Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study

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Summary

Background Near-infrared spectroscopy (NIRS) intravascular ultrasound imaging can detect lipid-rich plaques (LRPs). LRPs are associated with acute coronary syndromes or myocardial infarction, which can result in revascularisation or cardiac death. In this study, we aimed to establish the relationship between LRPs detected by NIRS-intravascular ultrasound imaging at unstented sites and subsequent coronary events from new culprit lesions.

Methods In this prospective, cohort study (LRP), patients from 44 medical centres were enrolled in Italy, Latvia, Netherlands, Slovakia, UK, and the USA. Patients with suspected coronary artery disease who underwent cardiac catheterisation with possible ad hoc percutaneous coronary intervention were eligible to be enrolled. Enrolled patients underwent scanning of non-culprit segments using NIRS-intravascular ultrasound imaging. The study had two hierarchal primary hypotheses, patient and plaque, each testing the association between maximum 4 mm Lipid Core Burden Index ($maxLCBI_{4mm}$) and non-culprit major adverse cardiovascular events (NC-MACE). Enrolled patients with large LRPs (≥250 $maxLCBI_{4mm}$) and a randomly selected half of patients with small LRPs (<250 $maxLCBI_{4mm}$) were followed up for 24 months. This study is registered with ClinicalTrials.gov, NCT02033694.

Findings Between Feb 21, 2014, and March 30, 2016, 1563 patients were enrolled. NIRS-intravascular ultrasound device-related events were seen in six (0·4%) patients. 1271 patients (mean age 64 years, SD 10, 883 [69%] men, 388 [31%] women) with analysable $maxLCBI_{4mm}$ were allocated to follow-up. The 2-year cumulative incidence of NC-MACE was 9% (n=103). Both hierarchical primary hypotheses were met. On a patient level, the unadjusted hazard ratio (HR) for NC-MACE was 1·21 (95% CI 1·09–1·35; p=0·0004) for each 100-unit increase $maxLCBI_{4mm}$) and adjusted HR 1·18 (1·05–1·32; p=0·0043). In patients with a $maxLCBI_{4mm}$ more than 400, the unadjusted HR for NC-MACE was 2·18 (1·48–3·22; p<0·0001) and adjusted HR was 1·89 (1·26–2·83; p=0·0021). At the plaque level, the unadjusted HR was 1·45 (1·30–1·60; p<0·0001) for each 100-unit increase in $maxLCBI_{4mm}$. For segments with a $maxLCBI_{4mm}$ more than 400, the unadjusted HR for NC-MACE was 4·22 (2·39–7·45; p<0·0001) and adjusted HR was 3·39 (1·85–6·20; p<0·0001).

Interpretation NIRS imaging of non-obstructive territories in patients undergoing cardiac catheterisation and possible percutaneous coronary intervention was safe and can aid in identifying patients and segments at higher risk for subsequent NC-MACE. NIRS-intravascular ultrasound imaging adds to the armamentarium as the first diagnostic tool able to detect vulnerable patients and plaques in clinical practice.

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Introduction

Despite advances in medical therapy and stenting, coronary artery disease remains the world's leading cause of death and causes extensive disability.[1] When ruptured and complicated by thrombosis, cholesterol-rich lipid core atheromas are strongly associated with myocardial infarction and cardiac death.[2–4] These coronary events led to the concept of a so-called vulnerable coronary plaque, defined as non-obstructive lesions that are at elevated risk of rupture.[5,6] The ability to predict which coronary segments or patients will subsequently have future events is weak; thus, the quest for detecting such coronary segments or patients at risk for secondary cardiovascular events (cardiac death and myocardial infarction) remains a high priority. It has been hypothesised that the prospective identification and treatment of such plaques could prevent subsequent coronary events.

The PROSPECT[7] and AtheroRemo-IVUS[8] studies tested the ability of greyscale and radio-frequency intravascular ultrasound to predict events in patients presenting with acute coronary syndrome and in stable patients undergoing an index percutaneous coronary intervention (PCI). Intravascular ultrasound measures of

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for English language articles published from database inception up until protocol finalisation (Dec 26, 2013) using the terms "coronary near-infrared spectroscopy", "coronary vulnerable plaque", "intravascular imaging." The search revealed no prospective cohort data showing whether or not the cholesterol content within the coronary artery wall was predictive of future events. Despite optimal medical therapy and risk-modification strategies, coronary events continue to occur. Many individuals with an apparently adverse risk factor profile remain asymptomatic. The quest for detecting patients at risk for secondary cardiovascular events (cardiac death and myocardial infarction) is a high priority. The unmet need within the intravascular imaging world is for a method to identify in vivo vulnerable patients and plaques. Lipid-rich plaque is associated with acute coronary syndromes and myocardial infarction and can be detected by near-infrared spectroscopy (NIRS). However, to date, only small studies using NIRS showed association between maximum 4 mm Lipid Core Burden Index (max$LCBI_{4mm}$) and non-culprit major adverse cardiovascular events (NC-MACE).

Added value of this study

The LRP study is the only study, to the best of our knowledge, to show the ability of NIRS to detect future cardiac events on the patient and on non-culprit plaque levels with a prespecified cutoff of the LCBI. The study also showed that the ability of NIRS to predict plaques vulnerable to events appears to be independent of intravascular ultrasound plaque burden or minimum lumen area within the site of max$LCBI_{4mm}$.

