Near-infrared spectroscopy-derived lipid core burden index predicts adverse cardiovascular outcome in patients with coronary artery disease during long-term follow-up

Anne-Sophie Schuurman*, Maxime M Vroegindewey*,[1,2] Isabella Kardys,[1,2] Rohit M Oemrawsingh, Jin Ming Cheng, Sanneke de Boer, Hector M. Garcia-Garcia, Robert-Jan M. van Geuns, Evelyn Regar, Joost Daemen, Nicolas M. van Mieghem, Patrick W. Serruys, Eric Boersma, K. Martijn Akkerhuis

*These authors contributed equally.

European Heart Journal, 2018;39(4):295-302

ABSTRACT

Aims: Near-infrared spectroscopy (NIRS) is able to quantify cholesterol within coronary arteries by the lipid core burden index (LCBI). We studied the prognostic value of NIRS-derived LCBI in patients with coronary artery disease (CAD) for adverse cardiac outcome during long-term follow-up.

Methods and results: During 2009-2013, NIRS was performed in a non-culprit artery of 275 patients undergoing coronary angiography for acute coronary syndrome (ACS) or stable angina. LCBI was quantified by an independent corelab for the region of interest ($LCBI_{ROI}$) and the 4 and 10 mm long segment with the maximum LCBI ($MaxLCBI_{4mm}$ and $MaxLCBI_{10mm}$). The primary endpoint was major adverse cardiac events (MACE), defined as the composite of all-cause death, non-fatal ACS, or unplanned revascularization. Hazard ratios (HR) were adjusted for age, gender, clinical risk factors and segment plaque burden based on intravascular ultrasound. During a median follow-up of 4.1 years, 79 patients (28.7%) had MACE. There was a statistically significant and independent continuous relationship between higher $MaxLCBI_{4mm}$ values and a higher risk of MACE. Each 100 units increase of $MaxLCBI_{4mm}$ was associated with a 19% increase in MACE (HR 1.19, 95%CI:1.07-1.32, p=0.001). Continuous $MaxLCBI_{4mm}$ remained independently associated with MACE after exclusion of target lesion-related events (HR 1.21, 95CI%:1.08-1.35), as well as after exclusion of adverse events related to the NIRS-imaged coronary segment (HR 1.19, 95%CI:1.06-1.34). Results for $MaxLCBI_{10mm}$ were comparable.

Conclusion: NIRS-derived LCBI is associated with adverse cardiac outcome in CAD patients during long-term follow-up independent of clinical risk factors and plaque burden.

INTRODUCTION

Coronary artery disease (CAD) is projected to remain the leading cause of mortality and morbidity worldwide. Patients with a history of CAD are at higher risk of subsequent adverse cardiovascular events, such as an acute coronary syndrome (ACS). In approximately 75% of all cases, an ACS is caused by rupture or fissure of a vulnerable, lipid rich core-containing plaque in the coronary arteries.[1,2] While coronary angiography (CAG) is unable to identify such lipid rich core-containing plaques in the coronary artery wall,[3] they can be identified by near-infrared spectroscopy (NIRS), a catheter-based intracoronary imaging technique based on diffuse reflectance spectroscopy.[4-6] Therefore, NIRS may be useful in identifying patients at increased risk of adverse cardiovascular outcome.[5-7]

The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis (ATHEROREMO) and the Integrated Biomarker Imaging Study 3(IBIS-3) studies were designed to investigate phenotypes and vulnerability of coronary atherosclerosis as determined by intravascular ultrasound (IVUS) and NIRS.[8,9] NIRS became available in our cardiac catheterization laboratory during the course of both the ATHEROREMO and IBIS-3 study.[10] In the current study, we performed long-term follow-up of both the ATHEROREMO-NIRS and IBIS-3-NIRS substudies, with the aim to investigate the long-term prognostic value of lipid rich core-containing plaques as assessed by NIRS in patients with CAD undergoing CAG.

METHODS

Study design and population

The current investigation combines the populations of the ATHEROREMO-NIRS and the IBIS-3-NIRS substudies. Both of these studies were conducted at the Erasmus Medical Center, Rotterdam, The Netherlands, and had similar enrollment criteria and baseline study procedures. The study designs and methods of ATHEROREMO-NIRS and IBIS-3-NIRS have been described in detail elsewhere.[8-10] Briefly, patients undergoing diagnostic CAG or PCI for ACS or stable angina pectoris (SAP) underwent baseline invasive imaging by NIRS and IVUS, and were subsequently followed-up on adverse cardiovascular events.[11,12] The obtained images were analyzed off-line, and findings were not used for patient care. In ATHEROREMO-NIRS, patient management was left to the discretion of the treating physician. In IBIS-3, as per protocol, high-dose rosuvastatin was prescribed during the first year after the index event. ATHEROREMO-NIRS enrolled 203 patients between April 2009 and January 2011, and IBIS-3-NIRS enrolled 131 patients between January 2010 and June 2013. Since 48 patients participated in both studies, a total of

286 patients were available. Of these patients, 275 patients had baseline data available on both NIRS and IVUS, and were therefore included in the current analysis.

