Special feature: Plaque characteristics

Clinical outcomes of calcified nodules detected by optical coherence tomography: a sub-analysis of the CLIMA study

Francesco Prati[1,2,3]*, MD; Laura Gatto[1,2], MD; Franco Fabbiocchi[4], MD;
Rocco Vergallo[5], MD, PhD; Giulia Paoletti[2,3], RN; Giovanni Ruscica[2], MD; Valeria Marco[2], RN;
Enrico Romagnoli[2,5], MD, PhD; Alberto Boi[6], MD; Massimo Fineschi[7], MD;
Giuseppe Calligaris[4], MD; Corrado Tamburino[8], MD; Filippo Crea[5], MD; Yukio Ozaki[9], MD;
Fernando Alfonso[10], MD; Eloisa Arbustini[11], MD

1. Department of Cardiovascular Sciences, San Giovanni Addolorata Hospital, Rome, Italy; 2. Centro per la Lotta Contro L'Infarto - CLI Foundation, Rome, Italy; 3. UniCamillus - Saint Camillus International University of Health Sciences, Rome, Italy; 4. Centro Cardiologico Monzino, IRCCS, Milan, Italy; 5. Department of Cardiovascular and Thoracic Sciences, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; 6. Interventional Cardiology Unit, Ospedale Brotzu, Cagliari, Italy; 7. Department of Cardiovascular Diseases, Azienda Ospedaliera Universitaria Senese, Siena, Italy; 8. Cardio-Thoracic Vascular Department, Azienda Ospedaliero-Universitaria "Policlinico Vittorio-Emanuele", University of Catania, Catania, Italy; 9. Department of Cardiology, Fujita Health University Hospital, Toyoake, Japan; 10. Department of Cardiology, Hospital Universitario de La Princesa, Madrid, Spain; 11. Centre for Inherited Cardiovascular Diseases, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-01120

Abstract

Aims: The goal of the present *post hoc* analysis of the CLIMA registry was to establish the relationship between calcified nodules (CNs) with (CND) or without (CNWD) disruption of the superficial intimal fibrous layer and one-year occurrence of target lesion myocardial infarction (MI) and/or cardiac death.

Methods and results: CND and CNWD were identified based on the presence or absence of superficial irregularities indicative of disruption of the intimal fibrous layer, with possible overlying local thrombus. In total, 222 CNs were found in the 1,776 non-culprit LAD plaques. CND had larger maximum calcific arc and smaller lumen area. Cardiac death and MI occurred in 20% of patients in the CND group versus 2.7% in the CNWD group and 3.3% in the group without CN (p<0.001). This figure was mainly due to the 13.3% incidence of cardiac death in the CND group versus 2.0% in the CNWD group and versus 2.2% in the group without CN (p<0.001). The presence of CND was confirmed as an independent predictor of events (HR 6.58, 95% CI: 2.7-15.8, p<0.001).

Conclusions: The presence of CND was associated with a high one-year incidence of cardiac death and/or target lesion MI.

Corresponding author: Cardiovascular Department, San Giovanni Addolorata Hospital, Via dell'Amba Aradam, 8, 00184 Rome, Italy. E-mail: fprati@hsangiovanni.roma.it

Abbreviations

ACS	acute coronary syndrome
CN	calcified nodule
CND	calcified nodule with disruption
CNWD	calcified nodule without disruption
FCT	fibrous cap thickness
FU	follow-up
IVUS	intravascular ultrasound
LAD	left anterior descending artery
MI	myocardial infarction
MLA	minimum lumen area
OCT	optical coherence tomography

Introduction

The presence of calcified nodules (CNs) is an established feature of plaque vulnerability in the coronary region. Based on histology data, over 5% of acute coronary syndromes (ACS) are caused by acute thrombosis occurring at the site of CN[1].

CNs are appreciated on optical coherence tomography (OCT) as intraluminal protrusion of calcific components with or without disruption of the intimal fibrous layer. CNs with disruption of the intimal fibrous layer (CND) show an irregular surface on OCT, probably due to overlying thrombus, whilst CNs without disruption of the intimal fibrous layer (CNWD) have a smooth regular surface[2-8]. Based on previous OCT reports, CNs may have superficial thrombus apposition, with this feature being more common in the presence of ACS[8].

