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Longer Duration of Statin Therapy is Associated with Decreased Carotid Plaque Vascularity by Magnetic Resonance Imaging

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Abstract

Objective—Plaque neovasculature is a major route for lipoprotein and leukocyte ingress into plaques, and has been identified as a risk factor for carotid plaque disruption. V_p, a variable derived from pharmacokinetic modeling of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), correlates with plaque neovasculature density. Because lipid-lowering therapy has been associated with regression of neovasculature in animal models, we sought to determine clinical correlates of carotid plaque neovasculature (as assessed by V_p) in participants on statin therapy for established cardiovascular disease.

Methods—98 participants from an AIM-HIGH sub-study underwent DCE-MRI of their carotid arteries. Expert readers who were blinded to all clinical variables analyzed the MR images to measure carotid plaque V_p in all participants. Associations between V_p and duration of statin therapy and other clinical risk factors were analyzed.

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CONFLICT OF INTEREST

Outside of the present study, Dr. Yuan reports grants from the NIH and Philips Medical. He also serves as a Member of Radiology Advisory Network, Philips. Mr. Hippe reports grants from GE Healthcare. No other authors have any other potential conflicts of interest to disclose.

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Results—Prior duration of statin treatment at enrollment ranged from <1 year (21%), 1-5 years (40%) and >5 years (39%). In univariate analyses, shorter duration of statin therapy (P=0.01), the presence of metabolic syndrome (P=0.02), and higher body mass index (P=0.01) and lipoprotein(a) (P=0.01) were all significantly associated with higher baseline V_p values. In multivariate analyses, significant associations remained between shorter duration of statin therapy (P=0.004) and lipoprotein(a) (P=0.04).

Conclusions—These are the first human, *in vivo* findings suggesting a relationship between duration of statin therapy and regression of carotid plaque neovasculature. Future longitudinal studies are warranted both to confirm this finding and to address whether changes in neovasculature may translate into change in risk for plaque disruption.

Keywords

statin; neovasculature; lipoprotein(a); magnetic resonance imaging; atherosclerosis

INTRODUCTION

Over the past two decades, there has been an increasing appreciation for how specific atherosclerotic plaque features increase risk for plaque disruption that result in clinical cardiovascular events.[1, 2] Among these plaque features are macrophages[3-5] and neovasculature.[6] Histological studies in human coronary arteries have documented associations between leukocyte adhesion molecules on neovascular endothelium and plaque inflammatory cell content,[7, 8] suggesting that neovasculature may be a major route by which macrophages enter atherosclerotic plaques. In addition, neovasculature has been linked to plaque vulnerability in humans.[9] Together, these findings suggest important roles for both neovasculature and macrophages in plaque development and disruption.

Concurrently, efforts have been made to develop non-invasive methods, such as magnetic resonance imaging (MRI), to image plaque components associated with vulnerability. To this aim, several groups also have devoted substantial effort to developing techniques to quantify plaque neovasculature and macrophages. In particular, preoperative, dynamic, contrast-enhanced-magnetic resonance imaging (DCE-MRI) of carotid arteries has been validated against post-operative immunohistochemistry performed on human carotid endarterectomy specimens. These studies have found strong correlations between DCE-MRI-derived markers of carotid plaque neovasculature (fractional blood volume, V_p),[10-12] and macrophages (transfer constant, K^{trans}).[11]

Statin therapy is associated with decreased risk for cardiovascular events[13, 14] and, in animal models, statin therapy decreases plaque macrophages[15, 16] and neovasculature.[17-20] Thus, we hypothesized that duration of prior statin therapy, as well as other baseline variables, might be associated with V_p and/or K^{trans} values measured at baseline (i.e., prior to randomization) in a sub-study of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) Trial.[21] Analyses were restricted to those participants who were on statins at baseline.

METHODS

Study Design

The objective was to evaluate neovasculature density and its association with clinical and laboratory measures in the AIM-HIGH participants who were on statins at baseline. Participants underwent baseline DCE-MRI scans within 3 months following randomization into statin alone or with statin plus extended-release niacin in the AIM-HIGH Trial. Fractional blood volume (V_p) estimated by kinetic modeling of DCE-MRI, previously found to correlate well with neovasculature content of plaques,[11] was the predefined primary endpoint. The transfer constant (K^{trans}), another kinetic model parameter that correlates with histological measurements of plaque inflammation,[11] was also estimated using DCE-MRI and included in the analysis.

Study Participants

Sub-study participants were recruited from a subset of 21 of 92 AIM-HIGH Trial (NCT00120289) clinical sites in the United States and Canada. Appendices 1 and 2 list the participating clinical and imaging sites and investigators. AIM-HIGH Trial inclusion and exclusion criteria have been published previously.[21] Briefly, the primary AIM-HIGH inclusion criteria included: 1) age 45 years or older, 2) documented stable coronary, cerebrovascular/carotid or peripheral arterial disease, and 3) “atherogenic dyslipidemia”, defined as HDL-cholesterol <40mg/dL in men or <50mg/dL in women, triglycerides 150-400 mg/dL; and LDL-cholesterol <180 mg/dL if not taking statin drugs. In total, 94% of AIM-HIGH participants were taking statins at baseline. The duration of statin therapy prior to entering the trial was also recorded as the categories <1 year, 1-5 years and >5 years. This categorization was determined by the AIM-HIGH Trial executive committee prior to data analysis in this study.