The medical ethics committee of the Erasmus MC approved both the ATHEROREMO-NIRS and IBIS-3-NIRS substudy. These two studies were performed in accordance with the declaration of Helsinki. All patients provided written informed consent for their participation and for compliance with the study protocols, including long-term follow-up. The ATHEROREMO study is registered in ClinicalTrials.gov, number NCT01789411, and the IBIS-3 study is registered in The Netherlands trial register, number NTR2872.

Near-infrared spectroscopy

Subsequent to the standard index CAG, invasive imaging with IVUS and NIRS was performed in a non-culprit coronary artery. The NIRS target segment in this non-culprit coronary artery was required to be at least 40 mm in length and without significant luminal narrowing (<50% stenosis) as assessed by on-line angiography. The study protocol predefined the order of preference for the selection of the non-culprit vessel.[8,9]

The NIRS system included a 3.2-F rapid exchange catheter, a console and a rotation and pullback device (InfraRedx, Burlington, Massachusetts). Images were acquired by the NIRS catheter that was automatically pulled back at a speed of 0.5 mm/s and 240 rotations per minute in a proximal segment of the non-culprit artery, as described in detail previously.[5,10] The fraction of yellow pixels obtained from the chemogram, an image map derived from the NIRS measurements, was multiplied by 1000 to compute the Lipid Core Burden Index (LCBI). Therefore, the 4 mm long segment with the maximum LCBI ($MaxLCBI_{4mm}$) ranged from 0 to 1000 representing the percentage of lipid core in the investigated segment.[6] Moreover, the 10 mm long segment with the maximum LCBI ($MaxLCBI_{10mm}$) was quantified, and the same was done for the region of interest ($LCBI_{ROI}$) of the investigated segment. NIRS data were analyzed off-line by an independent corelab (Cardialysis, Rotterdam, The Netherlands) blinded to all other patient and outcome data.

Intravascular ultrasound

After the standard index CAG, the non-culprit segment was first examined by IVUS. IVUS images were acquired by the Volcano Eagle Eye Gold IVUS catheter (20 MHz).[8] Analyses of the IVUS gray-scale data were performed using the pcVH 2.1 and qVH software (Volcano Corp., San Diego, CA, USA). Segmental plaque burden was defined as the plaque and media cross-sectional area divided by the external elastic membrane cross-sectional area.[8] IVUS gray-scale data were also analyzed off-line.

Study endpoints

The primary endpoint consisted of major adverse cardiac events (MACE), defined as the composite of all-cause death, non-fatal ACS, or unplanned coronary revascularization

during long-term follow-up. A secondary analysis was performed on the composite endpoint of cardiac death, non-fatal ACS, or unplanned revascularization. Furthermore, additional analyses were performed on these two endpoints after exclusion of definite target lesion-related events, as well as after exclusion of adverse events related to the NIRS-imaged coronary segment.

Follow-up was conducted in January 2015. Vital status of the patients was obtained from municipal civil registries. Follow-up questionnaires were subsequently sent to all living patients as a first screening method for identifying possible adverse events. Thereafter, hospital discharge letters were obtained if any hospitalization or possible event was reported. In patients who did not return the questionnaire, the local hospital records were investigated for possible events. Cause of death was obtained from hospital records, autopsy reports or general practitioners notes.

MACE were adjudicated based on original source data by a clinical events committee blinded to patient characteristics and NIRS and IVUS data. In accordance with the guidelines of the European Society of Cardiology, non-fatal ACS was defined as the clinical diagnosis of ST-segment Elevation Myocardial Infarction (STEMI), non-STEMI (NSTEMI), or unstable angina pectoris.[13,14] Unplanned coronary revascularization was defined as any PCI or coronary artery bypass grafting (CABG) that was not planned after the index angiography and enrollment in the study. Cardiac death was defined as any death due to proximate cardiac cause, unwitnessed death or death of unknown cause.

Furthermore, the clinical event committee adjudicated whether the cardiac events were related to the target lesion that was treated during the index procedure, as well as whether the events were related to the coronary artery segment that was imaged at baseline.

Statistical analysis

Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Normally-distributed continuous variables were reported as means and standard deviations. Non-normally-distributed continuous variables were reported as medians and interquartile ranges (IQR), categorical variables as numbers and percentages.

Patients that were lost to follow-up were censored at the date of last contact. The first event was considered in case a patient had multiple events. The Kaplan-Meier method was used to estimate cumulative event rate. All subsequent analyses were performed for each of the three LCBI variables. The log-rank test was used to compare cumulative event rates between quartiles of the LCBI variables and pairwise comparisons were performed when the overall log-rank test showed statistical significant differences.

The association between LCBI and the long-term incidence of study endpoints was analyzed by Cox proportional hazard regression analyses. Furthermore, to evaluate whether the association between LCBI and log(hazard) was linear enough to fit as a single

degree of freedom regression term, a spline was inserted in each full Cox proportional hazard regression model and visual inspection of the estimated relation was performed. No evidence was found for non-linearity with respect to $MaxLCBI_{4mm}$, whereas findings with respect to $MaxLCBI_{10mm}$ and $LCBI_{ROI}$ were borderline significant. Visual inspection of the estimated relation showed that categorization of LCBI in quartiles resulted in an acceptable piece-wise linearity for all endpoints. For Cox regression analyses, consecutively, unadjusted models and multivariable models containing clinical characteristics and IVUS derived plaque burden were used. Potential confounders were chosen based on existing literature. The multivariable models contained the following potential confounders: age, gender, indication for index CAG (ACS or SAP), diabetes mellitus, history of cerebrovascular accident, history of peripheral artery disease and IVUS derived segmental plaque burden. Hazard ratios (HRs) were reported with 95% confidence intervals (CIs). Although this study did not aim to develop a prognostic model per se, a C-index was reported for each multivariable model to provide some indication of the prognostic value of continuous LCBI in addition to clinical risk factors and plaque burden.