In the CLIMA study, a large prospective registry on plaque vulnerability assessed by means of OCT, patients with CNs tended to develop hard cardiac events more frequently, including acute myocardial infarction (MI) and/or cardiac death, although the difference was not significant[9].

The goal of the present *post hoc* analysis of the CLIMA registry was to study the relationship between calcified nodules with or without disruption of the intimal fibrous layer and the long-term occurrence of hard events (target lesion MI and/or cardiac death).

Methods

AIM AND STUDY DESIGN

The CLIMA study was a prospective observational, multicentre registry recruiting all consecutive patients undergoing assessment of the proximal left anterior descending artery segment by OCT in the context of clinically indicated coronary angiography. The CLIMA study aimed to explore criteria of plaque vulnerability that included minimum lumen area (MLA), fibrous cap thickness (FCT), lipid arc circumferential extension, presence of cluster of macrophages, cholesterol crystals, calcified nodules, intimal vasculature and intraplaque layered tissue.

Outcomes of the CLIMA study were defined according to the Academic Research Consortium guidelines and adjudicated blindly by a clinical events committee; any adverse event or hospitalisation during the follow-up was adjudicated accessing the relative source documents[10]. The project was approved by the local ethics board and registered in the ClinicalTrials.gov registry (ClinicalTrials.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 the 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 C7XR™ system or the OPTIS™ system (both St. Jude Medical, St. Paul, MN, USA) with a non-occlusive technique[4,5]. The acquired OCT coronary images were analysed off-line using a proprietary OCT console (St. Jude Medical) at an independent imaging core laboratory (Euroimage, Rome, Italy) by blinded expert readers. Only OCT pullbacks allowing accurate measurement of the 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. A mandatory inclusion criterion was the adequate OCT assessment of at least 30 mm of naïve proximal segment of left anterior descending artery free from significant stenosis on angiography.

Definitions and cut-offs for OCT parameters were derived from available consensus documents and from the main intravascular ultrasound (IVUS) and OCT studies[4,5,11].

Calcium was defined as a signal-poor or heterogeneous region with a sharply delineated outer border. On the basis of criteria established in the OCT consensus document[5], CNs were adjudicated in the presence of single or multiple regions of calcium that protruded into the lumen, frequently forming sharp, jutting angles.

Two subgroups of CNs (CND and CNWD) were identified based on the presence or absence of superficial irregularities indicative of disruption of the intimal fibrous layer with possible overlying tissue protrusion indicative of local thrombus[4,5,8] **(Figure 1)**.

Along the selected plaques we analysed plaque morphology applying the definitions utilised in the CLIMA study[9]. These included: 1) MLA <3.5 mm^2, 2) minimum FCT <75 μm, defined as a signal-rich homogeneous band overlying a lipid core and
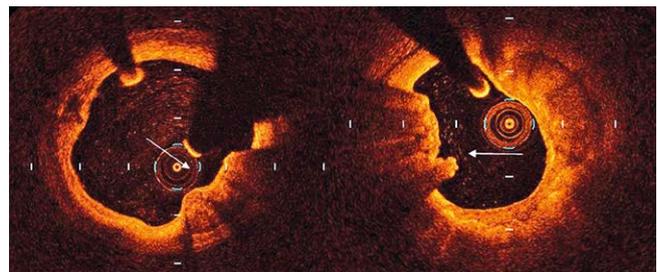

Figure 1. *An example of calcified nodule without fibrous layer disruption (arrow in the left panel) and with fibrous layer disruption plus thrombus (arrow in right panel).*

measured at the thinnest portion; 3) lipid plaque (LP) with lipid arc extension >180°, defined as a signal-poor region diffusely bordered by overlying signal-rich bands corresponding to an FC, and 4) presence of macrophage clusters defined on visual estimation as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise[12].

In the presence of CNs the following additional analyses were obtained: 1) lumen area (LA) at the CN site; 2) maximum arc of target lesion calcium measured in degrees with a protractor centred on the lumen at the CN site; 3) measurements of base and height, assuming for CN a trapezoid geometric shape.

STATISTICAL ANALYSIS

Numbers and percentages were used to report discrete variables, while mean (±standard deviation) was used to describe continuous variables in case of skewed or normal distribution, respectively. The Student's t-test, Mann-Whitney U test and χ^2 test were applied for bivariate analyses when appropriate. Clinical endpoints (cardiac death and target lesion anterior MI) were evaluated on a per-patient hierarchical basis, compared with the log-rank test, and summarised as Kaplan-Meier estimates. All variables reported in **Table 1** and **Table 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, Version 22.0 (IBM Corp., Armonk, NY, USA), adopting a two-tailed p-value <0.05 for statistical significance.

