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Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease

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ABSTRACT

Background: Near-infrared spectroscopy (NIRS) is capable of identifying lipid core-containing plaques, which can subsequently be quantified as a lipid core burden index (LCBI). Currently, no data are available on the long-term prognostic value of NIRS in patients with coronary artery disease (CAD).

Objectives: This study sought to determine the long-term prognostic value of intracoronary NIRS as assessed in a nonculprit vessel in patients with CAD.

Methods: In this prospective, observational study, NIRS imaging was performed in a nonculprit coronary artery in 203 patients referred for angiography due to stable angina pectoris (SAP) or acute coronary syndrome (ACS). The primary endpoint was the composite of all-cause mortality, nonfatal ACS, stroke, and unplanned coronary revascularization.

Results: The 1-year cumulative incidence of the primary endpoint was 10.4%. Cumulative 1-year rates in patients with an LCBI equal to and above the median (43.0) versus those with LCBI values below the median were 16.7% versus 4.0% (adjusted hazard ratio: 4.04; 95% confidence interval: 1.33 to 12.29; p = 0.01). The relation between LCBI and the primary endpoint was similar in SAP and ACS patients (p value for heterogeneity = 0.14). Similar differences between high and low LCBI were observed in pre-specified secondary endpoints.

Conclusion: CAD patients with an LCBI equal to or above the median of 43.0, as assessed by NIRS in a nonculprit coronary artery, had a 4-fold risk of adverse cardiovascular events during 1-year follow-up. This observation warrants confirmation by larger studies with extended follow-up.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a novel, catheter-based technique capable of identifying lipid core-containing plaques within the coronary artery wall (1). Currently, no data are available on the long-term prognostic value of NIRS in patients with coronary artery disease. We therefore performed a prospective study to assess the prognostic value of coronary plaque detection, as evaluated with NIRS, on the occurrence of major adverse cardiac and cerebrovascular events (MACCE) in the real-world setting of everyday clinical practice, in which patients with both stable angina and acute coronary syndrome (ACS) present for coronary angiography. Parallel to this objective, it was our aim to investigate whether imaging of a single segment without significant luminal narrowing of a nonculprit coronary artery could be used for risk stratification.

METHODS

Study population and design

The ATHEROREMO-NIRS (The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis–Near-Infrared Spectroscopy) substudy (2) was a prospective, single-center, observational study assessing the prognostic value of coronary NIRS, performed at the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. All patients had an indication, as determined by their treating physician (as part of routine clinical care), for diagnostic coronary angiography and/or percutaneous coronary intervention (PCI) due to either stable angina pectoris or an ACS. Detailed inclusion and exclusion criteria are listed in Supplemental table 1.

Subsequent to the standard angiography and PCI (when applicable), NIRS of a nonculprit coronary artery was performed. The NIRS target segment of the nonculprit coronary artery was required to be at least 40 mm in length and without significant luminal narrowing (<50% stenosis) as assessed by online angiography. The order of preference for selection of the nonculprit vessels was predefined in the study protocol: 1) left anterior descending artery; 2) right coronary artery; and 3) left circumflex artery. This study was approved by the Medical Ethics Committee of the Erasmus Medical Center, and performed in accordance to the Declaration of Helsinki (2008, 6th revision). Written informed consent was obtained from all participants.

Sample size

The ATHEROREMO-IVUS (The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis–Intravascular Ultrasound) study had a pre-specified sample size of 800 patients, and was designed to explore multiple relations between

genetic and serum biomarkers and coronary plaque characteristics (2). It was during the course of the ATHEROREMO-IVUS study that intracoronary NIRS became commercially available and accessible for our cardiac catheterization lab. The ultimate sample size of the ATHEROREMO-NIRS substudy (203 consecutively consenting patients) was not based on prior effect estimates but rather on the time point of availability and local institutional review board approval (April 2009) of the NIRS technique as ATHEROREMO evolved.

Near-infrared spectroscopy

The U.S. Food and Drug Administration–approved NIRS system, as used in this study, consists of a 3.2-F rapid exchange catheter, a pullback and rotation device, and a console (InfraReDx, Burlington, Massachusetts). Image acquisition was performed by a motorized catheter pullback at a speed of 0.5 mm/s and 240 rpm in a proximal segment of a nonculprit artery, starting distal to a side branch. The system performed 1,000 chemical measurements per 12.5 mm, in which each measurement interrogated 1 to 2 mm^2 of vessel wall from a depth of approximately 1 mm in the direction from the luminal surface toward the adventitia (1). Areas of the artery with spectral characteristics of a lipid core were displayed in yellow within the image map, called a chemogram. NIRS images were analyzed offline by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). Core laboratory personnel were blinded to all other patient and outcome data.

