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IVUS-Based FSI Models for Human Coronary Plaque Progression Study: Components, Correlation and Predictive Analysis

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Abstract

Atherosclerotic plaque progression is believed to be associated with mechanical stress conditions. Patient follow-up in vivo intravascular ultrasound coronary plaque data were acquired to construct fluid-structure interaction (FSI) models with cyclic bending to obtain flow wall shear stress (WSS), plaque wall stress (PWS) and strain (PWSn) data and investigate correlations between plaque progression measured by wall thickness increase (WTI), cap thickness increase (CTI), lipid depth increase (LDI) and risk factors including wall thickness (WT), WSS, PWS, and PWSn. Quarter average values (n=178–1016) of morphological and mechanical factors from all slices were obtained for analysis. A predictive method was introduced to assess prediction accuracy of risk factors and identify the optimal predictor(s) for plaque progression. A combination of wall thickness and plaque wall stress was identified as the best predictor for plaque progression measured by WTI. Plaque wall thickness had best overall correlation with WTI ($r=-0.7363$, $p<1e-10$), cap thickness ($r=0.4541$, $p<1e-10$), CTI ($r=-0.4217$, $p<1e-8$), LD ($r=0.4160$, $p<1e-10$), and LDI ($r=-0.4491$, $p<1e-10$), followed by plaque wall stress (with WTI: ($r=-0.3208$, $p<1e-10$); cap thickness: ($r=0.4541$, $p<1e-10$); CTI: ($r=-0.1719$, $p=0.0190$); LD: ($r=-0.2206$, $p<1e-10$); LDI: $r=0.1775$, $p<0.0001$). Wall shear stress had mixed correlation results.

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Conflict of Interest

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Keywords

Coronary; fluid-structure interaction; plaque rupture; plaque progression; IVUS

1. Introduction

Atherosclerotic plaque progression and rupture are believed to be associated with morphological factors, components, material properties, and mechanical stress conditions.^{1,4-7,11,13,15,17-19,21-22} However, mechanisms governing plaque progression and rupture are not well understood.^{5,22} Considerable advances in medical imaging technology and image-based plaque models have been made in recent years to identify vulnerable atherosclerotic plaques in vivo with information about plaque components including lipid-rich necrotic core (called necrotic core for simplicity), plaque cap, calcification, intraplaque hemorrhage, loose matrix, thrombosis, and ulcers, subject to resolution limitations of current technology.^{1,6,14-15,23,26,34} In vivo image-based coronary plaque modeling papers are relatively rare because clinical recognition of vulnerable coronary plaques has remained challenging.^{19,21,33} In a multi-patient IVUS-based follow-up study (n=20), by dividing slices into low, intermediate, and high wall shear stress (WSS) groups and comparing the low and high WSS groups with the intermediate-WSS group, Samady et al. found that low-WSS segments demonstrated greater reduction in vessel (P<0.001) and lumen area (P<0.001), and high-WSS segments demonstrated an increase in vessel (P<0.001) and lumen (P<0.001) area.¹⁹ In a follow-up study of 506 patients with acute coronary syndrome (ACS) treated with a percutaneous coronary intervention and in a subset of 374 consecutive patients 6–10 months later to assess plaque natural history, Stone et al. (2012) reported that increase in plaque area was predicted by baseline large plaque burden; decrease in lumen area was independently predicted by baseline large plaque burden and low wall shear stress.²¹ From the PROSPECT patient follow-up study (660 patients with complete IVUS data), Xie et al.³⁰ reported that although the minimum lumen area (MLA) was similar, the plaque burden was significantly greater in nonculprit lesions with a plaque rupture compared with nonculprit lesions without a plaque rupture (66.0% [95% confidence interval: 64.5% to 67.4%] vs. 56.0% [95% confidence interval: 55.6% to 56.4%]; p < 0.0001). IVUS-VH analysis revealed that a nonculprit lesion with a plaque rupture was more often classified as a fibroatheroma than a nonculprit lesion without a plaque rupture (77.1% vs. 51.4%; p < 0.0001). Secondary, nonculprit plaque ruptures were seen in 14% of patients with acute coronary syndrome (ACS) and were associated with a fibroatheroma phenotype with a residual necrotic core. Xu et al.³¹ used a morphology-based carotid atherosclerosis score (CAS) as a measure to predict high-risk plaque development and plaque progression. One hundred and twenty patients with 50% to 79% carotid stenosis underwent carotid magnetic resonance imaging scans at baseline and 3 years thereafter. CAS was found to have a significant increasing relationship with incident disrupted luminal surface (DLS) and plaque progression in this prospective study. We have published results based on follow-up studies showing that advanced carotid plaque progression had positive correlation with wall shear stress (WSS) and negative correlation with plaque wall stress (PWS) at follow-up.³² In a research design paper, Fernandez-Ortiz et al.² described The Progression and Early detection of Subclinical Atherosclerosis (PESA) study which is an observational, longitudinal and prospective cohort

study in a target population of 4000 to collect data and identify new imaging and biological factors associated with the presence and progression of atherosclerosis in asymptomatic people and will help to establish a more personalized management of medical care. Fleg et al. gave an authoritative review of findings from several large clinical studies for detection of high-risk atherosclerotic plaques, available techniques, findings from patient follow-up studies, and future recommendations.⁴

In this paper, intravascular ultrasound (IVUS) patient follow-up data were acquired and IVUS-based models with fluid-structure interactions (FSI) and cyclic bending were constructed to obtain plaque morphological features, wall shear stress and plaque stress/strain data and identify their possible associations with plaque progression, cap thickness and lipid-rich necrotic core changes. A predictive method is introduced to investigate if those parameters could be used to predict plaque progression. Their quantitative prediction accuracy will also be calculated. The correlation knowledge and prediction accuracy of the risk factors may be helpful for better diagnosis and prevention of atherosclerosis-related cardiovascular diseases.

2. Methods

2.1. IVUS Data Acquisition

Patient follow-up IVUS data of coronary plaques were acquired from 3 patients (3M, age: 52/71/68) at Cardiovascular Research Foundation (New York, NY) after informed consent was obtained. Vessel and multi-components detection was performed to obtain IVUS-VH (Virtual Histology) data using automated Virtual Histology software (version 3.1) on a Volcano s5 Imaging System (Volcano Corp., Rancho Cordova, CA). The frames from IVUS-VH data at the baseline (T1) and follow-up (T2) were processed to obtain contours for vessel lumen, out-boundary and plaque components for model construction using established procedures described in Yang et al. (2009).³³ The X-ray angiogram (Allura Xper FD10 System, Philips, Bothel, WA) was obtained at both baseline scan (T1) and follow-up scan (T2) prior to the pullback of the IVUS catheter to determine the location of the coronary artery stenosis, vessel curvature and cyclic bending caused by heart contraction. Fusion of angiography and IVUS slices was done using method similar to that described in Wahle et al.²⁸ except that we did not have biplane angiography. The view angle of the angiography was chosen so that the angiography plane was close to the principal tangent plane of the chosen coronary segment. Co-registration (both longitudinal and circumferential) of baseline and follow-up IVUS data were performed by IVUS expert using angiography movie, location of the myocardium, vessel bifurcation, stenosis and plaque component features. The location of the myocardium was used in circumferential co-registration. Figure 1 presents matched selected IVUS-VH slices from one patient at T1 and T2, the corresponding segmented contours, enlarged view of one slice, and the reconstructed 3D geometry of the plaque at T1. The X-ray angiogram and vessel bending curves with maximum and minimum curvature were shown by Figure 2.

