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CLINICAL RESEARCH
Coronary artery disease

Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study

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Aims The CLIMA study, on the relationship between coronary plaque morphology of the left anterior descending artery and twelve months clinical outcome, was designed to explore the predictive value of multiple high-risk plaque features in the same coronary lesion [minimum lumen area (MLA), fibrous cap thickness (FCT), lipid arc circumferential extension, and presence of optical coherence tomography (OCT)-defined macrophages] as detected by OCT. Composite of cardiac death and target segment myocardial infarction was the primary clinical endpoint.

Methods and results From January 2013 to December 2016, 1003 patients undergoing OCT evaluation of the untreated proximal left anterior descending coronary artery in the context of clinically indicated coronary angiogram were prospectively enrolled at 11 independent centres (clinicaltrial.gov identifier NCT02883088). At 1-year, the primary clinical endpoint was observed in 37 patients (3.7%). In a total of 1776 lipid plaques, presence of MLA <3.5 mm^2 [hazard ratio (HR) 2.1, 95% confidence interval (CI) 1.1–4.0], FCT <75 μm (HR 4.7, 95% CI 2.4–9.0), lipid arc circumferential extension >180° (HR 2.4, 95% CI 1.2–4.8), and OCT-defined macrophages (HR 2.7, 95% CI 1.2–6.1) were all associated with increased risk of the primary endpoint. The pre-specified combination of plaque features (simultaneous presence of the four OCT criteria in the same plaque) was observed in 18.9% of patients experiencing the primary endpoint and was an independent predictor of events (HR 7.54, 95% CI 3.1–18.6).

Conclusion The simultaneous presence of four high-risk OCT plaque features was found to be associated with a higher risk of major coronary events.

Keywords Optical coherence tomography • Clinical outcome • Coronary plaque • Personalized medicine • Registry

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Translational perspective

The CLIMA study prospectively explored the correlation between the simultaneous presence of four optical coherence tomography (OCT) plaque vulnerability features and an increased risk of future major acute coronary events [i.e. cardiac death and myocardial infarction (MI)]. The study demonstrated the negative impact of OCT-defined high-risk intermediate lesions of the proximal left anterior descending artery on following clinical outcome (hazard ratio 7.54 at 1-year follow-up). Thus, these data seemed to confirm OCT as potential tool to assess '*in vivo*' the risk profile of coronary plaques and help identify patients at high risk of future coronary events.

Introduction

Studies based on histology and intracoronary imaging modalities demonstrated that plaques prone to rupture are typically characterized by a large superficial lipid pool, that is delimited by a thin fibrous cap and often exhibit local signs of inflammation (superficial macrophages).[1–4] Apart from systemic factors, that can contribute identifying subjects at risk of cardiac events,[5] intravascular imaging techniques proved to be effective solutions to detect high-risk plaque, shedding light on the role of large lipid pool, plaque burden, and reduced lumen area for promoting acute coronary syndromes (ACS).[6–8]

Optical coherence tomography (OCT), with its capability of visualizing superficial plaque components at a high resolution is potentially capable of identifying high-risk plaques.[9–13]

The CLIMA study has been conceived to explore the correlation between multiple OCT criteria of high-risk plaque at non-culprit sites located in the proximal left anterior descending (LAD) artery and the risk of future acute coronary events.

Methods

Study design

The CLIMA is a prospective observational, multi-centre registry recruiting all consecutive patients undergoing assessment of proximal LAD atherosclerosis by OCT in the context of a clinically indicated coronary angiography. Supplementary material online, *Table S1* summarizes the inclusion/exclusion study criteria.

The aim of the CLIMA study was to assess whether the simultaneous presence of four predefined OCT high-risk features detected in the same non-culprit LAD plaque [including minimum lumen area (MLA), fibrous cap thickness (FCT), lipid arc circumferential extension, and macrophage infiltration] was associated with the future risk of target-segment MI and/or cardiac death (composite primary clinical endpoint). The present study is addressing the 1-year follow-up results.

The LAD artery was preferred over the other main coronaries for two major reasons: (i) it is easier to identify the culprit vessel in case of recurrent events and (ii) coronary events occurring in the proximal LAD segments are potentially the most ominous.

All patients received scheduled clinical visits by a physician during the first 12 months according to standard institutional guidelines. Endpoints were assessed by means of dedicated telephone-based interviews and/or office-based direct visits in case of adverse events. Thus, any adverse event or hospitalization during the follow-up was adjudicated accessing the relative source documents by operators blinded to OCT analyses. Outcomes were defined according to the Academic Research Consortium guidelines and blindly adjudicated by a clinical-event committee.[14]

The project was approved by the local ethics board and registered in the ClinicalTrial.gov registry (clinical trial.gov identifier NCT02883088). All patients provided written informed consent for the index procedure, follow-up, and anonymous data management. This work was supported by the Centro per la Lotta contro l'Infarto – Fondazione Onlus (CLI Foundation, Rome, Italy), and authors were solely responsible for the design, conduct, and final contents of this study.

