

# SYNTAX score in relation to intravascular ultrasound and near-infrared spectroscopy for the assessment of atherosclerotic burden in patients with coronary artery disease



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## KEYWORDS

- coronary artery disease
- intravascular ultrasound
- other imaging modalities
- risk stratification

## Abstract

**Aims:** The aim of this study was to examine the relationship between the anatomical SYNTAX score (SXscore), derived from all three coronary arteries, and coronary wall pathology measured by radio-frequency intravascular ultrasound (RF-IVUS) and near-infrared spectroscopy (NIRS) in a single non-culprit segment.

**Methods and results:** In patients referred for coronary angiography (N=88) or PCI (N=592) for stable angina or acute coronary syndrome, the SYNTAX score calculator ([www.syntaxscore.com](http://www.syntaxscore.com)) was used to determine the SXscore before PCI, if applicable. RF-IVUS and/or NIRS were performed in a non-stenotic 40 mm study segment following the clinically indicated angiography/PCI. After adjustment for multiple confounders, a higher SXscore was associated with higher segmental plaque volume in the study segment (2.21 mm<sup>3</sup> per SXscore point, 95% CI: 0.92-3.50, p-value 0.001), as well as with higher volume of fibrous (0.93 mm<sup>3</sup> per point) and fibro-fatty tissue (0.29 mm<sup>3</sup> per point). A higher SXscore was also associated with a higher NIRS-derived lipid core burden index (LCBI) in the full study segment (1.35 units per SXscore point, 95% CI: 0.22-2.47, p-value 0.019). Importantly, SXscore correlated with the fatty/fibro-fatty and LCBI signals despite adjusting for plaque burden.

**Conclusions:** In patients with CAD, higher SXscores are associated with higher atherosclerotic burden as assessed by RF-IVUS and NIRS in a single non-stenotic coronary artery segment.

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## Abbreviations

<b>ACS</b>	acute coronary syndrome
<b>ATHEROREMO-IVUS study</b>	The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - IVUS study
<b>CABG</b>	coronary artery bypass graft surgery
<b>CAD</b>	coronary artery disease
<b>CAG</b>	coronary angiography
<b>CI</b>	confidence interval
<b>IBIS-3 study</b>	Integrated Biomarker and Imaging Study 3
<b>IQR</b>	interquartile range
<b>LCBI</b>	lipid core burden index
<b>MACE</b>	major adverse cardiac events
<b>MLA</b>	minimal luminal area
<b>NIRS</b>	near-infrared spectroscopy
<b>PCI</b>	percutaneous coronary intervention
<b>RF-IVUS</b>	radiofrequency intravascular ultrasound
<b>SAP</b>	stable angina pectoris
<b>SD</b>	standard deviation
<b>STEMI</b>	ST-segment elevation myocardial infarction
<b>SXscore</b>	SYNTAX score
<b>TCFA</b>	thin-cap fibroatheroma(s)

## Introduction

The SYNTAX score (SXscore) is an angiographic tool that grades the complexity of coronary artery disease (CAD) and is also used for short- and long-term prediction of major adverse cardiac events (MACE) in patients undergoing percutaneous coronary intervention (PCI) and/or coronary artery bypass graft surgery (CABG)<sup>1,2</sup>. The severity and composition of coronary atherosclerosis as assessed by radiofrequency intravascular ultrasound (RF-IVUS) and near-infrared spectroscopy (NIRS) in one (non-) stenotic coronary artery segment have recently also shown prognostic value for MACE<sup>3-8</sup>. Furthermore, RF-IVUS and NIRS in one (non-)stenotic coronary artery segment have previously been used to evaluate the effects over time of antiatherosclerotic therapy under the assumption that these assessments are representative of the total coronary atherosclerotic burden<sup>9</sup>. However, how well the atherosclerotic burden as graded by NIRS and RF-IVUS measured in one (non-)stenotic coronary artery segment correlates with the atherosclerotic burden as assessed by the SXscore which is derived from all three coronary arteries has never been investigated in a large cohort.