2.2. The FSI model with cyclic bending and boundary conditions

There are several features that are worth mentioning for the models we are constructing for coronary plaques. First, arteries are subjected to dynamic pressure loading. Fluid-structure interaction should be included to study the impact of both wall shear stress and structural stress/strain on the biological processes under investigation.²⁵ Secondly, for models based on in vivo image data, a shrink-stretch process should be used to obtain no-load vessel geometry as the starting geometry for model construction.¹⁰ Thirdly, coronary arteries are subjected to cyclic bending caused by cardiac contraction/expansion. This has to be included in coronary models for accurate computational predictions.³³

In our FSI model with cyclic bending, blood flow was assumed to be laminar, Newtonian, and incompressible. The Navier-Stokes equations with arbitrary Lagrangian-Eulerian formulation were used as the governing equations. Pulsating pressure conditions were specified at the inlet and outlet using patient's systole and diastole arm pressure conditions. Catheter measurements of intravascular pressure condition was not available for these patients. Cyclic bending was specified by prescribing periodic displacement at the myocardium side of the vessel using data obtained from X-Ray angiography. The vessel material was assumed to be hyperelastic, anisotropic, nearly-incompressible and homogeneous. Plaque components were assumed to be hyperelastic, isotropic, nearly-incompressible and homogeneous for simplicity. No-slip conditions and natural traction equilibrium conditions were assumed at all interfaces. Our complete FSI model can be found from Yang et al. and are omitted here.³³

Biaxial testing was performed using eight coronary arteries from 4 cadavers (age: 50–81) to obtain realistic vessel material data for our model.¹² A modified Mooney-Rivlin model was used for the vessel fitting our biaxial data:^{12,33}

$$W = c_1(I_1 - 3) + c_2(I_2 - 3) + D_1[\exp(D_2(I_1 - 3)) - 1] + K_1/2K_2\{\exp[K_2(I_4 - 1)^2] - 1\}. \quad (1)$$

$$I_1 = \sum C_{ii}, \quad I_2 = \frac{1}{2} [I_1^2 - C_{ij}C_{ij}], \quad (2)$$

where I_1 and I_2 are the first and second invariants of right Cauchy-Green deformation tensor $\mathbf{C}$ defined as $\mathbf{C} = [\mathbf{C}_{ij}] = \mathbf{X}^T \mathbf{X}$, $\mathbf{X} = [\mathbf{X}_{ij}] = [x_i/a_j]$, (x_i) is current position, (a_i) is original position, $I_4 = C_{ij}(\mathbf{n}_c)_i(\mathbf{n}_c)_j$, $\mathbf{n}_c$ is the unit vector in the circumferential direction of the vessel, c_1 , D_1 , D_2 , and K_1 and K_2 are material constants. The parameter values used in this paper were: $c_1 = -1312.9$ kPa, $c_2 = 114.7$ kPa, $D_1 = 629.7$ kPa, $D_2 = 2.0$, $K_1 = 35.9$ kPa, $K_2 = 23.5$. Our measurements are also consistent with data available in the literature.^{8–9,22}

2.3. 3D Reconstruction of plaque geometry and mesh generation

The most time-consuming part in model construction is 3D mesh generation. All the segmented contour data were put into ADINA to reconstruct the 3D vessel geometry with finite element mesh using the procedures described in Yang et al.³³ Due to irregular geometries of the multi-component plaque, a component-fitting mesh generation technique

was developed to generate mesh for each plaque model. When a vessel has a component, the mesh has to be built around it. Using the component-fitting technique, the 3D vessel domain was divided into hundreds of small “volumes” to fit the irregular vessel geometry with plaque components inclusions. The element type used for structural models (vessel and plaque components) was 3D solid 8-node element while the element type used for the fluid model was 3D 4-node element, free formed mesh.

3D coronary plaque FSI models for the 3 patients (F1, F2, F3) at each scan were constructed and solved by ADINA (Adina R&D, Watertown, MA) to calculate flow and stress/strain distributions, using unstructured finite element methods for both fluid and solid model. Mesh analysis was performed by decreasing mesh size by 10% (in each dimension) until solution differences (measured by L_2 norms of solution differences of all mechanical factors, including stress, strain, displacements, flow velocity, and pressure) were less than 2%. Simulation for each plaque was run for 3 periods and the third period was almost identical to the second period and was then taken as the solution. More details of the computational models and solution methods can be found in Tang et al.²²

2.4. Plaque progression measurements and data extraction for statistical analysis

For each patient, IVUS slices at baseline (Time 1, T1) and follow-up (Time 2, T2) were matched up using vessel bifurcation, stenosis features and with careful review by the IVUS group. For simplicity, the vessel segment assembled using the selected slices is called the plaque. Each IVUS slice was divided into 4 quarters with each quarter containing 25 evenly-spaced nodal points taken on the lumen, each lumen nodal point was connected to a corresponding point on vessel out-boundary. Figure 3 shows the quarters with the connecting lines. The length of the connecting line at a point is defined as the wall thickness at the nodal point. If the line passes a necrotic core or calcification block, the distance between the lumen point and the first time the line meets the necrotic core or calcification is defined as cap thickness. The length of the line segment within the necrotic core (or calcification) is defined as the necrotic core depth at that nodal point. Very little calcification was found in the cases studied. Therefore, calcification was ignored in this study. Vessel wall thickness (WT), lipid-rich necrotic core depth (LD), cap thickness (Cap), WSS, PWS and PWSn values from 3D FSI model solution at each point were recorded for both baseline and follow-up scan. Average values of these 6 parameters for each quarter were obtained from all slices for statistical analysis. Plaque progression was measured by the point-wise vessel wall thickness increase (WTI) from baseline to follow-up at the matched nodal points. Cap thickness increases and lipid-rich necrotic core depth increases (LDI) were obtained in the same way for analysis.

2.5. Statistical methods for correlation analysis

The Linear Mixed-Effects (LME) model¹⁶ was used to study the correlation between a selected outcome variable (i.e., plaque progression measured by WTI, cap thickness, cap thickness increase, lipid depth, lipid depth increase) and the predictors (WT, WSS, PWS and PWSn) using their quarter average values at both baseline and follow-up. Here the observation unit is quarter, and all feature values of quarters were obtained by averaging the

corresponding feature values of nodes within the quarters. In the following, WTI is used as the outcome variable and PWS is used as the predictor, for demonstration purpose.

