The coronary substrate determines prognosis in acute coronary syndromes: the kaleidoscope has been shaken . . . again!

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This editorial refers to 'Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome', by G. Niccoli et al., on page 1377.

The identification of ‘vulnerable’ or ‘high risk’ coronary plaques has represented the quest for the Holy Grail in interventional cardiology for the past three decades. Plaque rupture (PR), plaque erosion (PE), and complicated calcified nodules (CNs) constitute the most common underlying substrates leading to coronary thrombosis and acute coronary syndromes (ACS).4–7 Despite the advent of novel intracoronary imaging techniques, which are able to disclose unique morphological insights and plaque features similar to those found in plaques already complicated with coronary thrombosis, their value in predicting future clinical events remains limited.4–7 Optical coherence tomography (OCT) is an emerging technique with unique spatial resolution (15–20 μm) that provides unsurpassed visualization of the coronary surface although with limited penetration in the underlying coronary wall.4–7 This technique is ideally suited to unravel even subtle fibrous cap disruptions, intracoronary thrombus, and the underlying necrotic cores. The thickness of the fibrous cap can be accurately measured and, therefore, thin-cap fibroatheromas (TCFAs) may be readily identified.4–7 However, the implications of the discovery of the various pathological substrates on the long-term prognosis of ACS patients remain unknown.

In this issue of the journal, Niccoli et al.8 sought to assess the prognostic implications of PR in ACS patients. OCT was systematically performed in patients presenting with ACS to detect the presence of PR vs. an intact fibrous cap (IFC) at the culprit lesion. The primary endpoint of this prospective observational study was the occurrence of major cardiac events at follow-up (composite of cardiac death, non-fatal myocardial infarction, unstable angina, and target lesion revascularization). A total of 139 consecutive ACS patients (47 ST-segment elevation and 92 non-ST-segment elevation ACS) with good quality pre-intervention OCT image analysis were included. Overall, PR was identified in 59% of patients. Interestingly, clinical and angiographic characteristics were similar in patients with PR and those with IFC. However, patients with PR more frequently had lipid-rich plaque, a thinner fibrous cap, and thrombus at the culprit lesion. Importantly, at clinical follow-up, adverse events occurred more frequently (39% vs. 14%, P < 0.001) in patients with PR. This was mainly driven by a higher risk of unstable angina and target vessel revascularization. Moreover, after adjusting for potential confounders, PR emerged as an independent predictor (odds ratio 3.7) of adverse events. The authors suggest that the presence of PR at the culprit lesion portends a poor prognosis and also that this information might be used to risk-stratify and manage ACS patients. This certainly represents a highly provocative study suggesting, for the first time, that in ACS patients the underlying pathological coronary substrate has major prognostic value.

Due to the potential clinical implications of these novel findings, the discussion of some methodological issues is of major interest. First, the authors should be commended for their strict methodology that enabled OCT information to be gained in relatively unselected ACS patients that would support the external validity of their findings. However, some selection bias appears unavoidable and it is likely that highly unstable patients or those with complex coronary anatomy would have been excluded from the study that required pre-intervention OCT imaging. In addition, this is an observational investigation with a relatively small sample size and, accordingly, the findings should be considered as hypothesis-generating and will require confirmation by future studies. Secondly, patients with a large thrombus burden represent a challenge for OCT examination.4–7 In most cases, this problem persists despite careful thrombus aspiration as significant residual red thrombus precludes a complete delineation of the underlying vessel wall (namely a localized PR might be hidden behind the shadow cast by a red thrombus). Therefore, the possibility of misclassification of some PR as IFC cannot be excluded. Reassuringly, however, intra- and interobserver
reproducibility of the main OCT diagnoses was excellent.8 Thirdly, in this study, patients with disruptions overlying a calcified plaque/nodule were included in the PR group. This is difficult to understand because usually the thrombus burden is less but calcification is extensive in such cases.6 In addition, their frequencies (PR = 60–75%; CN = 2–5%) are dramatically different. We and other investigators, however, consider these as distinct pathological entities with very little in common.5,7 Alternatively, the diagnosis of PE remains largely elusive.7 In this study, the presence of thrombus attached to an intact plaque was considered as ‘definitive’ PE, whereas luminal irregularities without thrombus and thrombus without underlying lipid/calcified plaque were considered as ‘probable’ PE. However, these definitions remain highly controversial, and the risk of OCT overdiagnosis exists.9 Too many different types of plaques were probably lumped together in the IFC category (Figure 1). Fourthly, the advancement of thromboaspiration catheters may certainly disrupt not only thrombus but also the underlying plaque.6 Actually it remains impossible to ascertain whether the observed PR was spontaneous or rather a result of a mechanical trauma (including a Dotter effect) on TCFAs. Last, but not least, the high event rate in the PR cohort was unexpected considering that second-generation drug-eluting stents (DES) were used in most cases. Even in patients with ST-segment elevation ACS new generation DES currently provide superb long-term clinical results. As the study might be underpowered for clinical events, these findings could also be a play of chance. In this regard, although the combined clinical outcome measure occurred more frequently in patients with PR, none of the individual clinical endpoints significantly differed between the two groups.

