Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics: The PREDICTION Study

**Running title:** Stone et al.; Prediction of CAD progression in man

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Abstract:

**Background** - Atherosclerotic plaques progress in a highly individual manner. The purposes of the PREDICTION Study were to determine the role of local hemodynamic and vascular characteristics in coronary plaque progression and to relate plaque changes to clinical events.

**Methods and Results** - Vascular profiling (VP), using coronary angiography and intravascular ultrasound, was employed to reconstruct each artery and calculate endothelial shear stress (ESS) and plaque/remodeling characteristics in-vivo. Three-vessel VP (2.7 arteries per patient) was performed at baseline in 506 patients with acute coronary syndrome (ACS) treated with a percutaneous coronary intervention (PCI) and in a subset of 374 (74%) consecutive patients 6-10 months later to assess plaque natural history. Each reconstructed artery was divided into sequential 3-mm segments for serial analysis. One-year clinical followup was completed in 99.2%. Symptomatic clinical events were infrequent: only 1 (0.2%) cardiac death; 4 (0.8%) patients with new ACS in non-stented segments; 15 (3.0%) patients hospitalized for stable angina. Increase in plaque area (primary endpoint) was predicted by baseline large plaque burden, decrease in lumen area (secondary endpoint) was independently predicted by baseline large plaque burden and low ESS. Large plaque size and low ESS independently predicted the exploratory endpoints of increased plaque burden and worsening of clinically relevant luminal obstructions treated with a PCI at followup. The combination of independent baseline predictors had a 41% positive- and 92% negative predictive value to predict progression of obstruction treated with a PCI.

**Conclusions** - Large plaque burden and low local ESS provide independent and additive prediction to identify plaques that develop progressive enlargement and lumen narrowing.

**Clinical Trial Registration Information** - clinicaltrials.gov; Identifier: NCT01316159.

**Key words:** atherosclerosis; endothelium; natural history; shear stress
Introduction

Atherosclerosis is a systemic disease with focal and eccentric manifestations. In a patient with coronary artery disease (CAD) and systemic risk factors each coronary lesion progresses, regresses, or remains quiescent in an independent manner, indicating that local vascular factors must be a major determinant responsible for the behavior of individual plaques.

The vascular endothelium is in a unique and pivotal position to respond to the extremely dynamic forces acting on the vessel wall due to the complex 3-D geometry of the artery associated with its natural curvature and the acquired presence of focal atherosclerotic obstructions. Mechanical forces in general, and fluid shear stress in particular, elicit a large number of humoral, metabolic and structural responses in endothelial cells. The response of a number of genes sensitive to local low endothelial shear stress (ESS) leads to creation of a raised plaque, subsequent hemodynamic forces created by the enlarging plaque may lead to a cycle of progressive atherogenesis, which may culminate in plaque rupture that may become clinically manifest as obstructive thrombus or rapid progression of a fixed obstruction.

Identification of an early coronary atherosclerotic plaque likely to acquire high-risk characteristics and precipitate a new coronary event may allow for development of preemptive strategies to avert adverse events. The recent PROSPECT Study demonstrated that coronary lesions responsible for new cardiac events in patients following a percutaneous coronary intervention (PCI) for an acute coronary syndrome (ACS) were associated with large plaque burden, a small lumen area, thin-cap fibroatheroma (TCFA) morphology, as assessed by intravascular ultrasound (IVUS), and minimal obstruction by angiography. This natural history study was limited, however, by acquisition of vascular characteristics at only a single point in time, and pathobiologic mechanisms potentially responsible for ongoing and progressive plaque...
instability, such as local ESS, were not investigated.

The purposes of the PREDICTION Study were to identify the detailed coronary hemodynamic and plaque characteristics in high-risk patients following a PCI for an ACS, to follow the serial natural history of the plaques over a 6-10 month period in a large number of consecutive patients, and to investigate whether high-risk lesions likely to rupture and cause an ACS or rapid progression of an obstruction could be identified early in its natural history.

Methods

Study Design

The PREDICTION Study was designed as both an anatomic natural history study and an event-attribution study. Patients with an ACS undergoing PCI for a culprit lesion were enrolled and underwent coronary vascular profiling (VP), as described below, at the time of the index catheterization procedure. A large subset of consecutive, unselected patients underwent followup VP after 6-10 months to assess anatomic natural history and antecedent vascular characteristics responsible for the natural history. All patients had clinical followup at one-year. The study was performed in Japanese clinical sites because Japanese patients routinely undergo followup catheterization and IVUS 6 months after successful PCI for an ACS and this clinical practice facilitated performance of a large natural history study.

Inclusion criteria included age >18 years, presentation with an ACS, CAD with at least one coronary segment requiring PCI according to usual clinical indications, and at least one vessel suitable for IVUS not planned for PCI. Exclusion criteria included heart failure NYHA Class III/IV, unstable clinical status, left main disease or 3-vessel disease, significant coronary calcification precluding IVUS evaluation, renal failure such that additional contrast material...
would be contraindicated, clinically significant valvular disease, and life expectancy <12 months.

Study Methods

Detailed ESS and plaque/arterial wall characteristics were identified using VP methods combining intracoronary IVUS and biplane coronary angiography, to represent the artery accurately in 3-D space and to measure flow, as previously described, and presented in detail in the On-line Supplement. In brief, the 3-D anatomy of the artery was reconstructed from digitized radiofrequency IVUS signals and biplane coronary angiography. The arterial lumen and outer vessel wall were reconstructed from digitized and segmented end-diastolic IVUS frames. A structured grid utilizing a body-fitted coordinate system was employed to represent the lumen volume. Coronary blood flow was calculated directly from the time required for the previously calculated, true 3-D volume of blood contained within the arterial section to be displaced by radio-opaque material during a contrast injection. The detailed intravascular flow characteristics were obtained by solving the transport equations governing the conservation of mass and momentum (Phoenics, CHAM, England). The ESS at the luminal surface of the artery was calculated as the product of viscosity (calculated from the measured hematocrit) and the gradient of blood velocity at the wall. The 3-D geometry of the outer vessel wall (area within the external elastic membrane [EEM]) was recreated in a manner similar to that described for the lumen geometry. The 3-D geometry of the plaque (plaque plus media thickness) was taken as the difference between the outer vessel wall and the lumen. The processes of data acquisition and analysis are highly reproducible.

Study Assessments

We divided the entire reconstructed artery into consecutive 3-mm segments starting at the ostium. We chose 3-mm segments since this length was methodologically reliable and would
also accurately reflect the local hemodynamic and plaque characteristics as well as the heterogeneous and highly focal changes occurring within the plaque over time. Within each 3-D segment we assessed local ESS, plaque characteristics, and vascular remodeling. The same coronary artery segments were evaluated at the time of the followup catheterization 6-10 months later to determine the change in vascular characteristics. Assurance that the arterial segments to be measured were identical at the initial and the followup procedures was accomplished by using fixed anatomic landmarks, primarily multiple arterial branches, as reference fiducial points.

Coronary artery natural history outcomes were analyzed utilizing a variety of different approaches to represent different magnitudes of CAD progression: (I.) Each 3-mm segment was evaluated to determine the effect of the baseline local ESS and plaque characteristics (as continuous variables) on the change in vascular outcome variables (as continuous variables) in the same segment. (II.) We analyzed the natural history of obstructions at baseline since arterial areas with a lumen narrowing at baseline may be particularly likely to exhibit worsening obstruction in followup. We analyzed those arterial areas of 5 sequential 3-mm segments at baseline within which a discrete luminal narrowing (“throat”) was present in the middle, surrounded by two 3-mm segments with progressive narrowing on either side of the throat. Each two 3-mm segments proximal (upstream) to the throat had to exhibit progressive decrease in lumen area >0.1 mm² compared to the preceding 3-mm segments and each 3-mm segments distal (downstream) to the throat had to exhibit progressive increase in lumen area >0.1 mm² compared to the preceding 3-mm segments. These baseline lumen narrowings were evaluated for change in obstruction at followup, and the baseline ESS was investigated to determine its role in the outcome. (III.) We identified those patients who underwent a PCI during the followup because of new clinical symptoms or substantial worsening of the luminal obstruction, and we investigated
the antecedent vascular characteristics responsible for the clinically relevant change in lumen obstruction.