Results

OCT showed CNs in 180 patients out of 1,003 (17.9%). Thirty patients (3.0%) had at least one CND, 150 (14.9 %) had CNWD, whilst the remaining 823 cases (82.0%) had no CNs.

Table 1. Patient characteristics.

	Patients without calcified nodules (823)	CND patients (30)	CNWD patients (150)	*p*-value
Cardiac risk factors				
Age, years	63.87±12.45	69.48±10.45	69.33±9.47	<0.001
Female gender, n (%)	201 (24.4)	8 (26.6)	38 (25.3)	0.939
Left ventricle ejection fraction, %	52.99±9.26	50.52±12.83	52.46±10.8	0.494
Hypertension, n (%)	545 (66.22)	25 (83.3)	108 (72)	0.064
Hypercholesterolaemia, n (%)	481 (58.44)	24 (80)	101 (67.3)	<0.01
Smoking habit, n (%)	239 (29.04)	10 (33.3)	30 (20)	0.063
Family history of CAD, n (%)	199 (24.17)	8 (26.6)	39 (26)	0.854
Diabetes mellitus, n (%)	182 (22.11)	3 (10)	38 (25.3)	0.173
CKD, GFR <60 ml/min/1.73 m², n (%)	119 (14.45)	8 (26.6)	22 (14.6)	0.178
Prior MI, n (%)	169 (20.53)	8 (26.6)	30 (20)	0.753
Prior revascularisation PCI, n (%)	236 (28.67)	13 (43.3)	51 (34)	0.112
Carotid disease, n (%)	63 (13.6)	7 (38.9)	20 (23.8)	0.002
Diagnosis				
Acute coronary syndrome, n (%)	446 (54.19)	13 (43.3)	77 (51.3)	0.430
STEMI, n (%)	172 (20.9)	5 (16.6)	22 (14.6)	0.193
NSTEMI, n (%)	161 (19.56)	6 (20)	32 (21.3)	0.882
Unstable angina, n (%)	113 (13.73)	2 (6.7)	23 (15.4)	0.449
Stable angina, n (%)	377 (45.81)	17 (56.7)	73 (48.7)	0.430
CAD-vessel disease, n (%)				
No significant disease	53 (6.4)	1 (3.3)	12 (8)	0.180
1-vessel significant disease	403 (49)	12 (40)	66 (44)	0.361
2-vessel significant disease	241 (29.3)	7 (23.3)	49 (32.7)	0.527
3-vessel significant disease	126 (15.3)	10 (33.4)	23 (15.3)	0.029
Left main disease	46 (5.6)	2 (6.6)	13 (8.6)	0.346
Therapy at discharge				
ASA, n (%)	812 (98.7)	28 (93.3)	147 (98.0)	0.066
P2Y$_{12}$, n (%)	746 (90.6)	24 (80.0)	132 (88.0)	0.114
Statins, n (%)	704 (85.5)	28 (93.3)	129 (86.0)	0.484

Values are expressed as number (%) or as mean±standard deviation. Carotid disease: presence of ≥50% stenosis and/or previous revascularisation. Hypercholesterolaemia: LDL-cholesterol ≥130 mg/dL. Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. CAD: coronary artery disease; CKD: chronic kidney disease; MI: myocardial infarction; NSTEMI: non-ST-elevation MI; PCI: percutaneous coronary intervention; STEMI: ST-elevation MI

In total, 222 CNs were found in the 1,776 analysed non-culprit LAD plaques (12.5%). In 146 patients out of 1,003 (14.5%), OCT showed only 1 CN along the analysed LAD segment; in 29 patients (0.3%) OCT identified 2 CNs and in 4 patients (2.7%) 3 CNs. In one case OCT analyses demonstrated 4 CNs. **Table 1** shows the demographic and clinical characteristics of the three groups. Patients without CNs were younger, whilst patients with CND were more frequently hypercholesterolaemic.