All statistical tests were two-tailed and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS statistics version 21.0 (IBM Corp., Armonk, New York).

RESULTS

Baseline characteristics

Mean age of the patients was 62.5 years and 76.7% were men (Table 1). A total of 42.5% of the patients presented with an ACS. $MaxLCBI_{4mm}$ values in the non-culprit artery ranged from 0 to 930, with a median of 227.0 (IQR:83.0-360.0). The $LCBI_{ROI}$ values ranged from 0 to 571, with a median of 40.0 (IQR:13.0-79.0). PCI was performed in 88.4% of the patients during the index procedure.

Incidence of primary endpoint

Median follow-up time was 4.1 (IQR:3.2-4.5) years. The follow-up questionnaire assessing the occurrence of MACE was completed by 90% of the patients. The primary composite endpoint of all-cause death, non-fatal ACS or unplanned revascularization occurred in 79 patients (28.7%). All-cause death occurred in 20 patients, non-fatal ACS in 40 patients and unplanned revascularization in 62 patients. The composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization occurred in 70 patients (25.5%).

Table 1. Baseline characteristics	
	N=275 patients
Clinical characteristics	
Age, years	62.5 ± 10.7
Men, n(%)	211 (76.7)
Diabetes, n(%)	59 (21.5)
Hypertension, n(%)	165 (60.0)
Dyslipidemia, n(%)	158 (57.5)
Current smoking, n(%)	69 (25.1)
Previous MI, n(%)	94 (34.2)
Previous PCI, n(%)	98 (35.6)
Previous CABG, n(%)	6 (2.2)
Previous CVA, n(%)	16 (5.8)
History of PAD, n(%)	15 (5.5)
History of renal impairment, n(%)	14 (5.1)
Laboratory measurements, (mmol/l)	
Median total cholesterol (IQR)	4.10 [3.60-5.00]
Median low-density lipoprotein (IQR)	2.42 [1.93-3.13]
Median high-density lipoprotein (IQR)	1.14 [0.92-1.35]
Procedural characteristics	
Indication for coronary angiography	
ACS, n(%)	117 (42.5)
Acute MI, n(%)	31 (11.3)
Unstable angina, n(%)	86 (31.3)
Stable angina, n(%)	158 (57.5)
PCI performed in non-imaged vessel, n(%)	243 (88.4)
Coronary artery disease	
No significant stenosis, n(%)	18 (6.5)
1-vessel disease, n(%)	144 (52.4)
2-vessel disease, n(%)	87 (31.6)
3-vessel disease, n(%)	26 (9.5)
NIRS characteristics	
Imaged coronary artery	
Left anterior descending, n(%)	96 (34.9)
Left circumflex, n(%)	97 (35.3)
Right coronary artery, n(%)	82 (29.8)
Median imaged segment length, mm (IQR)	56.4 [45.3-67.2]
Median $LCBI_{ROI}$ (IQR)	40.0 [13.0-79.0]
Median $MaxLCBI_{10mm}$ (IQR)	129.0 [48.0-234.0]
Median $MaxLCBI_{4mm}$ (IQR)	227.0 [83.0-360.0]
IVUS derived Segment Plaque Burden (%)	39.3 ± 11.0

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary bypass grafting; CVA, cerebrovascular accident; PAD, peripheral artery disease; ACS, acute coronary syndrome; NIRS, near-infrared spectroscopy; LCBI, lipid core burden index; IQR, interquartile range; IVUS, intravascular ultrasound.

Association between LCBI and MACE

The cumulative distribution of the $MaxLCBI_{4mm}$ values in patients with and without MACE shows that patients with MACE had higher $MaxLCBI_{4mm}$ values as compared to those without MACE (Figure 1).

Quartiles of $MaxLCBI_{4mm}$, $MaxLCBI_{10mm}$ and $LCBI_{ROI}$, and cumulative MACE incidence were pairwise compared. Pairwise comparisons consequently showed that patients in the third and fourth quartiles had significantly higher event rates compared to those in the first quartile (Figure 2). After adjustment for clinical characteristics and IVUS-derived plaque burden in the multivariable model, the third and fourth quartile of $MaxLCBI_{4mm}$ remained significantly associated with MACE (HR 3.09 (95%CI: 1.41-6.74) and HR 3.58 (95CI%: 1.67-7.70), respectively). Results for the $LCBI_{ROI}$ and $MaxLCBI_{10mm}$ were comparable (Table 2).

