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Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome

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Aims Patients presenting with acute coronary syndrome (ACS) may have different plaque morphologies at the culprit lesion. In particular, plaque rupture (PR) has been shown as the more frequent culprit plaque morphology in ACS. However, its prognostic value is still unknown. In this study, we evaluated the prognostic value of PR, compared with intact fibrous cap (IFC), in patients with ACS.

Methods and results We enrolled consecutive patients admitted to our Coronary Care Unit for ACS and undergoing coronary angiography followed by interpretable optical coherence tomography (OCT) imaging. Culprit lesion was classified as PR and IFC by OCT criteria. Prognosis was assessed according to such culprit lesion classification. Major adverse cardiac events (MACEs) were defined as the composite of cardiac death, non-fatal myocardial infarction, unstable angina, and target lesion revascularization (follow-up mean time 31.58 $\pm$ 4.69 months). The study comprised 139 consecutive ACS patients (mean age 64.3 $\pm$ 12.0 years, male 73.4%, 92 patients with non-ST elevation ACS and 47 with ST-elevation ACS). Plaque rupture was detected in 82/139 (59%) patients. There were no differences in clinical, angiographic, or procedural data between patients with PR when compared with those having IFC. Major adverse cardiac events occurred more frequently in patients with PR when compared with those having IFC (39.0 vs. 14.0%, $P = 0.001$). Plaque rupture was an independent predictor of outcome at multivariable analysis (odds ratio 3.735, confidence interval 1.358–9.735).

Conclusion Patients with ACS presenting with PR as culprit lesion by OCT have a worse prognosis compared with that of patients with IFC. This finding should be taken into account in risk stratification and management of patients with ACS.

Keywords Acute coronary syndrome • Plaque rupture • Optical coherence tomography • Prognosis

Introduction

Acute coronary syndromes (ACSs) are still a large burden of morbidity and mortality in patients affected by ischaemic heart disease.[1,2] Thrombotic occlusion of a coronary artery is the final common event leading to blood flow reduction to the underlying myocardium in ACS.[3] However, plaque causing thrombotic occlusion may have variable characteristics, and both postmortem studies and *in vivo* observations provided by intracoronary imaging modalities have suggested that thrombus may complicate a plaque with either a ruptured [plaque rupture (PR)] or intact fibrous cap (IFC).[4,5] Plaque rupture is, indeed, the most common substrate of coronary thrombosis in nearly 50% of patients,[6,7] but an eroded plaque is the substrate in up to one-third of patients with ACS, typically, women, younger,

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and smokers.[8] Of note, vasoconstriction at the level of the culprit plaque or of the microcirculation may also cause ACS with IFC, as suggested by recent studies that used a provocative test or biomarkers related to vasospastic angina.[9,10]

The advent of optical coherence tomography (OCT), an intracoronary light-based technology, has allowed to accurately characterize the plaque underlying coronary thrombosis, due to its high resolution.[11,12] Importantly, ruptured plaques when compared with IFC plaques have different severity, plaque and thrombus composition and pathogenesis that may drive different outcomes.[13–15] In particular, recent observations suggest that patients with PR may have widespread vulnerable features of the entire coronary tree.[16] However, studies focused on the prognostic role of PR vs. IFC are lacking. In this study, we aim at comparing clinical outcome of patients with ACS undergoing OCT evaluation of the culprit plaque according to the plaque morphology (either PR or IFC) that caused clinical instability.

Methods

Study design and patient population

We prospectively enrolled consecutive patients admitted to the Coronary Care Unit of the Policlinico Gemelli and San Giovanni Addolorata Hospital (Rome, Italy) with diagnosis of ST-elevation (STE)-ACS or non-ST-elevation (NSTE)-ACS, who underwent diagnostic coronary angiography followed by OCT of the culprit coronary stenosis between January 2010 and September 2012. Clinical and angiographic exclusion criteria as well as a detailed flow chart of screened and enrolled patients are reported in Supplementary material online, Appendix. Of note, the choice to perform OCT was left to the operator's decision.

All patients gave their informed consent, and the study was approved by the local Ethics Committee.

ST-elevation acute coronary syndrome patients had chest pain, new persistent ST-segment elevation, cardiac troponin T rise and fall, and/or new regional wall motion abnormalities. Non-ST-elevation acute coronary syndrome patients had at least two episodes of angina at rest or one episode lasting >20 min during the preceding 48 h and normal levels (unstable angina) or raise and fall [NSTE-myocardial infarction (MI)] of high-sensitivity troponin T levels.

Details about invasive treatment, OCT procedure, and clinical data collection of the study population are reported in Supplementary material online, Appendix.