Imaging acquisition and definition

Coronary angiographies were performed according to the standard techniques and OCT images were acquired by means of the FD C7 XR system or the OPTIS system (both St. Jude Medical, St. Paul, MN, USA) with a non-occlusive technique.[15] The acquired OCT coronary images were analysed off-line using a proprietary OCT console (St Jude Medical, Inc., USA) at an independent imaging core laboratory (Euroimage Research, Rome, Italy) by blinded expert readers. Only OCT pullbacks allowing accurate measurement of lumen (continuous arc of at least 270° around the centre of the lumen) and qualitative definition of the superficial plaque components were considered eligible and included in the final analyses. Each plaque identified at OCT and surrounded by at least 5 mm of healthy vessel was analysed individually. Mandatory inclusion criterion was the adequate OCT assessment of at least 30 mm of untreated proximal segment of LAD free from significant stenosis (>50%) at angiography.

Definitions and cut-offs for OCT parameters were derived from available consensus documents and from major intravascular ultrasound (IVUS)/OCT studies (Supplementary material online).[6,15,16] In particular, we considered as markers of high-risk plaques: *MLA* <3.5 mm^2 measured along the entire length of the assessed coronary segment, derived from the 4.0 mm^2 cut-off applied in the PROSPECT clinical study[6] and corrected for the relative IVUS overestimation[15,16]; *minimum FCT* <75 µm, defined as a signal-rich homogeneous band overlying a lipid core and measured at the thinnest portion[4,15–17]; *lipid plaque with lipid arc extension* >180°, defined as a signal-poor region diffusely bordered by overlying signal-rich bands corresponding to a fibrous cap[15,16]; and *presence of macrophage* clusters defined at visual estimation as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise.[16] According to the study design, the classification of OCT-defined high-risk plaques required the simultaneous presence of these four criteria. Other OCT features included: intimal vasculature defined as sharply delineated signal-poor voids that can usually be followed in multiple contiguous frames[16]; *intra-plaque layered tissue*, defined as deeper layers of tissue with a clearly layered structure[18]; *cholesterol crystals*, defined as thin linear regions of high intensity[16,19]; and *calcified nodules*, defined as an accumulation of nodular calcification with disruption of fibrous cap on the calcified plate.[16,20]

Statistical analysis

Percentages were used to report discrete variables, while mean (±standard deviation) or median (1st–3rd quartile) were used to describe

Table 1 Patient characteristics

	Population (1003)	Patients with clinical event[a] (37)	Patients without clinical event[a] (966)	HR (95% CI)	*P*-value
Cardiac risk factors					
Age (years)[b]	66 (56–74)	69 (58–81)	66 (56–74)	1.05 (1.0–1.1)	0.028
Female gender (%)	247 (24.6)	12 (32.4)	235 (24.3)	1.48 (0.7–2.9)	0.263
Left ventricle ejection fraction (%)[b]	55 (48–60)	55 (40–60)	55 (48–60)	0.96 (0.8–0.9)	0.034
Hypertension (%)	678 (67.6)	31 (83.8)	647 (67.0)	2.46 (1.1–5.9)	0.044
Smoking habit (%)	279 (27.8)	11 (29.7)	268 (27.7)	1.07 (0.5–2.2)	0.846
Family history of CAD (%)	246 (24.5)	7 (18.9)	239 (24.7)	0.71 (0.3–1.6)	0.421
Prior MI (%)	207 (20.6)	10 (27.0)	197 (20.4)	1.37 (0.7–2.8)	0.391
Prior PCI (%)	300 (29.9)	12 (32.4)	288 (29.8)	1.12 (0.6–2.2)	0.741
Diabetes mellitus (%)	223 (22.2)	10 (27.0)	213 (22.0)	1.31 (0.6–2.7)	0.462
CKD (GFR <60 mL/min/1.73 m^2) (%)	149 (14.9)	11 (29.7)	138 (14.3)	2.47 (1.2–5.0)	0.012
Hypercholesterolaemia (%)	606 (60.4)	19 (51.4)	587 (60.8)	0.68 (0.4–1.3)	0.241
Total cholesterol (mg/dL)[b]	177 (151–207)	161 (147–193)	177 (152–208)	0.99 (0.9–1.0)	0.275
LDL (mg/dL)[b]	110 (85–137)	107 (80–126)	110 (85–137)	1.00 (0.9–1.0)	0.509
HDL (mg/dL)[b]	42 (35–51)	39 (31–51)	42 (35–51)	0.98 (0.9–1.0)	0.229
Triglycerides (mg/dL)[b]	119 (88–169)	116 (80–155)	120 (89–169)	1.00 (0.9–1.0)	0.174
High-sensitivity C-reactive protein (mg/L)[b]	4.65 (1.5–12.1)	7.10 (1.7–12.9)	4.60 (1.5–12.0)	0.99 (0.9–1.1)	0.565
Diagnosis					
Acute coronary syndrome (%)	536 (53.4)	17 (45.9)	519 (53.7)	0.72 (0.4–1.4)	0.305
STEMI (%)	199 (19.8)	8 (21.6)	191 (19.7)	1.08 (0.5–2.4)	0.853
NSTEMI (%)	199 (19.8)	7 (18.9)	192 (20.0)	0.95 (0.4–2.2)	0.907
Unstable angina (%)	138 (13.8)	2 (5.4)	136 (14.0)	0.36 (0.2–1.4)	0.143
Stable angina (%)	467 (46.6)	20 (54.1)	447 (46.3)	1.40 (0.7–2.7)	0.305
CAD-vessel disease					
No significant disease	66 (6.5)	2 (5.4)	64 (6.6)	0.83 (0.2–3.5)	0.800
1-vessel significant disease	481 (48.0)	10 (27.0)	471 (48.8)	0.40 (0.2–0.8)	0.012
2-vessel significant disease	297 (29.6)	15 (40.6)	282 (29.2)	1.62 (0.8–3.1)	0.150
3-vessel significant disease	159 (15.9)	10 (27.0)	149 (15.4)	2.01 (1.0–4.2)	0.059
Left main significant disease	61 (6.1)	1 (2.7)	60 (6.2)	0.41 (0.1–3.0)	0.380

CAD, coronary artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non ST-Elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI.
[a]Composite of cardiac death and target LAD segment myocardial infarction.
[b]Expressed as median and interquartile range.

continuous variables in case of normal or skewed distribution, respectively.