For individual patients, the LME model was defined as

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + b_j + \varepsilon_{ij}, \quad (3)$$

where y_{ij} is the WTI value at the i th quarter on the j th slice, x_{ij} is the corresponding value of PWS. β_0 and β_1 are the fixed effects of PWS for the baseline and the changing rate of WTI, respectively. The WTI values y_{ij} at close spots are likely not independent; here we considered a sophisticated dependence structure among quarter observations. In particular, the random effect term b_j in (3) captures the clustering dependence among the quarters within each slice. Furthermore, an exponential isotropic variogram model is applied to account for the spatial dependence among quarters in the three-dimensional Euclidean space. This model is analogous to the autoregressive model for sequentially dependent observations.¹⁶ Specifically, the vector of random error terms (ε_{ij}) is assumed to follow a joint Gaussian distribution with mean 0, and the correlation between ε_{i1j1} and ε_{i2j2} is modeled by an exponential function φ^s , where s is the Euclidean distance between the 3-dimensional spatial locations of the two quarters (based on the average spatial location coordinates of the nodes in the quarters) on the vessel, φ is the correlation parameter to be estimated in the model fitting by the restricted maximum likelihood (REML) algorithm. In the statistical hypothesis test, the null hypothesis that no correlation exists between WTI and PWS (or other predictors) corresponds to $\beta_1 = 0$. A small p-value ($p < 0.05$) of the Student's t-test for the coefficient provides a strong statistical evidence to reject the null and accept the existence of correlation.

For the correlation analysis based on three patients together, the LME model is defined as

$$y_{ijk} = \beta_0 + \beta_1 x_{ijk} + b_{jk} + \varepsilon_{ijk}, \quad (4)$$

where y_{ijk} is the WTI value at the i th quarter on the j th slice of the k th patient, x_{ijk} is the corresponding value of PWS. β_0 and β_1 have the same meanings as those in equation (3). The random effects b_{jk} and b_k model a hierarchical clustering dependence - quarters are clustered within slices, which are further clustered within patients. The vector of error terms (ε_{ijk}) models the within-cluster spatial dependence of the observations. Specifically, the patients are assumed to be independent so the correlation between the error terms from different patients is 0. The correlation between ε_{i1j1k} and ε_{i2j2k} from the same k th patients is assumed an exponential function ϕ_k^s , where s is the Euclidean distance between the 3D spatial locations, ϕ_k is the patient-specific dependence parameter to be estimated in model fitting. To test the correlation between WTI and PWS, we again use the p-value for testing $\beta_1 = 0$. The LME model fitting was carried out with statistical software R by function `lme` in the R package `nlme` (fit and compare Gaussian linear and nonlinear mixed-effects models).¹⁶

To measure the direction and magnitude of the linear correlations between WTI and PWS, Pearson's correlation coefficient cannot be directly used because it assumes independent observations. Analogous to the Pearson's correlation coefficient, a dependence-adjusted correlation coefficient r is created to account for the spatial dependence structure among the quarter observations based on the above model (3).²⁴ Specifically, note that the Pearson's correlation coefficient between x and y can be written as:

$$\hat{c}or(x, y) = \hat{\beta} \sqrt{\frac{\hat{v}ar(x)}{\hat{v}ar(y)}}, \quad (4)$$

where $\hat{v}ar(x)$ and $\hat{v}ar(y)$ are the sample variances, and $\hat{\beta}$ is the estimated slope coefficient by fitting x to y with a simple regression that assumes independence among the observations. Now, following the same idea, the dependence-adjusted correlation coefficient r is given by

$$r = \hat{\beta}_1 \sqrt{\frac{\hat{v}ar(x)}{\hat{v}ar(y)}}, \quad (5)$$

where $\hat{\beta}_1$ is the estimated slope coefficient by fitting PWS to WTI with the LME model (3) for single patient analysis or (4) for multi-patient analysis. Because $\hat{\beta}_1$ is estimated in the models that have adjusted the clustering and spatial dependence structure among the observations, r is considered as the dependence-adjusted correlation coefficient. Note that because the null hypothesis of no correlation is equivalent to the null hypothesis that the true slope coefficient $\beta_1 = 0$, and because the term $\sqrt{\frac{\hat{v}ar(x)}{\hat{v}ar(y)}}$ converges in probability to a constant, to gauge the evidence for rejecting the null hypothesis of no correlation, the p-value p calculated based on the null distribution of $\hat{\beta}_1$ is equivalent to the p-value directly based on the null distribution of r .

2.6. Predictive Method

Generalized linear mixed models (GLMMs)^{16,20,27,29} were used to select best predictors by calculating and comparing their predictive sensitivity and specificity. Sensitivity of prediction is defined as the proportion of the true positive-outcomes that are predicted to be positive. Specificity of prediction is defined as the proportion of the true negative-outcomes that are predicted to be negative. Sensitivity and specificity have values from 0 to 1; higher combined values of these two measures indicate more accurate predictions. The best combination of predictors is the one whose model provides the highest sensitivity and specificity.

Our GLMMs extend generalized linear models for categorical responses (in our case, the binary outcomes of positive or negative WTI) to consider the dependence among observations. The model is defined as

$$y_{ijk} = E(y_{ijk} | b_{jk}, b_k) + \varepsilon_{ijk}, \quad (6)$$

$$\text{logit}(E(y_{ijk}|b_{jk}, b_k)) = \beta_0 + \beta_1 \text{Predictor1}_{ij} + \beta_2 \text{Predictor2}_{ij} + \dots + b_{jk} + b_k, \quad (7)$$

where $y_{ijk} = 1$ denotes the positive outcome $\text{WTI} > 0$ and $y_{ijk} = 0$ denotes the negative outcome $\text{WTI} < 0$ at the i^{th} quarter on the j^{th} slice of the k^{th} patient. The expectation of y_{ijk} is the probability of the positive outcome: $E(y_{ijk} | b_{jk}, b_k) = P(y_{ijk} = 1 | b_{jk}, b_k)$. The binomial

link function $\text{logit}(x) = \log\left(\frac{x}{1-x}\right)$. The fixed-effect term $\beta_1 \text{Predictor1}_{ij} + \beta_2 \text{Predictor2}_{ij} + \dots$ models the combined effects of the predictors. The random effects b_{jk} and b_k model the hierarchical clustering dependence and the error terms (ε_{ijk}) model the within-cluster spatial dependence of the observations, in the same way as the model (4). The GLMM model fitting (i.e., estimating the parameters in the model) was carried out with R function `glmmPQL` in package `MASS`.²⁷

The procedure for model fitting and predictor selection is described as follows. All quarter data from the three patients were combined together for analysis. A 5-fold cross-validation procedure was used to find the best predictor(s). Specifically, we randomly partition the quarters into five subgroups: four subgroups are used as training data to fit model, the remaining one is used as the testing data for evaluating the model. With the training set, the GLMMs are fitted using predictors' values at baseline (T1) to reach best agreement with outcomes from follow-up data (T2). In evaluating the model, we feed the testing data into the fitted model, obtain the predicted value of the response, and then deduce the sensitivity and specificity of the prediction. Specifically, the probability of positive outcome ($\text{WTI} > 0$) at each quarter was calculated by feeding the testing subgroup data into the fitted model. A positive outcome is predicted if the estimated probability of the positive outcome is higher than a threshold. The sensitivity and specificity of the model were thus obtained by comparing its predicted results with the true outcomes. We repeat this process five times (i.e., 5-fold) because each of the five subgroups is used once as the testing data. We exhaustively searched all 15 possible combinations among four candidate predictors WT, PWS, PWSn, and WSS. Sensitivity and specificity results (at the optimal thresholds that maximize sensitivity+specificity) of all combinations are given in Table 6.