It is important to realise that the three methods differ from each other in the assessment and quantification of CAD. The SXscore is an anatomical scoring tool that grades luminal coronary obstruction, directly from the coronary angiography (CAG). Therefore, it lacks detail with respect to coronary artery wall pathology. Conversely, RF-IVUS and NIRS have been shown to provide information on plaque morphology in the imaged coronary segment. However, both of these imaging techniques require additional intracoronary catheters, whereas the SXscore itself does not require instrumentation of the coronary lumen.

The aim of this study was to examine the relationship between the coronary atherosclerotic burden measured as luminal coronary obstruction graded by the SXscore, derived from all three coronary arteries, and the atherosclerotic burden by assessing coronary artery wall pathology measured by RF-IVUS and NIRS in one non-stenotic segment of a single non-culprit coronary artery.

## Methods

### STUDY POPULATION

This study constitutes a combined analysis of two cohorts, The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - IVUS (ATHEROREMO-IVUS) study and the Integrated Biomarker and Imaging Study 3 (IBIS-3). The design of both studies has been described elsewhere<sup>9-11</sup>. In total, 770 patients with an indication for diagnostic CAG and/or PCI due to either stable angina pectoris (SAP) or an acute coronary syndrome (ACS) were included and had an RF-IVUS and/or NIRS performed in a non-stenotic segment of a non-culprit coronary artery.

Both studies were approved by the Medical Ethics Committee of the Erasmus MC and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all included patients. ATHEROREMO-IVUS is registered at ClinicalTrials.gov (NCT01789411), and IBIS-3 is registered in the Netherlands trial register (NTR2872).

### CORONARY INTRAVASCULAR ULTRASOUND AND NEAR-INFRARED SPECTROSCOPY

RF-IVUS and NIRS methods have been described in detail previously<sup>9-11</sup>. For a comprehensive Methods section, refer to **Supplementary Appendix 1**.

### SYNTAX SCORE

The SXscore was calculated (pre PCI) for every CAG taken at study entry using the SYNTAX score calculator ([www.syntaxscore.com](http://www.syntaxscore.com)). Details concerning the calculation of the SXscore have been described elsewhere<sup>1</sup>. In brief, the three coronary arteries are divided into 16 segments, each with a corresponding weighting factor. If there is a lesion producing 50% or more luminal obstruction, the weighting factor is added. Moreover, other factors that reflect the severity of the atherosclerotic lesion and the possible difficulty of a percutaneous treatment, for example lesion length and diffuse disease of the vessel, are taken into account. Eventually, all points are summed to obtain the SXscore reflecting the complexity of the CAD of the patient.

As applied in other all-comers and ST-segment elevation myocardial infarction (STEMI) populations, lesions caused by in-stent restenosis were considered as *de novo* lesions<sup>12-14</sup>. Occlusions in patients presenting with ACS were scored as occlusions of unknown duration, as the analyst was blinded to all other patient information<sup>15</sup>.

In case of a co-dominant coronary artery circulation, the vessel mainly responsible for the perfusion of the posterior side of

the heart was designated as the dominant coronary artery. Lastly, patients with a pre-existing CABG, whose CAG was unquantifiable using the SXscore, were excluded.

The SXscores were determined by a trained analyst who was blinded with respect to other patient characteristics and clinical outcome.

## STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages. The distribution of the continuous variables, including RF-IVUS and NIRS parameters, was examined for normality with Kolmogorov-Smirnov tests. Normally distributed continuous variables are presented as mean±standard deviation (SD). Non-normally distributed continuous variables are presented as median and interquartile range (IQR). SXscores were categorised into tertiles based on the distribution of the SXscores in the particular group that was being examined. Kruskal-Wallis tests were used for multiple group comparison of continuous variables. Categorical variables were compared using Pearson chi-square tests or Fisher-Freeman-Halton exact tests when appropriate.