Sub-study specific inclusion criteria were: 1) eligible for main AIM-HIGH study, 2) medically able to undergo MRI procedure, 3) willing to provide informed consent for sub-study participation. Sub-study specific exclusion criteria were: 1) history of pacemaker or metallic implants, 2) history of bilateral carotid endarterectomy, or 3) estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. This study was approved by the AIM-HIGH Executive Committee and a local institutional review board or research ethics committee at each participating clinical site. Separate signed informed consent was obtained from each participant in this sub-study.

After DCE-MRI scans were obtained, participant scans were excluded from further analysis if image quality was inadequate for analysis based on a previously described 4-point scale[22] or there were significant violations of the DCE imaging protocol, including an incorrect time interval, too few time frames, failure to inject contrast agent and improper alignment of images. In addition, participants were excluded if carotid artery thickness was ≤1.0mm, as DCE-MRI measurements are considered unreliable in very thin vessel walls.

DCE-MRI Scan Protocol

MRI scans of carotid arteries were performed on 3T MRI scanners (GE HealthCare or Philips Healthcare). The DCE-MRI imaging protocol has been previously described.[23] Briefly, the protocol included an axial multi-slice 2D spoiled gradient recalled echo (SGRE) sequence to acquire DCE images. Depending on individual scanner configuration, 4 to 8 contiguous slices were acquired, centered on the bifurcation of the index carotid artery with acquisition parameters: field of view: 160*160mm, matrix 256*256, acquired resolution 0.625*0.625 mm, reconstructed image size 512*512, 2-3 mm slice thickness, repetition time 117-126 ms, echo time 5ms, flip angle 50°. The index artery was selected as the one with more visible plaque. Images were acquired at 18 time points separated by a repetition interval of 18s. Coincident with the third dynamic scan in the sequence, 0.05 mmol/kg of a gadolinium-based contrast agent was injected at a rate of 0.7 ml/s by a power injector. To impose a T1-dependent signal on inflowing blood, a spatial saturation band was used. Other contrast weightings were acquired with a standard multiple-contrast-weighted protocol that included 3D time of flight (TOF), 2D black blood T1-weighted, contrast enhanced 2D black blood T1-weighted, 2D black blood T2-weighted, and 2D black blood proton-density-weighted, and 3D Magnetization Prepared Rapid Gradient Echo (MP-RAGE) imaging, as previously described.[24]

Image Analysis

Image analysis was conducted by trained reviewers blinded to the corresponding subject's clinical and laboratory data using custom software (CASCADE)[25]. All images were co-registered using the index carotid bifurcation as a common landmark. Lumen and outer wall boundaries of the carotid artery were first manually traced using the structural multi-contrast images and were then mapped to the DCE-MRI images by an automatic registration algorithm.[23] The lumen and wall contours were then further manually adjusted, if needed, to better match the boundaries visible on the DCE-MRI images (illustrated in **Figure 1**). The contoured DCE-MRI images were processed to generate vasa vasorum (V-V) images as previously described.[26] This processing step is fully automated and includes registration and smoothing of the sequence of images, extraction of the arterial input function, and calculation of V_p and K^{trans} for each pixel based on the Patlak pharmacokinetic model. The resulting color-coded, parametric V-V images show V_p in red and K^{trans} in green (**Figure 1**). Lastly, aggregated values for V_p and K^{trans} were calculated by averaging all pixels within the vessel wall of each participant, except those within 1 mm of the lumen contour. This exclusion minimized any influence from the high intensity lumen signal due to partial volume effects, blurring, and motion. Note that the adventitial layer of the vessel is included within the outer wall boundary, so the average V_p and K^{trans} values include both plaque and the adventitia, as in other reports.[10-12, 23] Scan-rescan reproducibility of these measurements have been reported.[23]

Statistical Methods

Categorical variables were summarized as count (percentage) and continuous variables were summarized as mean ± standard deviation (SD) and median (range). Clinical and laboratory values were compared between the sub-study sample and the remainder of the

AIM-HIGH cohort sample using Fisher's exact test and the Mann-Whitney test. Plaque V_p and K^{trans} were compared between groups using two-sample t-tests or ANOVA while associations with continuous variables were assessed using Pearson's correlation coefficient. Highly right-skewed variables (triglycerides, lipoprotein(a), total : HDL cholesterol ratio, and apolipoprotein B : A1 ratio) were log-transformed prior to analysis. Multivariate analyses were conducted using linear regression. Variables significantly associated with V_p or K^{trans} during univariate analysis were included in a single multivariate model. Backwards elimination was then applied to identify variables independently associated with V_p or K^{trans}. A linear trend between plaque V_p and prior duration of statin therapy (a categorical variable) was tested using the linear component from the set of orthogonal polynomial contrasts. Residuals from the univariate and multivariate models were inspected to detect important departures from normality. All statistical calculations were conducted using R (version 2.14.1; The R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-tailed tests were used with statistical significance defined as $p<0.05$.