The PREDICTION Study is an observational natural history study. The primary endpoint when the study was designed in 2006 was change in plaque area, but we also identified a variety of secondary exploratory endpoints. We include plaque burden as an endpoint to reflect a combined endpoint of both plaque and EEM areas.

**Statistical Analysis**

Categorical variables are presented as counts and percentages; continuous variables are summarized as mean±SEM or median and interquartile range (IQR) as appropriate. Several statistical methods were used to correct for systematic error (non-independence of observations) introduced by the clustering of multiple arterial 3-mm segments or lumen narrowings within patients. First, to investigate the association of continuous response variables (e.g., change in plaque burden) with categorical variables (e.g., baseline ESS category), mixed-effects ANOVA with the patient and artery designated as random effects was used. *P* values were adjusted for multiple comparisons with the use of the Scheffé method. Second, to investigate the relationship between continuous response variables and continuous predictors (e.g., ESS magnitude), linear mixed modeling was employed. Third, to investigate the association of binary anatomic outcomes (e.g., progressive decrease in lumen area, worsening luminal narrowing treated with PCI) with baseline variables, mixed-effects logistic regression was implemented. Baseline variables associated with anatomic outcomes on univariable analysis at *P* level <0.1 were considered for entry in the respective multivariable models and final selection of independent predictors was performed with a backward stepping algorithm (criterion for retention: *P*<0.1). In logistic regression modeling, cut points for dichotomizing continuous anatomic variables were
selected by receiver operator characteristic (ROC) analysis which best predicted each outcome (ROC criterion: max[sensitivity+specificity]). All statistical tests were 2-tailed and an alpha level of 0.05 was used to determine statistical significance. All analyses were performed with Stata 10.0 (StataCorp LP, College Station, Tex) and SPSS 17.0 (SPSS Inc, Chicago, Ill).

The study was approved by the institutional review board at each hospital and each patient gave written informed consent.

Results

Enrollment was initiated on April 7, 2007 and the last subject followup visit was on October 18, 2010. Five hundred six subjects were enrolled at 17 clinical sites in Japan. The index ACS event included an ST-elevation MI (STEMI) in 291 patients (57.5%), non-STEMI in 60 patients (11.9%), and unstable angina in 155 patients (30.6%). One-year followup was completed in 502 (99.2%) patients. Two patients (0.4%) were lost to followup and 2 patients (0.4%) withdrew consent to participate.

Baseline VP data were obtained in all enrolled patients, and were analyzable for 496 (98.0%) patients: a total of 1,341 arteries were analyzable (2.7 arteries/patient). Followup VP data for serial anatomic natural history analyses were obtained in 374 (74%) consecutive patients. Baseline and followup VP data were analyzable for 329 (88.0%) of the 374 patients, including VP data from 824 pairs of arteries.

The reconstructed coronary arteries (mean length/artery 47.6±0.44 mm) were divided into consecutive 3-mm length segments (19,875 3-mm segments; 13,788 3-mm segments in native areas). Each segment was characterized by local predominant ESS value (defined as the minimum averaged ESS value over a 90° arc in each 3-mm segment), plaque and lumen area,
plaque burden (plaque area/EEM area) and remodeling pattern. For analysis of serial anatomic changes, each arterial segment at baseline was compared with the identical segment at followup (8,137 3-mm segments in native areas with available baseline and followup VP data).

This report focuses on the natural history and outcomes of the native (non-stented) coronary segments.

**Patient Demographics**

The patient characteristics are presented in Table 1. A majority of patients had substantial coronary risk factors, but only 59 (11.7%) had a history of prior CAD. Blood pressure at baseline was well-controlled and fasting lipids were modestly elevated. Cardiac risk, assessed by CRP, was low. At hospital discharge most patients were on dual anti-platelet therapy and routine vasculoprotective therapies (Table 2).

**Safety of Vascular Profiling Procedures**

895 VP procedures were performed. There were 5 complications (0.6%): coronary artery dissection in 3 and transient neurologic deficit in 2 patients. There were no long-term consequences from these complications and hospital stay was not prolonged.

**Analysis of Anatomic Natural History Outcomes**

I. Effect of baseline vascular characteristics on vascular outcomes at followup in each 3-mm segment (Table 3 and Supplemental Table 1S)

(a) Primary Endpoint - Change in Plaque Area

Plaque area increase at followup, after adjustment for the baseline plaque area, was independently associated with baseline large plaque burden, lumen area, and excessive expansive remodeling.(Table 3) Using baseline ESS as a categorical variable based on terciles, low ESS was not associated with a change in plaque area.(Figure 1A)
(b) Secondary Endpoint - Change in Lumen Area

Lumen area decrease, after adjustment for baseline lumen area, was independently associated with baseline large plaque burden, low ESS, excessive expansive remodeling and distal location of the segment. (Table 3) Baseline low ESS as a categorical variable was associated with a significant decrease in lumen area. (Figure 1B)

(c) Exploratory Endpoint - Change in Plaque Burden

Plaque burden increase, after adjustment for baseline plaque burden, was independently associated with baseline low ESS, excessive expansive remodeling, large lumen area and more proximal location of the segment. (Table 3) Using ESS as a categorical variable, baseline low ESS was associated with a significant increase in plaque burden. (Figure 1C)

II. Natural History of Baseline Discrete Luminal Narrowings Based on Local Vascular Characteristics

The majority of lumen obstructions (53%) at followup originated from areas with pre-existing mild lumen narrowing at baseline. In these baseline narrowings ESS was primarily moderate proximal to the throat; high just proximal to, and at, the throat; and low distal to the throat. (Figure 2)

Low ESS distal to the throat was significantly associated with different magnitudes of worsening of luminal area obstruction at followup. (Figure 3)

III. Natural History of Clinically Relevant Luminal Obstructions Treated with a PCI at Followup (Tables 4, 5 and Supplemental Table 2S; Figures 4 and 5)

PCI was performed in followup in 59 native lesions in 53 patients (10.5%) either for development of a new clinical event or because of identification of a significantly worsening obstruction in a patient who underwent routine followup coronary angiography. New clinical
events consisted of a new ACS in 13 patients (2.6%), which occurred in a native portion of the coronary artery in only 4 patients (0.8%); and worsening stable angina in 15 patients (3%), which occurred in a native segment in 10 patients (2%). Thirty-nine patients (7.8%) had a PCI performed in the absence of symptoms because a worsening native luminal obstruction was observed at the time of the routine followup cardiac catheterization (luminal %diameter stenosis measured by quantitative coronary angiography changed from 42.4±1.6% at baseline to 58.6±1.5% at followup; p<0.001).

Independent vascular predictors of baseline substantial luminal narrowings (i.e., minimal lumen area <6 mm², which corresponded approximately to the lower tercile of lumen area) treated with PCI for lesion progression or occurrence of symptoms during followup were large plaque burden and low ESS. (Table 5, Figure 4) There was no significant relationship between plaque burden at the throat and ESS distal to the throat.

The positive predictive value of baseline vascular characteristics to identify a lesion that progressed clinically at followup rose from 22% if only large plaque burden was present to 41% if both large plaque burden and low ESS were present. (Figure 5) Negative predictive value remained high if both large plaque burden and low ESS were absent. One hundred and ten patients (22.3%) had at least one substantial luminal narrowing with large plaque burden at baseline, 50 patients (10.0%) had a substantial luminal narrowing with low ESS at baseline, and 31 patients (6.2%) had a substantial luminal narrowing with both large plaque burden and low ESS.