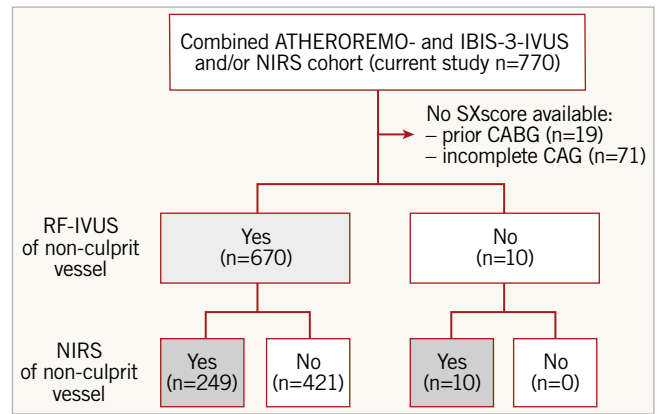
Linear and logistic regression analyses were applied to evaluate the relation between SXscore (explanatory) and RF-IVUS- and NIRS-derived (dependent) variables. Variables concerning plaque volume were first normalised for the imaged segment length (i.e., normalised plaque volume=plaque volume/imaged segment length\*median segment length of study population). In multivariable analyses, age, gender, hypertension, renal impairment, hypercholesterolaemia, diabetes mellitus, smoking, indication for CAG, history of PCI, as well as segmental plaque burden were entered as potential confounders/explanatory factors. Thus, the models allow a conclusion on the relation between SXscore and the RF-IVUS/NIRS imaging signals, irrespective of the patient's segmental plaque burden. Assumptions underlying linear regression models were evaluated by visual examination of the residuals.

All statistical tests were two-tailed and p-values <0.05 were considered significant. SPSS, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for all the analyses.

## Results

### BASELINE CHARACTERISTICS

The current study included 680 patients from the combined ATHEROREMO-IVUS and IBIS-3 cohorts (**Figure 1**). The overall SXscore ranged from 0 to 37.5 with a median of 7 (IQR: 3-13) and a mean of 8.6±7.4. Baseline clinical and angiographic variables were stratified according to tertiles reflecting the obtained SXscores (lowest tertile, ≤4; middle tertile, >4 to ≤10; highest tertile >10) (**Table 1**). The highest tertile comprised more men. As expected, more patients in the higher tertiles exhibited two- or three-vessel disease, whereas no significant stenosis or one-vessel disease was more frequently present in patients with the lowest SXscores. More patients with lower SXscores had previously undergone a PCI.



**Figure 1.** Patient inclusion. RF-IVUS was available in 670 patients (light grey) and NIRS was available in 259 patients (dark grey). ATHEROREMO-IVUS: The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis - IVUS study; IBIS-3: Integrated Biomarker and Imaging Study-3; NIRS: near-infrared spectroscopy; RF-IVUS: radiofrequency intravascular ultrasound; SXscore: SYNTAX score

### CORONARY INTRAVASCULAR ULTRASOUND IN RELATION TO SXSCORE

After adjustment for multiple confounders/explanatory factors, a higher SXscore was associated with a higher plaque volume in the study segment (2.21 mm<sup>3</sup> per SXscore point, 95% CI: 0.92-3.50, p-value 0.001) (**Table 2**). The relation between SXscore and plaque burden was consistent with this observation, although statistically non-significant (p-value 0.078). A higher SXscore was also associated with a higher volume of fibrous (0.93 mm<sup>3</sup> per SXscore point, 95% CI: 0.53-1.33, p-value <0.001) and fibro-fatty tissue (0.29 mm<sup>3</sup> per SXscore point, 95% CI: 0.17-0.42, p-value <0.001) (**Table 2, Figure 2**). Importantly, the SXscore correlated with the fatty/fibro-fatty signals despite adjusting for plaque burden. In contrast, we found no association between SXscore and necrotic core volume (p-value 0.16) or the presence of thin-cap fibroatheroma (TCFA) (p-value 0.46).

