Published in final edited form as:

Atherosclerosis. 2007 October ; 194(2): e34–e42.

Predictors of Carotid Atherosclerotic Plaque Progression as Measured by Noninvasive Magnetic Resonance Imaging:

Saam “Predictors of Carotid Plaque Progression”

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Abstract

The purpose of this in vivo MRI study was to quantify changes in atherosclerotic plaque morphology prospectively and to identify factors that may alter the rate of progression in plaque burden. Sixty-eight asymptomatic subjects with $\geq 50\%$ stenosis, underwent serial carotid MRI examinations over an 18 month period. Clinical risk factors for atherosclerosis, and medications were documented prospectively. The wall and total vessel areas, matched across time-points, were measured from cross-sectional images. The normalized wall index (NWI = wall area / total vessel area), as a marker of disease severity, was documented at baseline and at 18 months. Multiple regression analysis was used to correlate risk factors and morphological features of the plaque with the rate of progression/regression.

On average, the wall area increased by 2.2%/year ($P=0.001$). Multiple regression analysis demonstrated that statin therapy ($P=0.01$) and a normalized wall index >0.64 ($P=0.001$) were associated with a significantly reduced rate of progression in mean wall area. All other documented risk factors were not significantly associated with changes in wall area. Findings from this study suggest that increased normalized wall index and the use of statin therapy are associated with reduced

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Conflict of Interests: None

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rates of plaque progression amongst individuals with advanced, asymptomatic carotid atherosclerosis.

Keywords

magnetic resonance imaging; carotid arteries; atherosclerosis; plaque; progression

Introduction

Atherosclerosis is a progressive disease that starts early in life and is manifested clinically as CAD, cerebrovascular disorders or peripheral arterial disease(1). The disease may remain clinically silent for years as a result of arterial wall remodeling. In the mid-1980's, Glagov et al(2) proposed that early in atherosclerosis development, expansion of the outer wall boundary of the vessel permits growth of the lesion without corresponding reduction of luminal area or blood flow, and that in later stages, further progression overwhelms this process of compensatory enlargement and eventually leads to stenosis, hemodynamic compromise and possible occlusion(3). Nearly two decades later, little is known about plaque burden progression and remodeling in humans, as most of our knowledge is based on animal or autopsy studies. Furthermore, the majority of studies on human atherosclerosis progression have relied on monitoring change in the degree of lumen stenosis, which may, because of compensatory remodeling, significantly underestimate change in overall plaque burden.

Serial *in vivo* imaging of not only the lumen but the entire vessel wall would improve our understanding of the pathophysiology and time course of plaque burden progression during the sub-clinical phase, and enable assessment of factors that may affect the rate of disease progression. A number of studies have shown that MRI can accurately quantify vessel wall dimensions of atherosclerotic arteries *in vivo*(4), with measurement errors ranging from 4-6% for the lumen and wall, and 3.3% for total vessel area measurement(5,6). Thus, MRI provides a promising tool to study plaque progression and the remodeling process of atherosclerosis in humans in a non-invasive fashion.

In this prospective study, serial carotid MRI examinations were performed in a group of 74 asymptomatic subjects with 50-79% carotid stenosis by duplex ultrasound at the time of enrollment. The purpose of this study is to quantify the changes in atherosclerotic carotid artery wall morphology, and to identify factors that may alter the progression rate in plaque burden.

Material & Methods

Study Population

The 74 subjects were randomly selected from an ongoing prospective serial carotid MRI study referred to as PRIMARI. Requirements for inclusion in this analysis were at least two MRI scans (baseline and at 18 months) and sufficient image quality to identify the lumen, wall and the outer boundary of the arterial wall. Subjects for PRIMARI were recruited from the diagnostic vascular ultrasound laboratories at the University of Washington Medical Center, the Veterans Affairs Puget Sound Health Care System, and the Virginia Mason Medical Center after obtaining informed consent. The study procedures and consent forms were reviewed and approved by each site's Institutional Review Board. One side was chosen for serial MRI follow-up, referred to as the index carotid artery. Inclusion criteria for the study are: 1) 50-79% carotid stenosis by duplex ultrasound examination on the index carotid artery; and 2) asymptomatic with regard to their carotid artery disease within six months prior to enrollment. Exclusion criteria are: 1) prior carotid endarterectomy on the index carotid artery; 2) prior neck irradiation; and 3) contraindication for MRI.