Study endpoints

The pre-specified primary endpoint was the incidence of MACCE, defined as the composite of all-cause mortality, nonfatal ACS, stroke, and unplanned coronary revascularization during 1-year follow-up, exclusive of events related to the culprit lesion at the index angiography. Secondary endpoints included: 1) the composite of all-cause mortality and nonfatal ACS; 2) the composite of all-cause mortality, nonfatal ACS, and stroke; and 3) the composite of all-cause mortality, nonfatal ACS, and unplanned coronary revascularization during follow-up. Endpoints were adjudicated by a clinical events committee on the basis of original source data. Members of the clinical events committee were blinded to other patient data and NIRS imaging characteristics. Post-discharge survival status was obtained from municipal civil registries. Nonfatal ACS included ST-segment elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris as defined in accordance with the guidelines of the European Society of Cardiology (3,4). Stroke was defined according to the guidelines of the European Stroke Organization (5). Unplanned coronary revascularization was defined as PCI or coronary artery bypass grafting, which initially was not planned after the index angiography and enrollment in the study.

Whenever possible, all events were further adjudicated as related or unrelated to the coronary site that was treated during the index procedure. In case of follow-up

angiography, events were classified either as a definite culprit lesion–related (CLR) event or as related to a coronary site that was not treated during the index procedure (non-CLR event). In case angiographic information on the endpoint related coronary site was not available, the event was classified as indeterminate. The pathophysiological processes of definite CLR events (e.g., in-stent restenosis and stent thrombosis) differ from the pathophysiology of spontaneous plaque rupture. Therefore, data are presented both exclusive of definite CLR events (by default), as well as inclusive of definite CLR events.

Statistical analysis

Normally distributed continuous variables are presented as mean SD. Non-normally distributed continuous variables (e.g., the lipid core burden index [LCBI]) are presented as median (interquartile range [IQR]). Categorical variables are presented in numbers and percentages. Differences in baseline continuous variables between those with an LCBI below versus those equal to and above the median were analyzed by Mann-Whitney U tests, categorical variables by Fisher's exact and Pearson chi-square tests (in case of more than 2 categories). Log or square root transformations were applied whenever homoscedasticity was a required assumption of the used statistical test. Linear regression was used to determine predictors of LCBI. No prior data were ever reported on LCBI distribution of the nonculprit artery. The statistical analytical plan therefore prespecified the median LCBI value as cutoff between "low" and "high" LCBI groups, in case LCBI would appear to be non-normally distributed.

Patients lost to follow-up were considered at risk until the date of last contact, at which time point they were censored. For patients with more than 1 event, the first was counted. Cumulative event rates were estimated according to the Kaplan-Meier method and compared by the log-rank test. Backward stepwise regression analyses were used to determine the predictors of the primary endpoint. Univariable and multivariable Cox proportional hazards regression analyses were applied to evaluate the association between LCBI and 1-year outcome. Three models were used throughout the manuscript: an unadjusted model, an age- and sex-adjusted model, and a "full model." Given the number of events available, adjustment according to a propensity score was used in order to assure parsimony of the full model (6). Variables for the propensity score of the full model were selected on the basis of clinical relevance and significance after backward stepwise regression. The propensity scores were derived from predicted probabilities in logistic regression models with LCBI above the median as dependent variable (7). The propensity score that was entered into the full model accounts for age, sex, hypercholesterolemia, diabetes, hypertension, indication for index coronary angiography (stable angina pectoris versus ACS), history of myocardial infarction, peripheral artery disease (PAD) or stroke, and prior PCI. Crude and adjusted hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Discrimination of the full model with respect to event

prediction was evaluated with receiver-operating characteristic curves. Heterogeneity of the effect of LCBI on MACCE was tested between patients presenting with stable angina and those presenting with ACS at the time of enrollment (8). All statistical tests were 2-sided with a type I error level of 0.05. Analyses were performed with IBM SPSS statistics version 20.0 (IBM Corp., Armonk, New York).