The Student's *t*-, Mann–Whitney *U*, and χ^2 tests were applied for bivariate analyses when appropriate. Cohen's Kappa statistic was used to assess inter-observer agreement in macrophage infiltration adjudication in the first 100 consecutive patients. The receiver operating characteristic (ROC) curve and highest Youden's index (J) were used to confirm the selected OCT cut-offs.[21,22] Variance inflation factors were used to exclude multicollinearity among the selected OCT variables, and the added predictive value of the simultaneous 4-OCT selected criteria was evaluated using the Integrated Discrimination Improvement (IDI) index.

Clinical endpoint (cardiac death and target LAD segment MI) was evaluated on a per-patient hierarchical basis, compared with the log-rank test, and summarized as Kaplan–Meier estimates. The generalized mixed model analysis was performed to exclude difference due to lesion and patient level clustering. All variables reported in *Tables 1* and *2* were tested for bivariate association with the composite clinical endpoint and if nominally significant ($P < 0.05$) were simultaneously forced into a Cox regression model to identify independent outcome predictors and to calculate their adjusted hazard ratios (HRs). Statistical analyses were carried out using SPSS-PASW 22.0 (IBM, Armonk, NY, USA) and adopting a two-tailed *P*-value <0.05 for statistical significance.

Study sample size

Based on previous clinical studies testing clinical impact of OCT use during percutaneous coronary revascularization and preliminary experience of the steering committee we estimated an annual cumulative incidence of 7% for the composite clinical endpoint and of 5% for the OCT-defined high-risk plaque (i.e. simultaneous presence of the four criteria).[6,23] Assuming an expected detection of high-risk plaque features in about 20% of patients with the composite clinical endpoint and aiming to a two-sided alpha level of 0.05 and a power of

Table 2 Optical coherence tomography findings

	All population (1003)	Patients with clinical events[a](37)	Patients without clinical events[a](966)	HR (95% CI)	*P*-value
LAD vessel characteristics					
LAD culprit (%)	546 (54.4)	19 (51.4)	527 (54.6)	0.86 (0.5–1.6)	0.655
LAD stented in mid-distal segments (%)	775 (77.3)	27 (73.0)	748 (77.4)	0.78 (0.4–1.6)	0.507
Length of vessel assessed by OCT (mm)[b]	35.4 (32–47)	36.2 (34–52)	35.4 (32–49)	1.00 (0.9–1.1)	0.994
Length of stented segment (mm)[b]	18.0 (12–28)	18 (0–30)	18 (12–28)	0.99 (0.9–1.1)	0.539
OCT findings					
Total plaque length (mm)[b]	13.2 (6.6–20.6)	16.8 (8.5–26.1)	13.0 (6.5–20.6)	1.01 (1.0–1.1)	0.241
Minimum lumen area (mm^2)[b]	3.8 (2.8–5.3)	3.2 (2.3–5.0)	3.8 (2.8–5.3)	0.90 (0.8–1.1)	0.228
Minimum lumen area <3.5 mm^2 (%)	396 (39.5)	21 (56.8)	375 (38.8)	2.07 (1.1–4.0)	0.032
Fibrous cap thickness (μm)[c]	107 (±41)	76 (±26)	108 (±42)	0.96 (0.9–1.0)	<0.001
Fibrous cap thickness <75 μm (%)	183 (18.2)	19 (51.4)	164 (17.0)	4.65 (2.4–9.0)	<0.001
Maximum lipid arc (°)[c]	183 (±73)	213 (±77)	181 (±73)	1.01 (1.0–1.1)	0.009
Maximum lipid arc >180° (%)	410 (40.9)	24 (64.9)	386 (40.0)	2.40 (1.2–4.8)	0.017
Presence of macrophages (%)	577 (57.5)	30 (81.1)	547 (56.6)	2.66 (1.2–6.1)	0.027
Cholesterol crystal (%)	211 (21.0)	12 (32.4)	199 (20.6)	1.66 (0.8–3.4)	0.160
Intra-plaque layered tissue (%)	175 (17.4)	6 (16.2)	169 (17.5)	0.91 (0.4–2.2)	0.841
Calcified nodules (%)	180 (17.9)	10 (27.0)	170 (17.6)	1.73 (0.8–3.7)	0.147
Intra-plaque intimal vasculature (%)	518 (51.6)	21 (56.8)	497 (51.4)	1.24 (0.6–2.4)	0.527
Presence of all OCT-defined vulnerability criteria (%)[d]	36 (3.6)	7 (18.9)	29 (3.0)	7.54 (3.1–18.6)	<0.001

[a]Composite of cardiac death and target vessel myocardial infarction.
[b]Expressed as median and interquartile range.
[c]Expressed as mean and standard deviation.
[d]Simultaneous presence of minimum lumen area <3.5 mm^2, Fibrous cap thickness <75 μm, Maximum lipid arc >180°, and presence of macrophages.