Baseline Clinical Data and Laboratory Measures

Study subjects were asked, prior to the baseline MRI examination, to complete a detailed health questionnaire and physical examination. The following information was collected from each subject: age, gender, height and weight; current medications, hypertension, diabetes, smoking, hypercholesterolemia, family and subjects' history of CAD. Blood samples for laboratory measures were obtained after an overnight fast just prior to the MRI scan. Blood pressures were taken with the subject supine, after lying quietly for 5 minutes, in both arms, and repeated if they were not equal. Furthermore CRP levels at baseline were available in 26 subjects.

MRI Protocol

All MRI scans were performed at the University of Washington using a 1.5-T GE Signa Scanner (Horizon EchoSpeed, version 5.8, General Electric Healthcare, Milwaukee, USA) with phased-array surface coils (Pathway Medical Technologies Inc, Redmond, WA). A standardized protocol(7) was used to obtain cross-sectional images of the carotid arteries with four different contrast weightings: T1-weighted (T1W), proton-density weighted (PDW), T2-weighted (T2W), and three-dimensional time-of-flight angiography (3DTOF). All images were obtained with field-of-view of 13-16 cm, matrix size of 256, slice thickness of 2 mm, no inter-slice gap, best in plane pixel size $0.5 \times 0.5 \text{ mm}^2$, and two signal averages. Scan coverage was 2.4 cm for T1WI, 3.2 cm for TOF and 2.4-3.2 cm for PD- and T2WI. The scan was centered on the common carotid artery bifurcation to insure similar coverage of the common and internal carotid arteries, and to insure alignment and consistent coverage between scans. The level of the carotid bifurcation differs in most individuals, and given the limitations of longitudinal coverage (2.4 cm), consistent coverage could not be assured on the contralateral, non-index side. Therefore, analysis was limited to only the index carotid artery. Fat suppression was used for the black blood images (T1W, PDW, and T2W) to reduce signal from subcutaneous fat.

MRI Image Review and Criteria

Five experienced reviewers (N.T.; T.S.; B.C.; H.U.; J.C.) who were blinded to subject, time point, and clinical information analyzed the images. Image quality was rated per artery for each contrast weighting on a 5-point scale (1=poor, 5=excellent) dependent on the overall signal-to-noise ratio and clarity of the vessel wall boundaries(8). Images with an image quality ≤ 2 were excluded from the study. The serial scans of each subject's index carotid artery were reviewed simultaneously. To assist in registration between the serial scans, the common carotid artery bifurcation of the index side was used as an internal fiducial marker. The bifurcation level was assigned to the cross-sectional image just proximal (caudal) to the flow divider between the internal and external carotid arteries. In order to insure a similar coverage of the carotid artery for quantitative measurements, only image locations that could be matched across the two time points were reviewed.

Area measurements of the lumen and total vessel area of the index carotid artery were obtained using QVAS, a custom-designed image analysis tool(9,10). The total vessel area included lumen, intima, media and adventitia. Wall area was calculated as the difference between total vessel area and lumen area. The normalized wall index (NWI) was calculated by dividing the wall area by the total vessel area.

Grouping of Subjects

To evaluate the effect of treatment with HMG-coA reductase inhibitors ("statins"), subjects were grouped into a statin-treated group and a non-statin-treated group and depending on statin dosage into low, intermediate and high (see Table 1).

To compare subjects with less and more advanced carotid atherosclerosis, subjects were grouped according to the NWI, classified as $\leq$ or >0.64 . To accommodate for regression of the mean we used the mean of the NWI at baseline and at 18 months. The NWI normalizes the wall area to the total vessel area, and provides a measure of lesion burden that takes into account inherent differences in wall area amongst vessels of differing diameter (common carotid artery, carotid bulb, and internal carotid artery). A higher value for NWI is indicative of an artery with more atherosclerotic plaque burden (see figure 1). We used 0.64 as the cut-off point because half of the subjects had a NWI ≤ 0.64 (n=34) and the other half had a NWI >0.64 (n=34).