### NEAR-INFRARED SPECTROSCOPY IN RELATION TO SXSCORE

A higher SXscore was associated with a higher NIRS-derived lipid core burden index (LCBI) in the full study segment (1.35 units per SXscore point, 95% CI: 0.22-2.47, p-value 0.019) (**Table 2, Figure 3**). Consistent results were observed for the 10 and 4 mm segments with highest LCBI values. Again, it is relevant to note that the observed correlation between SXscore and LCBI signals was independent of segment plaque burden.

## Discussion

This is the first study, to our knowledge, to have examined systematically a large patient population for the correlation of coronary atherosclerotic burden as determined by the SXscore and the extent and characteristics of coronary atherosclerosis as assessed

Table 1. Baseline characteristics.

		Low SXscore ≤4 (n=236)	Mid SXscore >4 to ≤10 (n=221)	High SXscore >10 (n=223)	p-value
<b>Patient characteristics</b>					
Age, years		60.4±10.9	61.3±10.7	61.2±11.0	0.70
Men, n (%)		169 (71.6)	169 (76.5)	184 (82.5)	0.022
Risk factors	Diabetes mellitus, n (%)	48 (20.3)	42 (19.0)	40 (17.9)	0.79
	Hypertension, n (%)	130 (55.1)	130 (58.8)	107 (48.0)	0.064
	Hypercholesterolaemia, n (%)	119 (50.4)	138 (62.4)	118 (52.9)	0.028
	Smoking, n (%)	63 (26.7)	66 (29.9)	70 (31.4)	0.55
History	Positive family history, n (%)	138 (58.5)	117 (52.9)	101 (45.3)	0.018
	Previous myocardial infarction, n (%)	79 (33.5)	59 (26.7)	61 (27.4)	0.21
	Previous PCI, n (%)	94 (39.8)	63 (28.5)	52 (23.3)	<0.001
	Previous stroke, n (%)	15 (6.4)	12 (5.4)	15 (6.7)	0.84
	History of peripheral artery disease, n (%)	12 (5.1)	19 (8.6)	14 (6.3)	0.31
	History of renal insufficiency, n (%)	13 (5.5)	10 (4.5)	11 (4.9)	0.89
	History of heart failure, n (%)	8 (3.4)	4 (1.8)	5 (2.2)	0.56
<b>Procedural characteristics</b>					
Indication for coronary angiography	Stable angina, n (%)	130 (55.1)	95 (43.0)	88 (39.5)	0.001
	Acute coronary syndromes, n (%)	106 (44.9)	126 (57.0)	135 (60.5)	
Extent of coronary artery disease	No significant stenosis, n (%)	91 (38.6)	1 (0.5)	0 (0.0)	<0.001
	1-vessel disease, n (%)	134 (56.8)	138 (62.4)	72 (32.3)	
	2-vessel disease, n (%)	11 (4.7)	69 (31.2)	114 (51.1)	
	3-vessel disease, n (%)	0 (0.0)	13 (5.9)	37 (16.6)	
<b>Imaged coronary artery characteristics</b>					
Imaged segment length, mm		44.7±14.1	42.6±13.1	44.4±14.7	0.17
Imaged coronary artery for RF-IVUS	Left anterior descending, n (%)	107 (46.7)	76 (34.5)	64 (28.8)	0.004
	Left circumflex, n (%)	58 (25.1)	78 (35.6)	81 (36.5)	
	Right coronary artery, n (%)	65 (28.1)	65 (29.9)	76 (34.6)	
Imaged coronary artery for NIRS	Left anterior descending, n (%)	40 (44.4)	34 (39.1)	20 (24.4)	0.003
	Left circumflex, n (%)	22 (24.4)	36 (41.4)	31 (37.8)	
	Right coronary artery, n (%)	28 (31.1)	17 (19.5)	31 (37.8)	

CABG: coronary artery bypass graft; IQR: interquartile range; LCBI: lipid core burden index; NIRS: near-infrared spectroscopy; PCI: percutaneous coronary intervention; RF-IVUS: (radiofrequency) intravascular ultrasound; SXscore: SYNTAX score