Management-related issues also generate major practical interest. Stents implanted in lesions with PR or TCFA may have a higher risk for restenosis or thrombosis,3–6 although the rate of stent thrombosis was not reported in this study. In addition, patients with PR also exhibited more frequently TCFA, larger lipid arcs, and longer calcified plaques along the complete coronary segment. This would suggest a more diffuse and severe atherosclerotic process and, more importantly, a more vulnerable entire coronary tree. Although no significant difference was observed in the prevalence of diabetes, it tended to be higher in PR than in IFC (24.4% vs. 15.8%, respectively), which would suggest more diffuse disease and calcification in the PR group. In this regard, there was a strong trend for a higher rate of non-target lesion revascularization at follow-up in patients with PR. On the other hand, some investigators have proposed the use of intense antithrombotic

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**Figure 1** Categories called plaque rupture (PR) included cases of necrotic core (NC) with a discontinuous (arrow) thin fibrous cap and overlying thrombus (Th) (A), and a calcified nodule (B) with a luminal Th and a nodule of calcium (Ca2+) protruding into the lumen with a discontinuous fibrous cap. (C–E) Lesions included in the definition of intact fibrous cap (IFC). These are plaque erosion (C), healed (arrow) plaque rupture with underlying NC (D), and stable calcified plaque with a smooth lumen (E). Figures reproduced with permission from: (A) rupture, Arbab-Zadeh A et al. Circulation 2012;125:1147–1156; (B) calcified nodule, Falk, E. et al. Eur Heart J 2013;34:719–728; (C) erosion, Otsuka, F. et al. Nat Rev Cardiol 2014;11:379–389; and (D) healed rupture, Otsuka, F. et al. Nat Rev Cardiol 2014;11:379–389.
therapy alone (without additional stent implantation) in selected patients with IFC. This conservative management strategy may allow healing and complete restoration of the endothelial layer. Nevertheless, in this study all patients with IFC were treated with stents. A ‘lone thromboaspiration strategy’ could have been contemplated in selected patients with large lumens considering that on OCT the minimal lumen area was > 2 mm² in both groups. Of note, this cut-off value in minimal lumen area has been used to predict ischaemia-inducing lesions in stable patients. Whether a conservative strategy of ‘lone’ thromboaspiration followed by intense antithrombotic therapy might be more effective in selected patients with IFC vs. those with PR still remains to be elucidated.