Statistical Analysis

The summary statistics for the data are presented as mean $\pm$ SD. The statistics are presented as (i.) means: mean area of the whole artery (sum of all areas divided by the number of slices in an artery, summarized across all subjects) and (ii.) minima and maxima: minimum or maximum area across all locations from each artery, summarized across all subjects. All changes (both absolute and percentages) are presented as annualized rates. The one-sample t-test was used for the comparison of annual change to zero. The unpaired t test with equal or unequal variances –as appropriate– was used to compare the statin therapy group to the group without statin therapy. We used the Pearson's Correlation Coefficient to describe the association between absolute annual change of pairs of different artery measures and between artery measures and CRP levels in the subset of subjects with CRP levels at baseline (n=26). Multiple linear regression analysis was used to correlate progression with all clinical factors evaluated. The statistical significance of the relationship of percentage rates of change of the artery measures to NWI (dichotomous as $\leq$ or >0.64) was analyzed using linear regression. To avoid an induced (spurious) correlation between change rates in artery measures and NWI we used the mean of the NWI at baseline and at 18 months. Statistical significance was based on the p-value of the coefficient of the dichotomous NWI variable. To evaluate the intra- and inter-reader reproducibility the measurement errors for lumen, wall and outer wall areas were calculated as $100\% \cdot \sqrt{[\text{within-patient variance}] / \text{Mean (all measurements)}}$. The Intraclass correlation coefficient (ICC) was calculated to determine the level of intra-reader and inter-reader agreement between two measurements repeated within subjects in comparison to the variation in the measurements across subjects. An ICC close to 1.0 indicates that the CV is small relative to the range of values encountered. All calculations were made using SPSS 12.0 for Windows. Statistical significance was defined as a value of $P < 0.05$.

Experimental Results

MRI Scans and Image Quality

Scans of 6 out of 74 subjects were excluded due to an image quality of ≤ 2 . All data in this manuscript is based on the remaining 68 subjects with an image quality ≥ 3 . Mean time between the two MRI scans was 18.0 ± 1.3 months with a range of 16 to 26 months. Overall 1066 MR imaging locations were included in the analysis, resulting in an average matched coverage of 1.6 ± 0.3 cm.

Demographics and Risk Factors

Table 1 provides demographic information, including the risk factor profile and the lipid profile of the study population. Of note, 87% of the subjects were either smokers or former smokers. 69% of the subjects were on statin therapy, and the majority (86%) of the statin-treated group was prescribed simvastatin.

Annualized Progression Rate

Table 2 demonstrates the annual progression rate of carotid atherosclerosis in this study population. Overall, substantial progression was detected at 18 months, with mean wall area increasing by 2.2% per year ($P=0.001$) and mean NWI by 1.7% per year ($P<0.001$), and mean lumen area decreasing by -1.9% per year ($P=0.02$). However, the mean total vessel area did not change significantly (0.5% per year; $P=0.3$). Analysis of the minima and maxima results (slice-level analysis) demonstrated significant increases in maximum wall area (3.2% per year; $P=0.001$) and maximum NWI (1.9% per year; $P<0.001$), and decrease in minimum lumen area (-4.3% per year; $P=0.03$).

Substantial progression (figure 2a) and regression (figure 2b) was observed in individual subjects over a period of 18 months: changes in mean lumen area ranged from -25.6 to 13.3% per year and changes in mean wall area ranged from -7.9 to 14.6% per year.

Factors Associated with Plaque Progression Rate

Multiple regression analysis demonstrated that two factors were significantly associated with the rate of progression in mean wall area: statin therapy ($P=0.01$) and the NWI, classified as $>$ or ≤ 0.64 ($P=0.001$). Subjects on statin therapy ($n=47$) showed a slower increase in wall area compared to those not on statin therapy ($n=21$) (1.2% vs. 4.4% per year; $P=0.02$; table 3; figure 3). Conversely, subjects with a NWI ≤ 0.64 ($n=34$) had more rapid increase in mean wall area compared to those with a NWI >0.64 ($n=34$) (4.2% vs. 0.1% per year; $P=0.001$; table 4). A history of CAD, hypertension, hypercholesterolemia, smoking history, and family history of CAD were not significantly associated with changes in mean wall area.