There was a statistically significant continuous relationship between higher $MaxLCBI_{4mm}$ values and a higher risk of MACE (Table 3). After multivariable adjustment, $MaxLCBI_{4mm}$ remained significantly associated with MACE (HR 1.19 per 100 units increase in LCBI, 95%CI: 1.07-1.32), as well as with MACE after exclusion of target lesion-related events (HR 1.21 (95CI%: 1.08-1.35)). Similarly, $MaxLCBI_{4mm}$ remained also independently associated with MACE after exclusion of adverse events related to the NIRS-imaged coronary segment (HR 1.19 (95%CI:1.06-1.34)). Cox regression analysis with follow-up duration as time-dependent variable demonstrated that continuous $MaxLCBI_{4mm}$ also predicted MACE beyond 1-year of follow-up [HR (95%CI) 1.15 (1.00-1.33) versus 1.23 (1.07-1.42) for the first year].

The C-indices indicate that NIRS-derived LCBI has prognostic value in addition to clinical risk factors and IVUS-derived plaque burden, with C-indices of the models with only covariates ranging from 0.607 to 0.617 and C-indices of the multivariable models including continuous LCBI ranging from 0.674 to 0.704 (Table 3).

Association between LCBI and the composite endpoint of cardiac death, non-fatal ACS or unplanned revascularization

The cumulative incidence of the composite of cardiac death, non-fatal ACS or unplanned revascularization was higher in patients in the second (25.0%), third (31.3%) and fourth (35.7%) quartile of $MaxLCBI_{4mm}$ as compared to those in the first (10.3%) quartile of $MaxLCBI_{4mm}$ (log-rank pairwise comparisons p=0.031, p=0.002 and p=<0.001, respectively, Figure 3). The second, third and fourth quartiles of $MaxLCBI_{4mm}$ were significantly associated with the composite of cardiac death, non-fatal ACS or unplanned revascularization after adjustment for clinical characteristics and IVUS-derived plaque burden in the multivariable model (Table 4). A similar significant association was observed for $MaxLCBI_{4mm}$ as a continuous variable (Table 5). This association persisted after exclusion of target lesion-related events and after exclusion of events related to the imaged segment (Table

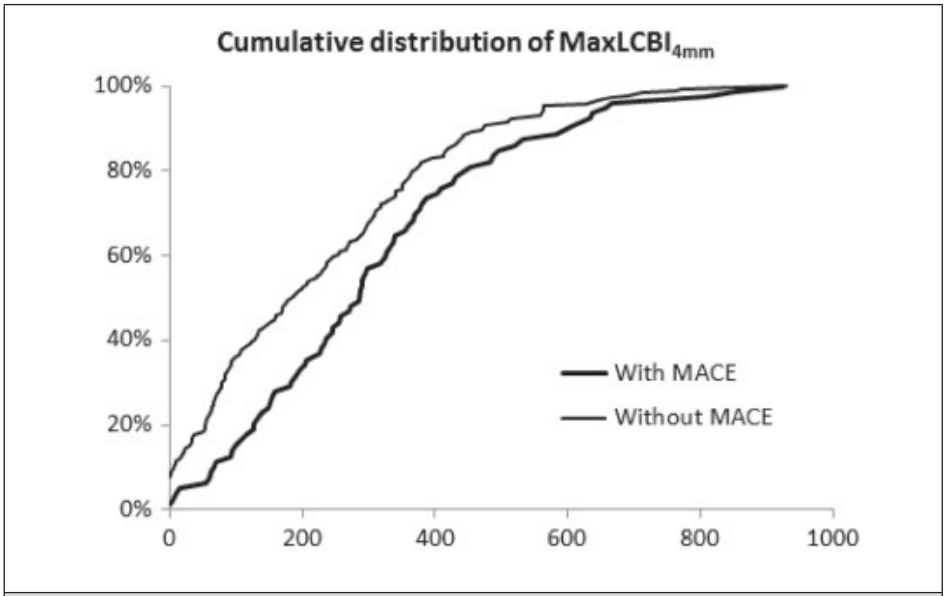

Figure 1. Cumulative distribution of the MaxLCBI$_{4mm}$ of patients with and without MACE (p=0.001, Mann-Whitney U test).
MACE: major adverse cardiac events, MaxLCBI$_{4mm}$: the 4 mm long segment with the maximum LCBI