There was no significant, meaningful association of clinical characteristics at baseline and subsequent vascular change. (Supplemental Tables 3S and 4S)

**Analysis of Clinical Outcomes**
Clinical events were infrequent during the one-year followup. (Table 6) There were a total of 7 deaths (1.4%) and only one (0.2%) cardiac death. An ACS occurred in 13 patients (2.6%; 4 patients [0.8%] with the culprit segment in a native vessel area). Hospitalization for worsening stable angina occurred in 15 patients (3.0%; 7 patients [0.8%] with the culprit segment in a native vessel area; 3 patients [0.6%] with both a native and a stented segment treated with revascularization).

There were too few patients with symptomatic clinical events to make meaningful statistical inferences between baseline vascular characteristics and symptomatic clinical outcome events.

Discussion

The PREDICTION Study is unique in that it presents the largest and most comprehensive serial anatomic natural history study of coronary atherosclerosis ever performed and utilized innovative methodologies to investigate potential pathophysiologic mechanisms responsible for CAD progression. The goal of these natural history investigations in consecutive patients with high-risk CAD was to identify the early plaque and arterial wall characteristics that precede the subsequent progression of lesions leading to acute plaque rupture or accelerated luminal obstruction. Our multi-tiered natural history analyses indicate that plaque burden is the most powerful predictor of plaque progression and luminal obstruction and that low ESS provides substantial additive independent prognostication. The combination of the independent baseline predictors of plaque burden and low ESS had a 41% positive predictive value to predict clinically relevant obstruction progression treated with PCI, but the combination of these vascular characteristics at baseline was infrequent (6%). Symptomatic clinical events were
uncommon in these patients well-controlled following an ACS and lack of statistical power precluded analyses to investigate the role of vascular characteristics at baseline to predict new symptomatic clinical events.

The changes in coronary plaque and arterial remodeling observed in the PREDICTION Study, and the prominent role of local ESS in the atherogenic processes associated with those changes in coronary anatomy, are remarkably similar to the observations in the atherosclerotic pig model\textsuperscript{2,7,15} and small pilot studies in man.\textsuperscript{16,17} In the diabetic, hypercholesterolemic pig low ESS was an independent predictor of the development of high-risk TCFAs and the magnitude of the atherogenic phenotype was inversely related to the magnitude of local ESS.\textsuperscript{7,15,18} The magnitude of progression of coronary lesions we observed in humans in the PREDICTION Study was not as marked as the progression observed in the pig model, but the pigs were rendered diabetic and intensely hypercholesterolemic (mean serum cholesterol 611±28 mg/dl), and the duration of followup was relatively prolonged.\textsuperscript{7,15} The central pro-atherogenic role of low ESS in man is underscored by the observation in the PREDICTION Study that baseline low ESS was an independent predictor responsible for plaque progression and worsening luminal obstruction both in the routine natural history of CAD and in the development of clinically relevant lesions treated with PCI. This relationship between local low ESS and atherosclerosis is particularly impressive since these coronary patients were followed clinically over a brief 12-month followup period (and assessment of anatomic natural history was performed only 6-10 months after the ACS), they were aggressively managed with vasculoprotective agents, and their cardiovascular risk was low.

Baseline large plaque burden and local low ESS were independently associated at followup with an increase in plaque burden and decrease in lumen area, as well as clinical...
worsening of luminal obstruction treated with a PCI. Local low ESS environment may lead to 
plaque development, progression, and formation of rupture-prone TCFA\(^2,7,15\) which initially 
may not obstruct the lumen, but may rupture and precipitate either a new ACS or rapid 
progression of a fixed plaque. Plaque progression may have occurred in these regions as a result 
of intraplaque hemorrhage, due to subclinical plaque rupture or disruption of intraplaque vasa 
vasorum, associated with consequent fibrosis and worsening luminal obstruction.\(^9,19,20\) Plaque 
progression with a decrease in lumen and EEM area may also result from a more direct 
phenotypic expression of fibrosis and scarring.

We did not observe that baseline high ESS was associated with plaque progression or 
progressive luminal obstruction. Other investigators have suggested that high ESS may promote 
transformation of a plaque to a high-risk phenotype.\(^21,22\) Small studies have observed that plaque 
rupture in the coronary and carotid circulations may be related to areas of high ESS.\(^23,24\)

We observed very few ACS events in our patients, despite the presence of substantial 
traditional risk factors and a recent ACS. This relatively benign outcome may be due to the 
effective vasculoprotective treatments provided to these patients or may reflect the relatively low 
genetic cardiovascular risk of the Japanese population compared to a Western population.\(^25\)

Although we did not observe an effect of systemic risk factors on coronary anatomic 
outcomes, local factors are only important in the context of the presence of systemic risk factors. 
Recent studies suggest that high-risk plaque characteristics in the carotid artery may be 
associated with adverse vascular outcomes in other vascular territories.\(^26\)

Although low ESS was an independent predictor of plaque burden increase in followup, 
we found that low ESS did not independently predict plaque area increase. The majority of 
patients in the PREDICTION Study were statin-naive prior to their index coronary event and
were administered statins only after their presentation with an ACS. There may have been global regression of atherosclerotic plaque area from the initiation of statins during the followup period\(^27\) (Figure 1A), as well as an additional effect of plaque morphology change or EEM shrinkage from local low ESS and associated pathobiology, manifesting as an associated increase in plaque burden and decrease in lumen area.(Figure 1C)

The observations in the PREDICTION Study are complementary to the recent observations in the PROSPECT Study, and provide new mechanistic insights that may elucidate the underlying pathobiology of plaque progression and the development of clinical events. In PROSPECT 697 patients with an ACS underwent 3-vessel coronary angiography and IVUS imaging after PCI.\(^10\) Multivariable analysis indicated that non-culprit lesions associated with subsequent major adverse cardiovascular events (MACE) were characterized at baseline by large plaque burden (≥70%), small minimal luminal area (≤4.0 mm\(^2\)), and appearance of a TCFA by radiofrequency IVUS. The hazard ratio for MACE at 3 years was high (11.05) if all 3 lesion characteristics were present at baseline, but only 4.2% of patients manifested these criteria. Assessment of local ESS was not performed in PROSPECT. As in PROSPECT, only 6% of PREDICTION patients manifested the highest risk lesion profile of large plaque burden and low ESS, but these patients had a 41% incidence of PCI for clinically relevant obstructions. We speculate that the small proportion (3.3%) of plaques with baseline large plaque burden that progressed to cause cardiac events in PROSPECT were those plaques exposed to a low ESS environment, which stimulated progressive inflammation and atherogenesis, culminating in an abrupt luminal change.

Although plaque characterization and estimation of TCFA by radiofrequency IVUS analyses were not available in the PREDICTION Study, large plaque burden was an independent
predictor of an adverse outcome in both PREDICTION and PROSPECT. In PREDICTION there was no relationship between plaque burden and low ESS. The variable of local ESS, uniquely available in the PREDICTION Study, provided substantial independent incremental predictive insight, with the combined presence of low ESS and large plaque burden having a positive predictive value of 41% to identify lesions at baseline likely to require PCI in the next year.

Limitations

The study is limited by the small number of clinical events which occurred in the 1-year followup. Many of the clinical events were also primarily asymptomatic and consisted of significant lumen progression treated with PCI. There were few patients with hard ischemic endpoints. There were only 14 (3%) symptomatic clinical events (related to native segments) in the one year followup. Furthermore, a number of the culprit lesions in native areas responsible for clinical events were either proximal or distal to the IVUS acquisition pullback and thus not available for detailed VP investigation (proximal, n=4; distal, n=7; left main coronary artery, n=3; VP data not available or usable, n=4). We are also limited by not having radiofrequency IVUS characterization of plaque constituents available, although the accuracy of the histologic correlation of such characterization has recently been called into question.28,29

Our predictive analyses utilize both continuous and categorical baseline variables since the continuous variables are essential to prove the pathobiological relationship between baseline vascular characteristics and outcomes, but the categorical variables, derived either by non-biased terciles or cut-points determined by ROC analyses, provide a way to compare the quantitative relationships we observed to the relationships in similar studies performed by investigators who utilize categorical baseline variables.2,21-23 We emphasize that this study is a natural history study and our conclusions are primarily exploratory. All of our analyses have been pre-specified,
but some of the specific threshold values of ESS, plaque area/burden, and lumen narrowings were determined post-hoc empirically within the PREDICTION dataset. Also, all patients were post-PCI for an ACS and we do not know how the findings translate to asymptomatic or stable patients.