Subjects who were not on statin therapy also exhibited greater luminal progression - expressed as reduction in mean lumen area - compared to subjects who were on statin therapy (-4.9% vs. -0.6% per year; $P=0.01$, Table 3; figure 3). The 4.9% per year decrease in mean lumen area amongst subjects who were not on statin therapy was significantly different from zero (no mean change, $P=0.006$). No significant differences were found for mean lumen and wall area progression for subjects on low, intermediate or high-dose statin therapy.

In the subgroup of subjects with CRP levels at baseline ($n=26$), a significant correlation was found for CRP levels and change in maximum wall area ($r=0.4$; $p=0.043$) and a correlation close to significance of mean wall area change and CRP levels at baseline ($r=0.37$; $p=0.065$). No other significant correlations were found between CRP levels and other measures of artery wall morphology.

When the lipid profiles were compared between subjects with and without statin therapy, no statistically significant differences were found for LDL cholesterol (77.8 vs. 87.2 mg/dl; $P=0.2$) or triglycerides (159.6 vs. 145.4 mg/dl; $P=0.6$). A trend was seen towards lower total cholesterol (170.5 vs. 188.3 mg/dl; $P=0.047$) and lower HDL cholesterol (39.2 vs. 45.7 mg/dl; $P=0.054$) in the subjects with lipid-lowering therapy. No significant association was found between progression rate and lipid levels at baseline.

Remodeling

The correlation between the mean wall area change and the mean lumen area change was close to zero (Pearson's $R=-0.09$; $P=0.5$). Despite the more rapid increase in mean wall area in subjects with a NWI ≤ 0.64 ($n=34$) compared to those with a NWI >0.64 , the rate of decrease in mean lumen area was identical in both groups (-1.9% per year; $P=1.0$, table 4). This might be due to the finding that subjects with a NWI ≤ 0.64 showed an increase of mean total vessel area compared to a slight decrease in subjects with a NWI >0.6 (1.4% vs. -0.5% ; $p=0.03$).

Figure 4a shows differences in remodeling in subjects grouped into tertiles according to their NWI. Subjects in the tertile with the lowest NWI had the largest % increase in mean wall area but demonstrate the smallest % lumen loss compared to the other tertiles. This can be explained by expansion of the total vessel area in subjects in the lowest tertile compared to no substantial change in total vessel area in other tertiles. These effects are mostly driven by subjects without statin therapy (figure 4b); no significant differences in remodeling pattern were found for subjects with statin therapy (data not shown).

Intra- and Inter-Reader Reproducibility

Ten randomly selected patients were re-evaluated 12 months after the initial review by two reviewers. ICC's for the intra-reader reproducibility were high for mean NWI (ICC=0.98; 95% CI=0.98-1.00), mean lumen area (ICC=0.99; 95% CI=0.98-1.00), mean wall area (ICC=0.97; 95% CI=0.89-0.99), and mean total vessel area (ICC=0.96; 95% CI=0.87-0.99). The intra-reader reproducibility study yielded measurement errors for NWI, mean lumen, wall and total vessel areas of 1.3%, 2.4%, 5.5% and 3.9%, respectively.

ICC's for the inter-reader reproducibility were high for mean NWI (ICC=0.99; 95% CI=0.98-1.00), lumen area (ICC=0.98; 95% CI=0.92-1.00), mean wall area (ICC=0.97; 95% CI=0.89-0.99) and mean total vessel area (ICC=0.99; 95% CI=0.94-1.00). The inter-reader reproducibility study yielded measurement errors for NWI, mean lumen, wall and total vessel areas of 3.6, 6.7%, 6.7% and 4.6%, respectively.

Discussion

This prospective study demonstrates the capabilities of *in vivo* MRI to quantify changes in atherosclerotic carotid artery wall morphology, and identifies potential factors that may influence the progression rate in plaque burden. Averaged across the 68 subjects in this study, the mean wall area increased by 2.2% per year (P=0.001) and the mean lumen area decreased by 1.9% per year (P=0.02). Measurements of the location with the most severe disease, such as the maximum wall and minimum lumen areas, showed even larger changes (3.2% and -4.3% per year, respectively), indicating that atherosclerotic disease progression and remodeling is focally enhanced. Two factors were significantly associated with decreased wall progression rate: statin therapy (P=0.01) and larger lesions, as defined by a NWI >0.64 (P=0.001). The rate of progression for mean wall area and for NWI was approximately four-times greater amongst the subjects who were not treated with statins, compared to the statin-treated group (4.4 vs. 1.2% per year, and 3.6 vs. 0.8% per year, respectively; figure 3).