Implications of all the available evidence

On the basis of the results of this study, NIRS-intravascular ultrasound imaging in mildly or non-obstructive coronary arteries can be used as a tool to identify both patients and non-culprit arteries at high risk for future events and should be considered for use in patients undergoing cardiac catheterisation with possible percutaneous coronary intervention. Studies for the use of NIRS-guided therapy should be done to address and mitigate the high risk for MACE of these patients and arteries.

endothelial shear stress also have been shown to predict lesion progression (PREDICTION),[9] but the practicality for routine clinical use was called into question.

The limited ability of intravascular ultrasound imaging modalities to accurately identify lipid core in plaques, considered to be a primary defining feature of vulnerable plaques, led to an effort to develop near-infrared spectroscopy (NIRS) for use in the coronary arteries of patients undergoing PCI.[10]

Autopsy studies showed and validated that cholesterol-rich atherosclerotic plaques have a specific NIRS chemical signature. NIRS was cleared as a means to detect lipid-core plaque by the US Food and Drug Administration (FDA) and is combined with simultaneous co-registered intravascular ultrasound. Preliminary, small-size studies showed the potential of NIRS to predict future events.[11–14] However, these studies were small and did not address the plaque-level hypothesis.

We did the Lipid-Rich Plaque (LRP) study to establish the ability of NIRS-intravascular ultrasound imaging at the time of cardiac catheterisation with possible PCI to predict subsequent major adverse cardiac events (MACE).[15] We report here the LRP study results assessing the ability of NIRS-intravascular ultrasound imaging to detect vulnerable patients and vulnerable plaques.

Methods

Study design and participants

The LRP prospective cohort study enrolled patients from 44 participating medical centres in Italy, Latvia, Netherlands, Slovakia, UK, and the USA (appendix p 2).

Patients with known or suspected coronary artery disease undergoing cardiac catheterisation with possible ad hoc PCI for an index event in whom it also was feasible to scan additional non-culprit territories were enrolled. Patients were formally enrolled after successful and uncomplicated PCI (or deferral) and after the physician-investigator established that at least 50 mm of non-stented NIRS-intravascular ultrasound imaging data had been obtained from at least two major coronary arteries.[15] All patients provided written informed consent before the start of the angiography and before catheterisation. The institutional review board or ethics committee at each participating centre approved the study.

Procedures

Unmasked NIRS-intravascular ultrasound imaging was done on culprit vessels or lesions, and imaging for study purposes began in non-culprit segments and vessels after all clinically indicated imaging or PCI (or both) was done. Study imaging results in arteries not suspected to be culprits were masked to the enrolling investigator for NIRS but not for intravascular ultrasound. All masked and unmasked images were submitted to the core laboratory (MedStar Cardiovascular Research Network NIRS/IVUS Core Laboratory. Washington, DC, USA). The follow-up allocation was returned to the enrolling institution via the electronic data collection system without disclosure of the maximum 4 mm Lipid Core Burden Index (max$LCBI_{4mm}$) value for the scanned artery segments determined by the core laboratory.[15]

The generation of the NIRS-intravascular ultrasound system (Infraredx, a Nipro Company, Burlington, MA, USA) used in the LRP study had rotational intravascular

ultrasound imaging at 960 rpm (16 fps), 0·5 mm/s pullback, acquired 160 NIRS spectra per s, and used a 3·2 Fr catheter with a 40 MHz ultrasound transducer (TVC Imaging System, Model TVC-MC-8). The system returned a spatial map of the probability of lipid-core plaque presence and quantified the amount of lipid-core plaque in the image as the Lipid Core Burden Index (LCBI) over any specified distance.

All enrolled patients with a large LRP ($maxLCBI_{4mm}$ ≥250) as detected by NIRS and a randomly selected half of the patients with a small LRP ($maxLCBI_{4mm}$ <250) were contacted at 2, 6, 12, and 24 months. Patients were randomly assigned to follow-up or no follow-up in a 1:1 ratio using a randomisation algorithm in the electronic data capture system.

Outcomes

The independent clinical event committee adjudicated all MACE reported up until 24 months. MACE comprised cardiac death, cardiac arrest, non-fatal myocardial infarction, acute coronary syndrome, revascularisation by coronary artery bypass grafting or PCI, and readmission to hospital for angina with more than 20% diameter stenosis progression related and unrelated to the treatment at index procedure. These events were adjudicated at both the patient and plaque levels for the hierarchal primary endpoints evaluation. Disease progression measurements were calculated offline by the core laboratory.

Once an event met the patient-level definition by the clinical event committee, all associated CT coronary angiograms, angiograms, or autopsies were sent to the core laboratory for plaque-level adjudication. If the follow-up culprit event location was identifiable by imaging or autopsy and this location was scanned at index with NIRS-intravascular ultrasound (eg, evaluation and co-registration) captured via the electronic data collection portal, then the event was adjudicated for the plaque-level endpoint by the clinical event committee, masked to the baseline NIRS data.

All NIRS-intravascular ultrasound index procedure analysis was done offline by an independent core laboratory (MedStar Cardiovascular Research Network, Angiographic and Invasive Imaging Core Lab, Washington, DC, USA) using a validated NIRS-intravascular ultrasound offline analysis software (QIVUS version 3.0.16.0, Medis Medical Imaging Systems, Leiden, Netherlands). In addition, each coronary artery with available NIRS-intravascular ultrasound imaging was divided into 30 mm segments (referred to as Ware segments), beginning from the proximal region or ostium of the artery. This segmentation was used for the plaque-level analysis.[15] Total scanned lengths available for all Ware segments, 30 mm in length or shorter, were included in the analysis if at least 4 mm of artery was available to measure $maxLCBI_{4mm}$. At the site of $maxLCBI_{4mm}$ within the Ware segment, the following intravascular ultrasound measurements were done: minimum lumen area, external elastic membrane area and volume, plaque area and volume, and plaque burden. These measurements were done at 1 mm intervals.