RESULTS

Between April 16, 2009, and January 28, 2011, a total of 203 patients were enrolled prior to coronary angiography. Median follow-up was 1 year and follow-up data were complete in 100% of the study sample. Mean age was 63.4 years. Men constituted 72.9% of the study sample and 46.8% of the patients presented with an ACS. A PCI was performed in 88.2% of the patients during the index coronary angiography.

LCBI values in the nonculprit vessel (median pullback length: 63.1 mm; IQR: 51.0 to 75.0 mm) ranged from 0 to 571, with a median of 43.0 (IQR: 15.0 to 90.0) (Figure 1). Regression analysis demonstrated that men and patients with a history of hypercholesterolemia, stroke, or PAD had higher LCBI values. Differences in baseline characteristics between patients with an LCBI below the median versus those with an LCBI equal to or above the median value are presented in Table 1. LCBI of the nonculprit imaged segment did not differ between patients presenting with stable angina (median: 35.0; IQR: 14.0 to 85.5) or ACS (median: 47.0; IQR: 16.0 to 90.0; p = 0.24).

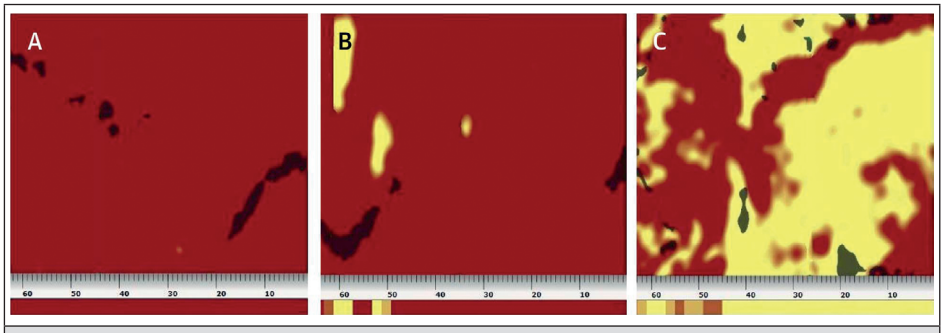

Figure 1. Intracoronary near-infrared spectroscopy displayed as a chemogram
The figures display the graphical result of coronary wall evaluation with near-infrared spectroscopy in 3 different patients. Spectral characteristics of lipid core– containing coronary plaques (LCP) are displayed along the length (x-axis, in mm) and circumference (y-axis, 0 to 360) of the scanned coronary artery. Yellow regions in the chemogram represent high probability for the presence of LCP, while red regions represent those with low probability. The lipid core burden index (LCBI) score is computed on the basis of the chemogram by multiplying the fraction of valid yellow pixels within the region of interest by 1,000. The LCBI for the different patients depicted are 0 (A), 43 (B), and 571 (C) (examples of the lowest, median, and highest value in our study, respectively).

Table 1. Baseline characteristics.