90%, a sample size of 540 patients was initially computed (using Fisher's exact test) and increased to 700 to accommodate for possible missing investigations or withdrawals. An interim analysis conducted on the first half of recruited patients to verify the statistical assumptions, revealed an annual clinical endpoint incidence lower (about 4%) than estimated; thus, the steering committee decided for a 40% sample size increase to maintain the original statistical power.

Results

Demographic and procedural data

From January 2013 to December 2016, 1003 patients undergoing OCT evaluation of the proximal LAD segment were enrolled at 11 independent centres and prospectively investigated to evaluate clinical outcome. Clinical and procedural characteristics of the study population are reported in *Tables 1* and *2*. Median age was 66 years and 24.6% of the patients were females. Clinical indication for the index procedure was ACS in 53.4% of patients and LAD was the identified culprit vessel in 54.4% of cases. Cumulatively, 77.3% of the patients received a stent implantation in the mid-distal segments of LAD, but none had indication for coronary revascularization in the proximal segment of LAD at the time of the enrolment. Most of patients were discharged with an indication to dual antiplatelet therapy and optimized lipid-lowering therapy (i.e. maximum tolerated dose) throughout the follow-up period (Supplementary material online, *Table SII*).

Optical coherence tomography and angiographic results

Optical coherence tomography assessment revealed 1776 non-culprit plaques in the analysed LAD with a mean plaque length of 13.2 (quartiles 6.6–20.6) mm. Quantitative analyses disclosed a MLA <3.5 mm^2 in 39.5% of lesions, fibrous cap thickness <75 μm in 18.2%, maximum lipid arc >180° in 40.9%, and macrophage infiltration in 57.5%. The simultaneous presence of all four high-risk criteria in at least one lipid plaque was observed in 36 lesions (3.6% of patients). Optical coherence tomography-defined macrophage infiltration was identified by two different readers with good accuracy (Kappa coefficient 0.62, 95% CI 0.77–0.47, $P < 0.001$, sensitivity of 78.0%, and specificity of 85.4%.

During the first year of follow-up, 37 patients (3.7%) experienced the primary endpoint events, including 2.5% cardiac mortality and 1.3% non-fatal target LAD segment MI (*Table 3* and *Figures 1 and 2*) due to the angiographically documented disease progression in the explored segment. Cumulatively, the rate of further revascularization in the target vessel, during 1-year follow-up was 2.5%.

Clinical predictors

Patients experiencing a clinical event during the first year of follow-up showed higher baseline risk profile including older age (HR 1.05, $P = 0.028$), lower left ventricle ejection fraction (HR 0.96, $P = 0.034$), higher prevalence of hypertension (HR 2.46, $P = 0.044$), chronic

Table 3 One-year clinical outcome

	All population (1003)	Plaques with MLA <3.5 mm^2, FCT <75 μm, lipid arc >180° and macrophages (36)	Plaques without MLA <3.5 mm^2, FCT <75 μm, lipid arc >180° and macrophages (967)	*P*-value
Cardiac death or target LAD segment MI (%)	37 (3.7)	7 (19.4)	30 (3.1)	<0.001 HR 7.54 (3.1–18.6)
Death (%)	34 (3.4)	4 (11.1)	30 (3.1)	0.015 HR 3.90 (1.3–11.7)
Non-cardiac death (%)	9 (0.9)	0 (0.0)	9 (0.9)	0.561 HR 0.0 (0.0–0.0)
Cardiac death (%)	25 (2.5)	4 (11.1)	21 (2.2)	0.003 HR 5.63 (1.8–17.4)
Myocardial infarction (%)	26 (2.6)	5 (13.9)	21 (2.2)	<0.001 HR 7.27 (2.6–20.5)
Non-target LAD segment related MI (%)	13 (1.3)	2 (5.6)	11 (1.1)	0.038 HR 5.11 (1.1–24.0)
Target LAD segment related MI (%)	13 (1.3)	3 (8.3)	10 (1.0)	0.002 HR 8.70 (2.3–33.1)
Target vessel revascularization (%)	25 (2.5)	2 (5.6)	23 (2.4)	0.245 HR 2.41 (0.5–10.7)

LAD, left anterior descending artery; MI, myocardial infarction.