Optical coherence tomography image analysis

Optical coherence tomography image analysis was performed offline by two expert investigators (G.N. and R.A.M.) who were blinded to the clinical presentation; discordance was resolved by consensus.

Optical coherence tomography analysis was conducted along the entire OCT pullback in order to categorize patients into two groups (PR vs. IFC) according to culprit lesion morphology and to collect additional features.

Culprit lesion was identified by means of angiography, electrocardiographic ST-segment alterations, and/or regional wall motion abnormalities on echocardiographic assessment. The culprit lesion was classified as PR or IFC. Plaque rupture was defined as the presence of fibrous cap discontinuity leading to a communication between the inner (necrotic) core of the plaque and the lumen.[17,18] Plaque rupture 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 according to recent proposed criteria.[19] On the other hand, IFC included both definite (the presence of an attached thrombus overlying an intact and visualized plaque) and probable erosions, defined as luminal irregularity without thrombus or thrombus without a superficial lipid or calcified plaque in the proximity of the thrombus.[20] Finally, IFC included also smooth plaques without evidence of rupture or thrombus as recently suggested.[20,21] Patients with other OCT imaged aspects at the culprit segment such as haematoma and dissections were excluded from the study. Additional features assessed by OCT are reported in Supplementary material online, Appendix.

Clinical follow-up and endpoint definition

A clinical follow-up was planned at 12, 24, and 36 months after discharge, and data about the follow-up were available for all patients. The primary endpoint was the incidence of major adverse cardiovascular events (MACEs) defined as the composite of death from cardiac causes, non-fatal MI, clinically driven target vessel revascularization (TVR), or rehospitalization due to unstable or progressive angina according to Braunwald Unstable Angina Classification.

Cardiac death was ascertained by contacting the family doctor or the hospital where the patient died. Myocardial infarction was diagnosed by the detection of raise and fall of cardiac biomarkers (preferably troponin) above the 99th centile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following criteria: ischaemic symptoms; electrocardiographic changes indicative of new ischaemia (new ST-T changes or new left bundle branch block); development of pathological Q waves in the electrocardiogram; and imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. Target vessel revascularization was carried out in the presence of a diameter stenosis of >50% in the culprit vessel in patients with recurrence of symptoms and/or evidence of inducible myocardial ischaemia. Target lesion revascularization (TLR) was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5 mm borders proximal or distal to the stent. All planned staged procedures in patients with multivessel diseases were performed during the index admission and were not included in MACE.

Statistical analysis

Data distribution was assessed according to the Kolmogorov–Smirnov test. Continuous variables were compared using an unpaired Student's *t*-test or Mann–Whitney *U*-test, as appropriate, and data were expressed as mean ± standard deviation or as median (range). Categorical data were evaluated using the χ^2 test.

In this study, there is only right censoring of the data, that is, MACE did not occur in the remaining patients before the end of follow-up, and the use of Cox proportional hazard ratio (HR) model is allowed with this type of data. Event-free survival was measured from the date of discharge to the occurrence of an MACE or to the date of last follow-up evaluation at 3 years. Thus, as primary analysis, we performed a simple Cox regression analysis using all variables on their original continuous scale to estimate the unadjusted HRs of all variables. We also calculated the 95% confidence interval (CI) of the coefficient of the Cox regression. Adjusted HRs were calculated by including the multivariable Cox regression analysis model variables showing $P \leq 0.15$ at univariate Cox regression analysis. Moreover, also the variables age and sex were included in the multivariable Cox regression analysis because considered biologically relevant. The validity of the proportional hazards assumption was tested adding a time-dependent interaction variable for each of the predictors, and estimates of the C-index for the Cox regression model were calculated. Survival curves using the Kaplan–Meier methods were produced for the presence of PR as the culprit lesion and compared by the log-rank test. Intra- and interobserver differences were investigated with kappa measure of agreement.

All tests were two-sided, and a *P*-value of <0.05 represented statistically significant differences. All analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical and angiographic findings in patients with plaque rupture vs. those with intact fibrous cap

Clinical characteristics of overall study population and according to the presence of PR as a culprit plaque are summarized in *Table 1*. One hundred and thirty-nine consecutive patients with ACS [mean age 64.3 ± 12.0 years, 102 (73.4%) males] were enrolled, 47 (33.8%) presenting with STE-ACS and 92 (66.2%) with NSTE-ACS. Eighty-two (59%) patients had a PR as a culprit lesion and 57 (41%) an IFC, as assessed by OCT analysis (*Figure 1*). Clinical and angiographic findings were similar between patients with PR and those with IFC (*Tables 1* and *2*).