The core laboratory also did serial quantitative coronary angiography analysis for the assessment of disease progression for lesions identified during the follow-up period. These independent calculations of absolute diameter stenosis change were added to the adjudication of the MACE category of readmission to hospital for progressive angina with lesion progression of more than 20%. All quantitative coronary angiography analysis was done via offline software, CAAS Workstation 7.3.

Statistical analysis

The LRP study tested two prespecified primary hypotheses: (1) the patient-level tested association between $maxLCBI_{4mm}$ (as a continuous value in 100 units) in all imaged arteries and patient-level non-culprit MACE (NC-MACE) during a 24-month follow-up; and (2) if the finding at the patient level was significant at the 5% level, then the plaque level would test the association between $maxLCBI_{4mm}$ (also as a continuous value in 100 units) in a segment and occurrence of NC-MACE in the same segment during 24-month follow-up.

Key prespecified secondary hypotheses were the following: (1) testing the association of $maxLCBI_{4mm}$ more than and less than a threshold of 400 with the risk of NC-MACE at the patient and plaque levels; and (2) testing whether plaque burden of 70% or more by greyscale intravascular ultrasound plus a $maxLCBI_{4mm}$ more than 400 in a coronary artery segment (Ware segment) is a stronger predictor of risk than $maxLCBI_{4mm}$ more than 400 alone.

The primary and secondary endpoints were assessed by Cox proportional hazard models. The Cox proportional hazard models will not be affected by the randomisation of only half of the patients with a $maxLCBI_{4mm}$ less than 250 to 24 months of follow-up. Additionally, a multivariable patient-level model was adjusted by age, male sex, diabetes, hypertension, smoking history, previous PCI, acute coronary syndrome presentation, and renal insufficiency. For the plaque-level analysis, within-patient clustering across segments was accounted for using the Wei-Lin-Weissfeld method.[16] In addition, a plaque-level model was constructed, and it was adjusted by the two intravascular ultrasound parameters, measured at the site of $maxLCBI_{4mm}$ within the Ware segments: plaque burden 70% or more and minimum lumen area 4·0 mm^2 or less. Cumulative incidence functions were used to describe the composite events of NC-MACE, stent-related MACE, and MACE of indeterminate origin throughout the 24 months of follow-up. Safety was monitored but was not prespecified as an endpoint. Data were managed at an independent data coordinating centre (appendix p 5). Analyses were done in SAS 9.4. This trial is registered with ClinicalTrials.gov, NCT02033694.

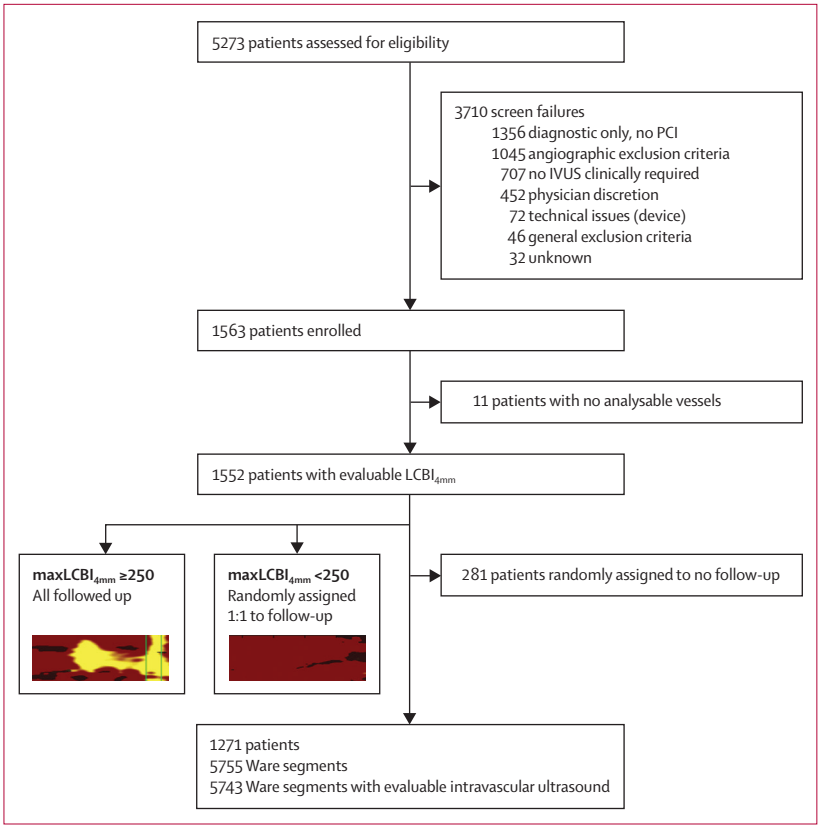

Figure 1: **Study profile**
The images are representative of the presence or absence of a large lipid-rich plaque detected by near-infrared spectroscopy at baseline. PCI=percutaneous coronary intervention. maxLCBI$_{4mm}$=maximum 4 mm Lipid Core Burden Index. IVUS=intravascular ultrasound.