3. Results

Figure 4 gives plots of PWS, PWSn, flow velocity and WSS from one plaque sample at T1 and T2 showing basic solution features from our FSI models. Using the morphological, tissue component and mechanical stress/strain data obtained from the FSI models, we investigated correlations between plaque progression measured by WTI, cap thickness (Cap), necrotic core depth (LD) and interested risk factors including WT, WSS, PWS and plaque wall strain (PWSn). We also attempted to find out which factors could better predict plaque progression. Correlation results concerning plaque burden increase (PBI) and plaque area increase (PAI) were also presented.

3.1 Correlations between plaque progression (WTI) and WT, WSS, PWS, and PWSn

Table 1 summarized the correlation results between WTI and four potential predictors: **WT, WSS, PWS, and PWSn**. Using the baseline (T1) values of the predictors, WT correlated

with WTI negatively (three patients together: $r=-0.7363$, $p<1e-10$; all three patients had significant correlations individually). WSS showed no correlation with WTI ($r=-0.0052$, $p=0.9250$). PWS showed positive correlation with WTI ($r=0.3000$, $p<1e-10$). PWSn also showed positive correlation with WTI ($r=0.2439$, $p<4e-8$), slightly weaker, compared to that of PWS.

Using follow-up (T2) data of the predictors, most of the correlations changed sign from T1. WT now correlates with WTI positively based on three patients together ($r=0.5692$, $p<1e-10$). Individually, we had 2 statistically significant positive correlations, and one statistically insignificant negative correlation. WSS showed positive correlations for all three individuals (overall: $r=0.3545$, $r<5e-10$). PWS now had overall negative correlation ($r = -0.3208$, $p<1e-10$). One patient had no significance correlation. Plaque strain again showed negative overall correlation ($r=-0.2500$, $p<2e-8$). Among the 4 predictors, wall thickness showed the strongest correlation, followed by plaque wall stress.

3.2. Correlation between plaque cap thickness (Cap) and WT, WSS, PWS, and PWSn

Table 2 shows that for the 6 plaques modeled, cap thickness showed positive correlation with WT ($r=0.4541$, $p<1e-10$), positive correlation with WSS ($r=0.5101$, $p<3e-8$), negative correlation with PWS ($r=-0.3359$, $p<1e-10$), and negative correlation with PWSn ($r=-0.1558$, $r=0.0019$). While WSS had the highest r value for the overall correlation, correlations from WT and PWS showed more consistent results from individual patients (all 6 positive for WT, and 4 negative for PWS). Negative correlation between PWS and cap thickness indicates that higher PWS values are likely linked to thinner cap thickness.

3.3. Correlation between plaque cap thickness increase (CTI) and WT, WSS, PWS, and PWSn

From our perspective, it is more important to know what to expect in the future. Correlations between cap thickness increase (CTI) and the 4 predictors are given in Table 3. After matching up the quarters with plaque caps, a total of 178 quarters were available for our analysis. Unfortunately, using the baseline data of the predictors, only WT showed significant correlation with CTI ($r = -0.4217$, $p<1e-8$). Using follow-up data, PWS and PWSn showed negative correlations with CTI ($r = -0.1719$, $p=0.0190$; $r = -0.1550$, $p = 0.0319$, respectively).

3.4. Correlation between lipid depth (LD) and WT, WSS, PWS, and PWSn

The size of lipid-rich necrotic cores is known to be related to plaque vulnerability. Table 4 shows lipid depth (LD) had significant correlations with all 4 predictors, with r -values equal to 0.4160, 0.0915, -0.2206 , -0.1802 for WT, WSS, PWS, and PWSn, respectively. WT turns out to be the best predictor, with the best r -value and most consistent individual plaque correlation results. The individual correlation results for PWS, PWSn and WSS all had many no-significance cases.

3.5. Correlation between lipid depth increase (LDI) and WT, WSS, PWS, and PWSn

Using all quarters combined from the 3 patients, Table 5 shows that WT, PWS and PWSn had significant correlations with LDI, while WSS had no significant correlation with LDI.

WT correlated with LDI negatively, with $r = -0.4491$ ($p < 1e-10$), while both PWS and PWSn showed positive correlations with LDI, with $r=0.1775$, and 0.2074 , respectively.

3.6. Sensitivity and specificity of possible predictors for plaque progression

Prediction accuracy (defined as sensitivity + specificity) of all 15 possible combinations of the candidate predictors WT, PWS, PWSn, and WSS for WTI are reported in Table 6. It turned out that a combination of WT and PWS had the best prediction accuracy (1.41) for WTI. For individual predictors, WT had the best accuracy (1.39) and WSS had the poorest accuracy (1.11).

3.7 Correlations between plaque burden increase (PBI) and related risk parameters

Another plaque geometrical parameter, plaque burden (plaque area / (plaque area + lumen area)), is a popular index measuring plaque progression in the medical and clinical community.²¹ Using slice average values of the parameters at baseline, Table 7 indicated that plaque burden increase (PBI) had negative correlation with WSS ($r=-0.7286$, $p<0.00001$), WT ($r=-0.5185$), plaque burden ($r=-0.5500$), plaque area ($r=-0.5566$), and plaque wall strain ($r=0.1181$, $p=0.1199$). PBI did not show significant correlation with plaque wall stress. Our correlation results involving PBI with WSS were consistent with results presented in Stone et al.²¹

3.8 Correlations between plaque area increase (PAI) and related risk parameters

Plaque area is also a popular index measuring plaque progression. Using slice average parameter values, Table 8 indicated that plaque area increase (PAI) also had negative correlation with WSS, WT, plaque burden, and plaque area. PAI did not show significant correlation with plaque wall stress and strain.

