Determinants of high cardiovascular risk in relation to plaque-composition of a non-culprit coronary segment visualized by near-infrared spectroscopy in patients undergoing percutaneous coronary intervention

Sanneke P.M. de Boer, Salvatore Brugaletta, Hector M. Garcia-Garcia, Cihan Simsek, Jung Ho Heo, Mattie J. Lenzen, Carl Schultz, Evelyn Regar, Felix Zijlstra, Eric Boersma, and Patrick W. Serruys*

Thoraxcenter Cardiology, Erasmus MC, ’s Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

Received 19 July 2013; accepted 12 August 2013; online publish-ahead-of-print 12 September 2013

Aim
The aim of this study was to determine the relationship between clinical and blood characteristics of a vascular inflammatory milieu and coronary plaque composition visualized by near-infrared spectroscopy (NIRS) in percutaneous coronary intervention (PCI) patients.

Methods and results
Between April 2009 and January 2011, we performed NIRS in 208 patients who underwent PCI or invasive diagnostic coronary exploration for various indications. Imaging was performed of one non-intervened coronary segment after the initial procedure. Univariate and multivariate linear regression analyses were applied to evaluate the relationship between the acquired NIRS-derived lipid core burden index (LCBI) and clinical and blood (lipids and hs-C-reactive protein) characteristics. Patients with a history of hypercholesterolaemia [median 48 (inter-quartile range 21–101) vs. 38 (13–70), P = 0.043] and multi-vessel disease [55 (24–104) vs. 32 (12–71), P = 0.012] had higher LCBI levels. Men had higher LCBI than women [48 (21–95) vs. 27 (9–59), P = 0.003]. Hypercholesterolaemia and gender remained significant in multivariate regression analysis, whereas also a history of non-cardiac vascular disease and beta-blockers were positively associated with LCBI. Altogether 23.2% of the variability in LCBI could be explained by clinical and blood characteristics.

Conclusion
Clinical characteristics reflecting patients with a high cardiovascular risk profile explained 23.2% of the variability in LCBI, whereas blood biomarkers added little. Further research is warranted to evaluate whether NIRS has the potential to provide additional prognostic information about patients’ cardiovascular risk.

Keywords
Near-infrared spectroscopy • Lipid core burden index • Percutaneous coronary intervention • Cardiovascular risk factors

Introduction
Acute coronary syndromes (ACSs) are a major cause of mortality and morbidity in Western countries.1–3 Rupture of vulnerable coronary plaques, often inflamed lipid-rich lesions with large necrotic cores with only a thin overlying fibrous layer of intimal tissue, are most likely to cause these ACSs.3–7 Several well-established and emerging cardiovascular risk factors have been related to the occurrence and progression of coronary atherosclerosis8–10 and the predisposition of patients to plaque rupture or acute coronary thrombosis.11 An important risk factor for the development of coronary atherosclerosis is the lipid profile,12 which accounts for ~50% of the population...
attributable risk of first acute myocardial infarction (AMI). A meta-analysis of 26 randomized trials showed that lowering low-density lipid (LDL) cholesterol is inversely associated with rates of both major coronary and vascular events. Therefore, the lipid profile is widely accepted as a determinant for risk stratification and primary target of therapy. Another established risk factor for coronary atherosclerosis is hs-C-reactive protein. Subjects with elevated levels of hs-C-reactive protein are at increased risk of coronary heart disease. Furthermore, as demonstrated by the Jupiter trial, rosuvastatin significantly reduced the incidence of major cardiovascular events in seemingly healthy persons without hyperlipidemia but with elevated hs-C-reactive protein levels.

Near-infrared spectroscopy (NIRS), a novel catheter-based imaging modality that determines composition of tissue, has the potential to identify lipid core containing coronary plaques (LCP) in patients. The accuracy of NIRS has been validated in coronary autopsy specimens and subsequently in vivo. This intra-coronary system utilizes the variation in reflection of the emitted near-infrared light to detect LCP, which is visualized as a (block) chemogram and qualified by a lipid core burden index (LCBI) score. Detection of these LCPs in coronary arteries might potentially be used for enhanced risk stratification, prevention, and treatment of coronary events. We have reported on the relationship between NIRS, Framingham Risk Score, and renal function in patients who underwent successful percutaneous coronary intervention (PCI) or invasive diagnostic coronary exploration.