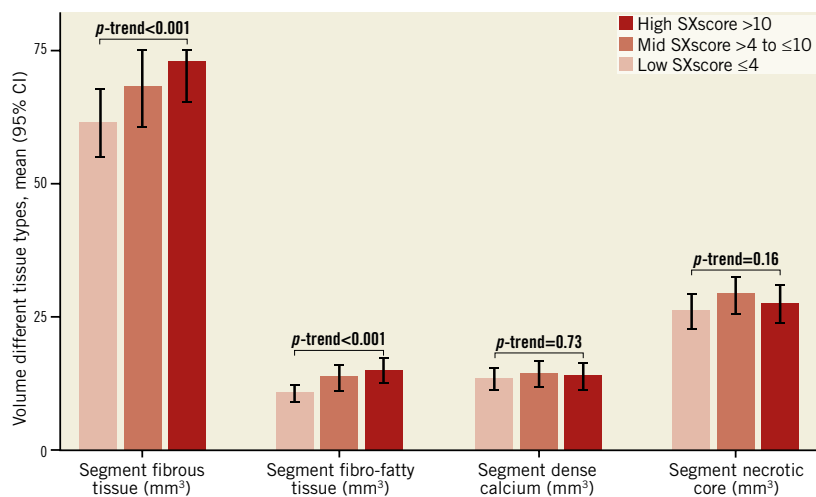
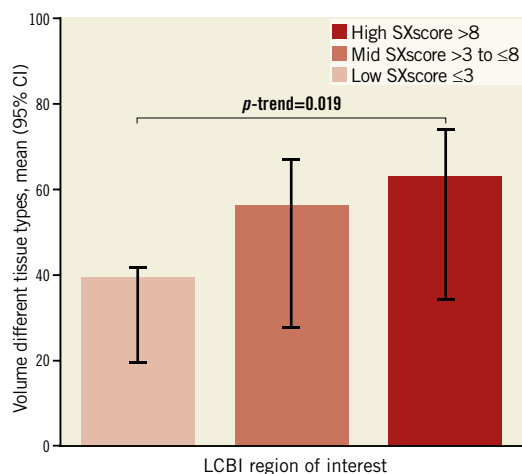


Figure 2. Distribution of RF-IVUS-derived plaque components across the SXscore categorised in tertiles. The mean volumes of the different plaque components (fibrous, fibro-fatty, dense calcium and necrotic tissue) are divided across the SXscore categorised in tertiles (cut-off points 4 and 10). RF-IVUS: radiofrequency intravascular ultrasound; SXscore: SYNTAX score