RESULTS

Participant Flow

A total of 225 participants from the AIM-HIGH trial met initial sub-study inclusion criteria and underwent baseline DCE-MRI scanning. Of these, 206 were on statin therapy at enrollment. After further excluding participants with insufficient image quality or DCE-MRI protocol violations (N=52) and those who failed to meet the minimum vessel thickness requirement of >1 mm (N=56), there were 98 subjects who met all inclusion/exclusion criteria available for analysis. Participant flow is shown in **Figure 2**.

Participant Demographics

Baseline demographics, clinical and laboratory variables are summarized in Table 1 of Ref [27]. The age of subjects ranged from 45 to 79 years (median: 62) and 86% of subjects were male. Duration of statin therapy prior to baseline was <1 year for 21% of subjects, 1-5 years for 40% of subjects and >5 years for 39% of subjects. Table 1 of Ref [27] also summarizes the distributions of these variables in the remainder of the AIM-HIGH cohort. Compared to this group, participants in the DCE-MRI sub-study tended to be younger (mean: 62 vs. 64 years, p=0.07), have shorter prior duration of statin therapy (p=0.052), were less likely to have a history of diabetes (22% vs. 34%, p=0.02) and had a lower body mass index (p=0.005), lower triglycerides (p=0.04) and lower ApoA-I (p=0.04).

Univariate Analyses

At baseline, average plaque V_p was 0.076 ± 0.047 and average plaque K^{trans} was 0.059 ± 0.025 min^{-1}. The results of the univariate analyses of the baseline DCE-MRI variables versus clinical and laboratory factors are shown in **Table 1**. A significant positive association was found between baseline K^{trans} and systolic blood pressure (p=0.04), but no other significant associations were found between clinical or laboratory variables and K^{trans}.

In contrast, significant univariate associations were found between baseline V_p and five demographic, clinical and laboratory variables: younger age, shorter prior duration of statin

therapy, presence of metabolic syndrome, higher body mass index and higher lipoprotein(a) (Lp(a)) (Table 2). There were no statistically significant associations of V_p with sex, race/ethnicity, tobacco use, prior niacin use, diabetes, BP, Total-C, NonHDL-C, HDL-C, TGs, apoB, apoA-I, Total:HDL-C ratio, or apoB:apoA-I ratio. Importantly, there also was no significant association of baseline V_p with LDL-C (p=0.7). **Figure 3** shows the inverse association of duration of prior statin therapy with baseline plaque V_p.

Multivariate Analysis

Factors significantly associated with V_p during univariate analysis were entered into a multivariate model (**Table 2**). After applying backwards elimination, only duration of statin therapy (p=0.004) and Lp(a) (p=0.04) remained independently associated with V_p.

DISCUSSION

This study demonstrates that DCE-MRI markers of carotid plaque neovasculature and inflammation can be reliably detected and quantified in a multi-center clinical trial. More importantly, it identifies potential links between specific clinical factors and the extent of carotid plaque neovasculature as represented by V_p. Specifically, the study finds, in patients with established cardiovascular disease, that: a) higher Lp(a) levels are positively associated with more extensive neovasculature, and b) longer duration of statin therapy is associated with less neovasculature.

Neovasculature long has been recognized as a feature of human atherosclerosis,[28] and studies in the 1990s demonstrated a strong association between neovasculature and leukocyte and lipoprotein deposition in human coronary atherosclerosis.[7, 8] Thus, neovasculature likely serves as a key route for lipoprotein and leukocyte infiltration into human atherosclerotic plaques.[6, 29] Moreover, neovasculature has been associated with increased risk for plaque disruption.[9, 30] However, if conditions are changed (e.g., marked reduction in plasma lipids) to facilitate atherosclerotic plaque regression,[31-33] neovasculature also likely serves as a route by which macrophages might remove cholesterol and other debris from atherosclerotic plaques.[34-36] Therefore, the ability to monitor therapy-induced changes in plaque neovasculature may represent a novel window into therapy-induced changes in plaque biology.

It is important to recognize that although these studies were performed in the context of the larger AIM-HIGH Trial, they were obtained very early in the trial, within three months of randomization either to statin or to statin plus extended-release niacin; therefore, it is unlikely that trial-specific therapy modified the major findings. No univariate association was found between prior niacin use with V_p. However, only 15 participants were on niacin prior to study entry, which limits the power of this comparison. It also is important to acknowledge that because AIM-HIGH was performed in patients with documented cardiovascular disease, the baseline rates of statin treatment in study participants was very high. Moreover, the average LDL cholesterol level in this population was only 72 mg/dL and blood pressure was well-controlled. Thus, the trial provided an excellent opportunity to examine potential relationships between a number of clinical, demographic and laboratory

variables with DCE-MRI parameters in carotid plaques of patients with established cardiovascular disease who were treated to contemporary risk reduction standards.