The aim of the current study was to provide a thorough and broad analysis of the patient characteristics that are (potentially) associated with NIRS-derived LCBI, in particular blood lipids and hs-C-reactive protein. Logically, we do expect higher LCBI levels in patients with a clinical profile corresponding with increased CHD risk.

Methods

Study population
We studied 208 patients who underwent NIRS, between April 2009 and January 2011, in the Thoraxcenter, Erasmus MC, Rotterdam, the Netherlands, a tertiary referral hospital. Patients were 18 years of age or older, had stable angina pectoris (AP) or an ACS and underwent successful PCI or invasive diagnostic coronary exploration of one or more lesions in one or two native coronary arteries. Patients who underwent CABG were not included in this study. After the initial procedure (PCI or invasive diagnostic coronary exploration), patients underwent invasive imaging (NIRS and intravascular ultrasound (IVUS)) of one non-culprit vessel (i.e. the vessel of interest for this study), with a diameter stenosis <50% throughout a target segment of at least 40 mm in length by angiographic visual estimation. These study vessels were accessible to the Lipiscan (InfraReDx, Burlington, MA, USA) catheters and per protocol selected in the following way:

- If left anterior descending coronary artery (LAD) vessel has been treated, right coronary artery (RCA) should be selected (if not possible: LCX).
- If RCA vessel has been treated, LAD should be selected (if not possible: LCX).
- If LCX has been treated, LAD or RCA should be selected.

In case patients underwent an invasive diagnostic procedure, the selection of the study vessel was left to the discretion of the interventional cardiologist.

The medical ethical committee of our hospital approved the study and a written informed consent was obtained of every patient.

Near-infrared spectroscopy
The NIRS system consists of a rapid exchange catheter, a pullback and rotation device, and a console. The catheter is 3.2 F in diameter and 165 cm in usable length. The catheter is intended to be introduced into the vasculature via a 0.014-inch coronary guidewire, which is allowed to exit ~25 mm proximal to the distal tip. Two low-profile polymer markers are placed on the stiff proximal shaft to aid the user in locating the exit of the distal tip through the tip of a guiding catheter.

All the study coronary vessels included were accessible to the Lipiscan (InfraReDx, Burlington, MA, USA) catheters and had a <50% reduction in lumen diameter by angiographic visual estimation throughout a target segment of at least 40 mm in length. Coronary vessels that received a bypass graft with a minimal lumen diameter <2 mm or with a diameter stenosis >50% by angiographic visual estimation in the segments to be analysed were excluded. There were no complications related to the imaging procedure. A motorized catheter pullback, at 0.5 mm/s and 240 rpm, was performed starting distal to a side branch and acquiring 1000 NIRS measurements/12.5 mm of the scanned coronary artery. The region of interest was defined as the longest coronary segment, between two clearly identifiable landmarks (i.e. side branches).

The measured probability of the LCP from each scanned coronary segment was displayed as a map, the chemogram; yellow regions represent those with highest probability for the presence of the LCP, while red regions represent those with lowest probability. The chemogram displays the pullback position against the circumferential position of the measurement in degrees (Figure 1).

Based on the chemogram, the LCBI was calculated, representing the fraction of valid pixels in the chemogram that are yellow, multiplied by a factor of 1000. The LCBI is a summary measure of the amount of LCP along the entire interrogated length of the vessel on a 0-to-1000 scale.

NIRS images were prospectively analysed offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) unaware of the clinical or lab data.

Intravascular ultrasound
Intravascular ultrasound was acquired with Volcano™ s5/s5i Imaging System using Volcano™ Eagle Eye™ Gold IVUS catheter (20 MHz) at a standard pull back speed of 0.5 mm/s with an automatic pullback system. During motorized catheter pullback, at 0.5 mm/s, greyscale IVUS and raw radiofrequency data capture gated to the R-wave were recorded.