Optical coherence tomography data in patients with plaque rupture vs. those with intact fibrous cap

Optical coherence tomography data referred to culprit lesion and culprit segment analysis are listed in *Table 2*. Patients with PR had a

Table 1 Clinical characteristics of overall study population and according to the presence of plaque rupture or intact fibrous cap

Variables	All patients (*n* = 139)	Patients with plaque rupture (*n* = 82)	Patients with intact fibrous cap (*n* = 57)	*P*-value
Age, mean ± SD, years	64.3 ± 12.0	65.1 ± 12.5	63.2 ± 11.2	0.36
Male, *n* (%)	102 (73.4)	63 (76.8)	39 (68.4)	0.27
Clinical presentation, *n* (%)				
STE-ACS	47 (33.8)	30 (36.6)	17 (29.8)	0.41
NSTE-ACS	92 (66.2)	52 (63.3)	40 (70.2)	
Risk factors, *n* (%)				
Smoking				0.98
Smoker	57 (41.0)	33 (40.2)	24 (42.1)	
Non-smoker	62 (44.6)	37 (45.1)	25 (43.9)	
Former smoker	20 (14.4)	12 (14.6)	8 (14.0)	
Hypertension	104 (74.8)	60 (73.2)	44 (77.2)	0.59
Hypercholesterolemia	79 (56.8)	51 (62.2)	28 (49.1)	0.13
Diabetes mellitus	29 (20.8)	20 (24.4)	9 (15.8)	0.22
Obesity (BMI >30)	38 (27.3)	20 (24.4)	18 (31.6)	0.35
Family history of CAD	46 (33.1)	26 (31.7)	20 (35.1)	0.68
Previous history, *n* (%)				
Previous CAD	38 (27.3)	22 (26.8)	16 (28.1)	0.87
Previous ACS	22 (15.8)	14 (17.1)	8 (14.0)	1.0
Previous PCI	21 (15.1)	12 (14.6)	9 (15.8)	0.85
Previous CABG	3 (2.2)	1 (2.0)	2 (5.9)	1.0
eGFR, mean ± SD, mL/min	68 ± 40	67 ± 38	70 ± 35	0.86
TnT, ng/mL	5.31 ± 14.29	5.44 ± 16.22	5.13 ± 11.3	0.35
Medications at the discharge, *n* (%)				
Beta-blockers	114 (82.0)	71 (86.6))	43 (75.4)	0.09
ACE inhibitors	99 (71.2)	59 (72.0)	40 (70.2)	0.82
ARB	20 (14.4)	13 (15.9)	7 (12.3)	0.63
Statins	126 (90.6)	72 (87.8)	54 (94.7)	0.24
Calcium blockers	23 (16.5)	12 (14.6)	11 (19.3)	0.47
Insulin	7 (5.0)	3 (3.7)	4 (7.0)	0.44
Oral hypoglycaemic agents	22 (15.8)	16 (19.5)	6 (10.5)	0.15
Follow-up time, months	31.58 ± 4.69	31.54 ± 4.46	31.63 ± 5.04	0.91

SD, standard deviation; STE, ST-elevation; NSTE, non-ST-elevation; ACS, acute coronary syndrome; ARB, angiotensin-receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; TnT, troponin T; ACE, angiotensin-converting enzyme.

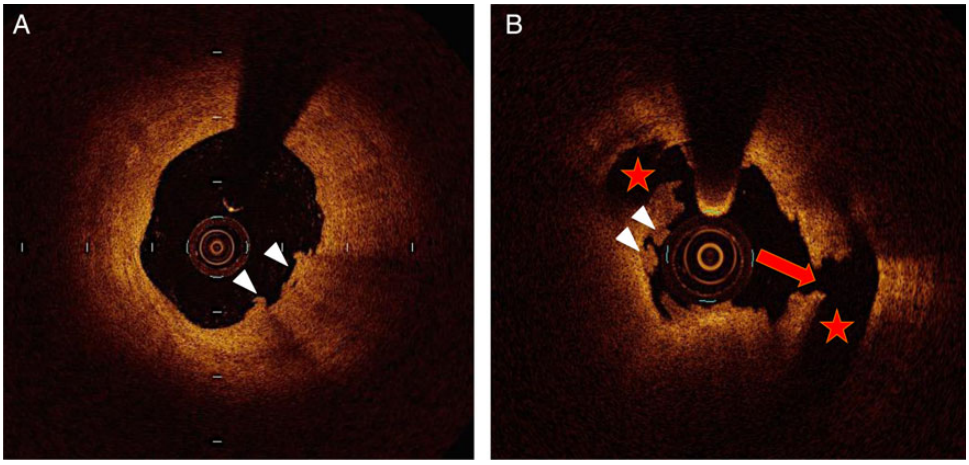

Figure 1 Representative optical coherence tomography images of intact fibrous cap and plaque rupture. In (*A*), an intact fibrous cap was imaged as a luminal thrombus (white arrowheads) over a fibrous plaque with a thick cap without evidence of disruption. In (*B*), a plaque rupture was observed as luminal thrombus (white arrowheads) associated with a fibrous cap disruption (red arrow) and a cavity formation (red asterisk).