Regarding the OCT plaque vulnerability criteria tested in the CLIMA study, CND lesions showed a thinner FCT as compared to the CNWD group and the group without CN (87.89±27.89 μm vs 102±35.90 μm vs 108.48±49.5 μm, respectively, p=0.012). Furthermore, plaques with CND showed a significantly smaller lumen area at the CN site, compared to CNWD (5.87±0.38 mm^2 vs 7.85±0.30 mm^2, p<0.01). This may in part be due to the presence of thrombus that, together with the calcified component, accounts for luminal reduction. No difference in terms of geometric measurements (base and height) was observed between CND and CNWD **(Table 2)**.

The composite incidence of cardiac death and/or target lesion MI occurred in 20% of patients in the CND group versus 2.7% in the CNWD group and 3.3% in the group without CN (p<0.001). This figure was mainly due to the 13.3% incidence of cardiac death in the CND group versus 2.0% in the CNWD group and versus 2.2% in the group without CN (p<0.001) **(Table 3)**.

Table 4 shows the OCT characteristics of CN according to the occurrence at one-year follow-up (FU) of the CLIMA hard composite endpoint (target lesion anterior MI and/or cardiac death).

Table 2. OCT findings (patient basis).

	Patients without calcified nodules (823)	CND patients (30)	CNWD patients (150)	*p*-value	*p*-value no CN vs CND	*p*-value no CN vs CNWD	*p*-value CND vs CNWD
OCT findings at the CN site							
Lumen area at calcific nodule site, mm^2	–	5.87±0.38	7.85±0.30	–	–	–	<0.01
Calcific nodule base, mm	–	0.84±0.38	0.77±0.30	–	–	–	0.292
Calcific nodule height, mm	–	0.29±0.10	0.30±0.09	–	–	–	0.870
OCT findings along the plaque							
Total plaque length, mm	14.71±5.23	18.16±13.63	15.57±11.02	0.220	0.115	0.502	0.260
Minimum lumen area, mm^2	4.39±5.91	4.01±1.90	4.11±1.78	0.344	0.415	0.0118	0.772
Minimum lumen area <3.5 mm^2, n (%)	327 (39.73)	11 (36.66)	58 (38.6)	0.922	0.736	1	0.837
Fibrous cap thickness, μm	108.48±49.5	87.89±27.89	102±35.90	0.012	0.001	0.034	0.052
Fibrous cap thickness <75 μm, n (%)	149 (19.6)	9 (32.1)	25 (18.2)	0.234	0.105	0.906	0.098
Maximum lipid arc, °	184.63±169.71	172.96±68.97	171.22±64.92	0.111	0.414	0.079	0.898
Maximum lipid arc >180°, n (%)	339 (44.7)	12 (42.9)	59 (43.1)	0.929	0.850	0.939	0.984
Maximum calcific arc, °	98.48±71.90	154.86±92.36	117.75±79.36	<0.01	0.003	0.022	0.026
Cholesterol crystal, n (%)	165 (21.7)	10 (35.7)	36 (26.3)	0.130	0.081	0.014	0.310
Macrophages, n (%)	457 (60.2)	21 (75.0)	99 (72.3)	0.010	0.116	0.001	0.767
Intraplaque layered tissue, n (%)	142 (17.3)	7 (23.33)	26 (17.33)	0.689	0.389	0.520	0.438
Intraplaque intimal vasculature, n (%)	416 (50.5)	17 (56.7)	85 (56.7)	0.330	0.510	0.053	1
Values are expressed as number (%) or as mean±standard deviation.							

Table 3. One-year clinical outcome (37 events).

	Patients without calcified nodules (823)	CND patients (30)	CNWD patients (150)	*p*-value
Cardiac death+target vessel MI, n (%)	27 (3.28)	6 (20)	4 (2.7)	<0.001
Death, n (%)	25 (3)	5 (16.63)	4 (2.7)	<0.001
Non-cardiac death, n (%)	7 (0.9)	1 (3.33)	1 (0.7)	0.353
Cardiac death, n (%)	18 (2.18)	4 (13.3)	3 (2)	0.001
Myocardial infarction, n (%)	22 (2.67)	2 (6.66)	2 (1.3)	0.228
Other vessel MI, n (%)	12 (1.45)	0 (0)	1 (0.7)	0.602
Target vessel MI, n (%)	10 (1.21)	2 (6.66)	1 (0.7)	0.022
Target vessel revascularisation, n (%)	22 (2.67)	2 (6.66)	1 (0.7)	0.108
MI: myocardial infarction				

Table 4. Characteristics of calcified nodules according to the composite endpoint.