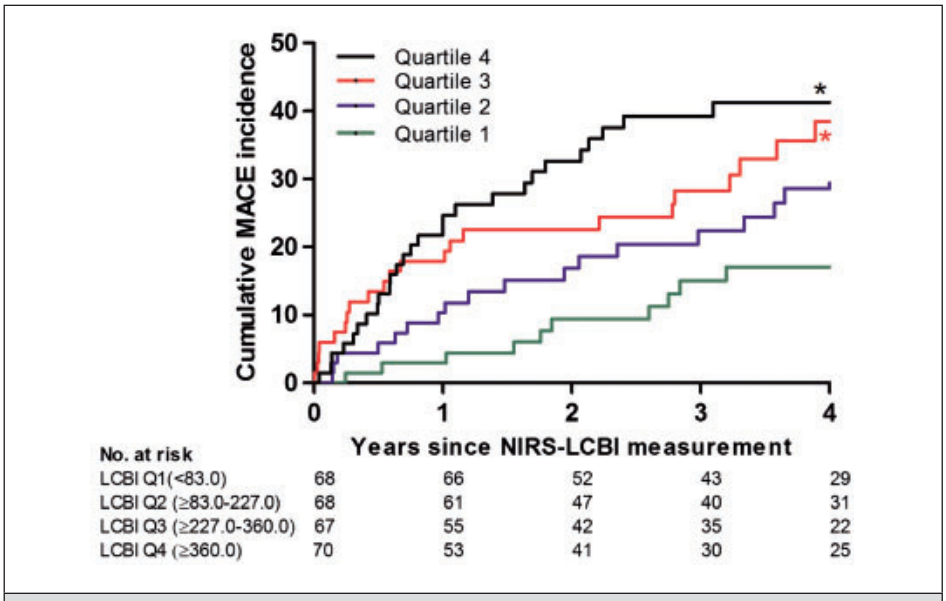

Figure 2. Assocation between quartiles of MaxLCBI$_{4mm}$ and the occurrence of MACE
*p<0.01 as compared to first quartile (reference).
LCBI: lipid core burden index, MACE: major adverse cardiac events

Table 2. Associations between quartiles of LCBI and risk of MACE at 4-years follow-up

	Cut-off LCBI value	Cumulative MACE incidence (%)	Unadjusted model		Multivariable model	
			HR (95%CI)	p-value	HR (95%CI)	p-value
$MaxLCBI_{4mm}$						
Quartile 1	0-83	14.7	1		1	
Quartile 2	≥83-227	27.9	1.99 (0.93-4.28)	0.078	2.11 (0.96-4.60)	0.062
Quartile 3	≥227-360	34.3	2.77 (1.32-5.81)	0.007	3.09 (1.41-6.74)	0.005
Quartile 4	≥360	38.6	3.22 (1.56-6.65)	0.002	3.58 (1.67-7.70)	0.001
$MaxLCBI_{10mm}$						
Quartile 1	0-48	13.2	1		1	
Quartile 2	≥48-129	30.9	2.56 (1.17-5.60)	0.018	2.66 (1.20-5.93)	0.017
Quartile 3	≥129-234	36.8	3.36 (1.57-7.20)	0.002	3.47 (1.59-7.61)	0.002
Quartile 4	≥234	34.3	3.06 (1.42-6.59)	0.004	3.27 (1.46-7.29)	0.004
$LCBI_{ROI}$						
Quartile 1	0-13	15.4	1		1	
Quartile 2	≥13-40	25.7	1.72 (0.79-3.73)	0.17	1.93 (0.88-4.25)	0.10
Quartile 3	≥40-79	37.1	2.90 (1.40-6.02)	0.004	3.24 (1.53-6.88)	0.002
Quartile 4	≥79	35.7	2.67 (1.28-5.56)	0.009	3.14 (1.43-6.87)	0.004

Cumulative MACE incidence by Kaplan-Meier method. P-values obtained with Cox regression analyses on pairwise comparisons between each quartile and first quartile (reference).
HR: hazard ratio, LCBI, lipid core burden index; MACE, major adverse cardiac events, ROI: region of interest

Table 3. Continuous LCBI values and risk of MACE at 4-years follow-up

	Unadjusted model		Multivariable model		C-index
	HR(95%CI)	p-value	HR(95%CI)	p-value	
MACE					
Covariates only					0.608
$MaxLBCI_{4mm}$	1.19 (1.08-1.31)	0.001	1.19 (1.07-1.32)	0.001	0.674
$MaxLBCI_{10mm}$	1.17 (1.04-1.31)	0.011	1.17 (1.03-1.34)	0.017	0.660
$LCBI_{ROI}$	1.18 (0.93-1.51)	0.18	1.24 (0.95-1.63)	0.12	0.652
MACE with exclusion of TLR-events					
Covariates only					0.617
$MaxLBCI_{4mm}$	1.22 (1.10-1.36)	<0.001	1.21 (1.08-1.35)	0.001	0.704
$MaxLBCI_{10mm}$	1.21 (1.07-1.37)	0.003	1.22 (1.06-1.40)	0.005	0.691
$LCBI_{ROI}$	1.24 (0.97-1.60)	0.087	1.31 (0.99-1.74)	0.059	0.683
MACE with exclusion of NIRS imaged segment-related events					
Covariates only					0.607
$MaxLBCI_{4mm}$	1.17 (1.06-1.30)	0.003	1.19 (1.06-1.34)	0.003	0.683
$MaxLBCI_{10mm}$	1.13 (0.99-1.28)	0.072	1.15 (1.00-1.33)	0.050	0.665
$LCBI_{ROI}$	1.09 (0.81-1.46)	0.58	1.18 (0.86-1.62)	0.31	0.659

Hazard ratios per 100 units increase in $MaxLCBI_{4mm}$, $MaxLCBI_{10mm}$ and $LCBI_{ROI}$.
HR: hazard ratio, LCBI: lipid core burden index, MACE: major adverse cardiac events, NIRS: near-infrared spectroscopy, ROI: region of interest, TLR: target lesion-related revascularization

Table 4. Associations between quartiles of LCBI and risk of composite of cardiac death, non-fatal ACS, or unplanned revascularization at 4-years follow-up