	Value
Age (years)	64 (10·3)
Median, IQR	64 (57–71)
Sex at birth	
Male	883/1271 (69%)
Female	388/1271 (31%)
Diabetes	464/1266 (37%)
Diabetes requiring insulin	162/1243 (13%)
Smoking history (any)	687/1249 (55%)
Current smoker	282/1249 (23%)
Hypertension	1019/1267 (80%)
Hyperlipidaemia	1013/1261 (80%)
Chronic renal insufficiency	101/1267 (8%)
Family history of coronary artery disease	637/1135 (56%)
Previous myocardial infarction	294/1253 (23%)
Previous PCI	569/1267 (45%)
Clinical presentation	
Stabilised STEMI	32/1271 (3%)
Non–STEMI	182/1271 (14%)
Unstable angina	468/1271 (37%)
Stable angina or positive stress test	589/1271 (46%)
Body-mass index	30·2 (6·5); n=1262
Cholesterol panel*	
Total cholesterol, mg/dL	163·5 (45·6); n=875
LDL, mg/dL	91·7 (40·4); n=846
HDL, mg/dL	44·7 (15·2); n=867
Triglycerides, mg/dL	152·3 (127·5); n=859
Number of diseased vessels	1 (0·7); n=1227
<70% in any epicardial artery	268/1227 (22%)
One	702/1227 (57%)
Two	228/1227 (19%)
Three	29/1227 (2%)
PCI done at index†	1111/1270 (87%)

Data are mean (SD) or n/N (%) unless otherwise specified. PCI=percutaneous coronary intervention. STEMI=ST-elevation myocardial infarction. *Aggregated (baseline cholesterol values or first cholesterol values within 24 months if patient was on statin therapy at enrolment). †Summary of PCI details in appendix p 9.

Table 1: **Baseline characteristics**

Role of the funding source

The study was jointly designed by the principal investigator (RW) and Infraredx, a Nipro Company. The investigators and funder were masked to the relation between the imaging data and the clinical endpoints until after data collection and primary analyses were completed. The funder participated in site selection, data monitoring, data analysis, and manuscript preparation but had no access to image analysis before unmasking. RW, RT, PEC, QZ, and PK had access to all the data. All authors agreed on the decision to submit the manuscript for publication.

Results

From Feb 21, 2014, to March 30, 2016, 1563 patients were enrolled, of whom 11 patients did not have analysable NIRS in any vessels scanned and were excluded from the endpoint analyses. Of the remaining 1552 patients, 1271 were followed up for up to 24 months and comprised the analyzable population (figure 1). By the study design, 281 patients with maxLCBI$_{4mm}$ less than 250 were randomly assigned to not be followed up (figure 1). The summary of baseline and core laboratory data for patients with maxLCBI$_{4mm}$ less than 250 randomly assigned to follow-up and no follow-up is listed in the appendix (pp 6–7).

22 of the 1271 patients underwent a planned staged procedure, which was a protocol deviation. In the primary analysis, these procedures were treated as clinical events. Hazard ratios (HRs) excluding these 22 patients were similar (appendix p 8).

The 1271 patients with evaluable maxLCBI$_{4mm}$ had a mean follow-up of 692 (SD 129) days. The baseline characteristics of the study cohort are shown in table 1. The median age was 64 years (IQR 57–71), 883 (69%) of 1271 were men and 388 (31%) were women, and 464 (37%) of 1266 had diabetes. PCI was done in 1111 (87%) of 1270 of patients. The procedural details and lesions stented are summarised in the appendix (p 9). The patients were discharged according to guideline-directed medical therapy with a high proportion of antiplatelet and lipid-lowering therapy (appendix p 9).

In the followed-up population, the mean number of arteries scanned per patient was 2·1 (SD 0·5) with 50 mm or more of eligible vessel in 89% (1135/1271) of the patients. Overall, the total scanned artery length per patient was 139 mm (45·2), and the total analysable (evaluable NIRS data in non-stented vessel) per patient was 97·8 mm (43·4; table 2). The mean $maxLCBI_{4mm}$ of these scanned vessels was 359·2 (SD 175·1), and 39% (493/1271) of the patients had $maxLCBI_{4mm}$ more than 400. In the enrolled population of patients with an evaluable $maxLCBI_{4mm}$ (n=1552), the mean $maxLCBI_{4mm}$ of these scanned vessels was 318·7 (SD 184·4), and 32% (495/1552) of the patients had $maxLCBI_{4mm}$ more than 400.

The mean length of imaged Ware segment was 21·2 mm (SD 9·1), with most scanned Ware segments in the left anterior descending artery. The mean Ware $maxLCBI_{4mm}$ was 165 (177·1), and in 11% (664/5755) of the Ware segments, the $maxLCBI_{4mm}$ was more than 400. Intravascular ultrasound analysis was done only at the location of $maxLCBI_{4mm}$ in each Ware segment and was analysable in 5743 of these segments with 1% (59/5743) having a plaque burden of 70% or more and mean minimum lumen area 6·6 mm² (SD 3·7). In the enrolled population of Ware segments with an evaluable $maxLCBI_{4mm}$ (n=6884), the mean Ware segment $maxLCBI_{4mm}$ was 147·5 (SD 169·7), and in 10% (666/6884) of the patients, the $maxLCBI_{4mm}$ was more than 400.

The safety of NIRS imaging was assessed in all 1563 patients, and NIRS-intravascular ultrasound device-related events were only seen in six patients (0·4%). Five events (0·3%) occurred in the index culprit artery, requiring treatment with three dissections, one intra-procedural ischaemic event, and one thrombosis after PCI, and one dissection (0·06%) occurred in a non-culprit artery being imaged as part of the additional procedure for the LRP study.