	All patients N = 203	LCBI < Median N= 101	LCBI ≥ Median N=102	P value
Patient characteristics				
Age, years	63.4 ±10.9	64.8 ±10.8	62.1 ±11.0	0.083
Male, n (%)	148 (72.9)	67 (66.3)	81 (79.4)	0.041
Diabetes Mellitus, n (%)	41 (20.2)	18 (17.8)	23 (22.5)	0.485
Hypertension, n (%)	114 (56.2)	56 (55.4)	58 (56.9)	0.888
Hypercholesterolemia, n (%)	115 (56.7)	53 (52.5)	62 (60.8)	0.259
Smoking, n (%)	50 (24.6)	23 (22.8)	27 (26.5)	0.805
Positive family history, n (%)	120 (59.1)	62 (61.4)	58 (57.4)	0.667
Previous MI, n (%)	79 (38.9)	36 (35.6)	43 (42.2)	0.389
Previous PCI, n (%)	78 (38.4)	39 (35.6)	39 (38.2)	1.000
Previous CABG, n (%)	6 (3.0)	4 (4.0)	2 (2.0)	0.445
Previous stroke, n (%)	6 (3.0)	1 (1.0)	5 (4.9)	0.212
Peripheral artery disease, n (%)	11 (5.4)	4 (4.0)	7 (6.9)	0.537
History of renal insufficiency, n (%)	12 (5.9)	5 (5.0)	7 (6.9)	0.767
History of heart failure, n(%)	9 (4.4)	6 (5.9)	3 (2.9)	0.331
Statin at discharge	181 (89.2)	91 (90.1)	90 (88.2)	0.82
Median total cholesterol (IQR)	4.20 (3.60-5.20)	4.20 (3.40-5.00)	4.30 (3.68-5.30)	0.301
Median low-density lipoprotein (IQR)	2.47 (1.95-3.21)	2.44 (1.85-3.14)	2.49 (2.03-3.39)	0.381
Median high-density lipoprotein (IQR)	1.14 (0.92-1.36)	1.15 (0.93-1.37)	1.09 (0.92-1.32)	0.455
Median triglycerides (IQR)	1.26 (0.91-1.80)	1.18 (0.89-1.73)	1.35 (0.95-1.91)	0.152
Procedural characteristics				
Indication for coronary angiography				0.261
ACS	95 (46.8)	43 (42.6)	52 (51.0)	
Acute MI, n (%)	67 (33.0)	15 (14.9)	13 (12.7)	
Unstable angina, n (%)	28 (13.8)	28 (27.7)	39 (38.2)	
Stable angina	108 (53.2)	58 (57.4)	50 (49.0)	
PCI / stent implantation	179 (88.2)	86 (85.1)	93 (91.2)	0.199
Extent of coronary artery disease				0.045
No significant stenosis, n (%)	16 (7.9)	10 (9.9)	6 (5.9)	
1-vessel disease, n (%)	106 (52.2)	58 (57.4)	48 (47.1)	
2-vessel disease, n (%)	58 (28.6)	28 (27.7)	30 (29.4)	
3-vessel disease, n (%)	23 (11.3)	5 (5.0)	18 (17.6)	
NIRS characteristics				
Imaged coronary artery				0.299
Left anterior descending, n (%)	74 (36.5)	42 (41.6)	32 (31.4)	
Left circumflex, n (%)	70 (34.5)	31 (30.7)	39 (38.2)	
Right coronary artery, n (%)	59 (29.1)	28 (27.7)	31 (30.4)	
Median LCBI (IQR)	43.0 (15.0-90.0)	15.0 (6.0-27.0)	88.5 (58.8-120.3)	<0.001

LCBI, Lipid Core Burden Index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; IQR, interquartile range, ACS, acute coronary syndrome.

Table 2. Clinical event distribution during one-year follow-up.

	All-cause mortality	Non-fatal ACS	Stroke	Unplanned coronary revascularization	All events (incl. CLR events)	All events (excl. CLR events)
Primary endpoint, *n (%)*						
All-cause mortality, non-fatal ACS, stroke and unplanned coronary revascularization	7 (3.4)	6 (3.0)	3 (1.5)	12 (5.9)	**28 (13.8)**	**21 (10.3)**
Secondary endpoint, *n (%)*						
All-cause mortality and non-fatal ACS	7 (3.4)	6 (3.0)	n.a.	n.a.	**13 (6.4)**	**10 (4.9)**
All-cause mortality, non-fatal ACS and stroke	7 (3.4)	6 (3.0)	3 (1.5)	n.a.	**16 (7.8)**	**13 (6.4)**
All-cause mortality, non-fatal ACS and unplanned coronary revascularization	7 (3.4)	6 (3.0)	n.a.	12 (5.9)	**25 (12.3)**	**18 (8.9)**

Percentages are given for the cumulative incidence. ACS, acute coronary syndrome; CLR events, culprit lesion-related events.

MACCE occurred in 28 patients (13.8%) during 1-year follow-up. Seven events (25% of the total number of events) were classified as definite CLR events, hence the primary endpoint (which excludes definite CLR events) occurred in 21 patients. The 1-year cumulative incidence of the primary endpoint was 10.4%. The frequencies of all first events are described in Table 2. Unplanned coronary revascularization (5.9%; all events were revascularized by PCI) occurred most frequently, followed by all-cause mortality (3.4%), nonfatal ACS (3.0%), and stroke (1.5%). Only LCBI, a history of stroke, and PAD were associated with the primary endpoint.