significantly thinner fibrous cap (76.2 ± 30.3 vs. 87.0 ± 30.7 μm, $P = 0.04$), more frequently thrombus [62 (75.6%) vs. 32 (56.1%), $P = 0.05$] and more frequently a lipid-rich plaque at the culprit lesion [70 (85.4%) vs. 31 (71.9%), $P < 0.001$] compared with IFC patients. Moreover, PR patients had a higher maximum lipidic arc (226.95 ± 109.6 vs. 189.9 ± 97.7°, $P = 0.03$) and a longer calcified segment (41.55 ± 45.25 vs. 27.0 ± 32.5 mm, $P = 0.05$) in the culprit vessel compared with IFC patients. Kappa measures of agreement for intraobserver variability were 0.92 ($P = 0.0001$) for PR and 0.96 ($P = 0.0001$) for thin cap fibroatheroma (TCFA), and for interobserver variability were 0.84 ($P = 0.0001$) and 0.86 ($P = 0.0001$) for PR and TCFA, respectively.

Clinical outcome in patients with plaque rupture vs. those with intact fibrous cap

Follow-up mean time was 31.58 ± 4.69 months in the overall population (31.54 ± 4.46 in the PR group and 31.63 ± 5.04 in the IFC group, $P = 0.91$). Overall, MACE rate was 28.8%, cardiac death 1.4%, non-fatal MI 7.9%, unstable angina 11.5%, and TVR 14.4%. Of importance, MACEs were significantly more frequent in PR patients compared with IFC patients [32 (39.0%) vs. 8 (14.0%), $P = 0.001$]. No significant differences in cardiac death [1 (1.2%) vs. 1 (1.8%), $P = 1$], non-fatal MI [9 (11.0%) vs. 2 (3.5%), $P = 0.2$], unstable angina [12 (14.6%) vs. 4 (7.0%), $P = 0.13$], and TVR [15 (18.3) vs. 5 (8.8%), $P = 0.14$] were observed (*Figure 2*). Overall, TLR rate was 10.1%, without significant difference between PR and IFC [10 (12.2%) vs. 4 (7.0%), $P = 0.4$]. Among patients with unstable angina, 10 underwent revascularization procedures, 8 patients in the PR group (5 non-TVR and 3 TLR) and 2 patients in the IFC group (1 non-TVR and 1 TLR). The non-TLR event rate (including TVR outside the target lesion and non-TVR) was 12% in the PR group vs. 3.5% in the IFC group ($P = 0.07$).

Univariate Cox regression analysis is reported in Supplementary material online, *Table S1*. The only significant predictor for the occurrence of MACE at the univariate Cox regression analysis was PR (HR = 2.60, 95% CI 1.195–5.644, $P = 0.02$). However, obesity (HR = 1.898, 95% CI 0.970–3.715, $P = 0.06$), stent length (HR = 1.05, 95% CI 0.993–1.103, $P = 0.09$), and history of previous percutaneous coronary intervention (HR = 1.90, 95% CI 0.865–4.185 $P = 0.11$) had a value of $P < 0.15$. Of note, in a multivariable Cox regression model including these variables, PR was the only independent predictor of MACE (HR = 3.735, 95% CI 1.358–9.735, $P = 0.010$; *Table 3*). The C-index for the multivariable Cox regression model was 0.755 (95% CI 0.727–0.783).

Finally, Kaplan–Meier analysis showed that patients with PR had a worse MACE-free survival compared with those having an IFC ($P = 0.02$; *Figure 3*).

Discussion

In this study, we show for the first time, to the best of our knowledge, that patients with an ACS having PR assessed by OCT as a mechanism of coronary instability have a worse prognosis after medium-term follow-up when compared with those having an IFC by OCT. This is mainly driven by a higher risk of unstable angina and of TVR at follow-up.