**Table 2. Associations between the SYNTAX score and RF-IVUS- and NIRS-derived variables in multivariable analyses.**

RF-IVUS-derived variables	Mean/OR (95% CI)						β/OR† (95% CI)		p-value‡	
	SXscore ≤4		4< SXscore ≤10		SXscore >10					
<b>No. of patients</b>	<b>230</b>		<b>219</b>		<b>221</b>		<b>670</b>			
Plaque volume, mm <sup>3</sup> ‡	230.1	(215.7-244.4)	246.0	(222.3-269.6)	242.4	(228.8-276.1)	2.21	(0.92-3.50)	0.001	
Plaque burden, % ‡	38.1	(36.8-39.5)	38.8	(36.7-40.9)	39.0	(37.0-41.1)	0.10	(-0.011-0.22)	0.078	
Plaque composition	Fibrous, mm <sup>3</sup>	61.4	(55.1-67.7)	68.0	(60.7-75.4)	72.6	(65.3-80.2)	0.93	(0.53-1.33)	<0.001
	Fibro-fatty, mm <sup>3</sup>	10.8	(9.3-12.3)	13.6	(11.3-15.9)	14.9	(12.6-17.2)	0.29	(0.17-0.42)	<0.001
	Dense calcium, mm <sup>3</sup>	13.3	(11.3-15.3)	14.3	(11.9-16.8)	13.9	(11.4-16.3)	0.023	(-0.11-0.16)	0.73
	Necrotic core, mm <sup>3</sup>	26.1	(22.8-29.3)	29.2	(25.7-32.6)	27.5	(24.0-30.9)	0.14	(-0.52-0.33)	0.16
Lesion morphology	TCFA	1		0.97	(0.63-1.50)	0.81	(0.53-1.24)	0.99	(0.97-1.01)	0.46
	MLA ≤4.0 mm <sup>2</sup> ‡	1		0.74	(0.44-1.23)	0.95	(0.59-1.54)	1.00	(0.97-1.02)	0.80
	Plaque burden ≥70%‡	1		1.05	(0.58-1.88)	1.47	(0.85-2.53)	1.02	(1.00-1.05)	0.092
<b>NIRS-derived variables</b>	<b>SXscore ≤3</b>		<b>3&lt; SXscore ≤8</b>		<b>SXscore &gt;8</b>					
<b>No. of patients</b>	<b>90</b>		<b>87</b>		<b>82</b>		<b>259</b>			
LCBI region of interest	39.4	(27.9-50.8)	56.0	(36.2-75.9)	62.7	(42.6-82.9)	1.35	(0.22-2.47)	0.019	
LCBI worst 10 mm	118.1	(90.9-145.3)	150.3	(106.4-194.3)	176.9	(132.2-221.6)	2.89	(0.39-5.38)	0.024	
LCBI worst 4 mm	190.4	(154.6-226.2)	231.3	(175.7-286.5)	266.6	(210.2-323.1)	3.83	(0.69-6.97)	0.017	

We present means and odds ratios with 95% CI based on multivariable models with SXscore included as categorical (explanatory) variable. In addition, we present βs and odds ratios with SXscore included as continuous (explanatory) variable. Multivariable models are adjusted for age, gender, hypertension, renal impairment, hypercholesterolaemia, diabetes mellitus, smoking, indication for CAG, history of PCI and plaque burden. †Based on multivariable models with SXscore included as continuous (explanatory) variable. ‡Multivariable model without adjustment for plaque burden. CI: confidence interval; LCBI: lipid core burden index; MLA: minimum luminal area; NIRS: near-infrared spectroscopy; No.: number; OR: odds ratio; RF-IVUS: radiofrequency intravascular ultrasound; SXscore: SYNTAX score; TCFA: thin-cap fibroatheromas



**Figure 3. Distribution of NIRS-derived LCBI across the SXscore categorised in tertiles. The mean LCBI of the region of interest is divided across the SXscore categorised in tertiles (cut-off points 3 and 8). LCBI: lipid core burden index; SXscore: SYNTAX score**

by RF-IVUS and NIRS in one non-stenotic segment of a single non-culprit coronary artery. This study shows that there is a significant and independent association between these entities in patients with CAD.

The SXscore is a well-established angiographic tool for the assessment of the severity and complexity of CAD<sup>2</sup>. It not only evaluates the number of significant stenoses but also lesion

length and the amount of calcification, amongst others. Still, as the SXscore is based on coronary luminography, it is limited in the assessment of the extent of (non-stenotic) plaque burden and plaque morphology, including the identification of high-risk plaque characteristics and vulnerable plaques. We demonstrated that the SXscore is associated with RF-IVUS- and NIRS-derived information on the extent and composition of coronary atherosclerosis in patients with CAD. The correlation between SXscore and the amount of fatty/fibro-fatty tissue as well as LCBI was most striking. In this respect, it is relevant to note the absence of relations between SXscore and plaque phenotype (necrotic core volume) and lesion morphology (TCFA).

