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Noninvasive Prediction of Atherosclerotic Progression: The PROSPECT-MSCT Study

Intravascular imaging-based natural history studies of atherosclerosis have provided insight into atherosclerotic evolution and demonstrated that local hemodynamic factors, plaque burden, and the composition of the atheroma regulate plaque growth and determine vulnerable plaque formation (1,2). However, intravascular imaging is time consuming, is associated with a risk of complications, and does not allow complete assessment of plaque pathophysiology. Recent reports suggest that multislice computed tomography (MSCT) provides useful prognostic information and permits reliable quantification of luminal dimensions and plaque burden, characterization of the composition of the plaque, coronary reconstruction blood flow simulation, and estimation of the local endothelial shear stress (ESS) (3). However, the potential of MSCT in identifying lesions that are prone to progress is undetermined.

The present analysis processed data from the patients enrolled in the PROSPECT-MSCT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree-MSCT) study in order to investigate the value of MSCT-derived variables in predicting plaque evolution (4). PROSPECT-MSCT recruited 32 patients with an acute coronary syndrome, who were enrolled in the PROSPECT study, and underwent MSCT imaging at baseline (after percutaneous coronary intervention of the culprit lesions responsible for the acute coronary syndrome),

TABLE 1 Univariate and Multivariate Analysis of the Variables Associated With Atherosclerotic Disease Progression

	Univariate Analysis			Multivariate Model	
	Associated Factor	**β (95% CI)**	**p Value**	**β (95% CI)**	**p Value**
Increase in lumen area (per 1 mm^2)	Presence of low endothelial shear stress at baseline	−1.06 −(−1.34 to −0.78)	<0.001	−0.47 (−0.78 to −0.16)	<0.001
	Baseline lumen area (per 1-mm^2 increase)	−0.28 (−0.33 to −0.23)	<0.001	−0.22 (−0.28 to −0.16)	<0.001
	Baseline outer vessel wall area (per 1-mm^2 increase)	−0.13 (−0.16 to −0.09)	<0.001	–	–
	Baseline plaque area (per 1-mm^2 increase)	0.08 (0.01 to 0.15)	0.029	–	–
	Baseline plaque burden (per 10% increase)	1.08 (0.88 to 1.28)	<0.001	–	–
	Presence of expanding remodeling at baseline	−1.04 (−1.38 to −0.70)	<0.001	−0.21 (−0.58 to 0.17)	0.277
Increase in plaque area (per 1 mm^2)	Baseline lumen area (per 1-mm^2 increase)	−0.04 (−0.9 to 0.01)	0.083	–	–
	Baseline outer vessel wall area (per 1-mm^2 increase)	−0.14 (−0.17 to −0.10)	<0.001	–	–
	Baseline plaque area (per 1mm^2 increase)	−0.42 (−0.48 to −0.37)	<0.001	−0.40 (−0.46 to 0.33)	<0.001
	Baseline plaque burden (per 10% increase)	−0.66 (−0.84 to 0.48)	<0.001	−0.23 (−0.41 to 0.05)	0.014
	Baseline % fibrofatty tissue (per 10% increase)	0.30 (0.05 to 0.55)	0.017	−0.07 (−0.29 to 0.16)	0.569
	Baseline % calcific tissue (per 10% increase)	−0.21 (−0.44 to 0.03)	0.081	–	–
Increase in plaque burden (per 10%)	Presence of low endothelial shear stress at baseline	0.28 (0.18 to 0.37)	<0.001	0.11 (0.02 to −0.21)	0.018
	Baseline lumen area (per 1-mm^2 increase)	0.05 (0.03 to 0.06)	<0.001	–	–
	Baseline plaque area (per 1-mm^2 increase)	−0.12 (−0.14 to 0.10)	<0.001	−0.10 (−0.12 to −0.07)	<0.001
	Baseline plaque burden (per 10% increase)	−0.46 (−0.53 to −0.40)	<0.001	−0.40 (−0.48 to −0.32)	<0.001
	Baseline % necrotic tissue (per 10% increase)	0.05 (0.01 to 0.09)	0.044	−0.03 (−0.08 to 0.01)	0.154
	Baseline % calcific tissue (per 10% increase)	−0.10 (−0.19 to −0.01)	0.035	0.22 (0.13 to 0.31)	<0.001
	Presence of expanding remodeling at baseline	0.20 (0.09 to 0.31)	<0.001	−0.04 (−0.15 to 0.07)	0.506
Increase in necrotic core (per 1 mm^2)	Presence of low wall shear stress at baseline	0.13 (−0.02 to 0.27)	0.097	0.01 (−0.14 to 0.17)	0.872
	Baseline plaque area (per 1-mm^2 increase)	−0.05 (−0.08 to −0.01)	0.017	−0.08 (−0.12 to −0.04)	<0.001
	Baseline plaque burden (per 10% increase)	−0.17 (−0.27 to −0.07)	0.001	−0.14 (0.25 to 0.03)	0.016
	Baseline % necrotic tissue (per 10% increase)	−0.25 (−0.31 to −0.18)	<0.001	–	–
	Baseline % fibrofatty tissue (per 10% increase)	0.16 (0.02 to 0.31)	0.028	0.17 (0.03 to 0.31)	0.016
	Baseline % fibrous tissue (per 10% increase)	0.22 (0.16 to 0.28)	<0.001	0.29 (0.23 to 0.36)	<0.001