4. Discussion

4.1 A paradigm change: predictive method and prediction accuracy of risk factors

Most studies for atherosclerosis progression and rupture were to find correlations between plaque progression and the potential risk factors. However, what we really need in clinical practice are predictive methods and potential predictors with their quantitative prediction accuracies. The predictive method introduced in this paper is an attempt in that direction. Due to small sample size, we used quarters as our data points to introduce our methods and perform our preliminary study. Optimized predictors were identified (wall thickness + plaque wall stress) with the best prediction accuracy achieved. The method could be easily extended to large-scale patient studies when data become available. The outcome event could also be other clinical events such as plaque rupture, increase of intraplaque hemorrhage, stroke, heart attack, etc. Risk factors could also include non-mechanical factors such as diabetes, cholesterol, drug effect, chemical factors in the blood, detectable inflammation on lumen surface, etc.

Our statistical approach has two novel contributions. First, for the correlation analysis, traditional regression model is not the ideal choice because it assumes the data observations to be independent. It is more appropriate to consider the dependence structure for the

observations of quarters. The linear mixed-effects (LME) model is an extension over regression model to properly consider the biologically meaningful dependence among quarters. In this study, our LME models considered the dependence due to hierarchical clustering effects (i.e., quarters in a slice and the slices in a patients are likely more homogeneous) as well as the spatial dependence (i.e., quarters next to one another are likely more similar than quarters far away from one another). The LME model was first introduced into the coronary plaque progression studies in a previous paper of ours.²⁴ The current work slightly improved it by more sufficiently modeling the hierarchical clustering effects.

Second, correlation analysis is used to find the most “explainable” factors related to the response variable. However, they are not necessarily the best ones for predicting future outcome. The clinically more important contribution of our study is to introduce predictive method to quantify prediction accuracy of risk factors. This paper is the first in literature to apply the generalized linear mixed models (GLMMs), which again sophisticatedly considered both clustering and spatial dependence structure of quarters, in predicting coronary plaque progression. Through fitting and comparing such predictive models, we provided interesting preliminary evidence on which factors are the best to predict coronary plaque growth in the future.

4.2. Wall thickness and plaque wall stress had better correlation with plaque progression than wall shear stress

Correlation between wall shear stress and plaque progression has attracted the most attention in the past. However, studies based on patient follow-up data have indicated that the effect of wall shear stress on plaque progression measured by wall thickness may not be as strong as previously believed.^{19,21,33} In this paper, wall thickness turned out to be the risk factor with the best correlation with plaque progression, cap thickness, cap thickness increase, lipid depth, and lipid depth increase. Wall thickness also had the best prediction accuracy for wall thickness increase among the 4 individual predictors. Between PWS and WSS, PWS had better correlation with WTI, lipid depth, and lipid depth increase than WSS did. In fact, WSS did not show significant correlation with WTI (at T1) and LDI. In their large patient study report (374 patients, about 800 vessels), Stone et al. reported that low WSS was not associated with plaque area increase (PAI).²¹ While WTI and PAI are different ways of measuring plaque progression, our observations were consistent with their findings.

4.3. Major limitation from IVUS-VH data

It is known that IVUS-VH cannot visualize thin caps: in fact, the lipid-rich tissue is often in ‘contact’ with the lumen. Since there is a commonly accepted 65 micron threshold value for cap thickness, we made cap with thickness about 50 micron when IVUS-VH data had lipid-rich core on the lumen. That was a kind of “best effort” we can make with the data IVUS-VH could provide.

4.4. Major limitation from lack of 3D vessel curvature data

One major limitation of the paper is the lack of biplane angiography that could be used to re-construct 3D vessel curvature. Our patient data were provided by Mintz’s group at Cardiovascular Research Foundation (CRF) with only one angiography image data acquired.

Care was taken to take the angiography with maximum curvature variations of the vessel segment of interest. However, we should definitely try to acquire angiography from two near orthogonal view angles to obtain accurate vessel curvature.

Effect of curvature variations was reported in our earlier paper by Yang et al.³³ Greater curvature could lead to up to 15% WSS decrease compared to the same vessel without curvature due to the increased flow resistance caused by the curvature. It should be noted that WSS distribution pattern on the lumen surface are more closely linked to lumen narrowing and remained similar for both curved and straight vessels. Therefore, correlation results would be affected less by the curvature data limitation, compared to the effect on actual WSS values. Accurate assessment would need to be done with real 3D curvature data when we get it.

4.5. Limitations

Some limitations of this study include: a) patient-specific and tissue-specific material properties were not available for our study; b) while the angiographic movie provided information for the position of the myocardium and partial information for curvature variations, two movies with different (preferably orthogonal) view angles are needed to reconstruct the 3D motion of the coronary and provide accurate curvature variation information; c) some data such as zero-stress conditions (opening angle), multi-layer vessel morphology and material properties were not possible to measure non-invasively in vivo; d) interaction between the heart and vessel were not included. A model coupling heart motion and coronary bending would be desirable when required data become available.

5. Conclusion

A predictive method was introduced to assess prediction accuracy of risk factors and identify the optimal predictor(s) for plaque progression and other target outcome. A combination of wall thickness and plaque wall stress was identified as the best predictor for the plaque samples studied. In search of correlations and mechanisms governing plaque progression and rupture, our results indicated that plaque wall thickness had best correlation with plaque progression, cap thickness, cap thickness increase, lipid depth, and lipid depth increase, followed by plaque wall stress in general performance. Wall shear stress had mixed correlation results for the positive correlation with wall shear stress and negative correlation with plaque wall stress. More patient follow-up data and large-scale studies are needed to continue our investigations.

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References

1. Cardoso L, Weinbaum S. Changing views of the biomechanics of vulnerable plaque rupture: a review. *Ann Biomed Eng.* 2014; 42(2):415–31. [PubMed: 23842694]
2. Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, Ordovás JM, Mocoroa A, Fernández-Friera L, Laclaustra M, García L, Molina J, Mendiguren JM, López-Melgar B, de Vega VM, Alonso-Farto