In summary, the PREDICTION Study demonstrated that routine 3-vessel IVUS can be safely performed in high-risk patients following successful PCI for an ACS, and that progression of plaque burden and luminal obstruction can be predicted on the basis of the presence of substantial plaque and low ESS at baseline. Most clinical events in followup in this population consisted of either asymptomatic or symptomatic progressive luminal narrowing with stable symptoms; ACS events were very infrequent. It remains to be confirmed whether early identification of high-risk lesions is enhanced by determination of local ESS and whether such insights will be clinically useful to guide patient management.

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Conflict of Interest Disclosures: None.

References


Table 1. Baseline Demographics and Clinical Characteristics

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<th>Characteristic</th>
<th>All Patients (N=506)</th>
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<td>Gender</td>
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<tr>
<td>Male, n (%)</td>
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<td>C-Reactive Protein, mg/dl</td>
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Continuous variable data are presented as median (interquartile range).

Table 2. Medications at Hospital Discharge

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<th>Medical Therapy</th>
<th>All Patients (n=506)</th>
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<tr>
<td>Statin, n (%)</td>
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<td>Other Lipid Lowering Medications, n (%)</td>
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<td>Acetylsalicylic Acid, n (%)</td>
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<tr>
<td>Beta Blocker, n (%)</td>
<td>169 (33.4)</td>
</tr>
<tr>
<td>Calcium Channel Blocker, n (%)</td>
<td>130 (25.7)</td>
</tr>
<tr>
<td>Long-Acting Nitrate, n (%)</td>
<td>98 (19.4)</td>
</tr>
<tr>
<td>ACE-Inhibitor/Angiotensin Receptor Blocker, n (%)</td>
<td>300 (59.3)</td>
</tr>
<tr>
<td>Ticlopidine, n (%)</td>
<td>146 (28.9)</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>347 (68.6)</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme
Table 3. Independent Baseline Predictors of the Change (follow-up measurement minus baseline measurement) in Anatomic Outcomes in 3-mm segments (n=8,137).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline Independent Predictor</th>
<th>Beta (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Plaque Area (mm²)</td>
<td>ESS (per 1 Pa decrease)</td>
<td>-0.02 (-0.06 to 0.02)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>0.06 (0.04 to 0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Area (per 1 mm² increase)</td>
<td>-0.16 (-0.18 to -0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>0.11 (0.04 to 0.19)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs. Compensatory/Constrictive</td>
<td>0.09 (0.001 to 0.176)</td>
<td>0.047</td>
</tr>
<tr>
<td>Change in Lumen Area (mm²)</td>
<td>ESS (per 1 Pa decrease)</td>
<td>-0.08 (-0.14 to -0.02)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>-0.23 (-0.26 to -0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>-0.09 (-0.17 to -0.02)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Arterial Location (per 10-mm increase)</td>
<td>-0.15 (-0.20 to -0.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs. Compensatory/Constrictive</td>
<td>-0.25 (-0.39 to -0.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in Plaque Burden (%)</td>
<td>ESS (per 1 Pa decrease)</td>
<td>0.25 (0.05 to 0.46)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>0.17 (0.09 to 0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>1.42 (1.61 to 1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Arterial Location (per 10-mm increase)</td>
<td>-0.13 (-0.26 to -0.01)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs. Compensatory/Constrictive</td>
<td>0.74 (0.32 to 1.15)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The results for change in plaque area are presented without removing the primary variable of interest (i.e., ESS), which was not significant, from the backward stepwise process of the multivariable analysis. Variables entered in the multivariable model: (A) Change in plaque area: ESS, lumen area, plaque area, plaque burden and remodeling pattern; (B) Change in lumen area: ESS, lumen area, plaque burden, longitudinal arterial location and remodeling pattern; (C) Change in plaque burden: ESS, lumen area, plaque area, plaque burden, longitudinal arterial location and remodeling pattern.

Table 4. Coronary Lesions Treated with PCI During Followup

<table>
<thead>
<tr>
<th>PCI Outcomes During Followup</th>
<th>Patients (N=502)</th>
<th>Treated Lesions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Acute Coronary Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native area</td>
<td>13 (2.6%)</td>
<td>13</td>
</tr>
<tr>
<td>Worsening Stable Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native area</td>
<td>4 (0.8%)</td>
<td>4</td>
</tr>
<tr>
<td>Absence of Symptoms but Substantial Obstruction Progression†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native area</td>
<td>102 (20.3%)</td>
<td>122</td>
</tr>
<tr>
<td>Data on patient classification are not mutually exclusive.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*A total of 59 native areas and 96 previously stented areas (in-stent restenosis or thrombosis) were treated with PCI at followup.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Substantial obstruction progression defined as: (i) lumen area decrease &gt;1.8 mm² or &gt;20% by 3D-model-based measurements in cases with available baseline and follow-up vascular profiling data; and (ii) lumen diameter decrease &gt;20% by angiography in cases without available follow-up vascular profiling data.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Baseline Anatomic Predictors (continuous data) of PCI for Clinically Relevant Baseline Luminal Narrowings (n=250)

A. Univariable Analysis

<table>
<thead>
<tr>
<th>Baseline Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Burden at Throat (per 10% increase)</td>
<td>2.61 (1.63-4.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS Distal to Throat (per 1 Pa decrease)</td>
<td>1.60 (0.97-2.63)</td>
<td>0.067</td>
</tr>
<tr>
<td>Plaque Area at Throat (per 1 mm² increase)</td>
<td>1.26 (1.13-1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen Area at Throat (per 1 mm² increase)</td>
<td>0.88 (0.56-1.39)</td>
<td>0.59</td>
</tr>
<tr>
<td>Longitudinal Arterial Location at Throat (per 10-mm increase)</td>
<td>0.78 (0.59-1.04)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

B. Multivariable Analysis

<table>
<thead>
<tr>
<th>Baseline Independent Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Burden at Throat (per 10% increase)</td>
<td>2.79 (1.69-4.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS Distal to Throat (per 1 Pa decrease)</td>
<td>1.59 (0.98-2.59)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Variables entered in the multivariable model: ESS distal to the throat; plaque area, plaque burden and longitudinal arterial location at the throat.

Table 6. Clinical Outcomes After One Year Followup

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up Complete</td>
<td>502 (99.2%)</td>
</tr>
<tr>
<td>Total Death</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Non-cardiac Death</td>
<td>6 (1.2%)</td>
</tr>
<tr>
<td>Acute Coronary Syndrome*</td>
<td>13 (2.6%)</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>11 (2.2%)</td>
</tr>
<tr>
<td>Non-ST-elevation MI</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Hospitalization for Stable Angina*</td>
<td>15 (3.0%)</td>
</tr>
</tbody>
</table>

*Data classification is not mutually exclusive.

Figure Legends:

Figure 1. Effect of Baseline ESS on Vascular Outcomes at Followup in Coronary Artery Segments. Cut-points for the 3 ESS categories were derived from the terciles of the frequency distribution in 3-mm segments. P values refer to the univariable analysis and are corrected for the clustering of arteries and segments within patients and for multiple comparisons. Error bars represent SEM.
Figure 2. Baseline ESS Patterns Along the Course of a Coronary Artery Obstruction. The 3 ESS categories (low: <1 Pa; moderate: 1-1.7 Pa; high: >1.7 Pa) in the bar graph were derived from the terciles of the ESS frequency distribution in 3-mm segments. NC, necrotic core.

Figure 3. Effect of Baseline ESS on Magnitude of Worsening Severity of Luminal Obstruction at Followup (408 narrowings in 241 patients). The 3 ESS categories (low: <1 Pa; moderate: 1-1.7 Pa; high: >1.7 Pa) were derived from the terciles of the baseline ESS frequency distribution in 3-mm segments. P values are for testing the independence between ESS category (3 groups) and the binary outcome.