New lessons in acute coronary syndrome patients: from imaging to pathophysiology

Optical coherence tomography provides unique insights on plaque characteristics. Fibrous plaques are characterized by bright homogeneous signals, lipid plaques as low-signal regions with diffuse borders, whereas calcium is characterized by well-delineated low intensity signals with sharp borders. All these OCT patterns have been validated by histological studies. However, despite important refinements in coronary imaging, identification of vulnerable plaques remains a moving target. OCT enables precise measurements of fibrous caps, and TCFAs are defined as lipid plaques covered by thin (< 65 μm) fibrous caps. Thrombi are visualized as irregular tissue protruding into the lumen with either high backscattering and major attenuation (red thrombus, rich red blood cells, and fibrin) or homogeneous backscattering without dorsal shadowing (white thrombus, platelet rich). OCT is able to detect not only the underlying lipid pools but also clusters of macrophages and free cholesterol crystals. The endothelial layer, however, is beyond the resolution of OCT and, therefore, exclusion of PR is usually required for the diagnosis of PE. This explains why some investigators prefer the term IFC, used in the study of Niccoli et al. Currently, however, there are no morphological features able to identify lesions prone to PE and thrombosis. Alternatively, calcified nodules are recognized on OCT as superficial calcification protruding into the lumen. Some authors required fibrous cap disruption for the diagnosis of CNs. However, other investigators suggest that only ‘complicated’ or ‘eruptive’ calcified nodules are associated thrombus or disruption of the overlying cap. This issue is of clinical relevance as recent observations suggest that some CNs may also induce major dorsal shadowing on OCT in the absence of disruption or associated thrombosis. In pathology, however, a CN is one with fibrous cap disruption and luminal thrombus whereas a “nodular calcification” has an intact fibrous cap and is usually located within the plaque but calcium is observed as nodules and not as sheets. Finally, intraplaque haemorrhage appears to be more closely related to plaque progression than to plaque complication or thrombosis, yet the OCT diagnosis of this substrate has not been validated.

Notably, many previous studies suggest that the underlying pathological substrate is associated with distinct clinical and pathophysiological characteristics (Figure 1). PR is the most frequent (2/3) substrate of coronary thrombosis. From a ‘clinical standpoint’ PR is more frequently seen in patients with sudden cardiac death and ST-segment elevation ACS. PE is more common in young patients, especially females, and appears to be associated with cigarette smoking. Alternatively, CNs are more prevalent in old patients and in those with diabetes or chronic kidney disease. From a ‘morphological standpoint’, PRs are associated with large plaque burden (> 75% cross-sectional area) frequently with expansive remodelling. PR occurs on lipid plaques and TCFAs where remnants of the ruptured cap and a residual cavity can be readily recognized. Although PR tends to occur at the shoulder of the plaque, the longitudinal location of the rupture has clinical implications. PRs with cavities facing the flow are associated with larger thrombus burden and ST-segment elevation ACS, whereas PRs with an opening looking towards the distal vessel are associated with less thrombus burden and non-ST-segment elevation ACS. Alternatively, in patients with PE, the underlying plaque is fibrotic or lipid but with a thick cap, where a denuded intimal surface exposes smooth muscle cells and the proteoglycan matrix to the flowing blood. Patients with PR usually present severe lumen compromise despite the occurrence of positive remodelling, whereas those with PE tend to have smaller plaque burden, constrictive remodelling, and larger residual lumen.

Inflammatory biomarkers are key players in the pathogenesis of ACS. Systemic levels of C-reactive protein and myeloperoxidase (a protein released by activated neutrophils) appear to predict prognosis in these patients. Interestingly, previous OCT studies suggested that levels of C-reactive protein are similar for patients with PR and PE whereas systemic levels of myeloperoxidase are significantly higher in patients with PE. Finally, the propagated thrombus characteristics may differ in patients with PR and PE. Platelet-rich thrombi occur in both PE and PR, but the latter shows a greater presence of fibrin in the propagated portion of the thrombus. Finally, thrombus overlying PE may exhibit different stages of healing and organization, with invasion of smooth muscle cells and the appearance of distinct thrombus layers.

Despite all these important pathophysiological differences, up to now the underlying substrate has not been correlated with the long-term outcome of ACS patients undergoing coronary interventions.

Conclusions

The study by Niccoli et al. provides reliable, provocative, and clinically relevant information. It is well established that OCT is able to unravel the underlying substrate of ACS patients and also may be used to optimize the results of coronary interventions. However, demonstrating that OCT-derived information on the underlying plaque substrate has prognostic implications may herald a paradigm shift in diagnosis and management. Previous studies suggested that selected patients with ACS and IFC have favourable outcomes on medical management alone. Now these favourable findings also extend to ACS patients with IFC undergoing coronary interventions. Once again the kaleidoscope has been shaken, unravelling unique novel information; but it might have been shaken too much, disclosing an unrealistic landscape. These findings certainly should stimulate additional research. Further studies are warranted to confirm that the underlying coronary substrate in ACS patients indeed correlates with late clinical outcomes. Whether tailoring antithrombotic therapy or the type of coronary intervention
according to the underlying pathological substrate might eventually improve the prognosis of ACS patients will require further research efforts.

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References