- JC, Guallar E, Sillesen H, Rudd JH, Fayad ZA, Ibañez B, Sanz G, Fuster V. The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design. *Am Heart J*. 2013; 166(6):990–8. [PubMed: 24268213]
3. Fitzmaurice, GM.; Laird, NM.; Ware, JH. *Applied Longitudinal Analysis*. Wiley-Interscience; Hoboken, NJ: 2004.
4. Fleg JL, Stone GW, Fayad ZA, Granada JF, Hatsukami TS, Kolodgie FD, Ohayon J, Pettigrew R, Sabatine MS, Tearney GJ, Waxman S, Domanski MJ, Srinivas PR, Narula J. Detection of high-risk atherosclerotic plaque: report of the NHLBI working group on current status and future directions. *JACC Cardio Imaging*. 2012; 5(9):941–55.
5. Friedman MH, Barger CB, Deters OJ, Hutchins GM, Mark FF. Correlation between wall shear and intimal thickness at a coronary artery branch. *Atherosclerosis*. 1987; 68:27–33. [PubMed: 3689481]
6. Friedman MH, Krams R, Chandran KB. Flow interactions with cells and tissues: cardiovascular flows and fluid-structure interactions. *Ann Biomed Eng*. 2010; 38:1178–1187. [PubMed: 20336826]
7. Fuster, V. The Vulnerable Atherosclerotic Plaque: Understanding, Identification, and Modification. In: Fuster, Valentin; Cornhill, JF.; Dinsmore, RE.; Fallon, JT.; Insull, W.; Libby, P.; Nissen, S.; Rosenfeld, ME.; Wagner, WD., editors. *AHA Monograph series*. Futura Publishing; Armonk NY: 1998.
8. Holzapfel GA, Mulvihill JJ, Cunnane EM, Walsh MT. Computational approaches for analyzing the mechanics of atherosclerotic plaques: a review. *J Biomech*. 2014; 47(4):859–69. [PubMed: 24491496]
9. Holzapfel GA, Sommer G, Regitnig P. Anisotropic mechanical properties of tissue components in human atherosclerotic plaques. *J Biomech Eng*. 2004; 126(5):657–665. [PubMed: 15648819]
10. Huang X, Yang C, Yuan C, Liu F, Canton G, Zheng J, Woodard PK, Sicard GA, Tang D. Patient-specific artery shrinkage and 3D zero-stress state in multi-component 3D FSI models for carotid atherosclerotic plaques based on in vivo MRI data. *Mol Cell Biomech*. 2009; 6(2):121–134. [PubMed: 19444328]
11. Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation: positive correlation between plaque location and low and oscillating shear stress. *Arteriosclerosis*. 1985; 5:293–302. [PubMed: 3994585]
12. Kural MH, Cai MC, Tang D, Gwyther T, Zheng J, Billiar KL. Planar biaxial characterization of diseased human coronary and carotid arteries for computational modeling. *Journal of Biomech*. 2012; 45(5):790–798.
13. Le Floc'h S, Cloutier G, Saijo Y, Finet G, Yazdani SK, Deleaval F, Rioufol G, Pettigrew RI, Ohayon J. A four-criterion selection procedure for atherosclerotic plaque elasticity reconstruction based on in vivo coronary intravascular ultrasound radial strain sequences. *Ultrasound Med Biol*. 2012; 38(12):2084–97. [PubMed: 23196202]
14. Loree HM, Kamm RD, Stringfellow RG, Lee RT. Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. *Circulation Research*. 1992; 71:850–858. [PubMed: 1516158]
15. Ohayon J, Finet G, Gharib AM, Herzka DA, Tracqui P, et al. Necrotic core thickness and positive arterial remodeling index: emergent biomechanical factors for evaluating the risk of plaque rupture. *Am J Physiol Heart Circ Physiol*. 2008; 295:H717–27. [PubMed: 18586893]
16. Pinherio, JC.; Bates, DM. *Mixed effects models in S and S-PLUS*. Springer Verlag; 2000.
17. Richardson PD. Biomechanics of plaque rupture: progress, problems, and new frontiers. *Ann Biomed Eng*. 2002; 30(4):524–36. [PubMed: 12086003]
18. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet*. 1989; 21;2(8669):941–4.
19. Samady H, Eshtehardi P, McDaniel MC, Suo J, Dhawan SS, Maynard C, Timmins LH, Quyyumi AA, Giddens DP. Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. *Circulation*. 2011; 124:779–788. [PubMed: 21788584]
20. Schall R. Estimation in generalized linear models with random effects. *Biometrika*. 1991; 78:719–727.

21. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, Takahashi A, Katsuki T, Nakamura S, Namiki A, Hirohata A, Matsumura T, Yamazaki S, Yokoi H, Tanaka S, Otsuji S, Yoshimachi F, Honye J, Harwood D, Reitman M, Coskun AU, Papafaklis MI, Feldman CL. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. *Circulation*. 2012; 126(2):172–81. [PubMed: 22723305]
22. Tang D, Kamm RD, Yang C, Zheng J, Canton G, Bach R, Huang X, Hatsukami TS, Zhu J, Ma G, Maehara A, Mintz GS, Yuan C. Image-based modeling for better understanding and assessment of atherosclerotic plaque progression and vulnerability: data, modeling, validation, uncertainty and predictions. *J Biomech*. 2014; 47(4):834–46. [PubMed: 24480706]
23. Tang D, Teng Z, Canton G, Yang C, Ferguson M, Huang X, Zheng J, Woodard PK, Yuan C. Sites of rupture in human atherosclerotic carotid plaques are associated with high structural stresses: an in vivo MRI-based 3D fluid-structure interaction study. *Stroke*. 2009; 40(10):3258–3263. Featured article on MDlinx.com. [PubMed: 19628799]
24. Tang D, Yang C, Canton G, Wu Z, Hatsukami TS, Yuan C. Correlations between carotid plaque progression and mechanical stresses change sign over time: a patient follow up study using MRI and 3D FSI models. *BioMedical Engineering Online*. 2013; 12:105.10.1186/1475-925X-12-105 [PubMed: 24125580]
25. Tang D, Yang C, Zheng J, Woodard PK, Sicard GA, Saffitz JE, Yuan C. 3D MRI-based multi-component FSI models for atherosclerotic plaques, a 3-D FSI model. *Annals of Biomed Eng*. 2004; 32(7):947–960.
26. Underhill HR, Hatsukami TS, Fayad ZA, Fuster V, Yuan C. MRI of carotid atherosclerosis: clinical implications and future directions. *Nature Reviews Cardiology*. 2010; 7(3):165–173.
27. Venables, WN.; Ripley, BD. *Modern Applied Statistics with S*. 4. Springer; New York: 2002.
28. Wahle A, Prause PM, DeJong SC, Sonka M. Geometrically correct 3-D reconstruction of intravascular ultrasound images by fusion with biplane angiography--methods and validation. *IEEE Trans Med Imaging*. 1999; 18(8):686–99. [PubMed: 10534051]
29. Wolfinger R, O'Connell M. Generalized linear mixed models: a pseudo-likelihood approach. *Journal of Statistical Computation and Simulation*. 1993; 48:233–243.
30. Xie Y, Mintz GS, Yang J, Doi H, Iñiguez A, Dargas GD, Serruys PW, McPherson JA, Stone BGW, Maehara A. Clinical outcome of nonculprit plaque ruptures in patients with acute coronary syndrome in the PROSPECT study. *JACC Cardiovasc Imaging*. 2014; 7(4):397–405. [PubMed: 24631511]
31. Xu D, Hippe DS, Underhill HR, Oikawa-Wakayama M, Dong L, Yamada K, Yuan C, Hatsukami TS. Prediction of high-risk plaque development and plaque progression with the carotid atherosclerosis score. *JACC Cardiovasc Imaging*. 2014; 7(4):366–73. [PubMed: 24631510]
32. Yang C, Canton G, Yuan C, Ferguson M, Hatsukami TS, Tang D. Advanced human carotid plaque progression correlates positively with flow shear stress: an in vivo MRI multi-patient 3D FSI study. *J Biomechanics*. 2010; 43(13):2530–2538.
33. Yang C, Bach R, Zheng J, El Naqa I, Woodard PK, Teng ZZ, Billiar KL, Tang D. In vivo IVUS-based 3D fluid structure interaction models with cyclic bending and anisotropic vessel properties for human atherosclerotic coronary plaque mechanical analysis, *IEEE Trans. Biomed Engineering*. 2009; 56(10):2420–2428.
34. Yuan C, Mitsumori LM, Beach KW, Maravilla KR. Special review: carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. *Radiology*. 2001; 221:285–299. [PubMed: 11687667]

Figure 1.