All baseline IVUS images were prospectively analysed offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands). The IVUS analyses were performed with the VIAS software (Volcano Corporation). Contour detection was performed by experienced IVUS analysts who were blinded to the NIRS results. Quantitative greyscale IVUS measurements included vessel area, lumen area, plaque area (vessel area – lumen area), and plaque burden ([plaque area/vessel area] * 100%).

Biomarker analysis
Routine blood for biomarker assessment was drawn prior to the index procedure and analysed at our department of medical microbiology and infectious diseases, diagnostic laboratory Erasmus MC, Rotterdam, the Netherlands (accreditation based on ISO/IEC 15189:2003 and CCKL-regulations).
Data analysis

We present patient-level analyses. NIRS and IVUS-VH data are derived from measurements in the non-culprit (study) vessel and are presented as one quantity for each patient.

Continuous variables are presented as means ± standard deviation or median and inter-quartile ranges (IQRs) as appropriate, categorical variables are expressed as numbers and percentages. The Kolmogorov–Smirnov test was used to analyse whether continuous data were normally distributed. Non-parametric continuous variables were compared using the Mann–Whitney U test, and are presented as median and IQR. If further statistical tests required normal distribution of the data, then log or square root transformations were applied.

We intended to obtain complete information in all patients, but failed to do so for the following seven variables: hs-C-reactive protein, high-density lipoprotein (HDL), LDL, creatinine, total cholesterol, triglycerides, and BMI. Using missing value analysis, we evaluated the extent of missing data and searched for patterns of missing data. Missing value analysis showed that there were 3.3% missing values on average.

For the patients with at least one of the variables of interest missing, we decided to impute the missing values by multiple imputation.23 (We also applied a complete case sensitivity analysis, showing consistent results, which we will not present.)

The baseline creatinine values were used to calculate the creatinine clearance according to the Cockroft and Gault formula: creatinine clearance (millilitres/minute) = (140 – age) × weight (kilograms)/72 × serum creatinine (milligrams/decilitre) (x0.85 for women).24

Correlation plots were constructed, and univariate and multivariate linear regression (LR) analyses were applied to reveal clinical characteristics that were related to LCBI. The lipid core burden index was considered the dependent variable, and all variables of interest (Table 1) were considered potential determinants. All baseline variables described in Table 1 entered the multivariate stage. All variables that had a P-value <0.5 in univariate analysis, based on Wald’s χ² test, were used to construct the multivariate model. The R² statistic is presented, which indicates the percentage of the variance in the dependent variable that can be ‘explained’ by the determinant.

Subsequently, we studied the correlation between NIRS-derived LCBI and IVUS-derived plaque burden. We present correlation plots and report Pearson’s correlation coefficient. This analysis has caveats, which are mainly due to the fact that we used different catheters for the IVUS-VH and NIRS measurements. The described correlation was based on segment-level data, whereas, for technical and logistic reasons, the analysed segments for IVUS-VH and NIRS were not synchronized at the level of frames. Furthermore, the length of the analysed segments was not necessarily the same for both techniques.

Univariate and multivariate LR analyses were applied to study the association between NIRS-derived LCBI and clinical risk factors (independent variables) and IVUS-derived plaque burden (dependent variable). The data of 12 patients could not be used, because of problems with the IVUS analysis software.

Finally, we studied the relation between blood lipid levels, hs-C-reactive protein and LCBI according to the quartiles of their distribution. For all tests, a two-sided P-value of 0.05 or less was considered significant. All statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Study population and baseline characteristics

The baseline and procedural characteristics of the included patients are presented in Table 1. The studied population consisted mostly of men (79.6%) and the mean age was 63.5 years. Most patients were treated for stable AP (52.9%) or non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (32.7%). Prior MI (38.0%) and prior PCI (38.9%) in the cardiac history were common. The prevalence of hypercholesterolaemia, positive family history for CHD, multi-vessel disease, and/or hypertension was >50%. Almost 20% of the patients were diabetic; the non-insulin dependent type was most common. The distribution of the studied coronary vessels (RCA 28.8%, LAD 36.1%, and LCX 35.1%) was about equally divided. The median total cholesterol level was 4.20 (IQR 3.60–5.20) mmol/L, LDL level 2.46 (1.92–3.20) mmol/L, HDL of 1.14 (0.92–1.35) mmol/L, triglycerides 1.27 (0.92–1.79) mmol/L, and a high-sensitive C-reactive protein 3.34 (1.26–5.78) (mg/dL). The median NIRS-derived LCBI was 42.5 (16.0–85.0).
Association between cardiovascular risk factors and lipid core burden index

