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Culprit plaque characteristics in younger versus older patients with acute coronary syndromes: An optical coherence tomography study from the FORMIDABLE registry

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Abstract

Objectives: Culprit plaque characteristics in young patients who experience an Acute Coronary Syndrome (ACS) evaluated by OCT (Optical Coherence Tomography) have to be defined. The OCT-FORMIDABLE is a multicentre retrospective registry enrolling consecutive patients with ACS who performed OCT in 9 European centres.

Methods: Patients were divided in two groups according to age at presentation: juvenile-ACS (age ≤ 50 years) and not juvenile-ACS (age > 50 years). Primary end-point was the prevalence of plaque rupture (PR). Secondary end point was the prevalence of thin cap fibro atheroma (TCFA), fibrocalcific and fibrotic plaque.

Results: 285 patients were included, 71 (24.9%) in juvenile-ACS group and 215 (75.1%) in not juvenile-ACS group. Younger patients showed a trend for a higher prevalence of TCFA (70 vs. 58%, $P = 0.06$) and thrombus presence (62 vs. 51%, $P = 0.1$), while no statistical difference concerning PR (70 vs. 64%, $P = 0.29$). Of interest patients younger that 35 years showed a higher prevalence of PR compared to patients aged between 35 and 45 or 45 and 50 years (100 vs. 72 vs. 55%, $P = 0.03$). Culprit plaque in juvenile-ACS group showed more frequently a reduced mean cap thickness (119 ± 66 vs. 155 ± 95 nm, $P = 0.05$) and less frequently fibrotic (32 vs. 57%, $P < 0.001$) or fibrocalcific (17 vs. 36%, $P = 0.003$) characteristics.

Conclusion: young patients with ACS show a trend for a higher prevalence of culprit PR, a thinner cap and less fibrotic or fibrocalcific components.

KEYWORDS

acute coronary syndrome, drug eluting stent, juvenile, optical coherence tomography, young

1 | INTRODUCTION

Acute coronary syndrome (ACS) is the most common reason for cardiac hospitalization in the western world and its prevalence is constantly increasing in European countries and United States of America. Approximately, 0.4–19% of these patients are young, and they have greater risk of long-term mortality than an age-matched background population [1,2].

Beyond the classical cardiovascular risk factors such as cigarette smoking, diabetes, hypertension, overweight and hyperlipidemia [3], pathophysiology of atherosclerosis in patients who experience ACS in young age deeply differ from the older patients by the presence of genetic abnormalities, concerning lipids metabolism, coagulations, and congenital coronary artery anomalies [4–6].

Optical Coherence Tomography (OCT) has emerged as the most accurate instrument for intracoronary evaluation [7]. Due to a resolution of ~10–20 μm [8] it has been largely exploited in the evaluation and characterization of plaque features, both in stable and acute coronary artery disease (CAD) [9,10]. OCT permitted to analyse stent's struts apposition, coverage, neointimal thickness [11] and stent thrombosis mechanisms [12]; however, its clinical impact is not completely understood [13].

The OCT-FORMIDABLE (OCT-Features Of moRphology, coMposItion anD instABility of culprit and pLaquE in ACS patients) study is a multicentre registry that enrolled all the patients with ACS undergone OCT on culprit plaque.

Aim of this study was to evaluate the differences of culprit plaque characteristics in patients with a juvenile ACS compared with older ACS patients.

2 | METHODS

The OCT-FORMIDABLE is a retrospective registry including all consecutive patients that perform OCT on culprit and not culprit plaque in any subset in patients with ACS between January 2014 and October 2016 in 9 centers (**see Web Appendix**).

Patients with poor image quality, incomplete pull-back or missing data were excluded. Of note, the choice to perform OCT was left to the operator's decision. Further, OCT was not performed in case of hemodynamic instability, left main disease, or para-ostial lesions of the main vessels, severe narrowing or tortuosity, which not permitted to the OCT probe to cross the lesion. Included patients were stratified in two groups according to age at presentation: juvenile-ACS (age ≤ 50 years) and not juvenile-ACS (age > 50 years).