Previously, a significant relation between atherosclerotic burden in one non-culprit coronary segment as assessed by RF-IVUS or NIRS and cardiovascular outcome was demonstrated which persisted after exclusion of culprit-related and imaged segment-related cardiac events<sup>5,7</sup>. This indirectly supported the assumption that the atherosclerotic burden in one non-culprit coronary segment may be representative of the atherosclerotic disease of the entire coronary tree. The current study shows a direct association between the angiographic atheroma burden of all three vessels and intravascular coronary wall evaluation of a non-culprit segment.

Although pre-specified high-risk plaque phenotypes (TCFA, MLA ≤4.0 mm<sup>2</sup> and lesions with a plaque burden of ≥70%) were not significantly associated with an increase in SXscore, the volume of fibrous and fibro-fatty tissue in plaques was higher in patients with a higher SXscore. Although a previous study has

shown that plaque morphology, as measured by three-vessel imaging by optical coherence tomography (OCT) or IVUS, is associated with and may be used for the identification of vulnerable plaques in patients with ACS<sup>16</sup>, it appears from our study that it is the amount of tissue type which is associated with SXscore and not plaque morphology (the layout of the tissue) *per se*. In the light of the relatively low overall angiographic burden of disease in our population, however, it needs to be considered that this finding may not be applicable in a patient population with more advanced CAD. Moreover, necrotic core and dense calcium did not show a significant association with a higher SXscore.

Previously, in one other small cohort, the relationship between NIRS and SXscore was explored but no association was found<sup>17</sup>. The relationship between NIRS and the SXscore has also been studied in a subset of patients from ATHEROREMO-IVUS<sup>18</sup>. The enrichment of the ATHEROREMO-IVUS cohort with the IBIS-3 cohort in the current study substantially increases the sample size and creates more robust data.

In most studies, SXscore is stratified in tertiles or even quartiles, reflecting the distribution of the scores found in the respective cohort<sup>2</sup>. The thresholds of the original SYNTAX trial (cut-off points: 22 and 33) have been incorporated in the guidelines for the decision making regarding CABG and PCI, but these thresholds apply to patients with left main and/or three-vessel disease<sup>19</sup>. Our population also consisted of patients with single- or two-vessel disease and hence, understandably, our mean SXscore and cut-off values for the tertiles were relatively low. Further research is warranted to assess which absolute SXscore thresholds are applicable in a heterogeneous population for risk prediction of adverse outcome in patients with CAD.

Furthermore, we argue that combined IVUS-NIRS intracoronary imaging holds promise for more precise detection and quantification of atherosclerotic burden in patients with CAD, and in the future may even be of interest for the prediction of adverse events. However, further research is warranted to assess the application of combined IVUS-NIRS intracoronary imaging for the prediction of adverse events.

## Limitations

This cohort, composed of two prospective studies, has broad inclusion criteria which enable the results to be applicable to a broad patient population with CAD. Data collection, processing and analyses were conducted by independent researchers blinded to patient and outcome data. However, a few limitations deserve consideration.

As indicated, our study includes patients with relatively low SXscores. This might induce an underestimation of the studied associations and insufficient power to reveal additional associations. However, a subgroup analysis with exclusion of patients without significant CAD showed results that were essentially similar. Moreover, the lowest tertile in this cohort contains significantly more patients with a previous PCI, which may indicate an underestimation of the severity of CAD caused by a low SXscore derived at study entry.

Furthermore, while the SXscore analyst was blinded to all patient information, occlusions in STEMI patients were scored as occlusions of unknown duration. In the MI SYNTAX score study, it was proposed to calculate occlusions in STEMI patients post wiring<sup>20</sup>. However, the MI SYNTAX score did not show better performance than the original SXscore calculated in STEMI patients.

Lastly, although the literature has demonstrated that experienced operators produce reasonable SXscores, the modest reproducibility of the SXscore in general has to be acknowledged<sup>21</sup>. However, because of the overall relatively low angiographic burden of disease in our study population, we expected a fair reproducibility of the SXscore in our study. To address the reproducibility of our SXscores, a second experienced operator, blinded to patient characteristics and previously scored SXscores, repeated SXscore analysis in a representative random sample. Cohen's kappa was shown to be 0.91, indicating a good interobserver agreement.