The univariate and multivariate association between baseline characteristics and LCBI is shown in Tables 2 and 3. When patients were stratified on indication for an invasive coronary procedure no differences (P = 0.49) in LCBI was observed: median (IQR) in stable angina 37.5 (15–94), NSTE-ACS 48 (16–94), and STEMI 36.5 (15–68).

Patients with a history of hypercholesterolaemia [median 48 (IQR: 21–101) vs. 38 (13–70), P = 0.043] and multi-vessel disease [55 (24–104) vs. 32 (12–71), P = 0.012] had higher LCBI levels. Men had higher LCBI than women [48 (21–95) vs. 27 (9–59), P = 0.003]. Except for multi-vessel disease, these variables remained significantly associated with LCBI after adjustment for the selected confounders in multivariate analysis. Also a significant association between a history of peripheral arterial disease (PAD) and/or cerebral vascular accident (CVA)/transient ischaemic attack (TIA), beta-blockers, and LCBI was found. Altogether 23.2% of the variability in LCBI could be explained by the variables that compose the model.

Lipid core burden index and intravascular ultrasound—derived plaque burden

Figure 2 shows the correlation between LCBI and IVUS-derived plaque burden, as well as the relationship between the quartiles of the distributions of LCBI and plaque burden. We observed a significant correlation between the two imaging modalities based on the data points in individual patients (Pearson’s r = 0.289, P < 0.001).
and the quartiles of the distributions of % plaque burden and LCBI, \( P < 0.001 \).

Except for a history of PAD and/or CVA/TIA none of the baseline characteristics was significantly associated with the IVUS-derived plaque burden in univariate analysis. This variable remained significantly associated with the IVUS-derived plaque burden after adjustment for the selected \((P < 0.5)\) confounders (age, sex, indication, hypertension, multi vessel disease, aspirin, clopidogrel, beta-blockers, and total cholesterol). Altogether 14.0\% of the variability in the IVUS-derived plaque burden could be explained by the variables that compose the model.

### Table 2  Baseline variables and their univariate association with lipid core burden index

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Beta</th>
<th>SE</th>
<th>( P )-value</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.035</td>
<td>0.025</td>
<td>0.16</td>
<td>0.010</td>
</tr>
<tr>
<td>Male</td>
<td>1.75</td>
<td>0.60</td>
<td>0.004</td>
<td>0.039</td>
</tr>
<tr>
<td>Indication for invasive coronary procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>1</td>
<td>0.34</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>0.76</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>-0.32</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac history</td>
<td>0.03</td>
<td>0.54</td>
<td>0.96</td>
<td>0.000</td>
</tr>
<tr>
<td>History of PAD and/or CVA/TIA</td>
<td>1.51</td>
<td>0.96</td>
<td>0.12</td>
<td>0.007</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>-0.17</td>
<td>0.63</td>
<td>0.79</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.11</td>
<td>0.55</td>
<td>0.85</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.38</td>
<td>0.54</td>
<td>0.011</td>
<td>0.031</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.02</td>
<td>0.68</td>
<td>0.98</td>
<td>0.000</td>
</tr>
<tr>
<td>Multi-vessel disease n, %</td>
<td>1.11</td>
<td>0.58</td>
<td>0.044</td>
<td>0.020</td>
</tr>
<tr>
<td>Family history</td>
<td>0.52</td>
<td>0.54</td>
<td>0.34</td>
<td>0.004</td>
</tr>
<tr>
<td>GFR</td>
<td>0.006</td>
<td>0.009</td>
<td>0.54</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.02</td>
<td>0.06</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2.14</td>
<td>1.76</td>
<td>0.23</td>
<td>0.007</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.00</td>
<td>1.08</td>
<td>0.36</td>
<td>0.004</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>-1.50</td>
<td>0.63</td>
<td>0.019</td>
<td>0.027</td>
</tr>
<tr>
<td>RAAS inhibitor</td>
<td>-0.96</td>
<td>0.60</td>
<td>0.11</td>
<td>0.012</td>
</tr>
<tr>
<td>Statin</td>
<td>-0.12</td>
<td>0.86</td>
<td>0.89</td>
<td>0.000</td>
</tr>
<tr>
<td>Blood lipid levels and hs-C-reactive protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>-0.33</td>
<td>0.29</td>
<td>0.26</td>
<td>0.009</td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>0.41</td>
<td>0.32</td>
<td>0.97</td>
<td>0.000</td>
</tr>
<tr>
<td>Low-density lipoprotein (mmol/L)</td>
<td>0.20</td>
<td>0.02</td>
<td>0.52</td>
<td>0.003</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.41</td>
<td>0.32</td>
<td>0.20</td>
<td>0.011</td>
</tr>
<tr>
<td>HS-C-reactive protein (mg/L)</td>
<td>0.026</td>
<td>0.02</td>
<td>0.25</td>
<td>0.035</td>
</tr>
</tbody>
</table>