It is intriguing that in multivariate analysis, Lp(a) was the only lipid variable found to be significantly associated with the baseline extent of plaque neovasculature. Epidemiologic[37, 38] and genetic[39, 40] studies have shown strong associations of Lp(a) with risks for cardiovascular diseases, including stroke. Multiple mechanisms by which Lp(a) might increase cardiovascular risk have been proposed, including lipid deposition in the artery wall,[41] with subsequent oxidative modification,[42] as well as a potential prothrombotic effect related to competitive inhibition of plasminogen by the structurally similar Kringle IV domains of apolipoprotein(a).[43] Interestingly, statin therapy alone has minimal to no effect on circulating Lp(a) levels[44] and, in contrast to other lipoprotein variables, only Lp(a) retained its on-trial relationship to risk for CV events in both arms of the AIM-HIGH Trial.[45, 46]

In both univariate and multivariate analyses, the most striking finding of this study was the statistically significant, inverse association of V_p with statin therapy duration. A small study of 28 humans observed a decrease, though not statistically significant, in V_p over 12 months of atorvastatin (0.068 to 0.059, p=0.3).[47] However, their measure of V_p was restricted to the region within 0.625 mm (1 pixel) of the outer wall boundary which targets the adventital layer, while the V_p measurement in this study included the vascularity of both plaque and adventitia. Animal studies have demonstrated that hypercholesterolemia increases plaque neovasculature,[29] while statin treatment has been shown to decrease neovasculature in hypercholesterolemic pig,[17] rabbit[19, 20] and apoE-deficient mouse[18] models of atherosclerosis. Intriguingly, the decreases in neovasculature seen in these models associated with statins were found to be independent of changes in plasma cholesterol. In our study, we found a strong inverse association between carotid plaque neovasculature, and duration of statin therapy, but no association between neovasculature and any lipid/lipoprotein variable other than Lp(a), the levels of which are unaffected by statins. Thus, the *in vivo* observations of this human study are consistent with the limited literature on the effects of statin intervention on neovasculature in animal models and humans.

While few associations with plaque K^{trans} were found, some trends were consistent with our previous report, including that K^{trans} values tended to be higher in current smokers and those with higher systolic blood pressure.[11] However, our previously finding of a significant negative correlation between HDL and K^{trans} was not seen in the present study. There are important differences between these two studies that limits their comparability. The present study selected patients with dyslipidemia and low HDL-C and this restricted range of HDL-C may have lowered power to detect an association with K^{trans}. In addition, plaques in the present study were much less advanced than those in the prior study, which examined carotid endarterectomy patients.

Reproducibility of V_p and K^{trans} measurements in the AIM-HIGH trial have recently been reported.[23] In that study, K^{trans} was found to be more reproducible than V_p overall, but the reproducibility of V_p was better in larger plaques, in particular those with area >25 mm^2 (ICC = 0.73). The reproducibility study had a median plaque size of 29 mm^2 while the

present study had a median size of 36 mm^2 (24% higher), so the overall reproducibility of the V_p measurements in this likely better than reported in the reproducibility sub-study. Nonetheless, the reproducibility of the kinetic parameters is generally lower than that for plaque morphology and composition measurements,[48] so some associations between the clinical factors and V_p and K^{trans} may have been missed due to diminished power.

The present study has some additional limitations that merit discussion. First, although performed in the context of a lipid intervention trial, this study examines associations of variables with neovasculature at baseline; therefore, it is not a randomized trial of statin intervention. Second, while the correlation of V_p with carotid plaque neovasculature has been histologically validated in highly stenotic carotid arteries,[10, 11] V_p has not been independently validated in arteries with more moderate disease, as encountered in this study. Third, the study is limited by the need to exclude a relatively large proportion of the potential study participants, due primarily to insufficient image quality or acquisition, as well as to atherosclerotic plaques that were insufficiently large for reliable analyses. This issue was also noted in the AIM-HIGH DCE-MRI reproducibility sub-study.[23] That study suggested that improved training for site MR technologists be performed which would allow them to better recognize poor quality and adjust; in addition, stricter quality controls measures could be adopted which monitor DCE-MRI protocol adherence as images are acquired and require repeat scans or retraining after protocol violations. Lastly, black-blood DCE-MRI protocols have recently been developed which may eliminate the need to exclude pixels within 1 mm of the lumen and thereby allow DCE-MRI of smaller, earlier lesions.[49, 50] Thus, it will be interesting to determine whether the findings might be replicated in randomized intervention trials and/or using newer agents or techniques that may potentially be more specific or sensitive markers of plaque neovasculature.