All patients gave their informed consent; the study was approved by the local Ethics Committee and registered on ClincalTrial.gov (NCT02486861). Clinical and OCT data were collected in the register according to the dataset. For the index admission, diagnosis was made according to ESC guidelines (STEMI, ST Segment Elevation Myocardial Infarction; NSTEMI, Non St Segment; and UA, unstable angina) [14].

Diabetes mellitus was defined according to the ADA criteria [15] [fasting blood glucose >126 mg/dl or treated diabetes mellitus (intake of a diabetic diet or oral hypoglycaemic agents), hypercholesterolemia as the total cholesterol >200 mg/dl or treated hypercholesterolemia and hypertension as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or treated hypertension.

2.1 | Invasive treatment and clinical data collection

All STEMI patients were treated with aspirin (300 mg) and clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (180 mg) on admission to the Emergency Department. Percutaneous coronary interventions were performed through a radial or femoral access according to operator preference, using a 6 French catheter. A bolus of 5,000 IU of heparin was administered. Glycoprotein IIb/IIIa inhibitors were administered after diagnostic angiogram at the start of percutaneous coronary interventions as well as manual thrombus aspiration, according to operator's decision.

All patients with NSTE-ACS received aspirin (300 mg, followed by aspirin 100 mg daily) and were treated with a loading dose of clopidogrel (600 mg) or or prasugrel (60 mg) or ticagrelor (180 mg), and fondaparinux or enoxaparin on admission to the Emergency Department according to physician's decision. Use of IIb/IIIa inhibitors was left to operator's decision.

2.2 | OCT procedure

A 0.014-inch guidewire was placed distally in the target vessel and an intracoronary injection of 200 μg of nitroglycerin was performed. Frequency domain OCT (FD-OCT) images were acquired by a commercially available system, which was advanced to the culprit lesion. The FD-OCT run was performed using the integrated automated pullback device at 75 mm/s. In case of STE-ACS patients, OCT was performed after vessel reopening with thrombus aspiration or balloon predilatation if necessary. During image acquisition, coronary blood flow was replaced by continuous flushing of contrast media directly from the guiding catheter at a rate of 3–4 ml/s with a power injector in order to create a virtually blood-free environment.

2.3 | OCT image analysis

OCT image analysis was performed offline by the operator that performed the pull-back (one for each centre) and by an independent investigator who was blinded to the clinical presentation; discordance was resolved by consensus. Culprit lesion was identified by means of angiography, electrocardiographic ST-segment alterations, and/or regional wall motion abnormalities on echocardiographic assessment.

Plaque rupture (PR) was defined as the presence of fibrous cap discontinuity leading to a communication between the inner (necrotic) core of the plaque and the lumen. PR included also fibrous cap disruption detected over a calcified plaque characterized by protruding calcification, superficial calcium, and the presence of substantive calcium proximal or distal to the lesion.

Thin cap fibro atheroma (TCFA) was defined as cap thickness < 65 nm. TCFA at rupture site was recorded.
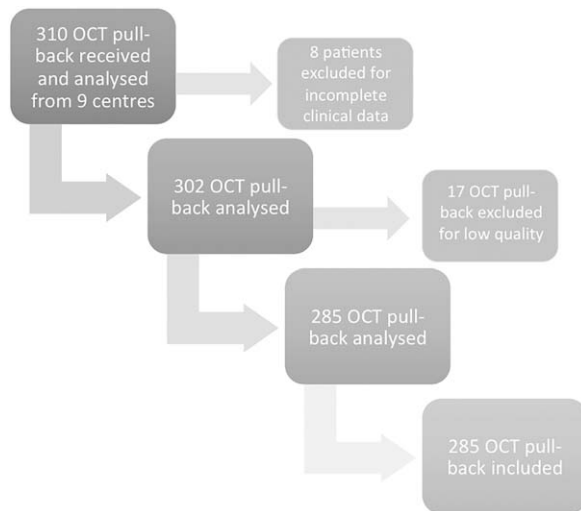
FIGURE 1 OCT pull-back analysis flow chart

Coronary spasm was considered as the absence at OCT analysis of significant plaque burden (considered as the ratio of plaque area/vessel area), PR, TCFA, or thrombus in presence of reversible coronary narrowing.