SE, standard error; MI, myocardial infarction; HS-C-reactive protein, high-sensitive C-reactive protein; GFR, glomerular filtration rate; LCBI, lipid core burden index.

### Table 3  Baseline variables and their multivariate association with lipid core burden index

<table>
<thead>
<tr>
<th>Multivariate</th>
<th>Beta</th>
<th>SE</th>
<th>( P )-value</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>0.03</td>
<td>0.23</td>
<td>0.232</td>
</tr>
<tr>
<td>Sex</td>
<td>1.62</td>
<td>0.61</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>History of PAD and/or CVA/TIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>1.12</td>
<td>0.65</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>-0.36</td>
<td>0.92</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>History of PAD and/or CVA/TIA</td>
<td>2.32</td>
<td>0.96</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.29</td>
<td>0.55</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>0.55</td>
<td>0.52</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>0.94</td>
<td>0.54</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2.31</td>
<td>1.65</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>-1.09</td>
<td>0.63</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>-1.91</td>
<td>0.63</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>RAAS inhibitor</td>
<td>-0.37</td>
<td>0.53</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.52</td>
<td>0.30</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.002</td>
<td>0.35</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>HS-C-reactive protein (mg/L)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

SE, standard error; MI, myocardial infarction; HS-C-reactive protein, high-sensitive C-reactive protein; LCBI, lipid core burden index; GFR, glomerular filtration rate.

**Figure 2** (A) Scatter plot of plaque burden (%) in relationship with lipid core burden index. (B) Quartiles of the distribution of lipid core burden index in relation to the quartiles of plaque burden (%).
Association blood biomarkers and lipid core burden index

Correlation plots (Figure 3) and regression analyses showed no (significant) correlation between blood biomarkers and LCBI. The $R^2$ for blood lipid levels and hs-C-reactive protein rated between 0.000 and 0.035 (Table 2), indicating that these variables only explain little of the variability in LCBI between the enrolled patients. Figure 4 shows the LCBI according to quartiles of blood lipid levels and hs-C-reactive protein. A weak, but non-significant relationship is visible between hs-C-reactive protein and LCBI: 40% of the patients in the lowest quartile (Q1) of hs-C-reactive protein had an LCBI in Q1, whereas 12% of the patients in the highest quartile (Q4) of hs-C-reactive protein had an LCBI in the first quartile. No relationships were visible between other blood biomarkers and LCBI.

Discussion

In this single-centre cross-sectional study clinical characteristics and blood biomarkers explained 23.2% of the variability in the NIRS-derived LCBI score, an indicator for LCP in coronary arteries. As increased levels of lipids and hs-C-reactive protein increase the likelihood of LCPs in the coronary vessel, relationships between these blood biomarkers and LCBI were expected. However, lipid profile and hs-C-reactive protein provided little additional information about the LCBI score in a non-intervened coronary artery segment; a maximum of 3.5% of the variability in LCBI could be explained by these biomarkers.