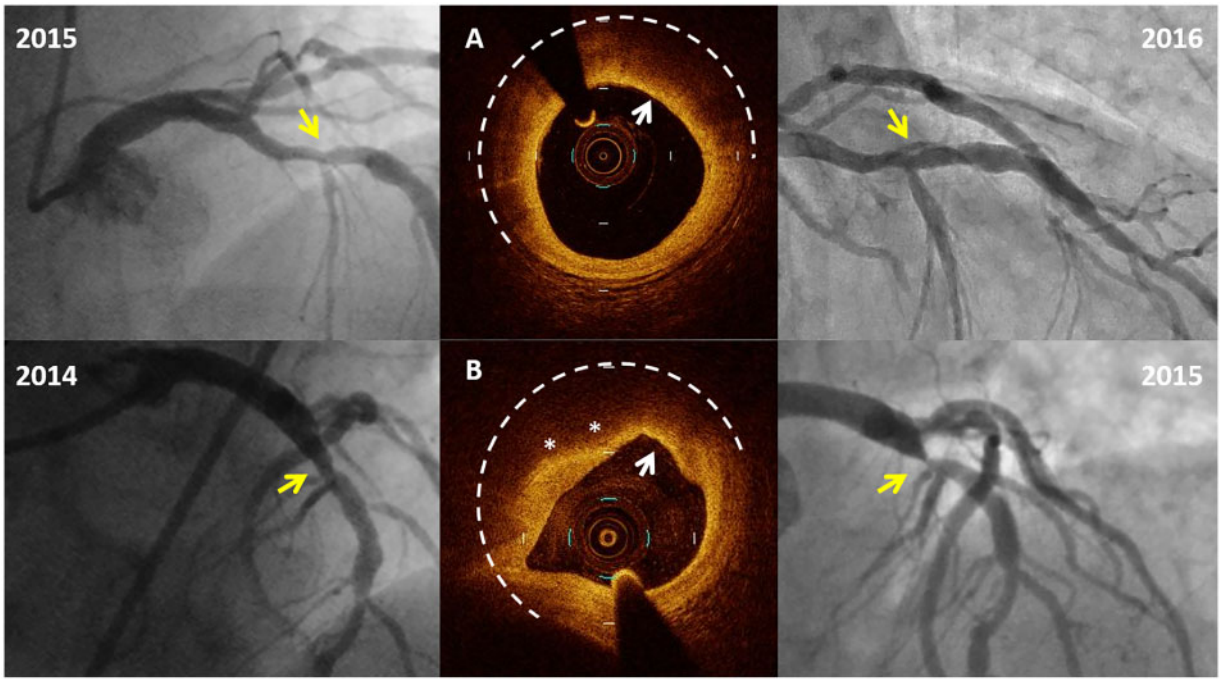


Figure 1 Optical coherence tomography criteria of high-risk plaque and subsequent risk of cardiovascular events. Upper panels. Evolution of an intermediate proximal left descending artery lesion (yellow arrow) exhibiting only two optical coherence tomography high-risk criteria (*A*): fibrous cap thickness 60 μm (white arrow), and circumferential lipid arc extension 200° (dotted line). The plaque did not show any angiographic progression at 1 year, remaining clinically silent. Lower panels. Evolution of an intermediate lesion in the proximal left descending artery lesion (yellow arrow) exhibiting the selected four optical coherence tomography high-risk criteria (*B*): minimum lumen area 2.64 mm^2, fibrous cap thickness 50 μm (arrow), circumferential lipid arc extension 206° (dotted line), and presence of optical coherence tomography-defined macrophage infiltration (asterisk). The plaque showed a significant stenosis progression causing an acute coronary syndrome within 1 year from the index angiogram.

kidney disease (HR 2.47, $P = 0.012$), and more frequent multi-vessel coronary disease (HR 2.51, $P = 0.009$), but comparable grade of LAD atherosclerosis (*Tables 1* and *2*).

Patients with events showed more frequently proximal LAD plaques with MLA <3.5 mm^2 (56.8% vs. 38.8% years, HR 2.07, $P = 0.032$), FCT <75 μm (51.4% vs. 17.0%, HR 4.65, $P < 0.001$), lipid arc extension >180° (64.9% vs. 40.0% years, HR 2.40, $P = 0.017$), and OCT-defined macrophage infiltration (81.1% vs. 56.6%, HR 2.66, $P = 0.027$). Other OCT features, such as cholesterol crystal, calcified nodules, intra-plaque intimal vasculature, or layered tissue, were not