Fibrocalcific, fibrotic plaque, lipid component or macrophage infiltration were defined according to International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT) Consensus standards [16].

2.4 ⎪ Clinical follow-up and end-points definitions

Clinical follow-up was assessed by clinical visit each 6 months or by phone call.

Primary end-point was the PR rate. Secondary end point was the TCFA rate and the fibrocalcific or fibrotic plaque rate.

2.5 Statistical analysis

Categorical variables are reported as count and percentages, whereas continuous variables as mean and standard deviations or interquartile range. Included patients were further divided into two groups according to age at presentation: juvenile-ACS (age $\leq$ 50 years) and not juvenile-ACS (age $>$ 50 years). We decide for this cut off because usual definition of juvenile AMI is $<$45 years old [16]. However we usually consider as family history of myocardial infarction an event before age 55 years. Therefore, we decided to put the cut off in the middle. Moreover, sensitivity analysis according clinical presentation (STEMI, NSTEMI, gender, and stratified for younger age) were performed. Gaussian or not Gaussian distribution was evaluated by Kolmogorov-Smirnoff test. The t-test has been used to assess differences between parametric continuous variables, Man-Whitney U test for non parametric variables, the chi-square test for categorical variables and Fisher exact test for 2 $\times$ 2 tables. Hazard Risk (HR) by Cox regression to assess clinical factor relevance on outcome. Furthermore, significant variables were compared with multiple Cox regression analysis to assess impact of OCT features on outcomes. Visual distribution of CPR according age was performed

dividing the CPR prevalence according the division of the age 15 percentile. Sensitivity analysis was performed for the presence of culprit PR on therapy efficacy. Intraobserver and interobserver differences were investigated with kappa measure of agreement. A two-sided *P* value $<$0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, NY).

3 ⎪ RESULTS

3.1 ⎪ Baseline clinical and OCT features according to age

Two hundred eighty-five patients were included (**see** Figure 1), 71 (24.9%) in juvenile-ACS group and 214 (75.1%) in not juvenile-ACS group. Patients in not juvenile-ACS group were less frequently male (77 vs. 89%, $P = 0.028$), hypertensive (37 vs. 65%, $p < 0.001$), diabetic (44 vs. 55%, $P = 0.02$). Patients in juvenile-ACS group presented more frequently smoking habit and family history. Older patients were more frequently medically treated (**see** Table 1).

Younger patients presented more often as STEMI (71.8 vs. 42.5%, $P < 0.001$) with culprit lesion on right coronary artery (51 vs. 43%, $P = 0.02$), compared with older patients, whom usually presented with diseased LAD (69 vs. 44%, $P < 0.0001$), thrombus aspiration was used similarly in the two subgroups (45 vs. 43.9%, $P = 0,89$ before OCT pull-back and 35 vs. 43%, $P = 0.3$ after the OCT pull-back). Most of the patients underwent to PCI with stenting (86 vs. 87%, $P = 0.6$) with drug eluting stent (75.4 vs. 77.8%, $P = 0.72$), while young patients underwent more of the to implantation of bioresorbable vascular scaffold (20 vs. 5.1% $P < 0.01$). In-hospital treatment was not different between the two groups, except for a more frequent administration of ticagrelor/prasugrel at discharge in younger patients (62 vs. 34%, $P < 0,001$). After a follow up of 700 days (450–890), there were no differences between the two groups in term of MACE (**see** Table 2), although younger patients showed a not significant trend for a lower mortality (0 vs. 3.7%, $P = 0.09$).

Juvenile-ACS patients showed a trend for a higher prevalence of TCFA (70 vs. 58%, $P = 0.06$) and thrombus presence (62 vs. 51%, $P = 0.1$), while no statistical difference concerning PR (70 vs. 64%, $P = 0.29$). Lipid core were more pronounced in younger patients (92 vs. 81%, $P = 0.035$).