Previous studies that use MRI have detected changes of atherosclerotic lumen and wall dimensions in subjects treated with lipid-lowering therapy. Corti et al(11) observed an 18% reduction in carotid wall area (15% reduction in aortic wall area) and a 5% increase in carotid lumen area (6% increase in aortic lumen area) in 51 subjects after two years of treatment with either 20 or 80 mg simvastatin. No significant difference in vessel wall changes was seen between the 20 and 80mg doses of simvastatin. Yonemura et al(12) reported significant regression of thoracic aortic plaques (-18%), and slight progression in abdominal plaques (+3%) in 19 subjects treated with 20 mg atorvastatin for one year. In a study conducted with intravascular ultrasound by Nissen et al(13), subjects treated with 40 mg of pravastatin showed significant progression in coronary arteries after 18 months of treatment (median increase in atheroma volume = +2.7%, mean = +5.4%), whereas subjects treated with 80 mg of atorvastatin demonstrated less progression (median = -0.4%, mean = +4.1%). Luminal changes were not reported(13).

Similar to the findings by Nissen et al(13) this study did not show significant regression in the subjects treated with statin therapy, though statin therapy was associated with absence of

progression in luminal narrowing and slowed progression in mean wall area, compared to those who were not on statins (table 3;figure 3). The subjects in this study were not statin-naïve and received different dosages and types of statins, which might explain the lack of plaque regression. Furthermore, based on the selection criteria of previously reported carotid MRI studies(14,15), subjects included in those trials most likely had less advanced disease than the subjects included in our study. While this study failed to show significant regression when the subjects were taken as a group, individual subjects did show regression (figure 2a), with mean lumen area increases of up to 19% and mean wall area decreases of up to 12% within 18 months. This study did not show any significant differences in mean lumen and wall areas, which might be explained by the small number of subjects on intermediate (n=12) and high dose statin therapy (n=2).

Findings from our study suggest that the rate of wall progression is affected by the disease severity, expressed as NWI. Subjects with a NWI ≤ 0.64 had more rapid increase in wall area compared to subjects with a NWI > 0.64 (4.2% vs. 0.1% per year; $P=0.001$). After adjustment of conventional risk factors for atherosclerosis and statin therapy, this finding remained significant ($P=0.001$).

Most of the concepts of arterial remodeling are based on histological studies (one time point data) of coronary arteries(2,16,17). Therefore, little is known about the change of arterial wall dimensions in the carotid artery over time. In this study, changes of the lumen area did not show any correlation with the changes of the wall area ($R = -0.09$; $P=0.5$). These findings support the theory(18,19) that luminal information alone provides an incomplete picture of the atherosclerotic disease process and that measuring change in luminal stenosis grossly underestimates progression or regression in overall plaque burden.

This study also found differences in remodeling patterns between subjects with earlier stages of disease as indicated by a lower NWI, as shown in Figure 4a. When grouped into tertiles of NWI, arteries with lowest NWI values (< 0.58) demonstrated the largest rate of increase in mean wall area but the smallest rate in reduction of lumen area. The figure demonstrates that this is possible because of overall increase in total vessel area (expansive remodeling). In the most advanced lesions, as defined by an NWI > 0.69 , no further change in total vessel area is observed, but lumen area reduction is greatest in this group. These findings are consistent with Glagov's hypothesis that expansive remodeling permits plaque burden increase without luminal encroachment early in the development of atherosclerosis, but that in later stages, expansive remodeling ceases, and further progression results in luminal narrowing(2). These effects can be mainly observed in subjects without statin therapy (figure 4b) which suggests that statin therapy alters arterial remodeling patterns.

Furthermore, findings from this study in the subgroup of patients with CRP levels at baseline showed that higher CRP levels were associated with a larger increase in maximum wall area. This gives further evidence that CRP levels are associated with progression of carotid atherosclerotic disease.

Limitations

All subjects in this study had advanced carotid atherosclerotic disease with $> 50\%$ stenosis by duplex ultrasound. It has yet to be determined whether a study of subjects with less advanced disease would reveal similar results. Furthermore, as this was an observational study, where the study participant's treatment plan was directed by their primary care provider, subjects were prescribed a variety types of statin drugs, and dosages were not standardized. Therefore, although significant associations between progression rates and treatment were demonstrated, a direct causal relationship between statin therapy and plaque regression cannot be established with our study.