During the 24-month follow-up, three event types were tracked. The cumulative incidence function for NC-MACE was 9% (n=103), culprit or previously stented MACE was 9% (n=104), and events with indeterminate coronary location were 2% (n=28). Figure 2 shows Kaplan-Meier estimates for NC-MACE components, which are summarised in the appendix (p 10). At the plaque level, there were 57 evaluable (with matched baseline chemogram) events (appendix p 11).[15]

Regarding vulnerable patient-level and vulnerable plaque-level endpoints, the independent correlates of NC-MACE during follow-up are shown in table 3. For the $maxLCBI_{4mm}$ as a continuous variable, the unadjusted HR was 1·21 (95% CI 1·09–1·35; p=0·0004) and the adjusted HR was 1·18 (1·05–1·32; p=0·0043) for experiencing an NC-MACE within 24 months with each 100-unit increase in $maxLCBI_{4mm}$. Patients with $maxLCBI_{4mm}$ more than 400 had an unadjusted HR of 2·18 (95% CI 1·48–3·22; p<0·0001) and an adjusted HR of 1·89 (1·26–2·83; p=0·0021) to have NC-MACE relative to patients with $maxLCBI_{4mm}$ of 400 or less. The estimated cumulative incidence functions for patients more than and less than the prespecified $maxLCBI_{4mm}$ cut point of 400 are presented in figure 3A.

	Patient-level and Ware segment-level values
Patient-level values (n=1271)	
Patient-level $maxLCBI_{4mm}$ in a masked artery scan	742 (58%)
Patient-level $maxLCBI_{4mm}$ in an unmasked artery scan	529 (42%)
Artery imaged	
Left main coronary artery	5 (0·4%)
Left anterior descending artery	1148 (90%)
Right coronary artery	546 (43%)
Left circumflex artery	967 (76%)
≥50 mm of eligible vessel	1135 (89%)
Number of vessels scanned	2·1 (0·5)
Total artery length scanned, mm	139 (45·2)
Total eligible vessel length, mm*	97·8 (43·4)
Patient-level $maxLCBI_{4mm}$	359·2 (175·1)
Median (IQR)	353 (257–476)
Patient-level $maxLCBI_{4mm}$ >400	493 (39%)
Number of Ware segments	4·5 (1·7); n=1270
Ware segment-level values† (n=5755)	
Scanned artery	
Left main coronary artery	6 (0·1%)
Left anterior descending artery	2662 (46%)
Right coronary artery	1280 (22%)
Left circumflex artery	1807 (31%)
Segment location	
Proximal	2248 (39%)
Mid	1927 (33%)
Distal	1246 (22%)
Far distal	334 (6%)
Ware segment length	
30 mm	2159 (38%)
<30 mm	3482 (61%)
>30 mm	114 (2%)
Ware segment length, mm	21·2 (9·1)
Plaque-level $maxLCBI_{4mm}$	165 (177·1)
Median, IQR	113 (0–283)
Plaque-level $maxLCBI_{4mm}$ > 400	664 (11%)
IVUS external elastic membrane within $maxLCBI_{4mm}$, mm^3	52·2 (27·4)
IVUS lumen volume within $maxLCBI_{4mm}$, mm^3	30·6 (17·1)
Plaque volume within $maxLCBI_{4mm}$, mm^3	21·5 (14·4)
Plaque area within $maxLCBI_{4mm}$, mm^2	5·4 (3·6)
Plaque burden within $maxLCBI_{4mm}$, %	38·9 (14·0)
Minimum lumen area within $maxLCBI_{4mm}$, mm^2	6·6 (3·7)

Data are n (%) or mean (SD) unless otherwise specified. $maxLCBI_{4mm}$=maximum 4 mm Lipid Core Burden Index. IVUS=intravascular ultrasound. *Summation of the total scanned length excluding the stented region and 5 mm edges. †Ware segment analysis restricted to only include segments with an evaluable $maxLCBI_{4mm}$ value.

Table 2: **Core laboratory data**

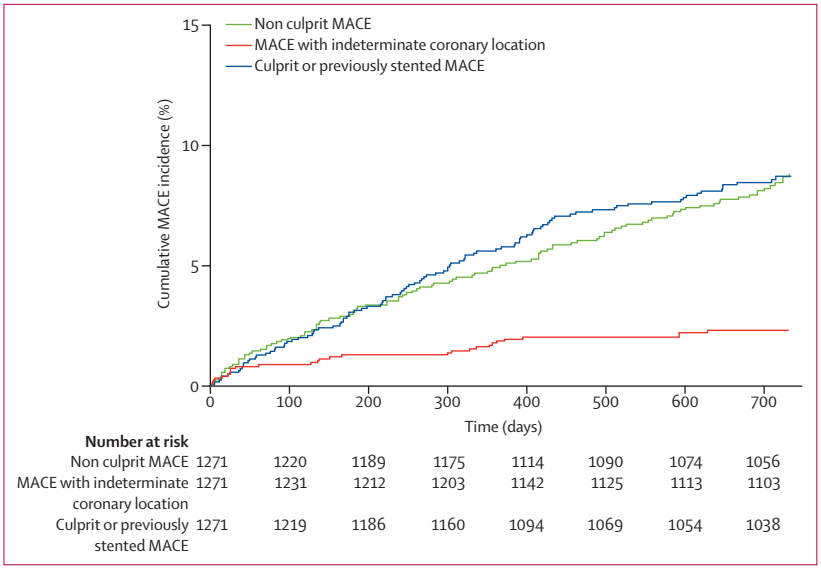

***Figure 2*: Cumulative incidence function by MACE type**
Non-culprit MACE, 9%; Culprit or previously stented MACE, 9%; MACE with indeterminate coronary location, 2%. MACE=major adverse cardiovascular event.