Culprit plaque in young patients was characterized by a reduced mean cap thickness (119 $\pm$ 66 vs. 155 $\pm$ 95 nm, $P = 0.05$) and showed less frequently fibrotic (32 vs. 57%, $P < 0.001$) or fibrocalcific (17 vs. 36%, $P = 0.003$) components (**see** Figure 2 and Table 3).

3.2 ⎪ Sensitivity analysis of OCT features for clinical presentation (STEMI and NSTEMI), gender and younger age stratifications ($\leq$35, 35–45, and 45–50 years old)

No significant differences in culprit PR and TCFA prevalence were found according to different ACS clinical presentations or gender (**see** Figures 3 and 4). It is worth noting that patients younger than 35 years showed a significantly higher CP rupture prevalence compared to

TABLE 1 Baseline feature of all ACS patients divided into two group (≤50 years old and older than 50 years old)

	All ACS patients		
	≤50 years (n = 71), mean ± sd, n (%)	> 50 years (n = 214), mean ± sd, n (%)	P value
Age (years)	44 ± 6	66 ± 9	<0,001
Female gender	8 (11%)	50 (23%)	0,028
Hypertension	26 (37%)	138 (65%)	<0,001
Hyperlipidemia	31 (44%)	117 (55%)	0,1
Diabetes mellitus	5 (7%)	40 (19%)	0,02
Smoke	55 (78%)	120 (56%)	0,001
Family history	39 (55%)	81 (38%)	0,001
LVEF (%)	56 ± 7	53 ± 9	0,06
Previously treated with statin	21 (30%)	129 (60%)	<0,001
Previously treated with ACE-I or ARB	13 (18%)	103 (48%)	<0,001
Previously treated with b-blockers	18 (25%)	104 (49%)	0,001
Previously treated with aspirin	19 (27%)	124 (58%)	<0,001
Culprit lesion			
Left Main	2 (3%)	11 (5%)	0,41
Left artery descendent	31 (44%)	147 (69%)	<0,001
Left circumflex	18 (25%)	63 (29%)	0,5
Right coronary artery	36 (51%)	91 (43%)	0,018
Therapy at discharge			
Statin	70 (99%)	211 (99%)	0.997
ACE-inhibitor	63 (89%)	169 (79%)	0.057
Aspirin	70 (99%)	214 (100%)	0.187
DAPT with new P2Y12i	44 (62%)	72 (34%)	<0.001
b-blocker	67 (94%)	187 (87%)	0.102

Abbreviations: ACE-I, angiotensin converting enzyme; ARB, angiotensin II receptor antagonist; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction.

patients aged between 35 and 45 years or 45 and 50 years (100 vs. 72 vs. 55%, P = 0.03) and a trend of higher TCFA prevalence (100 vs. 71 vs. 60%, P = 0.11).

Fibro-calcific components were more frequent in older patients independently from the clinical presentation (STEMI 1 vs. 26% P = 0.08, NSTEMI 25 vs. 43% P = 0.12) or gender (Female 1 vs. 44%

TABLE 2 Outcomes of all ACS patients at follow-up

	All ACS		
	≤50 years (n = 71), mean ± sd, n (%)	> 50 years (n = 214), mean ± sd, n (%)	P value
MACE (CV death, AMI, TVR)	8 (11.3%)	27 (12.6%)	0.76
Cardiovascular death	0 (0%)	8 (3.7%)	0.09
Target lesion revascularization	1 (1.4%)	9 (4.2%)	0.26
Target vessel stenosis	1 (1.4%)	2 (0.9%)	0.73
ACS	6 (8.5%)	15 (7.0%)	0.68
ACS on previous culprit lesion	1 (1.4%)	5 (2.3%)	0.45

Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; TVR, target vessel revascularization.
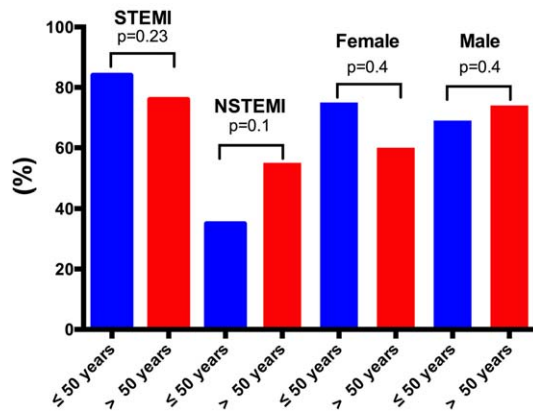
PR prevalence according clinical presentation

FIGURE 2 OCT features in ACS patients. TCFA: thin cap fibro atheroma, PR: Plaque rupture, ACS: Acute Coronary Syndrome, FCP: Fibro-calcific plaque, FP: fibrous plaque.