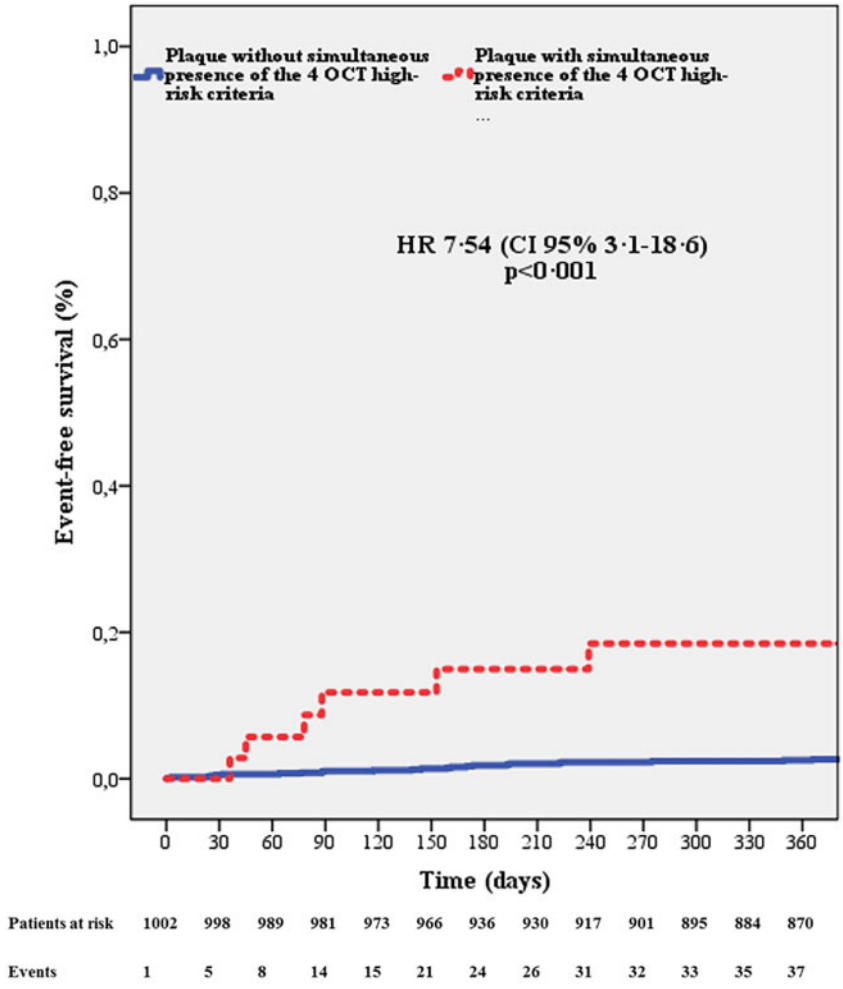


Figure 2 Clinical outcome. Survival free of cardiac death or target vessel myocardial infarction according to optical coherence tomography-defined high-risk plaque in proximal left descending artery segments.

Table 4 Predictive value of optical coherence tomography criteria for cardiac death or target left anterior descending artery segment myocardial infarction

OCT variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Minimum lumen area <3.5 mm^2	56.8	61.2	5.3	97.4
Minimum fibrous cap thickness <75 μm	51.4	81.5	10.4	97.6
Maximum lipid arc extension >180°	64.9	56.5	5.9	97.5
Presence of macrophages	81.1	38.3	5.2	98.0
Cholesterol crystal	32.4	77.6	5.7	96.5
Calcified nodules	27.0	82.4	5.6	96.7
Intra-plaque intimal vasculature	56.8	48.6	4.1	96.7
Layered tissue	16.2	82.5	3.4	96.3
Simultaneous presence of minimum lumen area <3.5 mm^2, fibrous cap thickness <75 μm, lipid arc >180°, and macrophages	18.9	97.5	19.4	96.9

NPV, negative predictive value; PPV, positive predictive value.

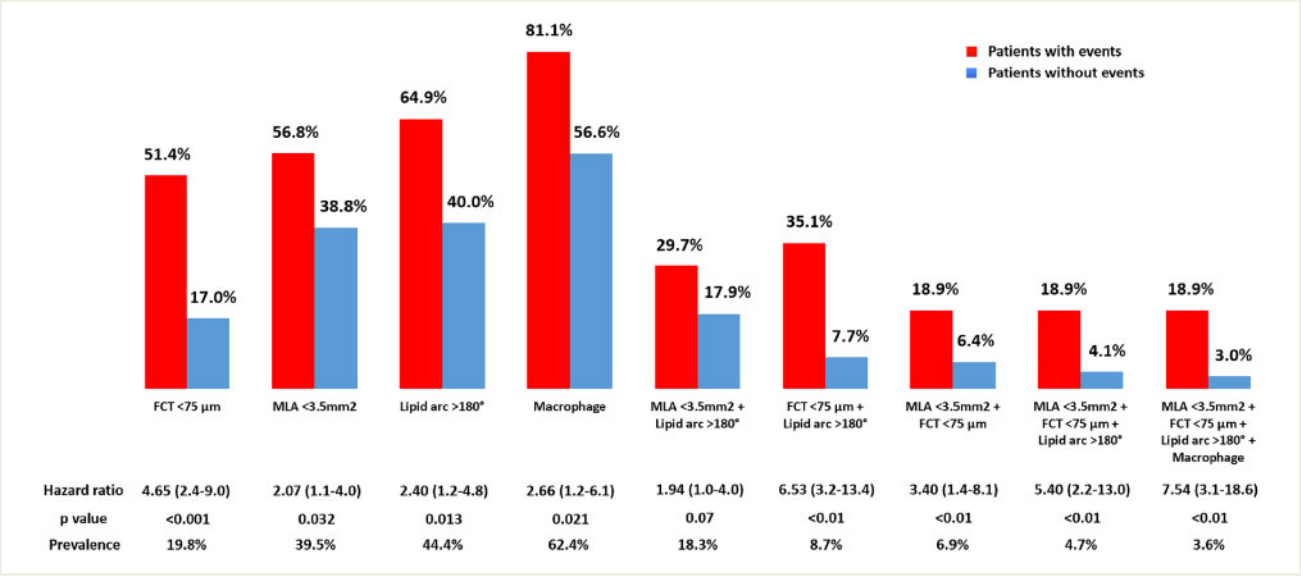


Figure 3 One-year event rates for lesions with and without optical coherence tomography-defined high-risk criteria.

associated with an increased risk of 1-year acute coronary events (*Table 2*).

The simultaneous presence of all the four high-risk OCT criteria in the same coronary plaque was significantly more frequent in patients experiencing the composite clinical endpoint during the first 12 months (18.9% vs. 3.0%, HR 7.54, 95% CI 3.1–18.6; $P < 0.001$). The combined high-risk criteria showed only a limited impact on predicting accuracy when compared with each individual OCT variable (relative IDI 11%, $P = 0.181$). Thus sensitivity was reduced, but specificity was significantly increased *Table 4*). In detail, 19.4% of OCT-defined high-risk plaques caused an acute event (i.e. positive predictive value). After correction for baseline clinical features, the simultaneous presence of MLA <3.5 mm^2, FCT <75 µm, lipid arc extension >180°, and OCT-defined macrophage infiltration in the same coronary plaque was confirmed as independent predictor of events (HR 6.12, CI 95% 2.1–18.1, $P < 0.001$). Furthermore, the risk of future cardiac events was proportional to the number of high-risk OCT criteria in the same plaque (*Figure 3*).