CONCLUSIONS

In summary, this study finds strong associations of shorter duration of statin therapy and higher Lp(a) levels with higher carotid plaque V_p, an MRI-derived marker of plaque neovasculature. The results suggest that this technique may hold promise in evaluating the potential value of neovasculature as a marker of plaque vulnerability, as well as the potential effects of therapies on this key player in both plaque atherogenesis and regression.

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APPENDIX 1. Participating AIM-HIGH clinical sites and investigators (by AIM-HIGH Site #)

2 - *Cardiology Consultants of Philadelphia* - Paul Grena, Sharon Budzinski; 9 - *Duke University* - John Guyton, Shubi Khan; 10 - *University of Calgary* - Todd Anderson, Bev Madden; 14/30 - *University of Pennsylvania /Philadelphia VA* - Richard Dunbar, Dalia Roberts, Monica Williams; 15 - *University of Southern California* - Colletti, Andrea Contreras; 21 - *University of Western Ontario* - William Kostuk, Cathy Bone; 34 - *Health Partners Riverside Clinic* - Chhavi Chadha, Maureen Busch; 35 - *St. Vincent's Charity Hospital* - Laurie Sadler, Mariellen DeSmit, Tania Zalatel; 37 - *St. Michael's, University of Toronto* - Lawrence Leiter, Leslie Berndl; 43 - *University of Maryland* - Michael Miller, Abby Roberts; 47 - *University of Washington* Cardiology - Xue-Qiao Zhao, Kevin O'Brien, Suzanne Peck; 48 - *University of Washington NW Lipid* Research Center - Robert Knopp, Pathmaja Paramsothy, Alice Dowdy, Barbara Twaddle; 49 - *Long Beach VA* - Moti Kahyap, Olaf Fallye, Sunil Kakadia; 51 - *Puget Sound VA* - Kenneth Lehmann, Julie LaGuire; 53 - *Vancouver General Hospital* - Anthony Fung, Rebecca Fox, Linda Axen; 55 - *Wake Forest University Endocrinology* - Robin Crouse, Donna Davis; 56 - *Wake Forest University Geriatrics* - Jamehl Demons, Tricia Wittmer; 58 - *Wake Forest University Cardiology* - David Herrington, Vickie Wayne, Lynda Doomy; 62 - *Baylor College of Medicine* - Peter Jones, Terry Techmanski, Diane Tanksley; 67 - *Christiana Care Health Services* - Edward Goldenberg, Jackie Laucirica; 69 - *McGuire VA* - Franklin Zieve, Melissa Kimmel; 71 - *Cardiovascular Consultants* - Chris Geohas, Rose Prasad, Annie Laborin; 72 - *Pennsylvania Cardiology Associates* - Robert Norris, Maureen Boyle, Julie Yoon; 74 - *Mayo Clinic* - Stephen Kopecky, Cindy Woltman, Dawn Shelstad; 77 - *Johns Hopkins University* - Peter Kwiterovich, Kathleen Byrne; 78 - *Heart Health Institute* - Patrick Ma, Maureen McRae, Donna Louch; 79 - *Methodist Hospital* - Alan Hoffman, Mary Rangel; 86 - *Kelsey Research Foundation* - Haroon-Ur Harry Rashid, Stacy Meadows.

APPENDIX 2. Participating AIM-HIGH imaging sites and investigators

BAR - *Barrows Neurological Institute* - Jim Pipe, Sharmeen Joomun; BAY - *Baylor School of Medicine* - Joel Morrisett, Karima Ghazzaly; CAL - *University of Calgary* - Richard Frayne, Brian O'Brien, Frances Raymond; JHU - *Johns Hopkins University* - Bruce Wasserman, Rena Geckle; MAY - *Mayo Clinic* - John Huston, Mandie Maroney-Smith; ROB - *Robarts Research Institute* - Brian Rutt, Cyndi Harper Little; UBC - *University of British Columbia* - Alex MacKay, Linda Chandler; UOW - *University of Washington* - Chun Yuan, Baocheng Chu, Niranjan Balu; USC - *University of Southern California* - Patrick Colletti, Samuel Valencerina; WFU - *Wake Forest University* - J. Robin Crouse, J. Greg Terry.

Abbreviations

AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging

K^{trans}	transfer constant
V_p	fractional plasma volume
SGRE	spoiled gradient recalled echo
TOF	time of flight
V-V	vasa vasorum

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HIGHLIGHTS

- Carotid plaque V_p is an imaging-based marker of neovasculature density, previously validated using histology
- V_p was measured in 98 subjects with established cardiovascular disease
- Longer prior duration of statin therapy was associated with lower V_p
- Higher lipoprotein(a) levels was independently associated with higher V_p