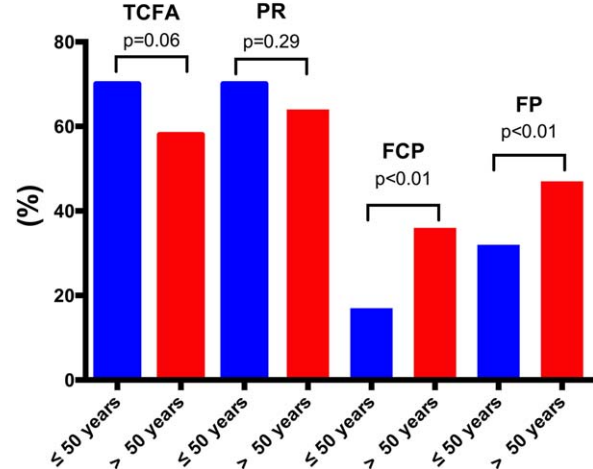## Oct feature in ACS patients

FIGURE 3 PR prevalence according the clinical presentation. STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, PR: Plaque rupture.

$P = 0.02$, 19 vs. 33% $P = 0.03$). The culprit PR prevalence presented a linear distribution through the different ages ($r^2 = 0.47$, $P < 0.01$).

We also performed an univariate and multivariate analysis for culprit PR predictors from which results that age and STEMI presentation were independent predictors of culprit PR (Table 4).

4 | DISCUSSION

The main findings of our study are (1) PR appears to be an age-related pathophysiologic mechanism of ACS, decreasing in prevalence as age

increase, and probably responsible for the more common presentation as STEMI in younger patients; (2) Younger ACS patients present plaques showing less fibrotic and calcific components, with a thinner cap making them more vulnerable; (3) Younger patients are less frequently affected by CVD risk factors, with a higher prevalence of smokers men with family history of CAD, thus reflecting a cluster of patients with an increase tendency to develop unstable plaque.

To our knowledge, this is the first OCT study evaluating culprit plaque morphology in patient aged less or more than fifty years. We

TABLE 3 OCT characteristics of all ACS patients

	All ACS patients		
	≤50 years (n = 71), mean ± sd, n (%)	>50 years (n = 214), mean ± sd, n (%)	P value
Thin cap but not PR	3 (4%)	19 (9%)	0.2
PR	50 (70%)	136 (64%)	0.29
Thin cap at rupture site	44 (82%)	100 (69%)	0.09
Thin cap in a different site from rupture site	14 (25%)	40 (27%)	0.73
Thin cap fibroatheroma coronary sites other than the culprit plaque	50 (70%)	124 (58%)	0.06
Length of PR (mm)	5.6 ± 5.1	8 ± 7.7	0.003
MLA	2.8 ± 1.9	2.4 ± 1.6	0.04
Cap Thickness (nm)	119 ± 66	155 ± 95	0.005
Fibro-calcification	12 (17%)	77 (36%)	0.003
Fibrous plaque	23 (32%)	122 (57%)	<0.001
Lipidic component	65 (92%)	173 (81%)	0.035
Necrotic core macrophage infiltration	18 (25%)	78 (37%)	0.08
Thrombus	44 (62%)	109 (51%)	0.1

Abbreviation: MLA, minimal lumen area.