	Cut-off LCBI value	Cumulative incidence (%)	Unadjusted model		Multivariable model	
			HR(95%CI)	p-value	HR(95%CI)	p-value
$MaxLCBI_{4mm}$						
Quartile 1	0-83	10.3	1		1	
Quartile 2	≥83-227	25.0	2.53 (1.05-6.11)	0.039	2.66 (1.09-6.50)	0.032
Quartile 3	≥227-360	31.3	3.60 (1.53-8.46)	0.003	4.07 (1.67-9.92)	0.002
Quartile 4	≥360	35.7	4.16 (1.80-9.62)	0.001	4.57 (1.90-10.98)	0.001
$MaxLCBI_{10mm}$						
Quartile 1	0-48	10.3	1		1	
Quartile 2	≥48-129	26.5	2.80 (1.17-6.70)	0.021	2.96 (1.21-7.21)	0.017
Quartile 3	≥129-234	30.9	3.60 (1.53-8.47)	0.003	3.73 (1.55-8.94)	0.003
Quartile 4	≥234	34.3	3.85 (1.66-8.93)	0.002	4.01 (1.66-9.67)	0.002
$LCBI_{ROI}$						
Quartile 1	0-13	10.8	1		1	
Quartile 2	≥13-40	21.4	2.05 (0.84-5.02)	0.12	2.30 (0.93-5.73)	0.073
Quartile 3	≥40-79	32.9	3.64 (1.56-8.49)	0.003	4.09 (1.72-9.73)	0.001
Quartile 4	≥79	35.7	3.73 (1.61-8.62)	0.002	4.18 (1.72-10.17)	0.002

Cumulative endpoint incidence by Kaplan-Meier method. P-values obtained with Cox regression analyses on pairwise comparisons between each quartile and first quartile (reference).
ACS: acute coronary syndrome, CI: confidence interval, HR: hazard ratio, LCBI: lipid core burden index, ROI: region of interest

Table 5. Continuous LCBI values and risk of composite of cardiac death, non-fatal ACS or unplanned revascularization at 4-years follow-up

	Unadjusted model		Multivariable model	
	HR(95%CI)	p-value	HR(95%CI)	p-value
$MaxLBCI_{4mm}$	1.21 (1.10-1.34)	<0.001	1.21 (1.08-1.35)	0.001
$MaxLBCI_{10mm}$	1.20 (1.06-1.35)	0.003	1.20 (1.05-1.37)	0.007
$LCBI_{ROI}$	1.24 (0.98-1.58)	0.078	1.29 (0.98-1.70)	0.065
Composite endpoint with exclusion of TLR-events				
$MaxLBCI_{4mm}$	1.25 (1.12-1.40)	<0.001	1.24 (1.10-1.39)	<0.001
$MaxLBCI_{10mm}$	1.25 (1.10-1.42)	0.001	1.25 (1.09-1.44)	0.002
$LCBI_{ROI}$	1.32 (1.03-1.68)	0.027	1.38 (1.04-1.83)	0.027
Composite endpoint with exclusion of NIRS imaged segment-related events				
$MaxLBCI_{4mm}$	1.20 (1.08-1.34)	0.001	1.22 (1.08-1.38)	0.001
$MaxLBCI_{10mm}$	1.16 (1.02-1.33)	0.026	1.19 (1.03-1.38)	0.022
$LCBI_{ROI}$	1.16 (0.87-1.55)	0.31	1.24 (0.90-1.70)	0.18

Hazard ratios per 100 units increase in $MaxLCBI_{4mm}$, $MaxLCBI_{10mm}$ and $LCBI_{ROI}$.
ACS: acute coronary syndrome, LCBI: lipid core burden index, NIRS: near-infrared spectroscopy, ROI: region of interest, TLR: target lesion-related revascularization

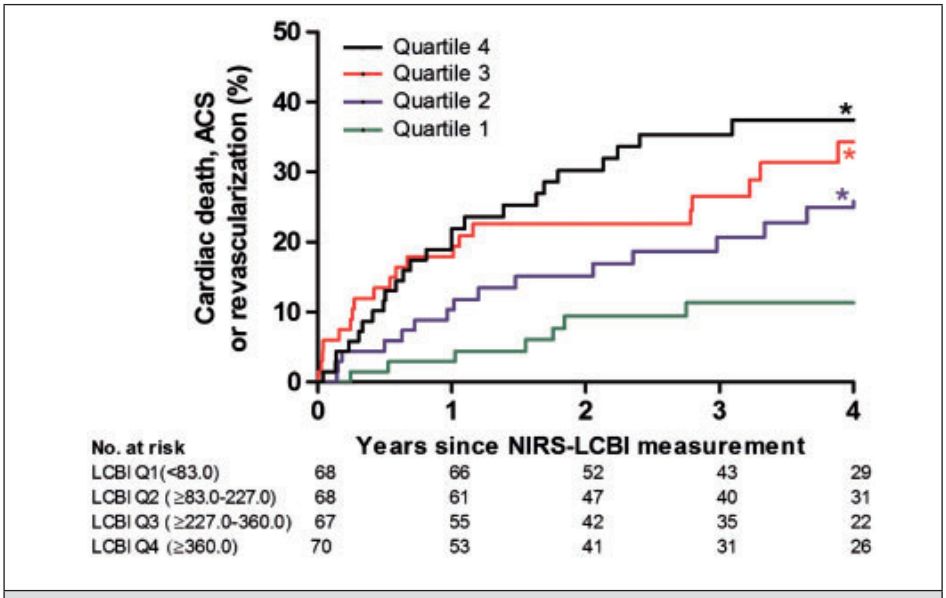

Figure 3. Assocation between quartiles of MaxLCBI$_{4mm}$ and the occurrence of *cardiac* death, non-fatal ACS and unplanned revascularization

*p<0.05 as compared to first quartile (reference).