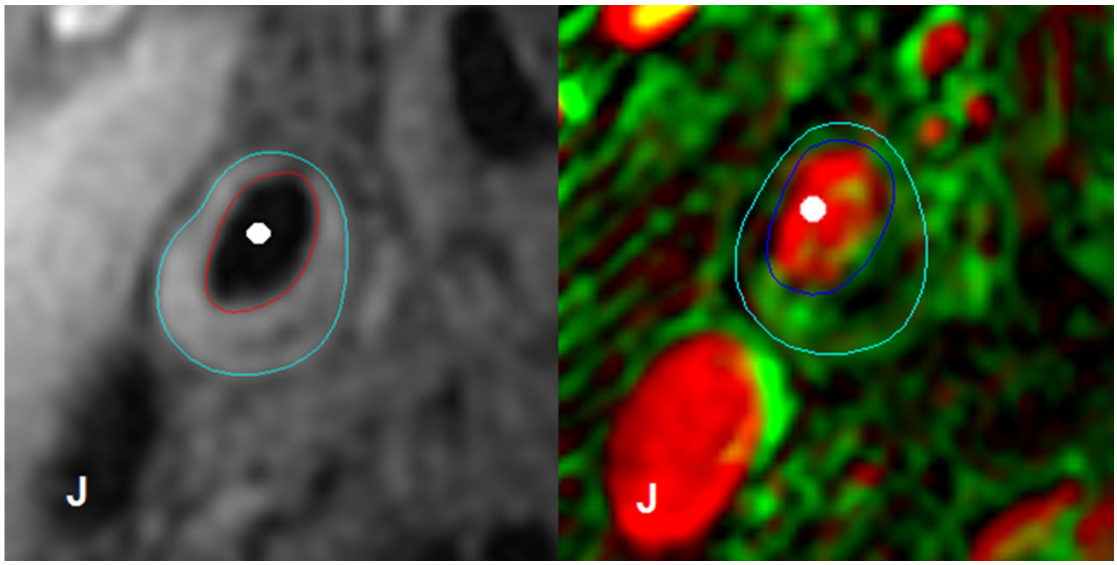

Figure 1. Pre-contrast T1-weighted image of the common carotid artery (left panel) and corresponding vasa vasorum (V-V) image derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (right panel) of a study subject

As described in the Image Analysis section of the methods, the lumen and outer wall boundaries were initially drawn using the structural multi-contrast images (red and blue boundaries in the left panel, respectively). These contours were then mapped to the DCE-MRI images and manually adjusted slightly to better fit the image, resulting in the final lumen and outer wall boundaries for DCE-MRI processing (dark and light blue boundaries in the right panel, respectively). The white circles indicate the arterial lumen and the "J" symbols indicate the jugular vein on both images. The Patlak pharmacokinetic model parameters V_p and K^{trans} are shown in red and green, respectively, as previously described[26]. Brighter pixels indicate larger values.