	Patients with events (37)	Patients without events (966)	p-value
Plaque length, mm	18.11±9.91	14.8±11.71	0.092
Calcified nodule base, mm	0.70±0.22	0.79±0.32	0.383
Calcified nodule height, mm	0.23±0.06	0.30±0.09	0.035
Maximum calcific arc, °	120.69±90.28	103.82±74.54	0.215
Lumen area at calcified nodule site, mm²	6.20±4.72	7.60±3.51	0.232
Calcified nodules with FC disruption, n (%)	6 (16.8)	24 (2.5)	<0.001
Calcified nodules without FC disruption, n (%)	4 (10.8)	146 (15.1)	0.471
Multiple calcified nodules, n (%)	3 (8.1)	30 (3.10)	0.094
Values are expressed as number (%) or as mean±standard deviation.			

The presence of fibrous layer disruption at the CN surface was higher in the patients who experienced the hard endpoint (16.8% vs 2.5%, p<0.001).

Also, after correction for the baseline clinical differences and the single or combined presence of the four CLIMA features of plaque vulnerability, the presence of CND was confirmed as an independent predictor of an event (HR 6.58, 95% CI: 2.7-15.8, p<0.001) **(Figure 2)**.
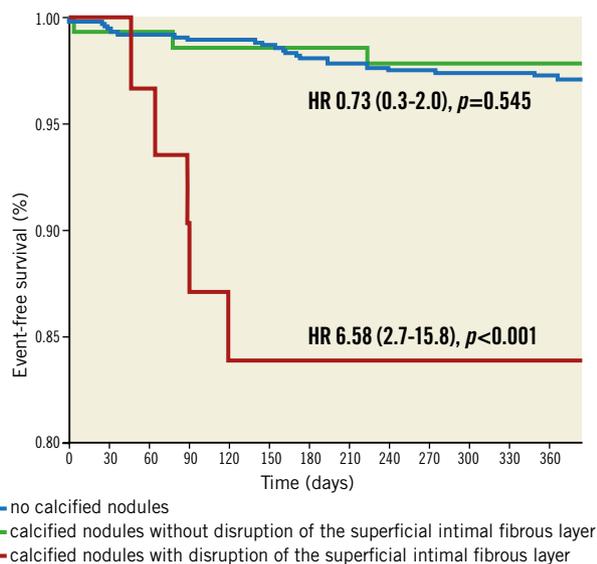

Figure 2. *MACE-free survival according to absence versus presence of calcified nodules with or without fibrous layer disruption.*

Discussion

The main finding of the present study, conceived as a *post hoc* analysis of the CLIMA trial, a large prospective registry on 1,003 patients, is that the presence of CND is related to a high incidence of cardiac death and/or target lesion anterior MI at one year, whilst the presence of CNWD does not identify a population at risk of hard endpoints.

Pathology studies of patients dying of sudden coronary thrombosis showed that ACS are caused by calcific nodules in about 5-6% of cases[1]. Such data have been confirmed in the last decade by OCT studies. OCT, thanks to an axial resolution in the range of 10-20 microns, accurately identifies calcific nodules and differentiates CN with loss of integrity of the intimal fibrous layer and possible superficial thrombus apposition (CND) from those with integrity of the intimal fibrous layer and absence of superficial thrombus apposition (CNWD)[3,4]. In other words, OCT identifies those CNs on which the thrombus has very likely stratified, due to the loss of the integrity of the intimal layer that covers the CN at the surface, distinguishing them from those with a smooth intimal surface on which thrombotic apposition is not seen.

Jia et al performed OCT in 126 patients with ACS. The prevalence of plaque rupture, OCT erosion, and OCT CN was 43.7%, 31.0%, and 7.9%, respectively[6]. In more detail, the authors found a 10% prevalence of CN culprit lesions in 50 patients with non-ST-segment elevation ACS and 0% in 54 patients with STEMI. In other OCT studies including only STEMI patients, the prevalence of CN in culprit lesions varied from 3.1% to 8.0%[7,13,14]. Lee et al compared culprit CN lesions in ACS and stable patients. The prevalence of thrombus was higher in the unstable setting (82.4% vs 20.0%; p<0.001)[8].