	maxLCBI$_{4mm}$ continuous	maxLCBI$_{4mm}$ >400
Vulnerable patient-level models		
Unadjusted LCBI alone		
maxLCBI$_{4mm}$	1·21 (1·09–1·35)	2·18 (1·48–3·22)
Multivariable-adjusted model		
maxLCBI$_{4mm}$	1·18 (1·05–1·32)	1·89 (1·26–2·83)
Age, years	0·99 (0·97–1·01)	0·99 (0·97–1·01)
Sex at birth		
Male	0·80 (0·52–1·22)	0·82 (0·54–1·25)
Female	1·25 (0·82–1·91)	1·22 (0·80–1·86)
Diabetes	1·33 (0·87–2·02)	1·33 (0·87–2·01)
Hypertension	2·09 (1·03–4·25)	2·07 (1·02–4·20)
Chronic renal insufficiency	1·97 (1·13–3·42)	1·97 (1·13–3·44)
History of smoking	1·48 (0·98–2·23)	1·48 (0·98–2·24)
Previous percutaneous coronary intervention	1·43 (0·96–2·13)	1·41 (0·94–2·10)
Presentation with acute coronary syndrome	0·82 (0·55–1·23)	0·84 (0·57–1·25)
Vulnerable plaque-level models*		
Unadjusted LCBI alone		
maxLCBI$_{4mm}$	1·45 (1·30–1·60)	4·22 (2·39–7·45)
Multivariable-adjusted model		
maxLCBI$_{4mm}$ >400	..	3·39 (1·85–6·20)
Plaque burden within maxLCBI$_{4mm}$ ≥70%†	..	3·99 (1·38–11·56)
MLA within maxLCBI$_{4mm}$ ≤4mm²‡	..	1·79 (1·02–3·16)

Data are hazard ratio (95% CI). maxLCBI$_{4mm}$=maximum 4 mm Lipid Core Burden Index. MLA=minimum lumen area. *Patient cluster adjusted via Wei Lin Weissfeld method. †Interaction between maxLCBI$_{4mm}$ >400 and plaque burden within maxLCBI$_{4mm}$ ≥70%, p=0·822. ‡Interaction between maxLCBI$_{4mm}$ >400 and MLA within maxLCBI$_{4mm}$ ≤4mm², p=0·512.

***Table 3*: Primary endpoints unadjusted and adjusted Cox proportional hazards models**

For the plaque level, the unadjusted HR for having a subsequent event in a coronary segment within 24 months was 1·45 (95% CI 1·30–1·60; p<0·0001) with each 100-unit increase in maxLCBI$_{4mm}$. A coronary segment with maxLCBI$_{4mm}$ more than 400 had an unadjusted HR of 4·22 (2·39–7·45; p<0·0001); the cumulative incidence functions for Ware segments more than and less than the prespecified maxLCBI$_{4mm}$ cut point of 400 is shown in figure 3B. When adjusted for plaque burden within maxLCBI$_{4mm}$ of 70% or more by intravascular ultrasound and minimum lumen area within maxLCBI$_{4mm}$ 4 mm² or less at the site of maxLCBI$_{4mm}$, the adjusted HR for maxLCBI$_{4mm}$ more than 400 remained significant and was 3·39 (95% CI 1·85–6·20; p<0·0001). There was no interaction between the maxLCBI$_{4mm}$ and plaque burden or minimum lumen area within maxLCBI$_{4mm}$ by intravascular ultrasound (table 3). An example of a plaque with more than 400 maxLCBI$_{4mm}$ at index procedure with corresponding plaque burden less than 70% that presented with NC-MACE at 1 year at the site of maxLCBI$_{4mm}$ is shown in the appendix (p 12).

Discussion

The LRP study is the largest prospective intracoronary imaging study to successfully identify patients and coronary segments at risk for future major coronary events. The study used a NIRS-intravascular ultrasound system in patients who underwent cardiac catheterisation with possible PCI. The study had several major findings. First, in patients with stable and acute coronary syndrome who presented for cardiac catheterisation for possible PCI and were treated medically by the guidelines, 9% had subsequent non-culprit events within 24 months. Multivessel NIRS-intravascular ultrasound can be easily and safely done to assess and identify vulnerable patients and vulnerable plaques. NIRS-intravascular ultrasound imaging in mildly obstructed or non-obstructive coronary arteries can identify both patients and non-culprit segments in the coronary arteries at high risk for future events. Lastly, a prespecified NIRS binary cutoff of 400 maxLCBI$_{4mm}$ is a reasonable predictor for subsequent events for the patient and the plaque levels.