CI = confidence interval.

and at 3-year follow-up. The MSCT data at baseline were used to estimate the luminal dimensions, plaque burden, and composition (3); reconstruct coronary anatomy; and perform blood flow simulation (1). The studied vessels were divided into 3-mm subsegments, and the baseline MSCT-derived plaque characteristics and predominant ESS (defined as the minimum averaged ESS in an arc of 90°) in each 3-mm subsegment were used to identify predictors associated with the changes in the luminal dimensions and atheroma burden and composition at follow-up (1). We define as significant disease progression an increase >21.6% of the plaque area at follow-up. This cutoff was selected based on the intraobserver variability (>2 standard deviations) of the expert who performed the analysis of the MSCT data (5).

The baseline characteristics of the studied population have been presented elsewhere (5). Fifty-eight coronary arteries (median length 41.3 [25.4 to 55.4] mm, 735 3-mm subsegments) that did not contain a treated culprit lesion were included in the analysis. The MSCT-derived variables associated with a reduction in luminal dimensions, an increase in plaque area and burden, and an increase in the necrotic core component are shown in **Table 1**. The plaque burden and composition appeared as independent predictor in most of the multivariate analyses. Low ESS was independently associated with the changes in lumen area and plaque burden, it was associated with the changes in the necrotic core component in the univariate, but not in the multivariate analysis, and it did not appear to affect the changes in plaque area.

At 3-year follow-up, 176 (23.9%) segments exhibited >21.6% increase in plaque area. Low ESS, plaque and burden, increasing % fibrofatty tissue component, and a decreasing % fibrotic tissue component appeared as predictors of disease progression. In the multivariate model only, decreasing plaque burden (odds ratio: 1.72; 95% confidence interval: 1.10 to 2.70; $p = 0.018$) and decreasing % fibrotic tissue component (odds ratio: 1.41; 95% confidence interval: 1.04 to 1.91; $p = 0.026$) were independently associated with plaque progression. The accuracy of the model created from the independent predictors of disease progression was 59.0%. The sensitivity, specificity, positive and negative predictive values, and the positive and negative likelihood ratios were 70.5%, 54.9%, 33.0%, 85.5%, 1.56, and 0.54, respectively.

The present analysis for the first time investigated the potential value of MSCT-derived plaque characteristics in identifying lesions that are likely to progress at 3-year follow-up. We found that: 1) low ESS and increased baseline lumen area were predictors of lumen decrease at follow-up; 2) decreased plaque area and burden were independently associated with an increase in plaque area at follow-up; 3) low ESS and decreased plaque area and burden and increased calcific tissue component were independently related with an increase in plaque burden at follow-up; and 4) a low plaque area and burden and an increased fibrofatty and fibrous tissue component were independently related to an increase in the necrotic core at follow-up. Interestingly, the results reported in this study are very similar to those presented in other invasive-based imaging studies (1,5). However, MSCT is a noninvasive modality, able to provide a holistic assessment of plaque burden and composition, and allows reconstruction of the entire coronary tree including coronary bifurcations. These unique features render it an attractive alternative for the study of atherosclerotic evolution. Our analysis showed that MSCT-derived variables had a moderate accuracy in detecting lesions that are likely to progress at follow-up. The potential value of this modality in the detection of vulnerable, prone-to-rupture plaques requires further investigation in the context of a large-scale natural history study of atherosclerosis.