The 1-year cumulative rate of the primary endpoint was 16.7% for patients with an LCBI equal to and above the median versus 4.0% for those with LCBI values below the median (log-rank p = 0.003) (Figure 2) (unadjusted HR: 4.56; 95% CI: 1.53 to 13.55). The secondary endpoint of all-cause mortality and nonfatal ACS occurred in 8.8% versus 1.0% in those with high versus low LCBI (p = 0.010) (Figure 2). Cumulative event rates for other secondary endpoints – also exclusive of definite CLR events – also are shown in Figure 2.

The association between LCBI equal to and above the median value and the primary endpoint remained significant after adjustment for age and sex (adjusted HR: 5.16; 95% CI: 1.73 to 15.42) and after adjustment for the full model (adjusted HR: 4.04; 95% CI: 1.33 to 12.29), as described in Table 3. LCBI values equal to and above the median were significantly associated with an increased risk of all secondary endpoints with point estimates of the (full model) adjusted HRs ranging from 3.56 to 10.59 (Table 3). With

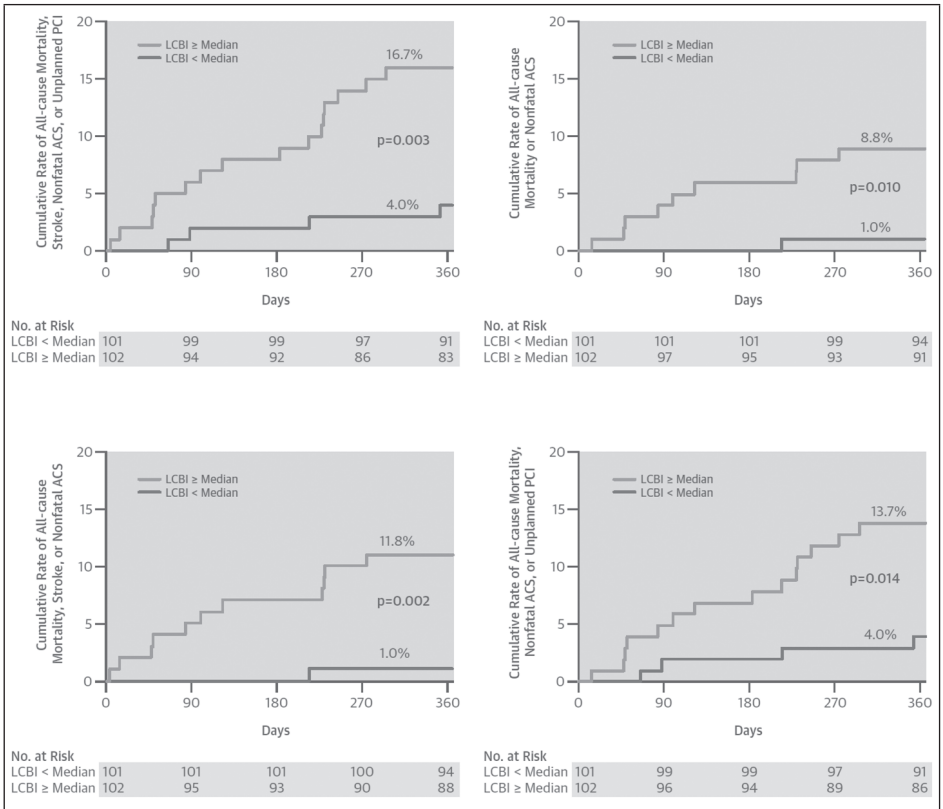

Figure 2. Time-to-event curves for the primary and pre-specified secondary composite endpoints exclusive of definite culprit lesion-related events

A 4-fold increase in major adverse cardiac and cerebrovascular events during 1-year follow-up was observed in patients with a lipid core burden index (LCBI) above the median, as assessed by near-infrared spectroscopy of a nonstenotic nonculprit coronary artery segment (16.7% vs. 4.0% event rate [adjusted hazard ratio: 4.04; 95% confidence interval: 1.33 to 12.29; p = 0.01]). ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

respect to prediction of the primary endpoint, the full model resulted in an area under the receiver-operating characteristic curve of 0.83 (95% CI: 0.75 to 0.92).

There was a statistically significant difference in mortality between those below and above the median in univariate analysis (1.0% vs. 6.9%; log-rank p = 0.032), but not after adjusting for the full model (adjusted HR: 6.2; 95% CI: 0.73 to 52.0; p = 0.10).