LCBI: lipid core burden index, MACE: major adverse cardiac events, NIRS: near-infrared spectroscopy

5). In general, the associations observed between MaxLCBI$_{4mm}$, MaxLCBI$_{10mm}$ and LCBI$_{ROI}$ and the occurrence of adverse events were stronger and more significant when the composite endpoint included cardiac death instead of all-cause mortality (Tables 2-5).

DISCUSSION

This study investigated the association between lipid rich core-containing plaques as identified by NIRS in a non-culprit coronary artery and the occurrence of adverse cardiac events during long-term follow-up in patients undergoing CAG. This study showed that LCBI values were significantly and independently associated with the incidence of adverse cardiac outcome in patients with CAD over 4 years of follow-up. To the best of our knowledge, this is the first study to investigate the association between LCBI in a non-culprit coronary artery and adverse cardiac outcome over 4 years of follow-up, which represents the longest follow-up period so far reported.

Studies on the relationship between LCBI and (long-term) follow-up are scarce. Recently, the COLOR study demonstrated that the MaxLCBI$_{4mm}$ obtained prior to stenting in a culprit coronary segment was not associated with culprit-related MACE during 2 years of follow-up.[15] Our study provides new evidence on the prognostic value of NIRS, since

we demonstrated that NIRS is predictive of MACE on the long-term by identifying high-risk lipid rich core-containing plaques in a non-culprit artery. The upcoming Lipid Rich Plaque (LRP) and PROSPECT-2 studies are also investigating the ability of NIRS-derived LCBI in non-culprit coronary arteries to predict adverse cardiovascular outcome during 2-year follow-up.

This study extends our previous 1-year follow-up data of the ATHEROREMO-NIRS study, which investigated the 1-year prognostic value of NIRS in that cohort and showed that high LCBI values were associated with an increased incidence of MACE.[10] The current study demonstrated that these results persist over a period of 4 years, suggesting that the increased risk at 1-year was not due to chance and LCBI of a non-culprit artery also has prognostic value beyond 1-year after the index CAG. As compared to the 1-year follow-up, the current study was conducted over a longer follow-up period, had a larger sample size and, consequently, a larger number of endpoints. The latter allowed us to investigate the associations between continuous LCBI values, as well as quartiles of LCBI, and adverse cardiac outcome instead of using a median split for LCBI. These analyses showed a significant and independent continuous relationship between higher LCBI values in a non-culprit coronary artery and adverse cardiac outcome. Importantly, this relationship persisted, and remained essentially unchanged, when target-lesion related adverse cardiac events (TLR) were excluded from the study endpoint, as well as when adverse events related to the imaged coronary segment were excluded. This indicates that LCBI values obtained in a non-culprit coronary artery segment are associated with adverse cardiac events throughout the entire coronary tree. As such, this finding supports the hypothesis that NIRS imaging in a non-culprit coronary artery segment may reflect vulnerability of the entire coronary tree.[8,16]

Previously, the ATHEROREMO-IVUS study demonstrated that IVUS-derived imaging parameters were predictive of MACE. For this reason, we included IVUS-derived plaque burden in the multivariable model to evaluate the independent prognostic value of NIRS. Given that progression of coronary atherosclerosis depends on multiple factors that are cumulative, interactive and nonlinear, a combination of these two imaging techniques is likely to result in a higher predictive value.

Other studies used NIRS to investigate the effect of anti-atherosclerotic therapy on the amount of lipid core-containing plaques. The YELLOW study demonstrated that patients with multivessel CAD treated for 6 to 8 weeks with rosuvastatin showed a reduction of lipid core in obstructive arteries.[17] The IBIS-3 study showed that high-dose rosuvastatin resulted in a neutral effect on lipid rich core-containing plaques as determined by NIRS.[18] Recently, it was shown that addition of a PCSK9-inhibitor to stable statin therapy resulted in a greater decrease of plaque burden as assessed by IVUS.[19] NIRS has improved ability to identify lipid core-containing coronary plaques as compared to other invasive imaging modalities including IVUS, since NIRS is able to distinguish cholesterol from other

tissue characteristics.[6] In this context, NIRS may be used to select patients with high LCBI values in future research to measure the effect of anti-atherosclerotic therapy on lipid rich core-containing plaques in the coronary artery wall and assess its association with adverse cardiac outcome. Ultimately, this may result in improved risk stratification and management of patients with CAD.

Limitations

Several study limitations warrant consideration. First, our study population also comprised patients from IBIS-3, who received high doses of rosuvastatin after the index procedure. This may also in part have affected the effect estimates. However, a post-hoc analysis did not display significant effect modification according to study.

