peripheral Arterial Disease*

	LRNC absent* (N= 235)	LRNC present* (N=68)	P value
Age	68.5 (±9.6)	67.5 (±11.5)	0.52
Male sex, %	63.0	82.4	0.003
Black race, %	34.3	39.0	0.50
Ankle brachial index, (SE)	0.67 (0.01)	0.64 (0.02)	0.14
Diabetes mellitus, %	37.8	43.8	0.38
Hypertension, %	92.8	88.3	0.24
Myocardial infarction, %	17.1	19.4	0.66
Stroke, %	16.4	15.9	0.91
Current smoker, %	21.4	35.9	0.02
Statin use, %	76.8	69.5	0.24
Antiplatelet use, %	79.1	75.9	0.58
Low-density lipoprotein cholesterol, mg/dl, (SE)	92.43(2.13)	90.29(3.76)	0.62
High-density lipoprotein cholesterol, mg/dl, (SE)	50.33(1.18)	46.18(2.09)	0.09
Body mass index, kg/m^2, (SE)	30.09(0.42)	28.98(0.78)	0.21

LRNC = lipid rich necrotic core, SE= standard error

* Data shown, other than mean age and sex, are age- and sex-adjusted means and standard errors. Continuous variables were based on general linear models, categorical variables were calculated with a logistic model.

Table 3

Atherosclerotic Plaque Characteristics in the Superficial Femoral Artery Associated with Presence or Absence of Lipid Rich Necrotic Core in Adults with Peripheral Arterial Disease (n=303)

	Analyses Adjusted for Age and Sex		
Normalized plaque measures, (SE)	**LRNC absent (n=235)**	**LRNC present (n=68)**	**P value**
Mean percent lumen area	33% (1%)	31% (2%)	0.42
Minimum percent lumen area	24% (1%)	22% (2%)	0.24
Mean wall area	0.70(0.01)	0.71 (0.02)	0.67
Maximum wall area	0.92 (0.03)	0.96 (0.05)	0.54

SE indicates standard errors; LRNC, lipid rich necrotic core. Mean and maximum wall areas are normalized for vessel size.

Table 4

Vessel Dimensions in Artery Cross-Sections with and without Lipid Rich Necrotic Core (n=778 cross-sections, n=68 participants)*

	Cross-sections without LRNC among participants with LRNC (n=576)	Cross-sections with LRNC present (n=202)	P value
Normalized mean wall thickness	0.22±0.01	0.25±0.01	<0.0001
Normalized maximum wall thickness	0.31±0.01	0.41±0.01	<0.0001
Lumen percent area	39% ± 1%	33% ± 1%	<0.0001

LRNC indicates lipid rich necrotic core

*Analysis was restricted to participants with LRNC

Table 5

Eccentricity index of cross sections with and without lipid rich necrotic core

	Eccentricity index	
	Unadjusted	**Adjusted**
LRNC present (n=192)	0.55	0.55
LRNC absent (n=3019)	0.36	0.36
P value	<0.001	<0.001

LRNC indicates lipid rich necrotic core

Concentric lesions were considered to have an eccentricity index <0.05; eccentric lesions were considered to have an eccentricity index ≥0.05.

Analyses were adjusted for age, sex, tobacco use, systolic blood pressure, use of antihypertensive medication, statin use, high-density and low-density lipoprotein cholesterol levels.