In addition the lack of association between progression rates and history of CAD might be explained by the more frequent use of statins in subjects with history of CAD.

Furthermore, CRP levels were only available in a subset of subjects and larger studies are necessary to confirm these preliminary results.

Finally, only MRI exams of at least average image quality (Image quality ≥ 3) were considered for review, resulting in the exclusion of six patients from analysis. In the future, improvements in pulse sequence design and in hardware (e.g. higher field MRI, coil design) should decrease the number of exclusions.

Conclusions

This study demonstrates the utility of noninvasive MRI for prospectively quantifying changes in carotid atherosclerotic plaque morphology. Among the risk factors for plaque progression investigated, use of statin therapy and more advanced lesions, as defined by a NWI greater than 0.64, were associated with a significantly lower rate of atherosclerotic wall progression in subjects with initially asymptomatic, $>50\%$ carotid stenosis. Furthermore, the lack of correlation between the change in lumen and wall areas confirms that measurement of lumen stenosis provides an incomplete picture of atherosclerosis progression and regression in subjects with 50-79% carotid stenosis. Finally, findings from this study provide confirmatory evidence of the expansive remodeling, specifically amongst arteries earlier in the stage of atherosclerosis development.

Acknowledgement

The authors wish to acknowledge Andrew An Ho for his help in preparing the manuscript.

Source of support: National Institutes of Health R01 HL61851 and R01 HL073401

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Figure 1.

T1-weighted images from subjects with normalized wall indexes (NWI) ranging from 0.43-0.79. Arrows point to the lesion and asterisks indicate the lumen. Subject with NWI=0.43 (top row) has a small eccentric lesion with a lumen area near to normal. Subject with NWI=0.60 has a substantially thickened wall with some luminal narrowing and the subject with NWI=0.79 has a very large lesion and severe luminal narrowing in the internal carotid artery.

Figure 2.

a.) MR images from a 73 year old subject who did not receive lipid-lowering therapy. The lumen area (asterisks) decreased by 14% and the wall area increased (arrow) by 19%, indicating significant progression over 18 months.

b.) MRI images of a 46 year old subject who received 5mg simvastatin. The lumen area (asterisks) increased by 18% and the wall area (arrow) decreased by 12%, indicating significant regression over 18 months.

Figure 3.

This graph demonstrates the annual change of mean lumen area versus mean wall area for subjects with (green dots) and without (red dots) lipid-lowering therapy.

*p=0.03 vs. Tertile with NWI ≥ 0.69

†p=0.06 vs. Tertile with NWI ≥ 0.69

NWI=Normalized Wall Index

*p<0.01 vs. Tertile with NWI ≥ 0.69

†p<0.05 vs. Tertile with NWI=0.59-0.68

NWI=Normalized Wall Index

Figure 4.

a.) Changes in lumen, wall and total vessel area in patients grouped into tertiles based on their normalized wall index (NWI). Although subjects in the lowest NWI tertile show a larger % increase in wall area compared to subjects in the tertiles with the medium and highest NWI, they show less lumen decrease and an increase in total vessel area which is suggestive of expansive remodeling. b.) This graph shows the changes in lumen, wall and total vessel wall area for the 21 subjects without statin therapy. The data suggests that expansive remodeling in patients in the lowest NWI tertile prevents a larger lumen decrease. No significant differences were found when subjects without statin therapy were grouped into tertiles based on their NWI (Data not shown).