The topic of vulnerable plaques has been controversial. Opposition to the concept often entangles a wide range of issues, including the difficulty in the development of commercially viable and reliable imaging technology, the practicality of scanning additional non-culprit coronary territory during a PCI or coronary catheterisation, the relatively unknown time-course of coronary atheroma progression, and the strategy of focal versus systemic treatment.[17–19] In agreement, based on autopsy, atheromas with cholesterol-rich lipid cores are involved in the majority of coronary deaths,[3] LRPs are focal and sparse in the coronary tree,[20] and it might be possible to detect them during cardiac catheterisation for purposes of secondary prevention. A previous study[21] identified thin cap fibroatheroma as the most probable substrate to be associated with a vulnerable plaque. Attempts to image thin cap fibroatheroma in vivo are limited by its

properties that match the fundamental capability of the imaging technique. Indeed, in PROSPECT,[8] non-culprit lesions having a plaque burden of 70% or more, a minimum lumen area of 4·0 mm² or less, and radiofrequency intravascular ultrasound identified thin cap fibroatheroma was associated with future events. Among these, plaque burden of 70% or more was the strongest correlate. These findings were corroborated in the VIVA[7] and AtheroRemo[22] intravascular ultrasound studies. Although successful in validating that characteristics of vulnerability to MACE can be found, these trials suffered from two issues potentially addressed by an alternative imaging modality. The specificity for vulnerable plaque phenotype was low, perhaps because intravascular ultrasound has limited ability to identify lipid core; and the methods used require a level of core laboratory analysis that is impractical in routine clinical practice. The ease and simplicity of the NIRS-intravascular ultrasound imaging system in the catheterisation laboratory overcomes both of these issues.

Optical coherence tomography, which is frequently claimed to be able to detect LRPs and thin cap fibroatheroma, has only scarce retrospective data to support its predictive ability for future non-culprit lesion-related MACE.[23] Because intravascular ultrasound and optical coherence tomography are primarily sensitive to structure and, to a lesser extent, the relatively non-specific variations in sound wave or photon propagation through media of differing densities, they are only inherently capable of detecting thin cap fibroatheroma by these characteristics.[24] By contrast, NIRS uses unique near-infrared spectral differences between cholesterol and collagen to readily identify LRP from normal vessels or fibrotic and calcified plaques. NIRS-intravascular ultrasound imaging was the first, and still is the only, technology to be rigorously prospectively validated for the detection of lipid-core plaque and holds a corresponding FDA label claim.

The development of intravascular NIRS, its fundamental basis, validation for detection of LRP, and the use of the LCBI have been described previously.[10] Briefly, the commercial version of NIRS used in the present study is a dual-modality probe with intravascular ultrasound, allowing simultaneous, co-registered structure and plaque composition. Previous small studies have consistently shown that the maxLCBI$_{4mm}$, a straightforward derivative of LCBI that is sensitive to the angular extent of a lipid-core plaque, is predictive of periprocedural myocardial infarction,[25,26] is a signature of ST-elevation myocardial infarction in culprit plaques,[27,28] and is predictive of future patient-level MACE.[11–14] Some of these studies suggested that the higher the maxLCBI$_{4mm}$, the higher predictability for a NC-MACE, and some supported a cutoff point of 400 maxLCBI$_{4mm}$ for prediction of subsequent events. Therefore, this cutoff point was prespecified as a secondary dichotomised endpoint in the LRP study.

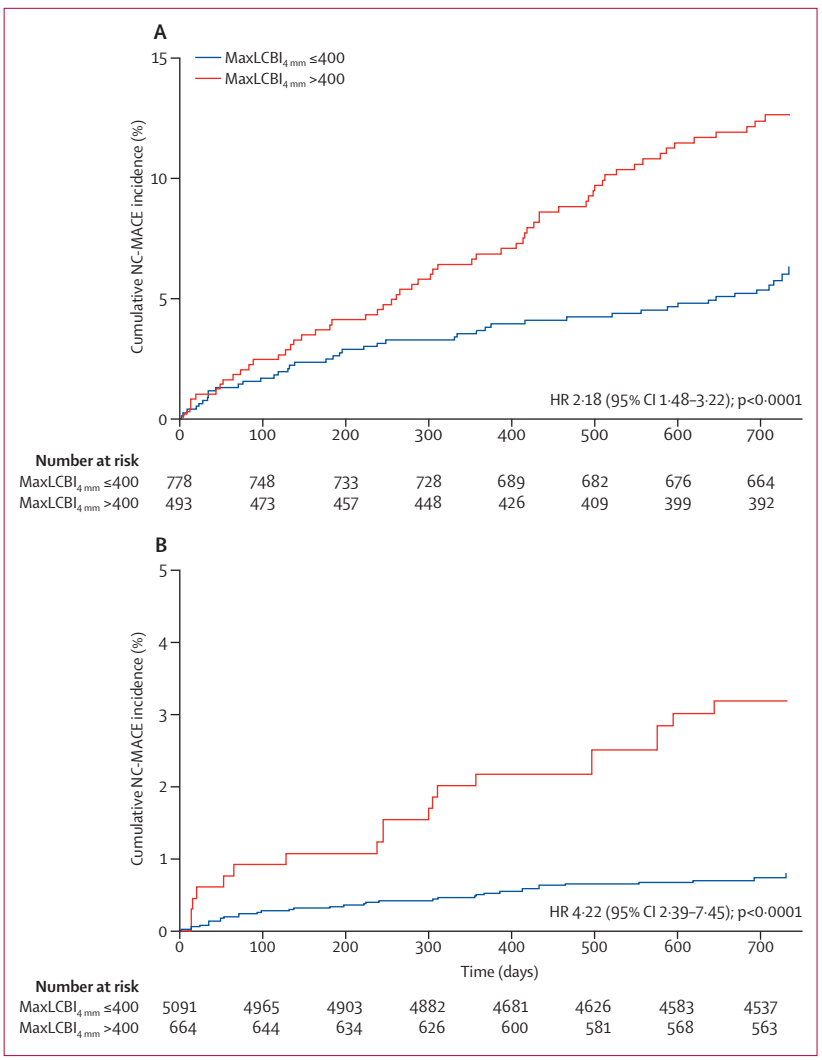

Figure 3: **Patient-level cumulative incidence of NC-MACE (A) and plaque-level cumulative incidence of NC-MACE (B)**

(A) Less than or equal to 400, 6%; greater than 400, 13%; p<0·0001. (B) Less than or equal to 400, 1%; greater than 400, 3%; p<0·0001. NC-MACE=non-culprit major adverse cardiovascular events. maxLCBI$_{4mm}$=maximum 4 mm Lipid Core Burden Index.