Discussion

This is the first OCT study exploring the correlation between the coronary plaque morphology and the risk of major cardiovascular event such as cardiac death and MI. The main findings of this registry are: (i) intravascular OCT is a potential tool for *in vivo* investigation of coronary plaques at risk of progression; (ii) OCT-defined high-risk plaque assessment showed an independent predictive value at 1-year follow-up; (iii) the use of multiple OCT high-risk plaque features can contribute to identifying patients at higher risk of acute coronary events (*Take home figure*).

Although OCT is not suited for plaque burden measurement due to its limited penetration, it can discriminate superficial plaque components at a microscopic level allowing the characterization of an high-risk plaque in terms of minimum lumen area, lipid pool extension, fibrous cap thickness, and OCT-defined macrophage content.[14,15,20,21]

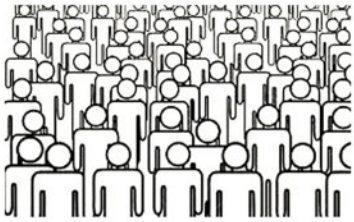
Multiple optical coherence tomography high-risk plaque features and cardiovascular events

Our registry confirmed that OCT has the potential to identify patients at higher risk for subsequent coronary events. Indeed, in this prospective case series we adopted as a pre-defined endpoint the simultaneous presence of four high-risk plaque criteria, including OCT-defined macrophages.[12] This high-risk pattern was observed in 3.6% of non-culprit plaques and identified about 20% of patients experiencing a major adverse coronary event during the first year of follow-up.[3] On the other hand, the combination of MLA <3.5 mm^2, FCT <75 µm, lipid arc extension >180°, and OCT-defined macrophage infiltration was observed only in 3% of patients with event-free survival. Thus, this OCT-based classification showed limited sensitivity (positive predictive value 19.4%), but high specificity (negative predictive value 96.9%) for the primary endpoint, and remained an independent predictor of 1-year events after correction for the other confounding variables.

The reasons for this limited positive predictive value might be intrinsic to the ability of OCT to characterize high-risk plaques, might be due to the positive effects of statins in promoting plaque stabilization or also reside in the short 1-year observation time, probably an insufficient period for plaques to cause events.

Comparison with other registries on high-risk plaque

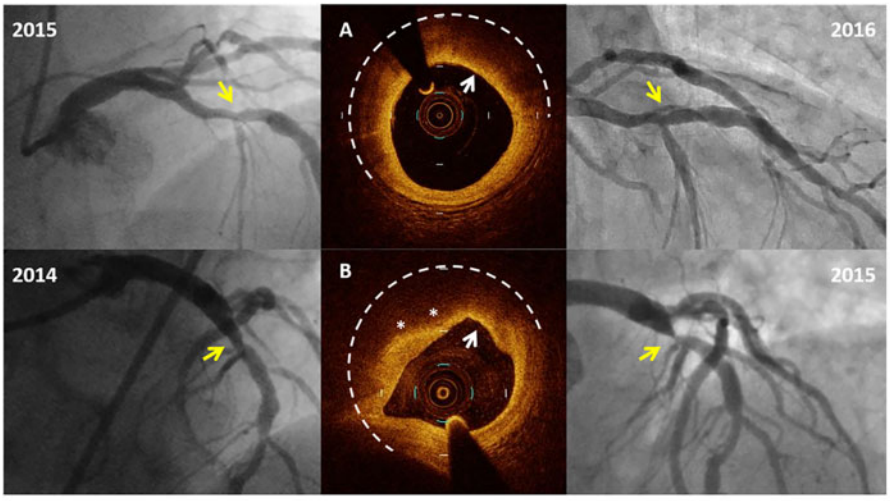
The utility of intravascular imaging in detecting high-risk plaque has been tested by three large studies. The PROSPECT study[6] showed that the simultaneous presence of three vulnerability features

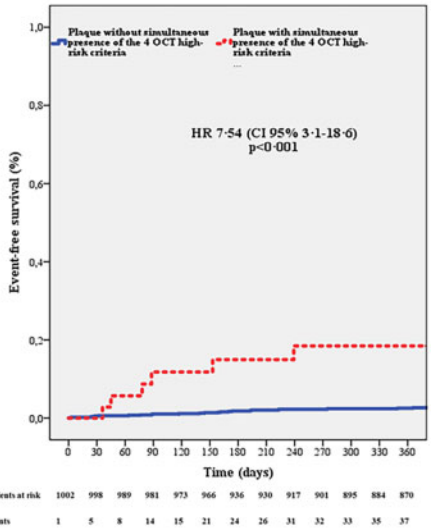


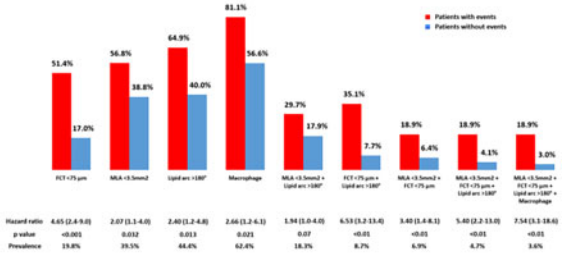
OCT LAD in 1003 patients with clinically indicated coronary angiogram from 11 independent centres enrolled from January 2013 to December 2016 (clinicaltrial.gov identifier NCT02883088).