The median LCBI in patients with stable coronary artery disease was 35.0 (IQR: 14.0 to 85.5) and did not differ significantly from the median of 47.0 (IQR: 16.0 to 90.0) in patients with ACS at index angiography (p = 0.44). We found no heterogeneity of the effect of LCBI on the primary endpoint between patients presenting with stable angina versus ACS patients at the time of enrollment (p value for heterogeneity = 0.14).

Table 3. LCBI levels equal to and above the median value and major adverse cardiac events (exclusive of definite culprit lesion-related events).

	Unadjusted model	P	Age and gender adjusted model	P	Full model	P
Primary endpoint	Hazard ratio (95% CI)	**value**	Hazard ratio (95% CI)	**value**	Hazard ratio (95% CI)	**value**
All-cause mortality, non-fatal ACS, stroke and unplanned coronary revascularization	4.56 (1.53-13.55)	0.006	5.16 (1.73-15.42)	0.003	4.04 (1.33-12.29)	0.014
Secondary endpoints						
All-cause mortality and non-fatal ACS	9.36 (1.19-73.87)	0.034	10.14 (1.27-80.67)	0.029	8.91 (1.10-72.33)	0.041
All-cause mortality, non-fatal ACS and stroke	12.67 (1.65-97.46)	0.015	14.58 (1.89-112.71)	0.010	10.59 (1.35-83.28)	0.025
All-cause mortality, non-fatal ACS and unplanned coronary revascularization	3.69 (1.21-11.20)	0.021	3.96 (1.29-12.11)	0.016	3.56 (1.14-11.20)	0.029

* Hazard ratios are given for patients with lipid core burden index (LCBI) levels equal to and above the median (n=102), versus those with LCBI below the median (n=101). Variables in the propensity score of the full model were age, gender, hypercholesterolemia, diabetes, hypertension, history of myocardial infarction, peripheral artery disease and stroke, indication for index coronary angiography (stable angina versus ACS) and prior PCI. ACS, acute coronary syndrome.

Analyses inclusive of definite culprit lesion-related events

Unplanned PCI was required for 4 culprit lesions that had been treated during the index catheterization; in 3 other patients, initially treated culprit lesions led to unstable angina, non-STEMI, and death, respectively.

When definite culprit lesion-related events were also taken into account, an overall 1-year cumulative rate of the primary endpoint was observed in 19.6% of the patients with an LCBI equal to and above the median versus 7.9% for those with LCBI values below the median (p = 0.015) (Supplemental Figure 1).

The secondary endpoint of all-cause mortality and nonfatal ACS occurred in 9.8% versus 3.0% in those with high versus low LCBI, respectively (p = 0.010). Similar results were observed for the other 2 secondary endpoints.

DISCUSSION

We observed that high LCBI levels were associated with a 4-fold increase in MAC(C)E during 1-year follow-up of a broad population of patients referred for coronary angiography.

This association between LCBI and adverse outcome was found by NIRS imaging of a single, nonstenotic segment of a nonculprit coronary artery.

Based on diffuse reflectance spectroscopy, NIRS provides a positive and specific chemical measure of cholesterol within the coronary vessel wall, as cholesterol has prominent molecular features in the near-infrared region that can be distinguished from other tissue constituents such as collagen (9). Its ability to recognize cholesterol monohydrate and cholesterol ester – both of which are abundant in necrotic cores and therefore key components of plaque vulnerability – appears to be superior to that of intravascular ultrasound (IVUS) – or optical coherence tomography-based techniques (10).

Against this background, the recently published, randomized YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial is of particular interest, as it is the first study to investigate whether a pharmacologic intervention may reduce lipid core plaque as assessed by intracoronary NIRS (11). High-dose statin therapy (vs. standard-of-care statin therapy) during 6 to 8 weeks in 87 patients resulted in a significant reduction of LCBI as measured at the site of untreated obstructive coronary lesions with a fractional flow reserve below 0.80 (11). It is important to emphasize, however, that the association between LCBI and MAC(C)E in our study was found through imaging of a segment of a nonculprit coronary artery without significant stenosis. Consequently, the median LCBI of 43.0 (IQR: 15.0 to 90.0) in our study is lower than the median LCBI values of 95.4 (IQR: 29.6 to 174.6) and 132.4 (IQR: 99.0 to 201.2), for the standard-of-care and high-dose statin therapy groups, respectively, as measured in the obstructive lesions in the YELLOW trial (11). The prognostic value of NIRS imaging of such obstructive lesions has not yet been investigated for risk prediction of adverse cardiovascular events during long-term follow-up.