Matched IVUS-VH and segmented contour plots of sliced from baseline (T1) and follow-up (T2). Plots also include enlarged view of a slice, and re-constructed 3D plaque geometry.

Colors used in IVUS-VH: Red - necrotic core; White - dense calcium; Dark Green – Fibrous; Light Green - Fibro-Fatty.

(a) T1, X-ray angiographic image showing vessel curvature.

(b) T1, Lumen center line extracted from X-Ray angiography.

(c) T1, Lumen center lines extracted from X-Ray angiography with max/min curvature.

(d) T1, Re-constructed 3D coronary segment with max/min curvature.

Figure 2.

X-Ray angiographic image, extracted centerlines of the coronary segment, and the re-constructed 3D geometry with maximum and minimum curvatures.

Figure 3. Sketch explaining definitions of quarters, wall thickness, cap thickness, and lipid depth (lipid-rich necrotic core depth).

Figure 4.

Plots of plaque wall stress, strain, wall shear stress and velocity on a mid-cut plane from baseline and follow-up FSI models showing basic solution features.

Table 1

Correlation results between plaque progression and four risk parameters (WT, WSS, PWS, and PWSn) using their quarter average values at baseline (T1) and follow up (T2).

WTI vs. WT						
Patient and Sample Size			T1		T2	
Patient	Slices	Quarters	r	p	r	p
F1	57	228	-0.3556	4.17E-08	0.5697	4.77E-22
F2	36	144	-0.9315	9.83E-35	0.6006	1.20E-14
F3	34	136	-0.7256	2.45E-27	-0.1020	2.36E-01
All	127	508	-0.7363	1.35E-48	0.5692	7.49E-28

WTI vs. WSS						
Patient and Sample Size			T1		T2	
Patient	Slices	Quarters	r	p	r	p
F1	57	228	-0.2187	0.0110	0.3358	3.86E-05
F2	36	144	0.1610	0.0609	0.3592	1.23E-05
F3	34	136	0.0481	0.6332	0.3739	1.76E-05
All	127	508	-0.0052	0.9250	0.3545	5.77E-10

WTI vs. PWS						
Patient and Sample Size			T1		T2	
Patient	Slices	Quarters	r	p	r	p
F1	57	228	0.2216	0.0004	-0.3872	1.05E-11
F2	36	144	0.4806	3.77E-07	-0.4255	1.65E-07
F3	34	136	0.4201	9.76E-06	0.0263	0.7455
All	127	508	0.3000	1.99E-10	-0.3208	8.33E-13

WTI vs. PWSn						
Patient and Sample Size			T1		T2	
Patient	Slices	Quarters	r	p	r	p
F1	57	228	0.3177	2.59E-07	-0.2469	6.81E-05

WTI vs. PWSn							
Patient and Sample Size				T1		T2	
Patient	Slices	Quarters		r	p	r	p
F2	36	144		0.2711	0.0029	-0.4329	9.69E-08
F3	34	136		0.2001	0.0167	-0.0424	0.5892
All	127	508		0.2439	4.22E-08	-0.2500	2.42E-08

Table 2
Correlation results between cap thickness and four risk parameters (WT, WSS, PWS, and PWSn) using their quarter average values.

Plaques	Qts	WT		WSS	
		r	p	r	p
P1	91	0.3142	0.0030	0.0538	0.6211
P2	23	0.9779	9.30E-09	0.3267	0.1587
P3	18	0.8301	0.0077	0.7182	0.0291
P4	20	0.7111	0.0036	0.6047	0.0135
P5	20	0.9359	9.13E-06	0.9717	1.15E-06
P6	89	0.4609	1.21E-05	-0.4036	2.40E-04
All	261	0.4541	1.00E-18	0.5101	3.33E-08

Plaques	Qts	PWS		PWSn	
		r	p	r	p
P1	91	0.1299	0.2375	0.1197	0.2697
P2	23	-0.5922	0.0126	-0.6006	0.0152
P3	18	-0.5642	0.0086	-0.5547	0.0093
P4	20	-0.6350	0.0088	-0.6831	0.0053
P5	20	-0.7923	0.0001	-0.7420	0.0002
P6	89	0.2171	0.0473	0.0003	0.9980
All	261	-0.3359	2.07E-11	-0.1558	0.0019

Table 3

Correlation results between cap thickness increase (CTI) and four risk parameters (WT, WSS, PWS, and PWSn) using their quarter average values at baseline (T1) and follow up (T2).

Predictor: Wall Thickness (WT)					
patient	Qts	T1 (baseline)		T2 (Follow Up)	
		r	p	r	p
F1	27	-0.6147	0.0026	0.2397	0.1844
F2	36	-0.3697	0.0385	-0.1230	0.4878
F3	115	-0.5444	8.23E-10	0.0928	0.3247
Combined	178	-0.4217	1.07E-08	0.0451	0.5469

Predictor: Wall shear stress (WSS)					
patient	Qts	r	p	r	p
F1	27	-0.2492	0.2767	0.2584	0.2974
F2	36	-0.0074	0.9673	-0.5297	0.0023
F3	115	0.2700	0.0076	0.4016	1.55E-05
Combined	178	0.0810	0.3618	-0.0227	0.8290

Predictor: Plaque Wall Stress (PWS)					
patient	Qts	r	p	r	p
F1	27	-0.2934	0.0135	-0.4412	0.0262
F2	36	0.0201	0.9115	0.1521	0.3777
F3	115	0.1248	0.1895	-0.3949	3.17E-06
Combined	178	-0.0243	0.7343	-0.1719	0.0190

Predictor: Plaque Wall Strain (PWSn)					
patient	Qts	r	p	r	p
F1	27	-0.3130	0.0153	-0.4383	0.0486
F2	36	-0.0237	0.8985	0.2102	0.2232
F3	115	0.0617	0.5125	-0.3483	0.0001
Combined	178	0.0215	0.7689	-0.1550	0.0319

Table 4
Correlation results between lipid depth (LD) and four risk parameters (WT, WSS, PWS, and PWSn) using their quarter average values.