MLA <3.5mm^2 + FCT <75µm + Lipid arc circumferential extension >180° + OCT defined macrophages

In 18.9% of patients who experienced the primary end-point the combination of the 4 findings was an independent predictor of events (HR 7.54, CI 95% 3.1-18.6).







Take home figure The CLIMA study explored the predictive value of multiple high risk plaque features in the same coronary lesion [minimum lumen area (MLA), fibrous cap thickness (FCT), lipid arc circumferential extension, and presence of macrophages] as detected by optical coherence tomography (OCT) in 1003 patients undergoing OCT evaluation of the untreated proximal left anterior descending coronary artery. At 1-year, the pre-specified combination of plaque vulnerability features was an independent predictor of events.

(thin-cap fibroatheroma, as determined by grey-scale and radiofrequency IVUS, large plaque burden, and small luminal area) were associated to a 3 years increase of a combined endpoint including cardiac death, target-vessel MI, and re-hospitalization due to ischaemia. However, such a combination of features was rather uncommon (4.2% of cases). In the Massachusetts General Hospital (MGH) OCT registry,[7] the incidence of a composite endpoint including cardiac death, acute MI, and ischaemia-driven revascularization was significantly more common in patients with lipid-rich plaques (3.5% vs. 1.8% at 2 years) and in presence of smaller minimal lumen areas ($P = 0.003$). The Lipid-Rich Plaque study[8] addressed lipid pool extension by means of near infrared spectroscopy (NIRS)[24,25] and showed at the adjusted patient-level analysis a 18% higher risk of experiencing non-culprit major adverse cardiac event (MACE) for each 100-unit increase in maximum lipid core burden index.[8]

In this context, the CLIMA study expands conclusions reached by these previous studies, addressing the clinical impact of local inflammation and FCT as additional high-risk features, besides presence and extension of lipid components.

Whilst in the published studies on plaque vulnerability progressive angina accounted for most of the events, the CLIMA registry, carried on with a high resolution imaging modality, was specifically conceived to address the impact of plaque features on the occurrence of major endpoints, such as target-vessel MI and cardiac death within the first year of follow-up.

Assessment of local inflammation

In the CLIMA study, the presence of plaque inflammation was used alongside with other conventional criteria to increase high-risk plaque classification in non-culprit lesions.[26] The detectability of macrophage clusters in the plaque layers explored by OCT has been a debated topic. However, the correspondence between histopathology and OCT images has been documented in several *ex vivo* studies,[27–29] and for this reason the ability of OCT to recognize presence of macrophages was acknowledged in the consensus document on OCT definitions.[16]

In the CLIMA registry, consistently with previous findings,[30] a substantial reproducibility for OCT-defined macrophage detection was obtained at the inter-observer analyses. Furthermore, the association between OCT-defined macrophage and higher risk of cardiac events was shown for the first time, with macrophage clusters being observed in about half of cases, and being related to the risk of adverse events (HR 2.66). More importantly, OCT-defined macrophage plaque infiltration further improved the classification of high-risk plaque phenotype; in-fact when added to the three other OCT variables, the risk of future adverse events increased from HR 5.40 to HR 7.54 (*Figure 3*).

Role of other optical coherence tomography features

According to previous studies calcified nodules can be a promoting site for local thrombosis,[3,20] while crystal of cholesterol and intimal vasculature are frequently found in lesions with signs of vulnerability,[19,31] but apparently not related to a worsened long-term outcome.[32] Consistently, in the present study crystal of cholesterol and calcific nodules were found more often in the group with cardiac events, although differences were not statistically significant.

Limitations

The observational nature represented the main limitation of the study. Indeed, this registry included patients with various clinical presentation and cardiovascular risk profile uniquely pooled by the intra-procedural OCT assessment of proximal LAD.

The combination of the four high-risk plaque features was rather uncommon, and showed at 1-year follow-up a limited positive predictive value for major cardiac events. The impact of medical treatment (e.g. statin) in determining favourable plaque composition changes should not be neglected.

The study did not require a three-vessel analysis; in fact, in line with previous studies only the target vessel was imaged.[7] This in keeping with the goal of promoting OCT as a practical and low-risk intracoronary imaging modality to be applied in clinical practice.

Consistently with other studies on plaque vulnerability it was not possible to relate cardiac death to a culprit lesion. However, even in the case target lesions were not responsible for the fatal event, high-risk plaque features in the analysed segment served as a marker of more advanced disease.

High-risk OCT features were searched in vessels that could have been treated with angioplasty. However only proximal target lesions located at a distance greater than 5 mm to the stent edges were imaged with OCT and entered the study.

Some definitions, although reflecting a validated methodology, might be considered arbitrarily taken. This is valid particularly for the FCT cut-off.

Conclusions

The CLIMA study showed the simultaneous presence of multiple OCT high-risk coronary plaque features in about 20% of patients with major coronary events in the first year of follow-up. Future larger studies with longer follow-up are needed to determine if these features provide incremental value over clinical variables and to understand whether personalized medical treatment or interventional procedures can improve clinical outcome in presence of such high-risk coronary plaques.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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