Plaque rupture is the most common substrate of ACS, as suggested both by pathological studies and more recently by studies performed *in vivo* and carried on with OCT.[22,23] The prevalence of PR is variable, depending on the clinical context, being more frequent in patients with sudden cardiac death compared with acute MI in postmortem studies, and in patients with STE-ACS compared with NSTE-ACS in *in vivo* studies.[24] Patients without PR exhibit different mechanisms of instability including thrombus at the site of plaque erosion, or intense vasoconstriction of epicardial arteries or of coronary microcirculation.[25,26] Importantly, we have recently found that the biomarker profile is different among patients with PR, with plaque erosion or with functional alterations of coronary circulation.[21]

Table 2 Angiographic, procedural, QCA and OCT data of overall study population and according to the presence of plaque rupture or intact fibrous cap

Variables	All patients (n = 139)	Patients with plaque rupture (n = 82)	Patients with intact fibrous cap (n = 57)	P-value
Angiographic data, *n* (%)				
Multivessel disease	77 (55.4)	47 (57.3)	30 (52.6)	0.58
Culprit artery				
LAD	81 (58.3)	48 (58.5)	33 (57.9)	0.75
LCx	30 (21.6)	19 (23.2)	11 (19.3)	
RCA	28 (20.1)	15 (18.3)	13 (22.8)	
B2/C lesion	104 (74.8)	65 (79.3)	39 (68.4)	0.15
Procedural data, *n* (%)				
Stent implanted				
DES	100 (71.9)	60 (73.2)	40 (70.2)	0.83
BMS	29 (20.9)	17 (20.7)	12 (21.0)	
POBA	10 (7.2)	5 (6.1)	5 (8.8)	
DES type				
First-generation DES	21 (21.0)	12 (20.0)	9 (22.5)	0.81
Second-generation DES	79 (79.0)	48 (80.0)	31 (77.5)	
Stent diameter, mm	3.07 ± 0.54	3.03 ± 0.16	3.12 ± 0.53	0.73
Total stent length, mm	20.33 ± 6.55	20.77 ± 6.50	19.66 ± 6.62	0.35
Use of IIb/IIIa glycoprotein inhibitor	58 (41.7)	35 (42.7)	23 (40.3)	0.86
QCA data				
RVD, mm	2.54 ± 0.52	2.52 ± 0.76	2.58 ± 0.55	0.46
MLD pre, mm	0.92 ± 0.11	0.89 ± 0.14	0.96 ± 0.21	0.55
DS% pre	70 ± 16	71 ± 12	68 ± 15	0.31
MLD post, mm	2.51 ± 0.41	2.50 ± 0.53	2.53 ± 0.67	0.8
DS% post	12 ± 8	12 ± 9	13 ± 10	0.77
Acute gain, mm	1.72 ± 0.31	1.69 ± 0.65	1.76 ± 0.78	0.32
Culprit lesion analysis by OCT				
MLA, mm^2	2.19 ± 1.35	2.14 ± 1.30	2.27 ± 1.44	0.58
Cap thickness, μm	80.7 ± 30.8	76.2 ± 30.3	87.0 ± 30.7	0.04
Plaque composition, *n* (%)				
Lipid-rich plaque	101 (72.7)	70 (85.4)	31 (54.4)	<0.001
Fibrous plaque	38 (27.3)	12 (14.6)	26 (45.6)	
Calcifications, *n* (%)	22 (15.8)	16 (19.5)	6 (10.5)	0.15
TCFA, *n* (%)	56 (40.3)	43 (52.4)	13 (22.8)	<0.001
Microchannels, *n* (%)	81 (58.3)	52 (63.4)	29 (50.9)	0.14
Thrombus, *n* (%)	94 (67.6)	62 (75.6)	32 (56.1)	0.05
White	47 (50)	19 (29.2)	28 (96.6)	<0.001
Red	47 (50)	46 (70.8)	1 (3.4)	
Culprit segment analysis by OCT				
Analysed length vessel, frames	187.5 ± 67.1	185.2 ± 61.5	190.9 ± 74.8	0.58
Minimum cap thickness, μm	76.3 ± 29.1	72.1 ± 26.9	82.3 ± 31.3	0.08
TCFA, *n* (%)	56 (40.3)	39 (47.6)	17 (29.8)	0.036
Lipidic length vessel, mm	99.1 ± 60.4	103.1 ± 58.4	93.4 ± 63.2	0.23
Lipidic arc,°	204.4 ± 125.3	218.9 ± 119.1	183.6 ± 131.9	0.13
Maximum lipid arc,°	211.75 ± 106.1	226.95 ± 109.6	189.9 ± 97.7	0.03
Calcifications, *n* (%)	104 (74.8)	65 (79.3)	39 (68.4)	0.15
Calcified length vessel, mm	35.6 ± 41.0	41.55 ± 45.25	27.0 ± 32.5	0.05
Maximum calcium arc,°	85.8 ± 78.3	91.3 ± 80.8	77.9 ± 74.5	0.27
Presence of microchannels, *n* (%)	81 (58.3)	46 (56.1)	35 (61.4)	0.53

ACS, acute coronary syndrome; BMI, body mass index; BMS, bare metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; DS, diameter stenosis; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; MLA, minimal lumen area; MLD, minimal lumen diameter; POBA, plain old balloon angioplasty; QCA, quantitative coronary angiography; RCA, right coronary artery; RVD, reference vessel diameter; TCFA, thin cap fibroatheroma; OCT, optical coherence tomography.