Figure 4. Independent Predictors of PCI for Clinically Relevant Baseline Luminal Narrowings. Prediction of PCI for baseline luminal narrowings with small minimal lumen area (<6 mm²; n=250). Variables entered in the multivariable model: ESS, plaque area, plaque burden and longitudinal arterial location. Cut-points for continuous baseline variables were selected by ROC analysis which best predicted PCI occurrence: low ESS (<0.98 Pa), large plaque area (≥7.30 mm²), large plaque burden (≥58.0%) and proximal arterial location (<25.4 mm). Error bars are 95% confidence intervals for odds ratios.

Figure 5. Incidence of PCI for Clinically Relevant Baseline Luminal Narrowings. Incidence of PCI (n=31) for baseline luminal narrowings with small minimal lumen area (<6 mm²; n=250) according to the presence of independent predictors: large plaque burden (n=131), low ESS (n=53) and their combination (n=32). P values are for comparing the incidence of PCI in baseline luminal narrowings with vs. without the predictor(s). Data on prevalence are for one or more such baseline luminal narrowings per patient.
Blood flow

Proximal (Upstream) Shoulder  Throat of Obstruction  Distal (Downstream) Shoulder

NC

Baseline ESS Category
- Low ESS
- Moderate ESS
- High ESS

Percent of Baseline Luminal Narrowings

30% 34% 36% 24% 67% 73% 36% 39% 25% 60% 31% 9%

2 segments Proximal to Throat  Segment Proximal to Throat  Segment at Throat  Segment Distal to Throat  2 segments Distal to Throat

3-mm Segment Along Course of Coronary Artery
Decrease in lumen area > 2.4 mm² (20th percentile; N=86) p=0.013

Decrease in lumen area > 3.6 mm² (10th percentile; N=40) p=0.021

Decrease in lumen area > 4.7 mm² (5th percentile; N=20) p=0.027

Baseline Endothelial Shear Stress Distal To Throat
PCI for Clinically Relevant Baseline Luminal Narrowings

Independent Predictors

Large Plaque Burden
At Throat

Low ESS
Distal to Throat

Odds Ratio

17.57
(3.67-84.20)
p<0.001

3.18
(1.20-8.43)
p=0.020
Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics: The PREDICTION Study


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SUPPLEMENTAL MATERIAL

Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics: The PREDICTION Study

Peter H. Stone, MD, Shigeru Saito, MD, Saeko Takahashi, MD, Yasuhiro Makita, MD, Shigeru Nakamura, MD, Tomohiro Kawasaki MD, Akihiko Takahashi, MD, Takaaki Katsuki, MD, Sunao Nakamura, MD, Atsuo Namiki, MD, Atsushi Hirohata, MD, Toshiyuki Matsumura, MD, Seiji Yamazaki, MD, Hiroyoshi Yokoi, MD, Shinji Tanaka, MD, Satoru Otsuji, MD, Fuminobu Yoshimachi, MD, Junko Honye, MD, Dawn Harwood, PhD, Martha Reitman, MD, Ahmet U. Coskun, PhD, Michail I. Papafaklis, MD, PhD, Charles L. Feldman, ScD, for the PREDICTION Investigators
Vascular Profiling Methods:

Intracoronary vascular profiling used methodology previously described and validated in vivo. In brief, the 3D anatomy of the coronary artery was reconstructed from intravascular ultrasound (IVUS) images and biplane coronary angiography. Intravascular ultrasound (IVUS) (Galaxy IVUS system with the Atlantis 40 MHz SR Pro IVUS catheter, Boston Scientific, Natick, MA) was performed with automated pullback at 0.5 mm/sec. The arterial lumen and external elastic lamina were segmented from digitized end-diastolic IVUS images. The physical 3D path of the IVUS transducer during pullback was reconstructed using the corresponding biplane angiographic projections, and the segmented IVUS images were located along this path and oriented appropriately. Lumen and external elastic membrane boundary points were connected by spline curves to rebuild the lumen and external elastic membrane geometry in 3D space, respectively. A structured grid was employed to represent the lumen volume. Coronary blood flow for the reconstructed arterial segment was calculated directly from the time required for the volume of blood contained within the segment to be displaced by radio-opaque material during a contrast injection. Blood was treated as a Newtonian fluid and its viscosity was estimated using the hematocrit and TC. Detailed intravascular flow characteristics were obtained by Computational Fluid Dynamics, solving the transport equations governing the conservation of mass and momentum (Phoenics, Cham Ltd, London, UK). The governing equations of blood flow were determined assuming that the arterial wall is stiff, blood is incompressible, and coronary blood flow is steady. The inlet velocity was assumed to be uniform, developed flow was assumed to be established after an entrance length of 3mm, and flow was ignored for the first 3 mm. The distortions introduced by these assumptions were insignificant at the Reynolds numbers observed in this study. Endothelial shear stress at the lumen surface of the artery was
calculated as the product of blood viscosity and the gradient of blood velocity at the wall. The reproducibility of our methodology of flow rate measurement has been previously reported.³
### Supplemental Tables

Table 1S. Univariable Analyses (Mixed-Effects Linear Regression) on the Relationship Between Change in Anatomic Outcomes and Baseline Anatomic Characteristics (3-mm segments; n=8,137)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline Predictor</th>
<th>Beta (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in Plaque Area (mm²)</strong></td>
<td><strong>Baseline Predictor</strong></td>
<td><strong>Beta (95% CI)</strong></td>
<td><strong>p value</strong></td>
</tr>
<tr>
<td></td>
<td>Endothelial Shear Stress (per 1 Pa decrease)</td>
<td>0.05 (0.014 to 0.086)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>0.020 (0.006 to 0.035)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Plaque Area (per 1 mm² increase)</td>
<td>-0.115 (-0.133 to -0.097)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>-0.28 (-0.33 to -0.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Arterial Location (per 10 mm increase)</td>
<td>-0.01 (-0.04 to 0.02)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs.</td>
<td>0.19 (0.09 to 0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Compensatory/Constrictive</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change in Lumen Area (mm²)</strong></td>
<td><strong>Baseline Predictor</strong></td>
<td><strong>Beta (95% CI)</strong></td>
<td><strong>p value</strong></td>
</tr>
<tr>
<td></td>
<td>Endothelial Shear Stress (per 1 Pa decrease)</td>
<td>-0.43 (-0.48 to -0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>-0.19 (-0.21 to -0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Area (per 1 mm² increase)</td>
<td>-0.01 (-0.03 to 0.01)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>0.32 (0.27 to 0.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Arterial Location (per 10 mm increase)</td>
<td>0.04 (0.01 to 0.09)</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs.</td>
<td>-1.07 (-1.25 to -0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Compensatory/Constrictive</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change in Plaque Burden (%)</strong></td>
<td><strong>Baseline Predictor</strong></td>
<td><strong>Beta (95% CI)</strong></td>
<td><strong>p value</strong></td>
</tr>
<tr>
<td></td>
<td>Endothelial Shear Stress (per 1 Pa decrease)</td>
<td>1.07 (0.90 to 1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Lumen Area (per 1 mm² increase)</td>
<td>0.43 (0.37 to 0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Area (per 1 mm² increase)</td>
<td>-0.28 (-0.35 to -0.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Plaque Burden (per 10% increase)</td>
<td>-1.58 (-1.78 to -1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Longitudinal Arterial Location (per 10 mm increase)</td>
<td>-0.12 (-0.25 to 0.012)</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>Remodeling Pattern: Excessive Expansive vs.</td>
<td>2.57 (2.12–3.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Compensatory/Constrictive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2S. Categorical Baseline Anatomic Predictors (Univariable Analysis; Mixed-Effects Logistic Regression) of Percutaneous Coronary Intervention for Clinically Relevant Baseline Luminal Narrowings (small minimal lumen area: <6 mm² at the throat; n=250).