Second, the follow-up questionnaire was completed by 90% of the patients. Although for the majority of the remaining patients, follow-up information was retrieved from our local hospital records, we cannot fully exclude the possibility that loss to follow-up was in part selective. However, a post-hoc analysis of clinical and NIRS characteristics of the non-responders as compared to those of the responders did not show any differences that indicated selective loss to follow-up.

Third, the sample size of this single-center study was relatively small. Nevertheless, our study had a large number of endpoints. This allowed us to analyse LCBI as quartiles and as a continuous variable, as well as to investigate the association with adverse cardiac outcome after exclusion of target lesion-related and imaged segment-related events. When the results of the LRP and PROSPECT-2 studies become available, a meta-analysis may provide more precise effect estimates. Furthermore, as the current study population comprises a broad spectrum of CAD patients, the results are expected to apply to a broad population of CAD patients.

Conclusions

In conclusion, this study demonstrates for the first time that LCBI, as assessed by NIRS in one non-culprit coronary artery segment, predicts adverse cardiac outcome, independent of clinical characteristics and IVUS, during long-term follow-up over 4 years in patients referred for CAG because of ACS or SAP.

REFERENCES

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;**20**(5):1262-75.
2. Falk E, Shah PK, Fuster V. Coronary Plaque Disruption. Circulation 1995;**92**(3):657-671.
3. Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, Detre KM, Wilensky RL. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. Circulation 2005;**111**(2):143-9.
4. Jaross W, Neumeister V, Lattke P, Schuh D. Determination of cholesterol in atherosclerotic plaques using near infrared diffuse reflection spectroscopy. Atherosclerosis 1999;**147**(2):327-337.
5. Waxman S, Dixon SR, L'Allier P, Moses JW, Petersen JL, Cutlip D, Tardif JC, Nesto RW, Muller JE, Hendricks MJ, Sum ST, Gardner CM, Goldstein JA, Stone GW, Krucoff MW. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results of the SPECTACL study. JACC Cardiovasc Imaging 2009;**2**(7):858-68.
6. Goldstein JA, Madden SP, Sum ST, Dixon SR, Madder RD, Muller JE. Assessment of Plaque Composition with Near-Infrared Spectroscopy. Current Cardiovascular Imaging Reports 2011;**4**(4): 298-308.
7. Moreno PR, Lodder RA, Purushothaman KR, Charash WE, O'Connor WN, Muller JE. Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. Circulation 2002;**105**(8):923-7.
8. de Boer SP, Cheng JM, Garcia-Garcia HM, Oemrawsingh RM, van Geuns RJ, Regar E, Zijlstra F, Laaksonen R, Halperin E, Kleber ME, Koenig W, Boersma E, Serruys PW. Relation of genetic profile and novel circulating biomarkers with coronary plaque phenotype as determined by intravascular ultrasound: rationale and design of the ATHEROREMO-IVUS study. EuroIntervention 2014;**10**(8): 953-60.
9. Simsek C, Garcia-Garcia HM, van Geuns RJ, Magro M, Girasis C, van Mieghem N, Lenzen M, de Boer S, Regar E, van der Giessen W, Raichlen J, Duckers HJ, Zijlstra F, van der Steen T, Boersma E, Serruys PW. The ability of high dose rosuvastatin to improve plaque composition in non-intervened coronary arteries: rationale and design of the Integrated Biomarker and Imaging Study-3 (IBIS-3). EuroIntervention 2012;**8**(2):235-41.
10. Oemrawsingh RM, Cheng JM, Garcia-Garcia HM, van Geuns RJ, de Boer SP, Simsek C, Kardys I, Lenzen MJ, van Domburg RT, Regar E, Serruys PW, Akkerhuis KM, Boersma E. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol 2014;**64**(23):2510-8.
11. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013;**34**(38):2949–3003.
12. The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;**35**(37):2541–2619.
13. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;**33**(20):2569–2619.

14. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;**37**(3):267-315.
15. Weisz G. Two-year results of the COLOR trial presented at TCT 2016: study indicates PCI of NIRS-defined lipid-rich plaque is safe and not associated with a greater incidence of adverse outcomes compared to PCI of non lipid-rich plaque. Cardiovascular Research Foundation 2016. https://www.eurekalert.org/pub_releases/2016-11/crf-tro110116.php (28 April 2017).
16. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, Uno K, Tuzcu EM, Nissen SE. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol 2010;**55**(21):2399-407.
17. Kini AS, Baber U, Kovacic JC, Limaye A, Ali ZA, Sweeny J, Maehara A, Mehran R, Dangas G, Mintz GS, Fuster V, Narula J, Sharma SK, Moreno PR. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol 2013;**62**(1):21-9.
18. Oemrawsingh RM, Garcia-Garcia HM, van Geuns RJ, Lenzen MJ, Simsek C, de Boer SP, Van Mieghem NM, Regar E, de Jaegere PP, Akkerhuis KM, Ligthart JM, Zijlstra F, Serruys PW, Boersma E. Integrated Biomarker and Imaging Study 3 (IBIS-3) to assess the ability of rosuvastatin to decrease necrotic core in coronary arteries. EuroIntervention 2016;**12**(6):734-9.
19. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. Jama 2016;**316**(22):2373-2384.