The clinical characteristics hypercholesterolaemia, male sex, use of beta-blockers, and history of peripheral artery disease PAD, and/or cerebral vascular accident/transient ischaemic attack (CVA/TIA) were all significantly associated with LCBI, reflecting patients with a high cardiovascular risk profile. Our finding of an association between a history of hypercholesterolaemia and LCP in the coronary vessels is in accordance with previous studies that found an association between (treated) hypercholesterolaemia and IVUS-derived necrotic core-rich coronary plaques. Simsek et al. found no ‘dose-dependent’ effect of creatinine (as a measure of renal function) on the NIRS-derived LCBI score in a previous report of this study.

The relationship between gender and LCBI supported other investigations that demonstrated that men have more severe structural

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/35/5/282/489485)
and functional atherosclerotic disease in epicardial coronary arteries than women. In fact, the pathophysiology of cardiovascular disease (in particular coronary artery disease) differs significantly between men and women. Several study reports suggest that signs and symptoms of CVD experienced by women are related to microvascular ischaemia and endothelial dysfunction, more so than in men. Symptomatic women usually have less flow limiting stenoses than men, and are more prone to have plaque erosion with subsequent thrombus formation. Myocardial ischaemia in the absence of obstructive coronary disease, but with an increased high risk of adverse outcomes, is an emerging paradigm for women. More research in this field is warranted.

None of the blood biomarkers was independently predictive of LCP in the coronary vessels. This lack of association might have various reasons. First, we might have studied the wrong biomarkers. However, both blood lipid levels and hs-C-reactive protein are well-established risk factors/markers for the development/identification of coronary atherosclerosis. A reason for this lack in association between blood biomarkers and LCBI might be that the vast majority of the patients (89%) were already treated with statins at the time of the procedure. We found relatively low level of cholesterol, LDL, and triglycerides in our study population. As shown previously there is a linear relationship between LDL cholesterol and annual changes in the plaque size; however, in patients with low LDL values, no plaque progression was found. Apparently, LDL levels influence plaque growth and probably consequently also plaque size. So, since patients treated with statins have lower levels of LDL, they might have as a result relatively small plaques. Furthermore, statins influence coronary plaques via other mechanisms as in patients without hyperlipidaemia the incidence of major cardiovascular events is also reduced by statin use. Consequently, the use of blood biomarkers in statin users as determinant for LCP may be confounded. In accordance, Nicholls et al. found no relationship between LDL cholesterol and hs-C-reactive protein and IVUS-derived disease burden. It should be noted that all the patients in this study were treated with statins.

Another explanation for the lack of association might be that we visualized 40 mm of a non-culprit vessel, in patients undergoing PCI or invasive diagnostic coronary exploration for various indications.
and therefore cannot exclude the possibility that the blood biomarkers are related to the culprit lesion. However, ex vivo as well as in vivo studies using IVUS in patients with myocardial infarction have demonstrated the presence of vulnerable plaques in other than the culprit lesion or even culprit artery. Also atherosclerosis in the peripheral vascular system or clinical circumstances can influence blood biomarker levels.

When patients were stratified on indication for an invasive coronary procedure (stable angina, NSTE-ACS, or STEMI) no difference in LCBI was observed. This is in contrast with Madder et al. who revealed that both target and remote LCPs were more common in patients with ACS than in those with stable angina. The expression of atherosclerosis is dependent on the interaction of multiple risk factors, including genetic susceptibility, abnormal lipid levels, and inflammation. Although we found no association between blood biomarkers and NIRS-derived LCBI, there is data to support the hypothesis that blood lipid levels and hs-C-reactive protein are independently associated with the promotion of plaque vulnerability.