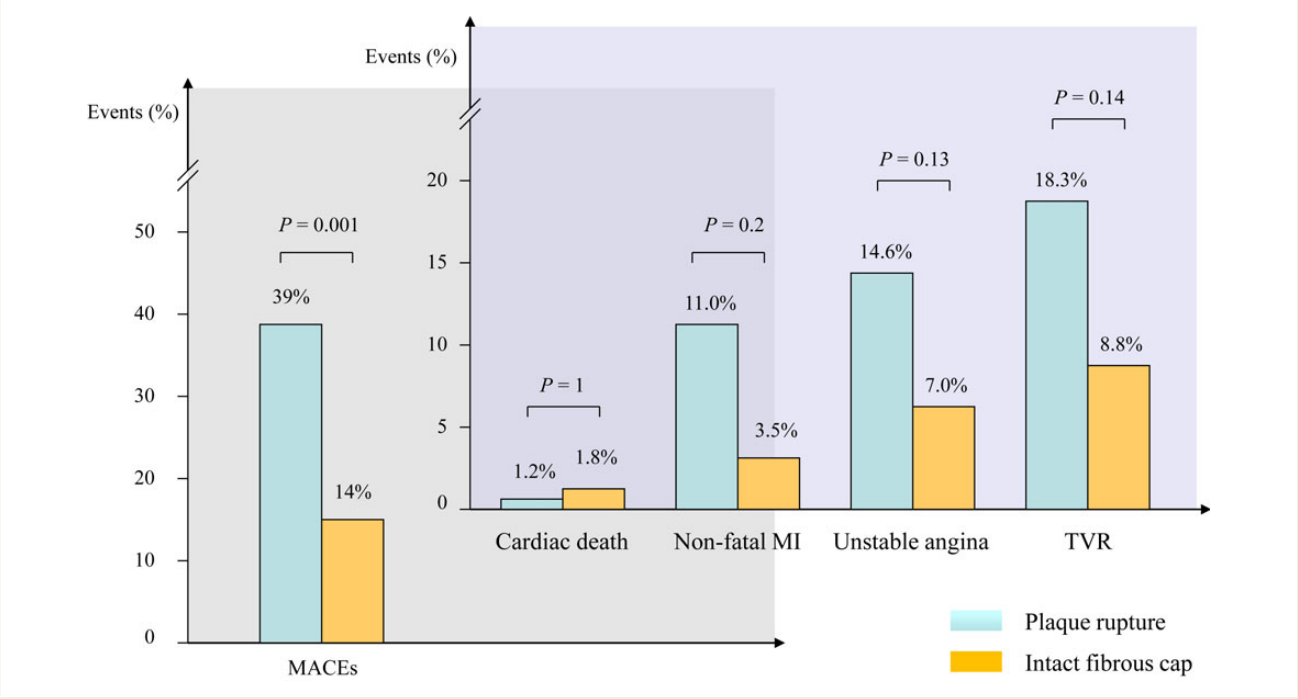

Figure 2 Major adverse cardiac event (MACE) rates in patients with plaque rupture and in those with intact fibrous cap. The rate of cardiac death, non-fatal myocardial infarction, unstable angina, and target vessel revascularization (TVR) in patients with plaque rupture and with intact fibrous cap.

Table 3 Predictors of major adverse cardiac events at 3-year follow-up at multivariable Cox regression analysis

Variables	HR	95% CI	*P*-value
Obesity (BMI >35)	1.688	0.822–3.845	0.15
Plaque rupture	3.735	1.358–9.735	0.010
Previous PCI	1.449	0.610–4.149	0.341
Stent length	1.028	0.980–1.081	0.262
Age	1.005	0.977–1.034	0.729
Sex (male)	1.36	0.335–1.591	0.765

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PCI, percutaneous coronary intervention.