<table>
<thead>
<tr>
<th>Baseline Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Plaque Burden (≥ 58.0%)* at Throat</td>
<td>18.42 (3.88-87.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large Plaque Area (≥ 7.30 mm²)* at Throat</td>
<td>9.61 (3.18-29.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Endothelial Shear Stress (&lt; 0.98 Pa)* Distal to Throat</td>
<td>3.52 (1.40-8.88)</td>
<td>0.008</td>
</tr>
<tr>
<td>Proximal (&lt; 25.4 mm)* Arterial Location at Throat</td>
<td>3.22 (1.17-8.87)</td>
<td>0.024</td>
</tr>
<tr>
<td>Small Lumen Area (&lt; 3.77 mm²)* at Throat</td>
<td>1.86 (0.73-4.71)</td>
<td>0.19</td>
</tr>
<tr>
<td>Remodeling Pattern at Throat: Constrictive vs. Compensatory/Excessive Expansive</td>
<td>1.72 (0.75-4.01)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Cut-points for continuous baseline variables were selected by ROC analysis which best predicted PCI occurrence.
Table 3S: Relationship Between Change in Anatomic Outcomes (3-mm segments; n=8,137) and Baseline Patient-Level Clinical Characteristics (Univariable Analysis; Mixed-Effects Linear Regression).

A. Change in Plaque Area:

<table>
<thead>
<tr>
<th>Baseline Clinical Variable</th>
<th>Beta (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>0.04 (−0.03 to 0.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender (Male vs. Female)</td>
<td>−0.096 (−0.304 to 0.113)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension History</td>
<td>0.08 (−0.09 to 0.25)</td>
<td>0.34</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>−0.24 (−0.47 to −0.01)</td>
<td>0.041</td>
</tr>
<tr>
<td>High LDL History</td>
<td>−0.09 (−0.28 to 0.09)</td>
<td>0.33</td>
</tr>
<tr>
<td>Low HDL History</td>
<td>−0.16 (−0.32 to 0.01)</td>
<td>0.063</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>−0.03 (−0.21 to 0.14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Insulin-dependence</td>
<td>0.31 (−0.23 to 0.85)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking History</td>
<td>−0.03 (−0.19 to 0.14)</td>
<td>0.74</td>
</tr>
<tr>
<td>Family History</td>
<td>0.28 (−0.03 to 0.59)</td>
<td>0.079</td>
</tr>
<tr>
<td>Coronary Artery Disease History</td>
<td>0.40 (0.14 to 0.66)</td>
<td>0.003</td>
</tr>
<tr>
<td>Statin use</td>
<td>−0.08 (−0.25 to 0.10)</td>
<td>0.41</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.23 (−0.02 to 0.48)</td>
<td>0.074</td>
</tr>
<tr>
<td>Total Cholesterol (per 10 mg/dl)</td>
<td>−0.003 (−0.022 to 0.016)</td>
<td>0.78</td>
</tr>
<tr>
<td>(available in 7,988 segments in 317pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (per 10 mg/dl) (available in 7,823 segments in 311pts)</td>
<td>−0.008 (−0.032 to 0.016)</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL (per 10 mg/dl) (available in 8,099 segments in 322 pts)</td>
<td>0.056 (−0.009 to 0.120)</td>
<td>0.090</td>
</tr>
<tr>
<td>C-Reactive Protein (per 1 mg/dl)</td>
<td>0.018 (−0.028 to 0.064)</td>
<td>0.44</td>
</tr>
<tr>
<td>(available in 7,841 segments in 312pts)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Change in Plaque Burden:

<table>
<thead>
<tr>
<th>Baseline Clinical Variable</th>
<th>Beta (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>−0.03 (−0.32 to 0.26)</td>
<td>0.83</td>
</tr>
<tr>
<td>Gender (Male vs. Female)</td>
<td>−0.27 (−1.09 to 0.54)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.52 (−0.14 to 1.18)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>−0.61 (−1.51 to 0.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>High LDL History</td>
<td>−0.22 (−0.96 to 0.52)</td>
<td>0.56</td>
</tr>
<tr>
<td>Low HDL History</td>
<td>−0.72 (−1.37 to −0.07)</td>
<td>0.031</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>−0.09 (−0.78 to 0.61)</td>
<td>0.81</td>
</tr>
<tr>
<td>Insulin-dependence</td>
<td>1.61 (−0.51 to 3.74)</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoking</td>
<td>−0.14 (−0.79 to 0.50)</td>
<td>0.66</td>
</tr>
<tr>
<td>Family History</td>
<td>0.33 (−0.91 to 1.57)</td>
<td>0.60</td>
</tr>
<tr>
<td>Baseline Clinical Variable</td>
<td>Beta (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.7 (−0.02 to 0.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Gender (Male vs. Female)</td>
<td>0.07 (−0.19 to 0.33)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.17 (−0.38 to 0.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>−0.06 (−0.34 to 0.23)</td>
<td>0.68</td>
</tr>
<tr>
<td>High LDL History</td>
<td>−0.10 (−0.33 to 0.14)</td>
<td>0.41</td>
</tr>
<tr>
<td>Low HDL History</td>
<td>0.07 (−0.14 to 0.28)</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>−0.02 (−0.24 to 0.21)</td>
<td>0.89</td>
</tr>
<tr>
<td>Insulin-dependence</td>
<td>−0.09 (−0.77 to 0.59)</td>
<td>0.79</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.03 (−0.17 to 0.24)</td>
<td>0.77</td>
</tr>
<tr>
<td>Family History</td>
<td>0.22 (−0.17 to 0.62)</td>
<td>0.27</td>
</tr>
<tr>
<td>Coronary Artery Disease History</td>
<td>−0.01 (−0.34 to 0.33)</td>
<td>0.98</td>
</tr>
<tr>
<td>Statin use</td>
<td>−0.08 (−0.31 to 0.14)</td>
<td>0.45</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>−0.07 (−0.38 to 0.25)</td>
<td>0.68</td>
</tr>
<tr>
<td>Total Cholesterol (per 10 mg/dl) (available in 7,988 segments in 317pts)</td>
<td>−0.02 (−0.04 to 0.01)</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL (per 10 mg/dl) (available in 7,823 segments in 311pts)</td>
<td>−0.02 (−0.05 to 0.01)</td>
<td>0.14</td>
</tr>
<tr>
<td>HDL (per 10 mg/dl) (available in 8,099 segments in 322 pts)</td>
<td>−0.06 (−0.10 to 0.01)</td>
<td>0.11</td>
</tr>
<tr>
<td>C-Reactive Protein (per 1 mg/dl) (available in 7,841 segments in 312 pts)</td>
<td>−0.01 (−0.06 to 0.04)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Table 4S. Univariable Analysis (mixed-effects logistic regression) of the effect of Baseline Patient-Level Clinical Characteristics on Percutaneous Coronary Intervention for Clinically Relevant Baseline Luminal Narrowings (small minimal lumen area: <6 mm$^2$ at the throat; n=250).