Unlike previous reports focusing on the prevalence of CN at a single time point, the CLIMA registry prospectively addressed the clinical impact of CN. Our data are consistent with a sub-analysis from the three-vessel PROSPECT imaging carried out with IVUS-virtual histology[15]. CNs were relatively common, being found in 18% of patients in the PROSPECT trial and in 17.9% in the CLIMA registry. In line with the PROSPECT trial, in the present study the presence of CN was not associated with a greater number of anterior MI and cardiac death at a one-year FU[15], being found in 27.0% of patients who experienced hard cardiac events versus 17.6% without, p=0.14, HR 1.73.

ROLE OF INTIMAL FIBROUS LAYER DISRUPTION

The hypotheses on the formation of CN include the possibility of non-plated, irregular growth of plaque calcifications or different remodelling of the calcifications themselves during their formation. This should not be an acute process, especially in cases of large calcifications visible on OCT. CNs are usually covered by a layer of intimal fibrous tissue with overlying endothelium, that is clearly distinguished in OCT images **(Supplementary Figure 1)**. The most likely thrombogenic bases of CNs are related more to the loss of the integrity of the fibrous layer that covers their intimal side than to their acute eruptive protrusions. This may lead to subsequent platelet adhesion and fibrin formation, and finally to thrombus generation. These features, initially described by pathologists[1], can be appreciated *in vivo* applying OCT that is able to characterise superficial plaque components[6,16].

Interestingly, we observed for the first time that CND seems to convey a worse clinical outcome than CNWD, with an HR for hard coronary events about eight times higher. OCT, therefore, is potentially able to identify a subgroup of vulnerable lesions with CN.

Based on this assumption, coronary plaques with CN that cause ACS are characterised at an early stage by a limited thrombus formation, which later on may progress to a thrombotic luminal obstruction, the ultimate step of ACS. Alternatively, the presence of CND may be simply a marker of more advanced disease. The fact that CND are observed more often in patients with greater age, triple vessel disease and more common features of plaque vulnerability may support this latter hypothesis. The adoption of a more aggressive medical treatment to stabilise atherosclerosis may be a reasonable solution in this scenario, to be preferred to the interventional treatment of vulnerable lesions.

UTILITY OF A PROSPECTIVE IN VIVO APPROACH

The prospective design of the study enabled exploring the role of CN in the pathophysiology of ACS, applying a different view angle. Unlike previous OCT studies that addressed the morphology of culprit plaques at a single time point in ACS patients, the CLIMA registry made it possible to relate plaque morphology in non-culprit segments to the clinical outcome. Also, intraluminal thrombus, found in the vast majority of ACS culprit lesions, is an obstacle to a precise OCT plaque characterisation and to the differentiation of the two entities of CN (CND and CNWD) which we have applied in the present study. These were the main limitations of single time point OCT studies performed in the unstable clinical setting.

Limitations

In the CLIMA trial and consistently in this *post hoc* analysis, we have applied a definition of calcified nodules that was suggested in the first OCT consensus document[4]. Other definitions have been adopted more recently, emphasising the presence of fibrous layer disruption as a distinctive feature that characterises calcified nodules[5,6]. Regardless of the adopted CN definition, the present prospective data bring evidence that focal regions of calcium protruding into the lumen and accompanied by fibrous layer disruption are found in patients with a worse clinical outcome. By study design, a short one-year observation time was adopted. We observed a high incidence of cardiac death and target lesion anterior MI, with the former being surprisingly high. Longer follow-up data will provide adjunctive understanding of the clinical impact of the loss of integrity of the fibrous layer that covers the intimal side of the CN.

Our study did not require a three-vessel analysis; in fact, only left anterior descending arteries were studied. This was in an effort to promote OCT as a practical and low-risk intracoronary imaging modality to be applied in clinical practice.

Consistent with other studies on plaque vulnerability, it was not possible to relate cardiac death to a culprit lesion. However, even in cases where target lesions were not responsible for the fatal event, the presence of CND served as a marker of more advanced disease.

According to pathological and OCT studies, CN is found more often in the mid right coronary artery where coronary torsion stress is maximum. However, this aspect does not seem to affect the study conclusions that establish a relation between the presence of CND and worse clinical outcome.