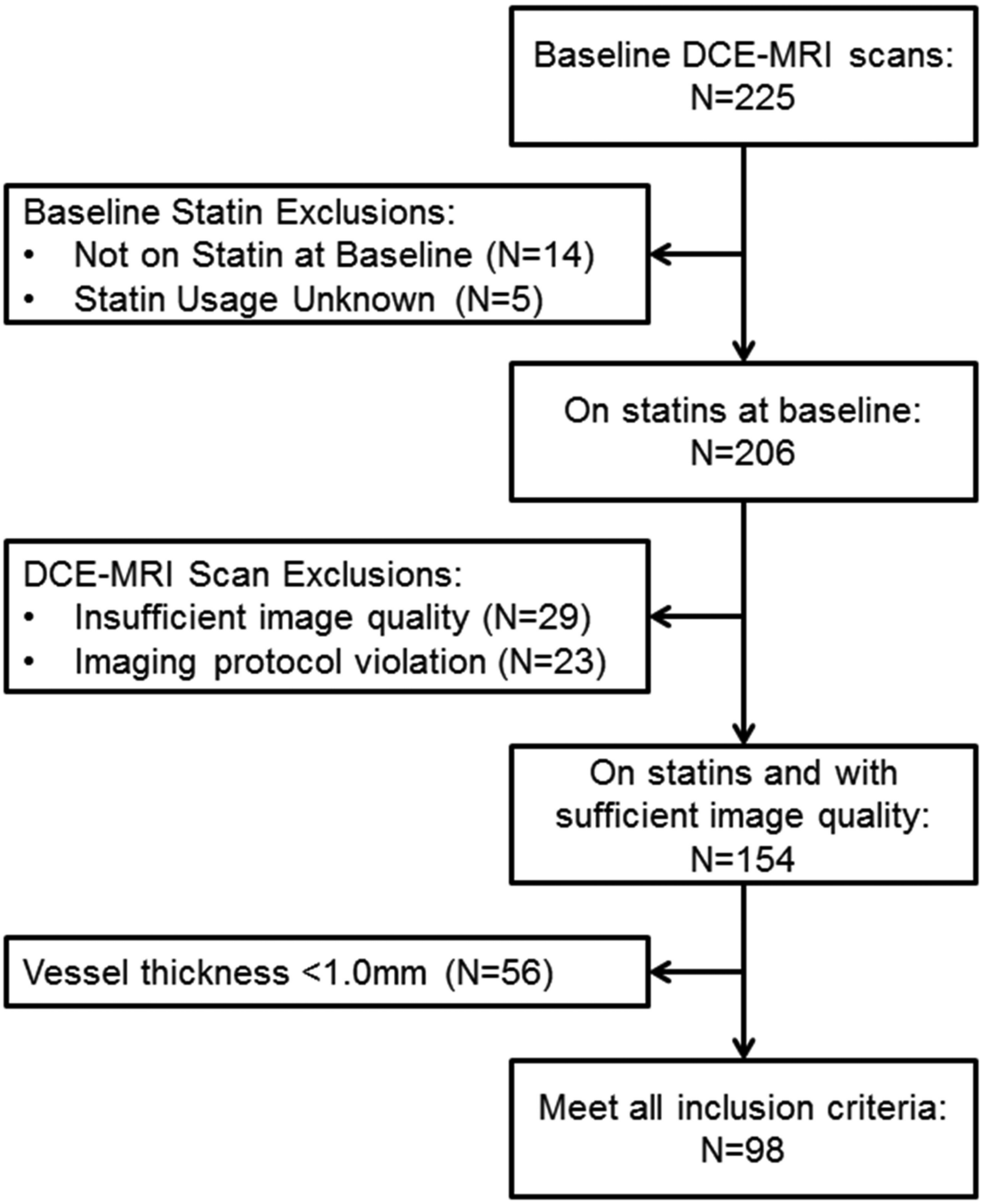

Figure 2. Sub-study participant flow

Flow diagram of participant progress through sub-study exclusion criteria.

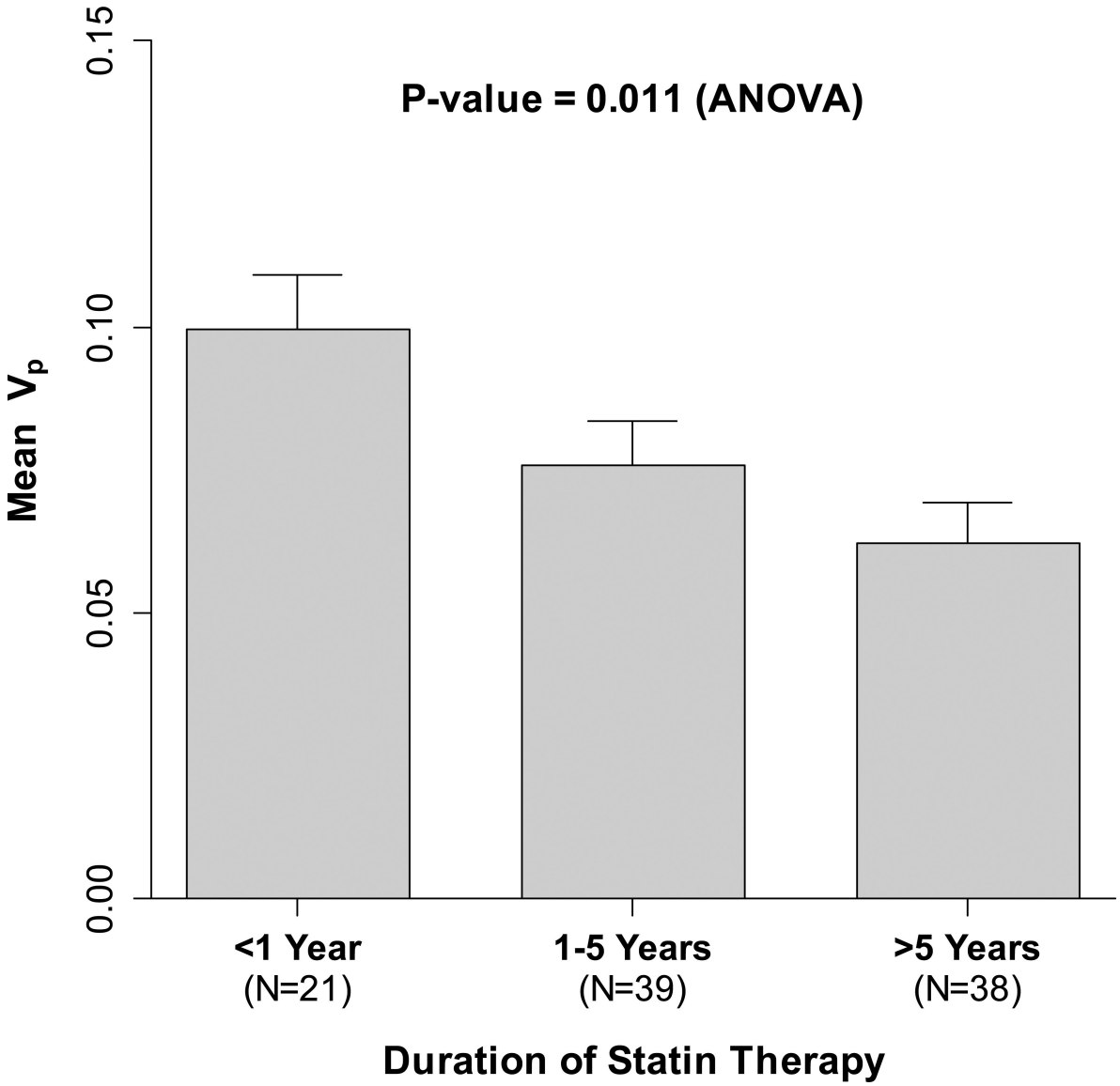

Figure 3. Plaque Neovasculature (V_p) at Baseline by Duration of Prior Statin Therapy