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Lumen Measurements From Quantitative Coronary Angiography and IVUS: A PROSPECT Substudy

Using multilesion, multivessel, multi-imaging modality data from PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) (1), we examined differences between angiographic and intravascular ultrasound (IVUS) lumen dimension measurements and factors that affected the discrepancy. Baseline grayscale and IVUS virtual histology studies in 3,017 nonculprit lesions (658 patients) were coregistered to the angiographic roadmap by an individual blinded to the IVUS and quantitative coronary angiography (QCA) analyses; IVUS and QCA measurements were performed at separate core laboratories (Cardiovascular Research Foundation, New York, New York) (2). The primary comparison was IVUS versus QCA in-lesion minimal lumen diameter (MLD) using a Passing-Bablok approach with differences between IVUS- and QCA-measured MLD assessed using Kendall's concordance coefficients and Bland-Altman plots. A model with a generalized estimating equation approach was used to compensate for potential cluster effects of multiple lesions in the same patient. IVUS pullback lengths were left anterior descending coronary artery (LAD) 72.9 ± 26.6 mm, left circumflex coronary artery (LCX) 61.2 ± 25.1 mm, and right coronary artery (RCA) 82.9 ± 30.6 mm; distances from the ostia were grouped in tertiles to identify proximal, mid, and distal segments. Statistical analyses, except Passing-Bablok regressions, were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina); Passing-Bablok analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) using the ggplot2 package version 1.0.0 and mcr package version 1.2.1.

There was a strong concordance between IVUS MLD and QCA MLD (Kendall's $W = 0.89$, $p < 0.001$) (**Figure 1A**); however, QCA underestimated MLDs in small vessels and overestimated MLDs in large vessels compared with IVUS. The "intersection MLD" was 3.8 mm, with smaller vessels having an MLD <3.8 mm and larger vessels an MLD >3.8 mm. The Bland-Altman plot of IVUS minus QCA MLD (**Figure 1B**) indicated that QCA underestimated MLD compared with IVUS: mean difference 0.21 ± 0.48 mm and median difference 0.23 mm (interquartile range [IQR]: −0.05 to 0.52]. In lesions with IVUS MLD >QCA MLD, the median difference was 0.39 mm. In lesions with IVUS MLD <QCA MLD, the median difference was −0.26 mm. The overall discrepancy was 16.5 ± 13.9% or a median of 13.1% (IQR: 6.2% to 22.5%).

There was a strong concordance between IVUS versus QCA MLD in the LAD, LCX, and RCA, separately: LAD, QCA MLD 2.55 ± 0.80 mm versus IVUS MLD 2.71 ± 0.60 mm, Kendall's $W = 0.88$, $p < 0.001$; LCX, QCA MLD 2.50 ± 0.73 mm versus IVUS MLD 2.72 ± 0.60 mm, Kendall's $W = 0.89$, $p < 0.001$; and RCA, QCA MLD 2.73 ± 0.70 mm versus IVUS MLD 2.99 ± 0.61 mm, Kendall's $W = 0.88$, $p < 0.001$. There was also a strong concordance in each proximal, middle, and distal subsegment ($p < 0.001$; data not shown); however, the mean discrepancy between IVUS MLD and QCA MLD in the proximal LAD was smaller than the mid or distal LAD (median 0.07 mm [IQR: 0.74 mm], 0.24 mm [IQR: 0.56 mm], 0.30 mm [IQR: 0.52 mm], respectively) or the proximal, mid, or distal LCX (median 0.21 mm [IQR: 0.49 mm], 0.22 mm [IQR: 0.56 mm], 0.21 mm [IQR: 0.54 mm], respectively) or RCA (median 0.22 mm [IQR: 0.61 mm], 0.30 mm [IQR: 0.53 mm], 0.31 mm [IQR: 0.55 mm], respectively) subsegments. Conversely, scatter was greatest in the proximal LAD subsegment (range [min-max MLD difference]): LAD, proximal 3.89 mm (−2.61 to 1.29 mm), mid 3.07 mm (−1.38 to 1.69 mm), distal 3.24 mm (−1.82 to 1.42 mm); LCX, proximal 3.16 mm (−1.40 to 1.75 mm), mid 3.43 mm (−1.14 to 2.29 mm), distal 2.75 mm (−1.41 to 1.34 mm); and RCA, proximal 3.41 mm (−1.47 to 1.94 mm), mid 2.87 mm (−1.28 to 1.59 mm), distal 3.26 mm (−1.60 to 1.66 mm).

An IVUS MLD minus QCA MLD difference >0.23 mm (median) and an IVUS >QCA MLD were associated with longer lesions ($p = 0.001$, $p = 0.0016$,