## Conclusions

In patients with CAD, there is a clear and significant correlation between a higher SXscore and a higher atherosclerotic burden as assessed by RF-IVUS and NIRS in one non-stenotic segment in a single non-culprit coronary artery.

### Impact on daily practice

This study shows that RF-IVUS and NIRS imaging in one non-culprit coronary artery segment reflects overall coronary atherosclerotic burden in patients with CAD. Our findings may support the use of RF-IVUS and NIRS in one single non-culprit coronary artery segment for the evaluation of the atherosclerotic burden in patients with CAD over time. However, trials are needed to investigate the suitability of assessing dynamic changes in plaque composition to predict outcome benefit with therapeutic interventions.

## Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard and University Paris VII, Paris, France.

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## Conflict of interest statement

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## Supplementary data

**Supplementary Appendix.** Methods.

The supplementary data are published online at:  
[http://www.pcronline.com/eurointervention/146th\\_issue/255](http://www.pcronline.com/eurointervention/146th_issue/255)





## **Supplementary data**

### **Supplementary Appendix 1. Methods**

#### **Coronary intravascular ultrasound**

Following CAG, IVUS was performed in a proximal non-stenotic (<50% stenosis) segment of at least 40 mm of a non-culprit artery. The order of preference used for selection of the non-culprit vessel was predefined in the study protocol: 1) left anterior descending artery; 2) right coronary artery; 3) left circumflex artery. All IVUS data were obtained with the Volcano s5/s5i Imaging System (Volcano Corp., San Diego, CA, USA) using a Volcano Eagle Eye Gold IVUS catheter (20 Mhz). An automatic pullback system was used with a standard pullback speed of 0.5 mm per second. The baseline IVUS images were sent to an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) for offline analysis. The core laboratory personnel were blinded for baseline patient characteristics and clinical outcome. The RF-IVUS analysis was performed using pcVH 2.1 and qVH (Volcano Corp., San Diego, CA, USA) software.

The external elastic membrane and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). Plaque burden was defined as the plaque and media cross-sectional area divided by the external elastic membrane cross-sectional area. A coronary lesion was defined as a segment with a plaque burden of more than 40% in at least 3 consecutive frames. The composition of atherosclerotic plaque was characterised into 4 different tissue types: fibrous, fibro-fatty, dense calcium and necrotic core [22]. Three types of high-risk lesions were identified: 1) thin-cap fibroatheroma (TCFA) lesion, defined as a lesion with presence of >10% confluent necrotic core in direct contact with the lumen; 2) lesion with large plaque burden,

defined as a lesion with a plaque burden of  $\geq 70\%$ ; 3) stenotic lesion, defined as a lesion with a minimal luminal area (MLA) of  $\leq 4.0 \text{ mm}^2$  [4,23].

### **Near-infrared spectroscopy**

In a subset of patients, NIRS imaging was performed in the same segment as IVUS. The NIRS system used consists of a 3.2 Fr rapid exchange catheter, a pullback and rotation device and a console (Infraredx, Burlington, MA, USA), approved by the U.S. Food and Drug Administration. Image acquisition was performed by a motorised catheter pullback at a speed of 0.5 mm/s and 240 rpm. The system performed 1,000 chemical measurements per 12.5 mm. Each measurement interrogated 1 to 2 mm<sup>2</sup> of vessel wall from, approximately, 1 mm in depth from the luminal surface towards the adventitia [4,5].

The NIRS measurements were used to create a chemogram. The fraction of yellow pixels from the chemogram was multiplied by 1,000, to calculate the lipid core burden index (LCBI). Thus, the LCBI value, with a range between 0 and 1,000, represents the amount of lipid core in the assessed segment [24]. In addition, within this region of interest, the 10 mm and 4 mm segment with the highest LCBI was defined.

NIRS images were analysed offline by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). Core laboratory personnel were blinded to all other patient and outcome data.