<table>
<thead>
<tr>
<th>Baseline Clinical Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>0.87 (0.60-1.28)</td>
<td>0.48</td>
</tr>
<tr>
<td>Gender (Male vs. Female)</td>
<td>1.53 (0.47-4.93)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.15 (0.48-2.76)</td>
<td>0.75</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.26 (0.59-8.65)</td>
<td>0.24</td>
</tr>
<tr>
<td>High LDL History</td>
<td>1.31 (0.49-3.46)</td>
<td>0.59</td>
</tr>
<tr>
<td>Low HDL History</td>
<td>1.70 (0.73-3.98)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.84 (0.34-2.07)</td>
<td>0.70</td>
</tr>
<tr>
<td>Insulin-dependence</td>
<td>1.87 (0.31-11.27)</td>
<td>0.49</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.91 (0.39-2.08)</td>
<td>0.81</td>
</tr>
<tr>
<td>Family History</td>
<td>1.98 (0.53-7.36)</td>
<td>0.31</td>
</tr>
<tr>
<td>Coronary Artery Disease History</td>
<td>0.82 (0.21-3.19)</td>
<td>0.78</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.72 (0.30-1.71)</td>
<td>0.46</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.87 (0.28-2.73)</td>
<td>0.81</td>
</tr>
<tr>
<td>C-Reactive Protein (per 1 mg/dl) (available in 240 narrowings in 181 patients)</td>
<td>0.84 (0.55-1.28)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
**Supplemental References:**


Commentaire éditorial

A la recherche de la plaque vulnérable

Gregg W. Stone, MD

Entre 1970 et 2010, le nombre de décès de cause cardiovasculaire enregistrés aux États-Unis est passé de quelque 450 pour 100 000 habitants à environ 125, soit une diminution de plus de 70%. Cette forte réduction de la mortalité cardiovasculaire constitue l’un des vrais succès de la médecine moderne. L’allongement de l’espérance de vie tant des hommes que des femmes est essentiellement imputable à la prévention des décès liés, au premier chef, aux événements coronaires et, en deuxième lieu, aux accidents vasculaires cérébraux, la contribution des autres pathologies étant nettement plus faible. La diminution de la mortalité de cause coronaire semble devoir être portée au crédit du traitement des syndromes coronaires aigus (SCA) et des coronaropathies chroniques, mais aussi à la prise en charge des facteurs de risque. Nous n’en demeurons pas moins au cœur d’une épidémie de maladie coronaire dans la mesure où, chaque jour, plus de 2 200 Américains décèdent d’une maladie cardiovasculaire (ce qui représente près d’un décès toutes les 39 secondes).

Chez la plupart des patients décédés d’une cause cardiovasculaire, on constate la présence d’une plaque d’athérosclérose coronaire thromboscée. Aux plaques présentant un haut risque de thrombose imminente (que le délai de survenue de celle-ci se compte en jours, en semaines ou en mois) a été donné le nom de « plaques vulnérables ». Bien que l’athérosclérose soit un trouble panvasculaire secondaire à une inflammation généralisée, les plaques vulnérables ne sont pas présentes partout ; leur nombre est limité, et elles siègent le plus souvent au niveau des segments proximaux et moyens des vaisseaux coronaires épicaudiques (et dans la portion distale de l’artère coronaire droite). Bien que l’on ait identifié plusieurs types de plaques ayant une propension à la thrombose, les études histopathologiques ont montré que ces plaques sont en majorité des fibroathéromes à chape mince (TCFA pour thin-cap fibroatheroma) qui se caractérisent par l’existence d’un gros noyau nécrotique et d’une chape fibreuse de faible épaisseur (moins de 65 µm) principalement constituée de collagène de type I auquel s’ajoutent quelques cellules musculaires lisses et dans laquelle ont migré des macrophages et des lymphocytes T. La production cellulaire de métalloprotéases matricielles et d’autres enzymes digestives, exacerbée par les importantes forces de cisaillement et par les foyers de calcification présents au sein de la chape, provoque la rupture de la plaque avec libération de facteurs tissulaires et formation simultanée d’un thrombus. Il est, en revanche, plus rare que la thrombose coronaire soit imputable à un épaississement pathologique de l’intima ou à une plaque fibreuse ou fibrocalcifiée. Les fibroathéromes formés d’un noyau nécrotique et d’une épaisse chape fibreuse sont considérés comme exposés à un risque de rupture intermédiaire. Ces vingt dernières années, ce concept a été à l’origine de multiples travaux visant à identifier les propriétés structurelles, morphologiques, chimiques et physiques des TCFA in vivo, l’objectif final étant de se doter des moyens thérapeutiques propres à prévenir l’infarctus du myocarde aigu et la mort subite.

Nonobstant les nombreuses techniques d’exploration non invasive proposées à cette fin (la plus récente étant la tomodensitométrie multibarrette), il est possible d’améliorer le rapport signal sur bruit en plaçant une sonde d’imagerie endovasculaire à proximité d’une lésion athéromateuse. De multiples méthodes de cathétérisme fondées sur ce principe ont été expérimentées chez l’Homme, qui, pour la plupart, ont dû être abandonnées pour des raisons techniques, pratiques ou commerciales ; il en a été ainsi de la thermographie, de l’imagerie endovasculaire par résonance magnétique, de la palpographie, de l’angioscopie et de l’imagerie des vaisseaux. Néanmoins, trois de ces techniques ont émergé du lot et ont été agréées par la Food and Drug Administration des États-Unis sur la base de leur capacité théorique à objectiver certaines des caractéristiques d’un TCFA ; il s’agit de l’échographie endovasculaire par radiofréquence (radiofrequency intravascular ultrasound : IVUS-RF), de la tomodigraphie par cohérence optique (TCO) et de la spectroscopie en proche infrarouge (SPIR). A la différence de l’IVUS en échelle de gris, qui analyse uniquement l’amplitude de l’onde sonore rétrodiffusée, l’IVUS-RF renseigne également sur le domaine de fréquence, ce qui lui confère une plus grande exactitude diagnostique. La TCO est similaire à l’IVUS, mais le vecteur utilisé est ici la lumière et non l’onde sonore, ce qui assure une résolution axiale nettement plus grande (10–20 µm au lieu de 150–200 µm) au détriment, toutefois, de la profondeur de pénétration. La SPIR permet d’étudier la signature chimique sous-jacente à l’athérome et a été conçue de manière à pouvoir identifier les « plaques à noyau lipidique » et celles dont le noyau est nécrosé. Contrairement à l’IVUS-RF et à la TCO, la SPIR ne fournit pas une image tomographique de la lésion, mais un « chimigramme » de la paroi vasculaire sous forme d’une signature spectroscopique composite pondérée s’étendant.
de l’intima à l’adventice. Chacune de ces trois approches procure d’intéressantes images transversales, longitudinales et sagittales censées figurer les lésions d’athérosclérose coronaire à haut risque chez l’Homme. Dès lors, comment y a-t-il lieu de valider l’éventuel apport de ces techniques d’imagerie à l’identification des plaques vulnérables ?

Pour acquérir la certitude que l’image obtenue par une approche invasive ou non invasive correspond bien à une plaque vulnérable, il est nécessaire de procéder en quatre étapes. Dans un premier temps, il convient de pratiquer des études cartographiques sur des pièces autopsiques de coronaires humaines afin de s’assurer que la technique est à même d’identifier des éléments tissulaires particuliers de la plaque d’athérosclérose avec une précision satisfaisante, d’abord en procédant pixel par pixel puis en analysant la lésion dans sa globalité (identification du phénotype propre à la plaque). Il faut ensuite que la plupart des plaques responsables de SCA présentent, lors de l’événement, les caractéristiques d’imagerie en faveur d’une rupture pathologique de TCFA (avec formation d’un thrombus), les plaques à l’origine d’un syndrome coronaire stable devant, en revanche, être pour l’essentiel dépouvrues de ces caractéristiques. Une approche complémentaire consiste à démontrer que le pourcentage de lésions non coupables (LNC) qui s’avèrent être des fibroathéromes est plus élevé chez les patients atteint d’un SCA que chez ceux présentant une maladie coronaire stable, comme l’a établi l’examen histopathologique. Troisièmement, il y a lieu de mener des études prospectives de suivi de l’évolution naturelle des lésions, dans lesquelles les LNC seront classées en fonction de l’imagerie comme étant ou non à haut risque (c’est-à-dire vulnérables) et feront ensuite l’objet d’un suivi longitudinal afin de vérifier si les images recueillies ont effectivement mis en évidence les lésions enclines à rapidement progresser, à se rompre, à se thrombose et à provoquer des événements cardiovasculaires majeurs (ECM). Enfin, et c’est le point le plus ambitieux, il convient qu’au moins une modalité de traitement par voie générale ou loco-régionale des plaques identifiées comme vulnérables par la technique d’imagerie se montre à même de prévenir la survenue de futurs ECM dans le cadre d’essais prospectifs randomisés.