The LRP study is the first study to use the NIRS chemogram to show predictive ability for future NC-MACE, both for the patient and plaque levels. There are fundamental differences between the LRP and PROSPECT studies. In PROSPECT,[8] only patients with acute coronary syndrome were enrolled, all three major coronary vessels were scanned, and patients were followed up for events at a median of 34·9 months. By contrast, in the LRP study, patients who were stable (nearly half of the population) and patients who were unstable with acute coronary syndrome were included, only a mean of 2·1 vessels were scanned per patient, and the follow-up was limited to 24 months. Despite these differences and limitations, the results of the LRP study were robust and could have pointed to a higher patient-level HR if more vessels had been scanned and

if follow-up had been extended beyond 24 months. The cumulative incidence curves for the 400 maxLCBI$_{4mm}$ continue to separate for both the patient and plaque levels and suggest potentially higher hazards for future events at later timepoints. Further, the severity of the coronary events in the LRP study was substantial and included cardiac death and non-fatal myocardial infarction.

With the evidence around plaque burden of 70% or more as a predictor for future events from the PROSPECT and AtheroRemo-intravascular ultrasound studies, a secondary endpoint in the LRP study was prespecified to include this variable in the plaque-level model. The addition of plaque burden of 70% or more did not alter the HR or have an interaction with maxLCBI$_{4mm}$ more than 400. Our data might suggest that NIRS has an edge over plaque burden to detect vulnerable plaques because some of the lesions with high plaque burden might have a low LCBI. Additionally, in the LRP study, the number of patients with plaque burden of 70% or more was smaller than in PROSPECT; however, lesions that were followed up in PROSPECT had a baseline identification criterion of at least 40% plaque burden with the mandatory three-vessel imaging. A minimum plaque bruden was not a prerequisite in the LRP study. In the LRP study, all arteries were scanned irrespective of the presence of plaque burden. This factor might explain the absence of interaction between the NIRS and plaque burden in the LRP study. The same was applied to minimum lumen area of 4 mm² or less as shown in table 3. A previous study reported that the LCBI at the site of the plaque burden added to the intravascular ultrasound-derived plaque burden improved detectability of thin cap fibroatheromas; however, plaque burden at the site of maxLCBI$_{4mm}$ does not have any interaction with the LCBI for NC-MACE up to 24 months.[29]

The questions are as follows: What should be the impact of these findings on clinical practice? Are we ready to use LCBI as a discriminator for systemic or local therapy to reduce future events? And should we use LCBI as a surrogate marker for event reduction with medical therapies such as high-dose statin or PCSK9 inhibitors? One study is investigating the effect of a PCSK9 inhibitor to abolish or reduce LCBI and alter optical coherence tomography findings: The PACMAN-AMI trial (NCT03067844), which examines the effects of the PCSK9-inhibiting antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction with NIRS, intravascular ultrasound, and optical coherence tomography imaging modalities. In addition, there are two ongoing randomised studies of optimal medical therapy alone versus localised stenting plus optimal medical therapy for future non-culprit MACE reduction guided by intracoronary imaging: PROSPECT II and PROSPECT ABSORB (NCT02171065), which has a randomised arm that based its treatment algorithm on the PROSPECT I criteria but collected NIRS data, and PREVENT (NCT02316886), which includes multi-modality entry criteria including NIRS with a maxLCBI$_{4mm}$ cutoff of 315.

We believe that the results of the LRP study should prompt outcome trials incorporating NIRS-guided systemic drug or biologics therapy or localised stent placement to effect outcomes or to change the NIRS imaging finding from baseline. FDA granted a device label expansion in April, 2019, for this device on the basis of the results from this study. The NIRS-intravascular ultrasound catheter is the only FDA-cleared dual-modality catheter and imaging system indicated for the identification of patients and plaques at increased risk of MACE.

In conclusion, non-culprit events continue to occur, and early detection of these events with intravascular imaging remains a challenge. The use of intravascular ultrasound-NIRS has shown its ability to detect NC-MACE in patients undergoing cardiac catheterisation and possible PCI and should be considered as a tool to guide patients and lesions at risk for unanticipated subsequent MACE.

Contributors

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafted the work or revised it critically for important intellectual content; and granted final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

RW has served on advisory boards for Amgen, Boston Scientific, Cardioset, Cardiovascular Systems, Medtronic, Philips Volcano, and Pi-Cardia; has served as a consultant for Amgen, Biosensors, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems, Medtronic, Philips Volcano, and Pi-Cardia; and has received grant support from AstraZeneca, Biotronik, Boston Scientific, and Chiesi; and has participated at a speakers bureau for AstraZeneca and Chiesi; is an investor in MedAlliance. CDM reports grants from Infraredx during the conduct of the study and grants from Medtronic, Abbott, Daiichi Sanyo, and Shockwave outside the submitted work. ZAA reports grants from St Jude Medical (now Abbott), personal fees from St Jude Medical (now Abbott), and Acist Medical, grants and personal fees from Cardiovascular Systems Inc, outside the submitted work. PS reports personal fees from Infraredx during the conduct of the study. All other authors declare no competing interests.

Data sharing

Data collected for the study will not be made available to others.

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