The currently ongoing IBIS-3 (Integrated Biomarker and Imaging Study-3) study is designed to assess the efficacy of high-dose rosuvastatin on the reduction of the necrotic core and LCBI in a nonculprit coronary segment of patients who have undergone diagnostic angiography or PCI (12).

Our data were prospectively obtained and the conclusions seem applicable to a broad range of patients, including those with stable angina or ACS at the time of index angiography. Of great importance is that NIRS evaluation was performed in an independent, dedicated core lab with personnel blinded for patient and outcome data. An independent and blinded clinical event committee adjudicated the events. Statistics were performed by authors who were not, in any way, involved with the study until the time of transfer of the finalized database.

Study limitations

There are several limitations to our findings. The small sample size and corresponding number of events are a limitation, although this study does represent the largest cohort of patients with NIRS analysis and long-term follow-up so far.

Furthermore, the ATHEROREMO-NIRS substudy was a single-center study by virtue of design. External validation, preferably in a larger sample size, is a fundamental prerequisite before any of our conclusions may be considered for possible future clinical implications.

Our cutoff value was based on the median LCBI value, similarly to a recent post hoc analysis of the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs. Atorvastatin) trial, which evaluated the median value of IVUS-derived percent atheroma volume as cutoff for predicting future MAC(C)E (13). We do not propose 43 as an absolute cutoff value. Larger sample sizes are required to determine and validate the sensitivity and specificity of NIRS imaging at different cutoff LCBI values.

Accordingly, future research will have to demonstrate whether the strength of NIRS is determined by its capability to detect or to rule out an increased risk for MAC(C)E during long-term follow-up.

Previous studies with IVUS have repeatedly demonstrated that IVUS-derived plaque volume in comparable nonstenotic, nonculprit coronary segments was associated with incident MAC(C)E during longterm follow-up (13,14). Similarly, the ATHEROREMO protocol proposed NIRS imaging in at least 4 cm (median pullback length: 63.1 mm) of only 1 proximal segment of a nonculprit coronary artery. Nevertheless, it should be emphasized that our findings relate to an increased risk of MAC(C)E throughout the entire coronary tree and not necessarily at the imaged segment or a lesion-specific risk. We did not aim to identify all "vulnerable" and potentially treatable plaques. Our study does not allow conclusions on whether the events during follow-up originated from regions of relatively high or low LCBI or whether more proximal cholesterol accumulation is associated with an increased event rate. Three-vessel NIRS imaging at index angiography and follow-up coronary angiography (or autopsy) at the moment of an endpoint are ideally required for such conclusions.

From an etiologic point of view, it is important to emphasize that the specificity of in vivo detection of potentially vulnerable plaques and knowledge about their temporal stability generally is limited given the current state of the art (15). As we did not repeat NIRS imaging of the same segment at a later time point, no conclusions can be drawn on temporal plaque stability and dynamics. Rather than an etiologic exploration to identify all coronary plaques and assess their temporal stability, our analyses should be seen as an evaluation of the prognostic value of NIRS imaging used as a global marker of intracoronary disease burden, which is not seen in the form of luminal narrowing on angiography.

The majority of the endpoints in this study were due to unplanned revascularization. Future studies with a higher incidence of mortality and nonfatal ACS are required to properly assess the prognostic value of NIRS for these events.

Formal testing demonstrated that there was no heterogeneity of the ability of LCBI to predict outcome between the stable angina and ACS groups, although the interaction test may have been underpowered.

Intracoronary NIRS became commercially available during the course of ATHEROREMO. Thus, understandably, we were not able to enroll all ATHEROREMO patients in this NIRS substudy. The characteristics, treatment, and outcomes of the substudy cohort and the remaining ATHEROREMO patients were similar. Hence, differential selection is unlikely, although it cannot be excluded with absolute certainty.

A limitation of the NIRS technique is that the chemograms only provide plaque information in a 2-dimensional manner and do not provide information on the depth of the cholesterol accumulation within the coronary artery wall. IVUS may therefore be used for additional evaluation of luminal stenosis, vessel remodeling, and plaque architecture.

CONCLUSIONS

This prospective observational study suggests that coronary LCBI, as assessed by NIRS in a nonculprit coronary artery, is associated with MAC(C)E during 1-year follow-up in patients referred for coronary angiography. However, our results are hypothesis generating and need confirmation by larger trials that overcome the limitations of our study.