Previous studies[24,25] report that PR is detected more commonly in STE-ACS compared with NSTE-ACS. In particular, the largest OCT study hitherto published including 126 patients with ACS, reported a 44% prevalence of PR in the overall population, with a higher rate in patients with STE-ACS (70%) compared with those having NSTE-ACS (30%).[20] At variance with previous data,[24,25] in our study, we did not observe any significant difference in culprit plaque morphology between the two groups of patients. This result should be interpreted with caution, taking into account the higher proportion of NSTE-ACS patients enrolled in the study (66.2%), compared with those presenting STEMI (33.8%), that might lead to underrate the correct difference between groups. Of note, the longitudinal morphology of PR is an important determinant of coronary artery occlusion and clinical presentations of ACS. Indeed, PR in the proximal shoulder site was more often seen in STE-ACS than in NSTE-ACS.[24]

We found that patients with PR had different features of both culprit site and culprit segment when compared with those having an IFC. Indeed, they exhibited more frequently lipidic plaques with TCFA and thrombus at the culprit site, whereas along the culprit segment they exhibited more frequently the presence of TCFA, bigger maximum lipidic arc, and calcified vessel length suggestive of more diffuse atherosclerotic process. These findings are in keeping with those provided by previous studies using OCT, intravascular ultrasound, or multislice computed tomography.[22,27,28] Importantly, a recent study by Vergallo *et al.*[16] showed that patients with ACS and PR when compared with those not having PR had more frequently TCFA in the entire coronary tree explored by three-vessel OCT. Moreover, Ozaki *et al.*[28] showed that patients with PR had more frequently positively remodelled plaques with large plaque burden when compared with those having an IFC. Taken together, these observations suggest that patients with PR share a common phenotype of more diffuse and vulnerable atherosclerosis. In our study, we could not assess multifocal instability as OCT interrogation was limited to the culprit epicardial segment.

In contrast with previous reports, we failed to show more severe stenosis at the culprit site in patients with PR when compared with those having an IFC.[20] This may be related to different patient populations (different prevalence of NSTE-ACS vs. STE-ACS) or different OCT classifications of culprit stenosis with IFC. Furthermore, minimal lumen area of both study groups was >2 mm^2, a cut-off suggested for ischaemia-inducing lesions.[29] This finding may be explained by the intrinsic dynamic nature of ACS with thrombus and vasoconstriction-modulating stenosis severity (while the

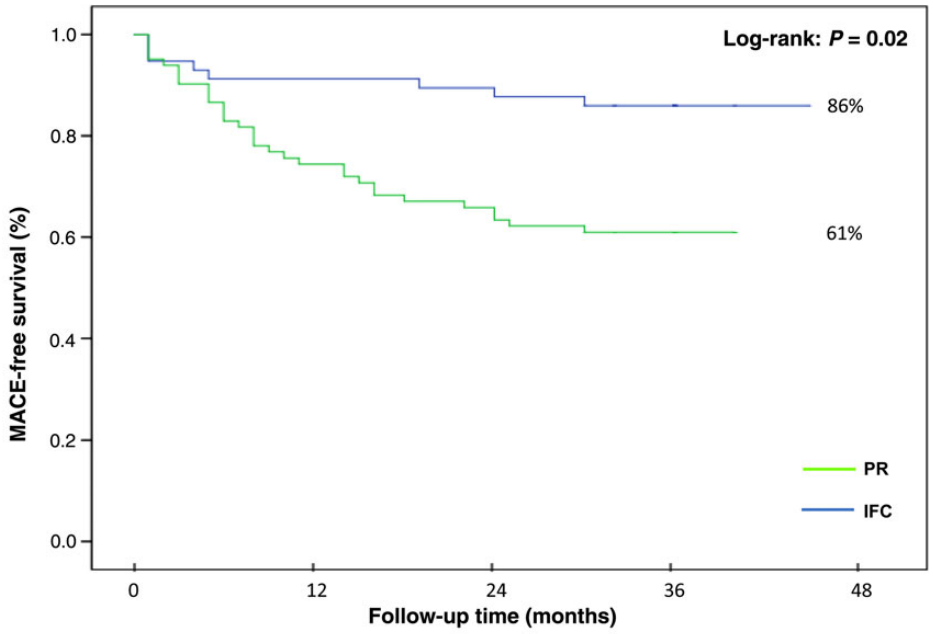

Figure 3 Major adverse cardiac event (MACE)-free survival Kaplan–Meier curves according to the presence of plaque rupture or intact fibrous cap. Curves are compared by the log-rank test.

above-mentioned cut-off has been defined in stable patients) and by the use of thrombus aspiration and IIb–IIIA inhibitors that may enlarge the lumen mechanically or by thrombus dissolution, respectively.[24,30,31]