Table 1**Baseline Clinical Data (68 Subjects)**

Demographics and Risk Factors	Mean $\pm$ SD or %	Range or Dosage (if applicable)
Age, (years)	70.3 $\pm$ 8.9	48-88
Male sex, (%)	93%	
Height (m)	1.74 $\pm$ 0.07	1.58-1.90
Weight (kg)	81.8 $\pm$ 15.2	49-127
Body mass index, kg/m ²	26.8 $\pm$ 3.7	18.9-35.3
Hypertension, (%)	82%	
Diabetes, (%)	25%	
Smoking Status		
active, (%)	40%	
quit, (%)	47%	
never smoked, (%)	13%	
History of CAD, (%)	47%	
Hypercholesterolemia, (%)	84%	
Family History of CAD, (%)	57%	
Statins, (%)	69%	
Statins (Type)		
Simvastatin	86%	5-80 mg
Atorvastatin	6%	10-20 mg
Cerivastatin	4%	0.4 mg
Fluvastatin	2%	40 mg
Lovastatin	2%	40 mg
Statins (Dosage)		
None	31%	
Low	48%	
Intermediate	18%	
High	3%	
Total Cholesterol, (mg/dl)	176.0 $\pm$ 34.1	107-253
LDL Cholesterol, (mg/dl)	80.6 $\pm$ 26.0	30-146
HDL Cholesterol, (mg/dl)	41.2 $\pm$ 11.1	25-72
Triglycerides, (mg/dl)	155.2 $\pm$ 90.5	40-496
Blood Pressure (mm hg)		
Systolic / Diastolic right	145.8 $\pm$ 21.8 / 73.6 $\pm$ 15.2	
Systolic / Diastolic left	145.6 $\pm$ 23.5 / 72.0 $\pm$ 10.8	

CAD=coronary artery disease; Low Dose=Simvastatin 5-20 mg, Atorvastatin 10 mg; Intermediate Dose=Simvastatin 40 mg, Atorvastatin 20 mg, Cerivastatin 0.4 mg; High Dose = Simvastatin 80 mg

Table 2

Progression Rate per Year (68 Subjects)

	Baseline ± 1 SD	Δ/year absolute ± 1 SD	Δ/year in % ± 1SD	p- value *
<i>Means (Data based on all matched locations)</i>				
Lumen [mm ²]	32.4±12.7	-0.6±2.2	-1.9±6.7	0.02
Wall [mm ²]	52.3±15.4	1.0±2.9	2.2±5.2	0.001
Total Vessel [mm ²]	84.7±23.4	0.4±3.5	0.5±3.6	0.3
Normalized Wall Index	0.63±0.09	0.01±0.02	1.7±3.3	<.001
<i>Minima or Maxima (Data based on 1 location per artery)</i>				
Min. Lumen [mm ²]	17.0±10.6	-0.5±1.9	-4.3±16.2	0.03
Max. Wall [mm ²]	71.0±19.7	2.0±5.8	3.2±7.9	0.001
Max. Total Vessel [mm ²]	115.9±32.7	0.7±6.8	0.9±7.4	0.3
Max. Normalized Wall Index	0.75±0.11	0.01±0.03	1.9±4.0	<.001

* One sample t-test vs. 0 for percentage change/year;

Comparison of Subjects with and without Statin Therapy (Percent Change of Areas per Year)

Table 3				
	Statins (S ⁺ ; n=47)	No Statins (S ⁻ ; n=21)	P [*] (S ⁺ vs. S ⁻)	P [†] (S ⁺ vs. 0)
<i>Means (Data based on all matched locations)</i>				
Lumen Area	-0.6±6.1	-4.9±7.3	0.01	0.006
Wall Area	1.2±4.7	4.4±5.8	0.02	0.002
Total Vessel Area	0.3±3.7	0.9±3.4	0.5	0.2
Normalized Wall Index	0.8±2.9	3.6±3.5	0.001	<.001

Values are mean ± 1 SD; S⁺=Subjects with statin therapy; S⁻=Subjects without statin therapy

* Unpaired t-test (equal variances assumed)

† One-Sample t-test vs. 0

Table 4Comparison of Subjects with Normalized Wall Index $>$ and ≤ 0.64 (Percent Change of Areas per Year)

	NWI >0.64 (n=34)	NWI ≤ 0.64 (n=34)	P^* (>0.64 vs. ≤ 0.64)
<i>Means (Data based on all matched locations)</i>			
Lumen Area	-1.9 $\pm$ 8.0	-1.9 $\pm$ 5.3	1.0
Wall Area	0.1 $\pm$ 3.5	4.2 $\pm$ 5.8	0.001
Total Vessel Area	-0.5 $\pm$ 3.1	1.4 $\pm$ 3.8	0.03
Normalized Wall Index	0.8 $\pm$ 2.9	2.6 $\pm$ 3.5	0.02

Values are mean $\pm$ 1 SD; NWI=Wall area divided by total vessel area

* Linear Regression, see methods