L’IVUS-RF, la TCO et la SPIR se sont montrées toutes trois capables de reconnaître in vitro les éléments constitutifs des plaques d’athérosclérose, tout comme l’examen histologique, et permettent, en outre, de caractériser le phénotype de ces dernières avec un bon degré de précision.12-14 Des travaux ont montré que chacune de ces techniques, selon ses critères propres, met en évidence la présence d’une plaque vulnérable chez la majorité des patients atteints d’un SCA.12,13,15 A ce jour, seule l’IVUS-RF s’est révélée à même d’identifier les lésions à l’origine de futurs ECM dans les études prospectives de suivi de l’évolution naturelle.16,17 Aucun essai n’a encore été entrepris pour examiner si le fait de traiter les plaques « à risque » contribue ou non à améliorer le pronostic à long terme des lésions ou des patients.

Dans Circulation: Cardiovascular Imaging, Kato et al18 ont apporté d’importants éclairages sur la morphologie des LNC chez les patients présentant un SCA et chez ceux atteints d’une maladie coronaire stable. En s’appuyant sur les données d’un registre multicentrique prospectif dont les patients avaient fait l’objet d’explorations triturationnelles par TCO avec analyse des images en aveugle dans un laboratoire central, les auteurs démontrent de façon probante que les LNC des patients atteints d’un SCA se distinguent de celles observées chez les patients coronariens stables par l’existence d’un plus grand arc lipidique, d’un noyau lipidique plus étendu et d’une plaque fibreuse plus mince. La fréquence des TCFA non coupables est apparue plus élevée dans les cas de SCA que chez les autres patients, tout comme celle des ruptures de plaques non diagnostiquées avec présence d’un thrombus. Ces observations complètent donc celles recueillies lors de précédentes études ayant fait appel à l’IVUS-RF et à la SPIR.12,15 Mais ce travail fournit également de nouvelles données dans la mesure où il démontre que les LNC des patients atteints d’un SCA se caractérisent plus fréquemment par la présence de macrophages ainsi que de microcanaux contigus à la lumière artérielle. Bien qu’il soit permis de mettre en doute la spécificité de la TCO en termes de détection des macrophages et que l’on ignore les conséquences que peut avoir la présence de microcanaux à proximité de la lumière (d’autant qu’aucune différence statistique n’a été relevée entre les deux groupes quant à cet élément), les caractères qui accompagnent ces anomalies (à savoir la composante lipidique étendue et la mince chape fibreuse) confèrent une certaine crédibilité à leur possible implication dans le processus conduisant à rendre la plaque vulnérable.

Bien que les auteurs aient reconnu que leur étude présentait d’importantes limites (tenant à un biais de sélection, au nombre relativement réduit de patients atteints d’un SCA, à l’évaluation non quantitative de plusieurs constitutants majeurs et à l’absence de données sur les segments les plus proches de l’arborisation coronaire, dont les études histopathologiques ont pourtant montré que ce sont ceux où siègent les TCFA),2 deux autres problèmes doivent être mentionnés. En premier lieu, le défaut majeur de la TCO provient de sa réalisation limitée et de son incapacité à quantifier le volume des plaques.13,19 Les auteurs minimisent cet inconvénient en considérant que « les caractéristiques morphologiques contribuant au plus fortement à la vulnérabilité d’un plaque sont celles des éléments de surface ». Cela n’est pas forcément vrai ; dans l’étude PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree [Recueil d’observations régionales pour identifier les facteurs prédictifs d’événements coronaires]), le facteur indépendant ayant le plus puissamment contribué au risque d’ECM a été l’activité de la plaque ;16 la même observation a été secondairement publiée par les investigateurs de l’étude VIVA (VH-IVUS in Vulnerable Atherosclerosis [Application de l’IVUS-RF à l’étude des plaques d’athérosclérose vulnérables]).17 De même, l’indice de volume lipidique mesure que par TCO a été établi en multipliant la valeur moyenne de l’arc lipidique par la longueur du noyau lipidique, ce qui constitue au plus un médiocre substitut de l’évaluation effective du volume et demande à être requalifié. Deuxièmement, un important biais qui n’a pas été mentionné tient au fait que les prescriptions de statines ont été plus nombreuses dans le groupe des coronariens stables ; or, l’on sait que ces médicaments augmentent l’épaisseur de la chape...
fibreuse et diminuent l’athérome et la teneur des plaques en lipides.20,21 L’étude aurait mérité que des ajustements multivariés soient pratiqués en fonction de ces différences et de certaines autres présentes à l’inclusion.

En dépit de ces points critiquables, il y a lieu de féliciter les auteurs pour cette étude menée avec soin qui fait progresser nos connaissances dans ce domaine. Plusieurs questions demeurent cependant sans réponse. Quelles caractéristiques d’une lésion mises (éventuellement) en évidence par la TCO dans cette étude sont le plus puissamment prédictives de la future survenue d’un ECM imputable à cette lésion ? L’arc lipidique ou la longueur du noyau lipidique ? L’épaisseur de la chape fibreuse ? La densité en macrophages ou la présence de microcanaux ? Une étude prospective de suivi de l’évolution naturelle doit être réalisée pour clarifier ce point. Quelle est la stabilité temporelle des critères de vulnérabilité d’une plaque évaluées par TCO ? Il semblerait, en effet, que la composition et le phénotype des plaques déterminées par IVUS-RF évoluent en quelques mois (vers des caractères morphologiques plus stables ou vers l’instabilité).22 Les résultats fournis par un laboratoire central de TCO pourraient-ils être transposés en salle de cathétérisme ? De fait, un observateur peu expérimenté (ou même chevronné) peut avoir de la difficulté à faire la distinction entre élément lipidique, dépôt calcique et perte de signal. L’absence d’écoulement sanguin peut être assimilée à tort à un thrombus. Un logiciel automatisé ou semi-automatisé assurant la détection des contours et la reconnaissance des formes serait ici d’une grande utilité. Les paramètres explorés par la TCO sont-ils plus ou autant prédictifs de la vulnérabilité d’une plaque que ceux fournis par l’IVUS-RF ou par la SPIR ? La concordance entre ces trois techniques d’imagerie en termes d’évaluation des caractéristiques et du phénotype des plaques est loin d’être parfaite.23,24 L’association de ces approches peut permettre d’obtenir des informations synergiques, par exemple, en combinant les données fournies par l’IVUS sur l’activité de la plaque à l’épaisseur de la chape fibreuse mesurée par TCO ou au volume du noyau lipidique déterminé par SPIR.

Surtout, il y aura lieu d’entreprendre des essais randomisés chez des patients porteurs de plaques à haut risque (identifiées par la technique d’imagerie considérée) en vue d’évaluer l’intérêt de nouvelles thérapeutiques systémiques plus efficaces (les inhibiteurs de la proprotéine convertase subtilisin/kexine de type 9 [PCSK9] pouvant être appelés en cela à jouer un rôle,25 sachant que la plupart des patients atteints d’athérosclérose coronaire sont d’ores et déjà traités par des statines à forte dose) ou d’approches interventionnelles loco-régionales (fondées, entre autre, sur l’emploi des actuels stents à libération de principe actif, des supports vasculaires bioréabsorbables qui font leur appariation ou encore des thérapies photodynamiques26,27 aﬁn de démontrer que traiter les plaques vulnérables avant qu’elles ne se rompent permet de prévenir eﬃcacement la survenue ultérieure d’un SCA, d’un infarctus du myocarde ou d’un décès de cause cardiaque. En l’absence de ces données, l’exploration tritonculaire invasive telle qu’elle a été réalisée dans PROSPECT et dans la présente étude ne saurait être préconisée hors du cadre de la recherche en raison des risques faibles mais réels que comporte l’intervention (dissection coronaire, emploi de produit de contraste et exposition aux rayonnements). Au-delà de ces considérations, la perspective de pouvoir réduire encore davantage le fardeau mondial que représente la pathologie cardiovasculaire justifie les énormes efforts de recherche qui sont accomplis dans le domaine des plaques vulnérables.

Délégations
Le Dr Stone expose ses fonctions de consultant auprès d’InfraRedx, St. Jude, Volcano, Abbott Vascular, Boston Scientiﬁc et Medtronic.

Références