Thrombus was more common in our study in patients with PR when compared with those having an IFC. This might be related to different pathogenetic mechanisms operating in these two settings. In particular, PR was found to be associated with early thrombus formation in postmortem studies, suggesting a strong pro-thrombotic stimulus probably related to rupture and release of tissue factor and of other potent pro-thrombotic substances from the culprit plaque.[14,32] Conversely, thrombus formation in erosion is associated with late thrombi in pathological studies suggesting repetitive less intense thrombotic stimuli, which may have left time to thrombus dissolution caused by spontaneous fibrinolysis.[33] Accordingly, a recent study suggested that residual thrombus burden 1 day after fibrinolysis was greater for rupture when compared with erosion.[34] Moreover, different biomarker profiles characterize patients with PR or IFC, with myeloperoxidase being more elevated in patients with plaque erosion suggesting intense neutrophil activation in this patient subset.[21,35]

The reasons why patients with PR have a worse prognosis when compared with those having an IFC after coronary stenting are probably multiple. In our study, the higher MACE rate in the former was driven by a higher rate of TVR and readmission for unstable angina, thus suggesting that both stent failure and disease progression are enhanced in patients with PR.

The increased rate of TVR in patients with PR may be accounted for by the different plaque composition and lipid and thrombus burden when compared with those having IFC, as quantitative coronary angiography analysis failed to show differences in acute gain between patients with PR or IFC, thus excluding a contribution of different acute angiographic stent results to the outcome. In particular, PR is often associated with a thin cap and a large lipid pool both related to enhanced inflammatory activity. Independently of plaque activity, plaque burden appears to be higher in patients with PR than in those with IFC, as suggested in previous studies.[7] The higher baseline plaque burden may lead to residual plaque beyond the stent that is a well-known predictor of stent failure in previous intravascular ultrasound studies. Finally, the risk of stent thrombosis according to the plaque type is obviously not detectable in our study, due to the small sample size; however, it is well known that stent implanted during an ACS especially in case of STE-ACS are at higher risk of stent thrombosis and PR may be the underlying substrate in 70–80% of case.[36] Future studies on a larger population should address the issue of risk of stent failure according to the underlying plaque morphology in ACS.

The increased risk of unstable angina in patients with PR compared with those having IFC might be related, again, to different plaque features. In particular, as suggested by the study of Vergallo *et al.*,[16] the presence of multiple TCFA is more frequent in patients with PR than in those with IFC, thus predisposing to plaque growth and recurrent instability.[16] This notion is supported also by the PROSPECT study that utilized intravascular ultrasound virtual histology to study the natural history of coronary atherosclerosis in patients treated by coronary stenting.[37]

Finally, different mechanisms of instability may explain the higher rate of recurrence in patients with PR when compared with those

having IFC. In particular, we recently found that patients with PR were characterized by higher levels of C-reactive protein and matrix metalloproteinase 9, those with plaque erosion by higher levels of myeloperoxidase, and those with a smooth plaque by higher levels of Cystatin C[21] associated with vasospasm in a recent Japanese study.[38] PR is thus related to inflammatory mechanisms that may lead to plaque growth and destabilization. This happens in at least two-thirds of patients with PR, while the remaining one-third is more probably characterized by mechanical rupture of the fibrous cap, as recently proposed by our group.[27,39] Patients with PR and raised CRP levels may be at an increased risk of future cardiovascular events despite conventional therapy of ACS due to persistent inflammation. This is in keeping with the well-known negative prognostic value of CRP in ACS patients.[40,41] On the other hand, patients with IFC may have a better prognosis as they are largely constituted by OCT-defined plaque erosion where a single occasional thrombotic stimulus occurs; thus, its recurrence might well be prevented by antithrombotic therapies without coronary stenting, as recently suggested.[42,43] Finally, the better prognosis of patients with IFC associated with smooth stenosis without rupture or thrombus may be due to the use of vasodilators that prevent coronary vasoconstriction recurrence or relieve of ischaemia by coronary stenting in high-grade fixed stenosis.

Our study has some important limitations. First, we did not perform routine follow-up angiography. Secondly, the higher prevalence of patients with NSTE-ACS, compared with those having STE-ACS, did not allow us to clearly establish the prevalence of PR in these two clinical presentations of ACS. Thirdly, the small sample size increases the risk of type 1 or 2 statistical errors. Indeed, the MACE rate in our study was higher than that of previous study, although it was similar that reported in a contemporary registry in invasively treated patients with ACS.[44] Moreover, the absence of endothelial cells is a key pathological criterion for erosion. Despite its high resolution, the current OCT technique cannot detect individual endothelial cells. As a result, the OCT definition of plaque erosion was based primarily on a diagnosis of exclusion requiring the absence of a fibrous cap rupture. Finally, we cannot exclude that in some patients PR was iatrogenic being caused by thrombus aspiration.

In conclusion, the relevant clinical message of our study is that patients with ACS and PR are at higher risk of MACE when compared with those having IFC, thus different tailored therapies should be investigated in these profoundly different patient subsets.

Supplementary material

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

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