Conclusions

In a *post hoc* analysis of the CLIMA study, the presence of CNs with loss of integrity of their fibrous intimal layer was found to be associated with a high one-year incidence of cardiac death and/or target lesion MI.

Impact on daily practice

Calcified nodules with disruption of fibrous layer can be easily identified using OCT, a high-resolution invasive imaging modality. The presence of calcified nodules with disruption is related to a higher risk of clinical endpoints and is therefore a relatively uncommon marker of plaque-patient vulnerability.

Funding

Conflict of interest statement

F. Prati has served as a consultant for Abbott/St. Jude and Amgen. The other authors have no conflicts of interest to declare.

References

1. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol.* 2006;47:C13-8.

2. Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation.* 2005;111:1551-5.

3. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW; Expert's OCT Review Document. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J.* 2010;31:401-15.

4. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, Costa MA, de Silva R, Dijkstra J, Di Mario C, Dudek D, Falk E, Feldman MD, Fitzgerald P, Garcia-Garcia HM, Gonzalo N, Granada JF, Guagliumi G, Holm NR, Honda Y, Ikeno F, Kawasaki M, Kochman J, Koltowski L, Kubo T, Kume T, Kyono H, Lam CC, Lamouche G, Lee DP, Leon MB, Maehara A, Manfrini O, Mintz GS, Mizuno K, Morel MA, Nadkarni S, Okura H, Otake H, Pietrasik A, Prati F, Räber L, Radu MD, Rieber J, Riga M, Rollins A, Rosenberg M, Sirbu V, Serruys PW, Shimada K, Shinke T, Shite J, Siegel E, Sonoda S, Suter M, Takarada S, Tanaka A, Terashima M, Thim T, Uemura S, Ughi GJ, van Beusekom HM, van der Steen AF, van Es GA, van Soest G, Virmani R, Waxman S, Weissman NJ, Weisz G; International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT). Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol.* 2012;59:1058-72.

5. Johnson TW, Räber L, di Mario C, Bourantas CV, Jia H, Mattesini A, Gonzalo N, de la Torre Hernandez JM, Prati F, Koskinas KC, Joner M, Radu MD, Erlinge D, Regar E, Kunadian V, Maehara A, Byrne RA, Capodanno D, Akasaka T, Wijns W, Mintz GS, Guagliumi G. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary

angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J.* 2019;40:2566-84.

6. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park SJ, Jang YS, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi SY, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R, Jang IK. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol.* 2013;62:1748-58.

7. Higuma T, Soeda T, Abe N, Yamada M, Yokoyama H, Shibutani S, Vergallo R, Minami Y, Ong DS, Lee H, Okumura K, Jang IK. A Combined Optical Coherence Tomography and Intravascular Ultrasound Study on Plaque Rupture, Plaque Erosion, and Calcified Nodule in Patients With ST-Segment Elevation Myocardial Infarction: Incidence, Morphologic Characteristics, and Outcomes After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv.* 2015;8:1166-76.

8. Lee T, Mintz GS, Matsumura M, Zhang W, Cao Y, Usui E, Kanaji Y, Murai T, Yonetsu T, Kakuta T, Maehara A. Prevalence, Predictors, and Clinical Presentation of a Calcified Nodule as Assessed by Optical Coherence Tomography. *JACC Cardiovasc Imaging.* 2017;10:883-91.

9. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y, Marco V, Boi A, Fineschi M, Fabbiocchi F, Taglieri N, Niccoli G, Trani C, Versaci F, Calligaris G, Ruscica G, Di Giorgio A, Vergallo R, Albertucci M, Biondi-Zoccai G, Tamburino C, Crea F, Alfonso F, Arbustini E. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J.* 2020;41: 383-91.

10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

11. Lee JB, Mintz GS, Lisauskas JB, Biro SG, Pu J, Sum ST, Madden SP, Burke AP, Goldstein J, Stone GW, Virmani R, Muller JE, Maehara A.

Histo-pathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. *Am J Cardiol.* 2011;108:1547-51.

12. Prati F, Gatto L, Romagnoli E, Limbruno U, Fineschi M, Marco V, Albertucci M, Tamburino C, Crea F, Alfonso F, Arbustini E. In vivo vulnerability grading system of plaques causing acute coronary syndromes: An intravascular imaging study. *Int J Cardiol.* 2018;269:350-5.