Bar heights correspond to mean V_p values and the error bars correspond to one standard error of the mean (SEM). Longer durations of prior statin therapy were associated with significantly lower mean V_p on the baseline DCE-MRI scans.

Table 1

Univariate analysis results for baseline plaque V_p and K^{trans}.

	V_p		K^{trans}		
Variable	**r or Mean ± SD**	**P Value**	**r or Mean ± SD**	**P Value**	**No.**
Sex		0.86		0.54	98
Male	0.075 ± 0.046		0.060 ± 0.025		84
Female	0.078 ± 0.051		0.055 ± 0.024		14
Age	−0.24	**0.020**	0.05	0.63	98
Race		0.70		0.27	98
White	0.075 ± 0.047		0.060 ± 0.025		90
Non-white/Other	0.082 ± 0.040		0.050 ± 0.021		8
Ethnicity		0.70		0.40	97
Hispanic or Latino	0.084 ± 0.045		0.048 ± 0.029		4
Not Hispanic or Latino	0.075 ± 0.047		0.059 ± 0.025		93
Tobacco use		0.51		0.21	98
Current	0.085 ± 0.047		0.067 ± 0.028		21
Former (quit > 1 year ago)	0.071 ± 0.046		0.058 ± 0.023		48
Never used	0.077 ± 0.049		0.055 ± 0.024		29
Duration of statin therapy		**0.011**		0.50	98
<1 year	0.100 ± 0.043		0.056 ± 0.023		21
1 - 5 years	0.076 ± 0.047		0.057 ± 0.025		39
>5 years	0.062 ± 0.044		0.063 ± 0.026		38
Prior use of niacin		0.41		0.72	98
Yes	0.066 ± 0.022		0.057 ± 0.020		15
No	0.077 ± 0.050		0.059 ± 0.026		83
Metabolic syndrome		**0.016**		0.83	98
Present	0.081 ± 0.047		0.059 ± 0.025		79
Absent	0.053 ± 0.040		0.060 ± 0.025		19

Variable	V_p		K^{trans}		
	r or Mean ± SD	P Value	r or Mean ± SD	P Value	No.
History of diabetes		0.49		0.70	98
Yes	0.070 ± 0.047		0.057 ± 0.024		22
No	0.077 ± 0.047		0.059 ± 0.025		76
Body mass index	0.25	**0.013**	0.10	0.35	98
Systolic blood pressure	0.10	0.34	0.20	**0.044**	97
Diastolic blood pressure	0.14	0.16	0.03	0.73	97
Total cholesterol	0.04	0.70	0.01	0.89	98
LDL cholesterol	0.04	0.69	−0.04	0.68	98
Non-HDL cholesterol	0.06	0.58	0.01	0.96	98
Log(Triglycerides)	0.04	0.70	0.08	0.41	98
Log(Lipoprotein(a))	0.25	**0.013**	0.11	0.28	96
ApoB	0.17	0.092	0.01	0.96	96
HDL cholesterol	−0.05	0.63	0.04	0.73	98
ApoA-I	−0.01	0.92	0.02	0.84	96
Log(Total : HDL ratio)	0.09	0.40	−0.04	0.68	98
Log(ApoB : ApoA-I ratio)	0.17	0.094	−0.03	0.75	96

r = Pearson's correlation coefficient.

Table 2

Multivariate analysis results for baseline plaque V_p as the outcome variable.

	Model 1			Model 2		
Variable	**β**	**(95% CI)**	**P Value**	**β**	**(95% CI)**	**P Value**
Duration of statin therapy			0.056*			**0.004***
1-5 years vs. <1 year	−0.0189	(−0.045, 0.007)		−0.0238	(−0.048, 0.000)	
>5 years vs. <1 year	−0.0282	(−0.057, 0.000)		−0.0365	(−0.061, −0.012)	
Log(lipoprotein(a)), per 1 SD increase	0.0091	(0.000, 0.018)	**0.049**	0.0096	(0.001, 0.019)	**0.040**
Age, per 10 year increase	−0.0024	(−0.014, 0.009)	0.69	-		
Body mass index, per 1 SD increase	0.0014	(−0.001, 0.004)	0.25	-		
Presence of metabolic syndrome	0.0149	(−0.010, 0.040)	0.25	-		

Model 1: initial model containing all variables significantly associated with *Vp* in univariate analysis;

Model 2: final model after applying backwards elimination to model 1;

β: regression coefficient;

*Trend test.