Historical predictors, like blood lipid levels, are frequently used as determinants of cardiovascular risk. If we had demonstrated a strong correlation between these factors and LCP, then NIRS would not provide additional information about a patients’ cardiovascular risk. Consequently, as NIRS has the potential of identifying LCP in coronary arteries, indicative of plaque vulnerability, this novel imaging technique might be a promising tool to provide additional information about patients’ cardiovascular risk, independent of blood lipid levels. It should be noted, however, that NIRS has not yet proved to provide additional information about a patient’s cardiovascular risk.

This study has some limitations. First, as only one non-culprit vessel was imaged, we lack information on the culprit artery, which may flaw our efforts to assess a relationship between LCBI and blood biomarkers. For the same reason, we were unable to assess the correlation of clinical presentation with LCBI findings as reasons for intervention are closely related to the culprit lesion. Secondly, this study might lack power to show strong correlations. Thirdly, this is a cross-sectional study; therefore, no information is available on the (reversed) progression of LCPs and its relationship with lipid levels in this population over time. Future research might focus on the effect of lipid level changes on LCP. Finally, although we had unique information on NIRS-derived and IVUS-derived parameters in the same segment, the observed results should be interpreted with caution, because the analysed segments were not synchronized at the level of frames.

The single-centre design of this study guarantees limited variability in the NIRS and blood collection procedures (consistent environment and care protocols) and the use of an independent core laboratory to analyse the NIRS images, assumes an independent and accurate analysis according to uniform standards.

Concluding, clinical characteristics reflecting patients with a high cardiovascular risk profile explained 23.2% of the variability in LCBI, whereas blood biomarkers added little. Further research is needed whether NIRS has the potential to provide additional information about patients’ cardiovascular risk.

Acknowledgements
We would like to thank the following interventional cardiologists and technical staff for their contribution to this study: Eric Duckers, MD, PhD; Robert-Jan van Geuns, MD, PhD; Willem van der Giessen, MD, PhD; Peter P.T. de Jaegere, MD, PhD; Nicolas van Mieghem, MD; Evelyn Regar, MD, PhD; Carl Schultz, MD, PhD; Patrick W. Serruys, MD, PhD and Felix Zijlstra, MD, PhD. We are indebted to Professor Willem van der Giessen, who had a valuable contribution in the design and completion of the study, but passed away before finalization of this work.

Conflict of interest: none declared.

References
lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52
14. Cholesterol Treatment Trials C, Baigent C, Blackwell L, Emberson J, Holland LE,
Reith C, Bhala N, Petra R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of
more intensive lowering of LDL cholesterol: a meta-analysis of data from 270,000
15. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Pre-
diction of coronary heart disease using risk factor categories. Circulation 1998;97:
1837–1847.
16. National Cholesterol Education Program Expert Panel on Detection E, Treatment of
High Blood Cholesterol in A. Third report of the national cholesterol education
program (NCEP) expert panel on detection, evaluation, and treatment of high
blood cholesterol in adults (adult treatment panel III) final report. Circulation 2002;
106:3143–3142.
17. Buckley DJ, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor
for coronary heart disease: a systematic review and meta-analyses for the U.S. pre-
18. Ridker PM, Danielson E, Fonseca FA, Genest J, Goto AM Jr, Kastelein JJ, Koenig W,
Lipid Coreburden indexand framinghamscore:can a systemic risk score
for coronary vascular reactivity and functional capacity in women: results from the
NHLBI women’s ischemia syndrome evaluation (wise) study. J Am Coll Cardiol 2006;
47:544–549.
19. Gardner CM, Tan H, Hull EL, Lisauskas JB, Sum ST, Meese TM, Jiang C, Madden SP,
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine.
Angiographic coronary artery disease prevalence and serum cholesterol levels as assessed with serial long-term (> or ≈12 months) follow-up intravascular ultrasound. Circulation 2003;108:
2757–2762.
Wang CC, Norton M, Tansios F, Nissen SE. Relationship between cardiovascular
risk factors and atherosclerotic disease burden measured by intravascular ultra-
Cardiol 2006;98:3Q–9Q.
23. Madder RD, Smith JL, Dixon SR, Goldstein JA. Composition of target lesions by near-
infrared spectroscopy identifies high risk of peripro-