13. Kajander OA, Pinilla-Echeverri N, Jolly SS, Bhindi R, Huhtala H, Niemelä K, Fung A, Vijayaraghavan R, Alexopoulos D, Sheth T. Culprit plaque morphology in STEMI - an optical coherence tomography study: insights from the TOTAL-OCT substudy. *EuroIntervention.* 2016;12:716-23.

14. Wang L, Parodi G, Maehara A, Valenti R, Migliorini A, Vergara R, Carrabba N, Mintz GS, Antoniucci D. Variable underlying morphology of culprit plaques associated with ST-elevation myocardial infarction: an optical coherence tomography analysis from the SMART trial. *Eur Heart J Cardiovasc Imaging.* 2015;16:1381-9.

15. Xu Y, Mintz GS, Tam A, McPherson JA, Iñiguez A, Fajadet J, Fahy M, Weisz G, De Bruyne B, Serruys PW, Stone GW, Maehara A. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation.* 2012;126:537-45.

16. Kobayashi N, Takano M, Tsurumi M, Shibata Y, Okazaki H, Shirakabe A, Goda H, Uchiyama S, Tani K, Takano M, Shimizu W. Features and Outcomes of Patients with Calcified Nodules at Culprit Lesions of Acute Coronary Syndrome: An Optical Coherence Tomography Study. *Cardiology.* 2018;269:356-61.

Supplementary data

Supplementary Figure 1. Example of a calcified nodule with and without disruption of the superficial intimal fibrous layer on OCT.
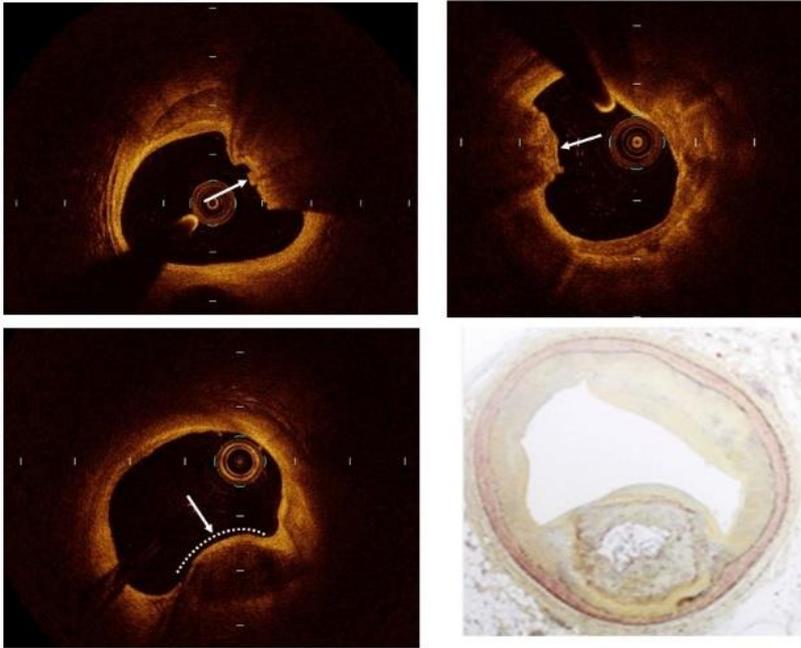
The supplementary data are published online at:
https://eurointervention.pcronline.com/
doi/10.4244/EIJ-D-19-01120

Supplementary data

Supplementary Figure 1.

Example of calcified nodule with and without disruption of the superficial intimal fibrous layer on OCT.

The two upper panels show how difficult it is to determine whether a fibrous intimal layer is present between a superficial calcified nodule and thrombus (arrows). The presence of a thin intimal layer with superimposed thrombosis makes the diagnosis of disruption a very likely hypothesis. Vice versa, the two lower panels show how, in the absence of superficial thrombosis, the intimal fibrous layer that usually covers calcified nodules is sharply visible with OCT. The pathologic panel is just an example that shows a superficial calcified nodule (bordered in brown) covered by a non-disrupted layer of intimal fibrous tissue. Thus, OCT consistently sees the intimal fibrous layer, even when it is very thin (arrow in the lower left panel), on superficial calcified nodules, while it does not accurately distinguish the intimal fibrous border on calcific nodules covered by thrombus. Fibrous layer disruption in the presence of thrombus is therefore more deductive than demonstrated with images.