Plaques	Qts	LD vs. WT		LD vs. WSS	
		r	p	r	p
P1	136	0.5710	6.82E-13	0.3928	5.03E-06
P2	144	0.2977	0.0003	0.0531	0.5471
P3	144	0.1596	0.0568	0.0389	0.6439
P4	228	0.3452	1.20E-07	0.3807	4.37E-09
P5	228	0.4344	1.41E-11	0.1679	0.0113
P6	136	0.7205	3.31E-21	0.1390	0.1073
Combined	1016	0.4160	1.68E-42	0.0915	0.0056

Plaques	Qts	LD vs. PWS		LD vs. PWSn	
		r	p	r	p
P1	136	-0.3556	5.78E-06	-0.2787	0.0001
P2	144	-0.1267	0.1314	-0.1389	0.0995
P3	144	-0.0818	0.3304	0.0079	0.9255
P4	228	0.0151	0.8222	0.0511	0.4453
P5	228	0.1164	0.0783	0.1281	0.0545
P6	136	-0.4957	1.87E-09	-0.4002	1.92E-06
Combined	1016	-0.2206	2.27E-16	-0.1802	1.99E-11

Table 5

Correlation results between lipid depth increase (LDI) and four risk parameters (WT, WSS, PWS, and PWSn) using their quarter average values at baseline (T1) and follow up (T2).

Predictor: Wall Thickness (WT)				
Patient	Qts	T1 (Baseline)		T2 (Follow Up)
		r	p	r p
F1	228	-0.2903	1.08E-05	-0.3392 1.93E-07
F2	144	-0.1095	0.1921	-0.0637 0.4487
F3	136	-0.6393	6.05E-16	-0.3177 0.0002
Combined	508	-0.4491	5.95E-22	-0.1928 0.0001

Predictor: Wall Shear Stress (WSS)				
Patient	Qts	T1 (Baseline)		T2 (Follow Up)
		r	p	r p
F1	228	-0.4094	2.28E-10	-0.2464 0.0003
F2	144	0.0377	0.6538	-0.1329 0.1129
F3	136	-0.0100	0.9084	0.1885 0.0286
Combined	508	-0.0856	0.1187	-0.0524 0.2998

Predictor: Plaque Wall Stress (PWS)				
Patient	Qts	T1 (Baseline)		T2 (Follow Up)
		r	p	r p
F1	228	0.0563	0.3995	0.1580 0.0178
F2	144	-0.0617	0.4629	0.0807 0.3367
F3	136	0.3123	0.0002	0.3074 0.0003
Combined	508	0.1775	4.20E-05	0.1475 0.0005

Predictor: Plaque Wall Strain (PWSn)				
Patient	Qts	T1 (Baseline)		T2 (Follow Up)
		r	p	r p
F1	228	0.0624	0.3496	0.1552 0.0203

Predictor: Plaque Wall Strain (PWSn)					
Patient	Qfs	T1 (Baseline)		T2 (Follow Up)	
		r	p	r	p
F2	144	-0.0686	0.4145	0.1061	0.2062
F3	136	0.3548	2.76E-05	0.1305	0.1306
Combined	508	0.2074	7.48E-07	0.1069	0.0148

Table 6

Prediction sensitivity and specificity of 15 combinations of predictors WT, PWS, PWSn, and WSS for plaque progression (WTI) showing that WT+PWS has the best prediction accuracy.

Predictor	ProbCutoffs	Sensitivity	Specificity	Sensi+Speci
WT	0.4279	0.8100	0.5806	1.3906
WSS	0.4756	0.8936	0.2164	1.1100
WT+WSS	0.3725	0.8474	0.5027	1.3501
PWS	0.4611	0.6910	0.5672	1.2582
WT+PWS	0.4388	0.8051	0.6048	1.4100
WSS+PWS	0.4810	0.6064	0.6102	1.2166
WT+WSS+PWS	0.3615	0.8526	0.4960	1.3485
PWSn	0.5140	0.5474	0.7030	1.2504
WT+PWSn	0.4489	0.7910	0.6116	1.4026
WSS+PWSn	0.5269	0.5192	0.7352	1.2544
WT+WSS+PWSn	0.3945	0.8308	0.5188	1.3496
PWS+PWSn	0.4554	0.6859	0.5780	1.2639
WT+ PWS+PWSn	0.4601	0.7526	0.6210	1.3735
WSS+ PWS+PWSn	0.5050	0.5590	0.6680	1.2270
WT+WSS+ PWS+PWSn	0.3871	0.8423	0.5188	1.3611

Table 7

Correlation results between plaque burden increase (PBI) and six risk parameters (WSS, WT, plaque burden, plaque area, PWS, and PWSn) using slice average values at baseline (T1).

Patient	PBI vs. WSS		PBI vs. WT		PBI vs. Plaque Burden	
	r	p	r	p	r	p
F1 (57 slices)	-0.4511	<0.0001	-0.7559	0.0000	-0.8624	<0.0001
F2 (36 slices)	-0.6047	0.0025	-0.3212	0.0311	-0.6966	0.0039
F3 (34 slices)	-0.5870	0.0041	-0.3430	0.1440	-0.6086	0.0026
All (127 slices)	-0.7286	<0.0001	-0.5185	2.96E-07	-0.5500	<0.0001

Patient	PBI vs. Plaque Area		PBI vs. PWS		PBI vs. PWSn	
	r	p	r	p	r	p
F1 (57 slices)	-0.8242	<0.0001	0.6487	0.0001	0.2347	0.0304
F2 (36 slices)	-0.5763	0.0409	-0.0952	0.7788	-0.2154	0.4254
F3 (34 slices)	0.0452	0.8455	-0.3429	0.2921	0.1698	0.3252
All (127 slices)	-0.5566	<0.0001	0.2142	0.1464	0.1181	0.1199

Table 8

Correlation results between plaque area increase (PAI) and six risk parameters (WSS, WT, plaque burden, plaque area, PWS, and PWSn) using slice average values at baseline (T1).

Patient	PAI vs. WSS		PAI vs. WT		PAI vs. Plaque Burden	
	r	p	r	p	r	p
F1 (57 slices)	-0.3496	0.0327	-0.7284	0.0000	-0.7864	0.0000
F2 (36 slices)	-0.4629	0.0660	-0.4705	0.2193	-0.9492	0.0287
F3 (34 slices)	-0.0494	0.7920	-0.1554	0.2633	-0.2573	0.3091
All (127 slices)	-0.3711	0.0187	-0.6426	0.0005	-0.6465	0.0000

Patient	PAI vs. Plaque Area		PAI vs. PWS		PAI vs. PWSn	
	r	p	r	p	r	p
F1 (57 slices)	-0.8375	0.0000	0.5495	0.0004	0.1873	0.0728
F2 (36 slices)	-0.9595	0.0189	-0.2709	0.3680	-0.2994	0.2095
F3 (34 slices)	-0.2757	0.0578	-0.0426	0.8547	0.1262	0.2070
All (127 slices)	-0.5796	0.0000	0.0418	0.7557	0.0915	0.1763