TCFA prevalence according clinical presentation
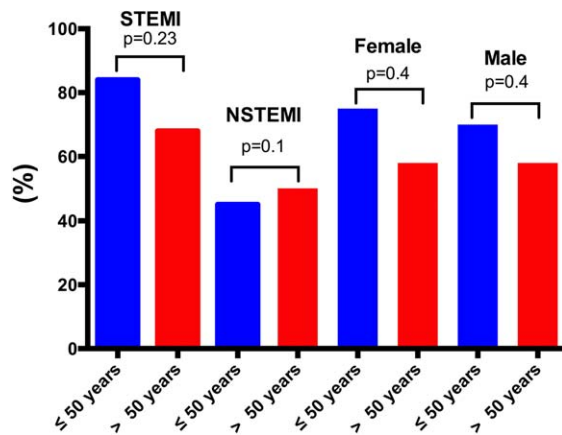
FIGURE 4 TCFA prevalence according the clinical presentation. STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, TCFA: thin cap fibro atheroma.

chose this conventional cut-off, making reference to the published literature, ranging from 45 to 55 years for juvenile ACS and 55–60 years for defining familiarity [1,16,17].

PR or erosion with superimposed thrombus is the pathological hallmark of ACS [18] and it's well known that the characteristics of a vulnerable plaque prone to rupture include a thin fibrous cap with macrophage infiltration and a large lipid core [10] (see Figure 5). The rupture of the culprit lesion is more frequent in STEMI patients regardless of age [18], but despite this traditional paradigm, the pathophysiologic differences in plaque characteristics and plaque course in ACS spectrum and between age groups are not completely understood. Age may play a role for the following considerations. Our data demonstrated a sort of "age-related gradient" of CP rupture rates significantly higher in patients younger than 35 years compared to older patients, as confirmed at multivariate analysis. A

significantly thinner cap in younger ACS patients may influence the hazard and depth of the rupture, despite shorter lesions and a less extensive disease. With aging, fibrosis and calcification seems to enforce the plaque and thicken the cap. In particular as shown in Figures 2 and 3 young female have a trend forward a higher prevalence of PR and TCFA which are associated with instable plaque rather than with classic obstructive plaque. On the other side, they have a lower prevalence of fibro-calcific plaque. Unfortunately, a specific subanalysis of young versus old female with STEMI (excluding NSTEMI and UA) is not feasible due to the limited samples (just 18 patients.). Nevertheless our results strengthened the idea that the pathophysiology of young females with STEMI or non-STEMI may be different than in men, with greater importance of plaque characteristic rather than conventional cardiovascular risk factors. Furthermore, older patient more frequently take cardiovascular therapies, which probably help to stabilize the plaque and could partially explain these differences (especially statin use). In this setting the pathological trigger is probably related to an evolution of the deeper part of the plaque, in terms of lipid core enlargement and inflammatory cells infiltration. This statement is consistent with the traditional construct of Virmani et al., whereby the atherosclerotic lesion progresses from a low-risk to a high-risk phenotype before PR [19]. The aggressiveness and the speed of a plaque evolution is unpredictable, but in young people it may occur in thinner and lipid rich soft plaque compared with older patients.

Our data are not conclusive for hypothesizing two different atherosclerotic pathways, but looking at the baseline characteristic we see that these pathological features may be based on genetics and behavioural aspects. In our series patients suffering of ACS at younger age are more frequently smokers and presented a family history of CAD. Some years ago several studies identified genetic predisposition in an estimated frequency between 5 and 14% in white Caucasian populations and considered hyperomocisteinemia as a marker of genetic risk [20,21]. The association with a familiar cluster may be particularly

TABLE 4 Univariate and multivariate analysis for CPR predictors

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	P value	HR	CI 95%	P value
Older Age	0.91	0.89–0.95	**0.02**	0.92	0.81–0.95	**0.05**
Female gender	0.84	0.46–1.52	0.56			
Hypertension	1.39	1.23–1.66	**<0.01**	1.6	1.31–2.1	0.06
Hyperlipidemia	0.76	0.43–1.15	0.16			
Diabetes mellitus	0.85	0.44–1.65	0.64			
Smoke	1.76	1.1–2.9	**0.02**	1.5	0.96–2.62	0.19
Family history	0.82	0.4–1.5	0.49			
previously treated with statin	0.38	0.23–0.64	**<0.01**	0.62	0.33–1.15	0.32
previously treated with ACE-I or ARB	0.39	0.24–0.64	**<0.01**	0.67	0.37–1.22	0.19
STEMI	3.4	2.1–5.8	**<0.01**	2.25	1.2–4.22	**0.01**