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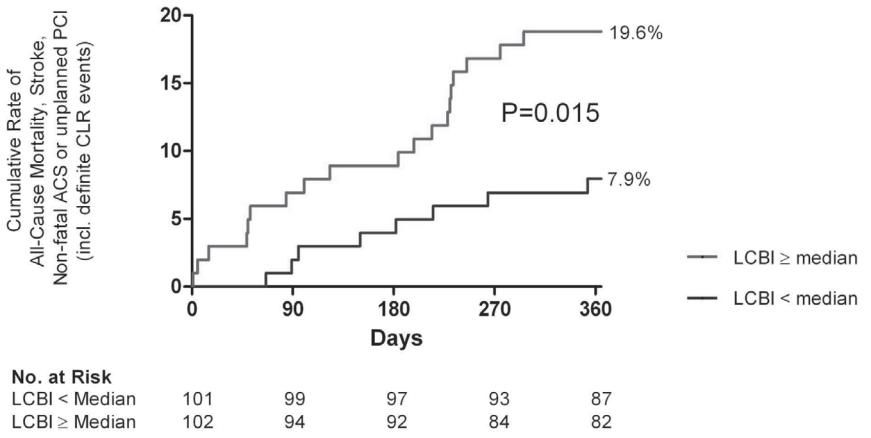
SUPPLEMENTAL TABLES AND FIGURES

Supplemental Table 1. Inclusion and exclusion criteria

Inclusion criteria:
8. Aged 21 years or older. 9. Presenting with stable angina pectoris (CCS angina class 1, 2, 3 or 4), unstable angina pectoris (Braunwald class 1-3, B-C), documented silent ischemia or acute myocardial infarction (STEMI and NSTEMI). 10. Eligible for coronary revascularization in the native coronary artery/arteries. 11. Willing and able to comply with the specified follow-up evaluation. 12. Willing to sign informed consent. 13. Presence of a flow-limiting stenosis (diameter stenosis ≥50% by QCA or visual estimate) that is held responsible for angina pectoris or acute coronary syndrome 14. The study vessel has not undergone percutaneous coronary intervention in the last 8 months.
Exclusion criteria:
17. Angina caused by a non-cardiac illness (Braunwald class IA, IIA, IIIA). 18. Pregnant women or women of childbearing potential who do not use adequate contraception. 19. Known allergies to aspirin, clopidogrel, ticlopdine, heparin, stainless steel, copper or a sensitivity to contrast media which cannot be adequately pre-medicated. 20. Previous participation in this study or participation in another study with any investigational drug or device within the past 30 days (study participation ends after completion of the final follow-up). 21. Life expectancy of less than one year or factors making clinical and/or angiographic follow-up difficult. 22. Planned or being status post coronary bypass surgery. 23. Planned major non-cardiac surgery. 24. Impaired renal function (creatinine>2 mg/dl or ≥150 µmol/l). 25. History of bleeding diathesis or coagulopathy. 26. History of disabling stroke within the past year.
Exclusion criteria for intravascular ultrasound and near-infrared spectroscopy:
27. Three-vessel coronary artery disease or left main disease with ≥50% stenosis. 28. Minimal lumen diameter <2mm in the segments to be analyzed within the study vessel. 29. Diameter stenosis >70% or total occlusion of the study vessel. 30. In case the study-vessel has been stented previously (>8 months ago), more than 1/3 proximal of the study vessel (at least 40mm in length) should be available for examination (i.e. outside the length of the stent plus 5mm proximal to the stent). 31. Poor left ventricular function as assessed by echocardiography or by angiography. 32. Moderate or severe tortuosity of the study segment (i.e. 2 bends >75° or one bend > 90°). 17. Known tendency for coronary vasospasm.

CCS: Canadian Cardiovascular Society; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; QCA: quantitative coronary angiography.



Supplemental Figure 1. Time-to-Event curves for the composite of all-cause mortality, stroke, non-fatal ACS or unplanned PCI, including definite culprit lesion-related events, during one-year follow-up of 203 patients.

The cumulative event rate applies to the analysis in which all 28 events, including the definite culprit lesion-related events, were assessed. LCBI = Lipid Core Burden Index; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; CLR events = culprit lesion-related events.