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI: ST-elevation myocardial infarction.
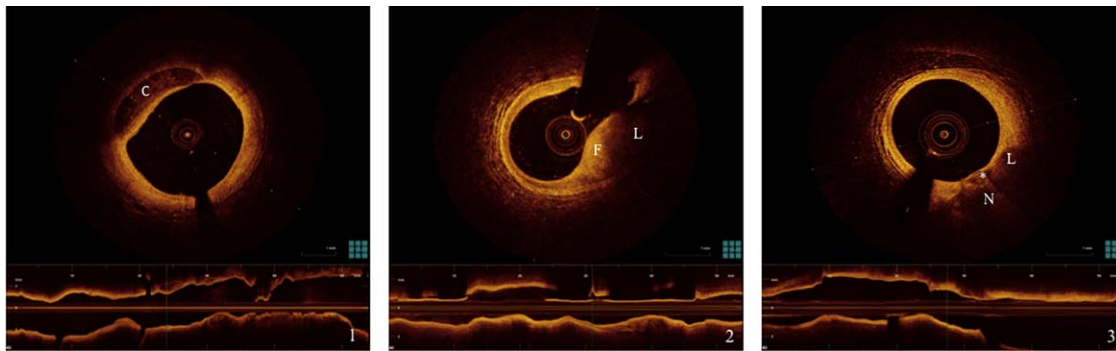
FIGURE 5 Samples of calcific plaque, lipid rich plaque, and necrotic core with macrophage infiltration. Panel 1 large calcified nodule (C) at 11 o'clock, Panel 2 large fibrous (F) and lipid (L) rich eccentric plaque at 5 o'clock characterized by a thick cap, Panel 3 eccentric plaque characterized by a lipid component and a necrotic core (N) with hyperintense signal due to macrophage infiltration (*) and a thin cap.

evident in patients with early onset CAD [1,17]. We did not investigate lipid profile and the correlations between plasmatic lipids and plaque characteristics, though it was reported as a common risk factors in younger patients with ACS [22]. Risky lifestyle factors, such as smoke and dyslipidaemia, in predisposed people should be early detected and prevented, before they develop into juvenile ACS [23,24].

On the basis of our findings, OCT evaluation in younger patient disclose a soft lipid rich plaque with thin cap on which smoke could act as a trigger for PR. On the contrary, older patients usually present chronic, fibrotic, and thicker plaque on which the triggers appear to primarily be hypertension and diabetes. The recipe is the same across the age, but ingredients change.

5 | CONCLUSION

In a select cohort of patients with ACS referred for coronary angiography with OCT evaluation, a significantly different clinical and virtual histology profile has been detected in patients stratified by age (more or less than 50 years old). Patients with premature CAD commonly have different risk profile and show higher prevalence of culprit PR, a thinner cap and less fibrotic or fibrocalcific components.

6 | LIMITATIONS

Our study has several limitations: firstly, a limited sample size probably underpowered the results and a selection bias limited the generalizability of our results. It is a retrospective, observational study. Each centre used a different OCT platform, and we lack of a real central core lab. PR or other structures may be obscured behind thrombi, when they are present. We also collected all the PR irrespective of the presence of a calcified plaque. Furthermore, because the primary endpoint of the study was the PR and its difference between age group we decided to not consider the plaque erosion, considering also the difficult diagnosis and the different definition that exists. The presence of thrombus could reduce the quality of the OCT pull-back, patients with poor image quality were excluded by the registry, thus the presence of PR could be

underestimated. Indeed, despite the use of thrombus aspiration or pre-dilatation could have determined jatrogenic PR, dissections or thrombus underestimations, it was used similarly in the two subgroups, so it should not have impact on our results.

CONFLICTS OF INTEREST

The authors report no conflicts of interest regarding the content herein.

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