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CLINICAL REVIEW
Imaging

Plaque erosion: a new *in vivo* diagnosis and a potential major shift in the management of patients with acute coronary syndromes

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Pathology and *in vivo* imaging studies have identified superficial plaque erosion as a frequent and important mechanism underlying acute coronary syndromes (ACS). In contrast with plaque rupture, the pathophysiological mechanisms leading to plaque erosion remain poorly understood. The advent of intravascular imaging techniques, particularly optical coherence tomography, has aided understanding of this mode of ACS *in vivo* by complementing previous insights from pathology studies. Appreciation of the distinct biological and clinical mechanisms of plaque erosion points to the possibility of tailored management strategies for patients presenting with ACS.

Keywords Acute coronary syndrome • Atherosclerosis • Intact fibrous cap • Intravascular imaging • Optical coherence tomography • Plaque erosion

History and pathology data

Ischaemic heart disease remains a major source of morbidity and mortality worldwide. Patients with acute coronary syndromes (ACS) can have a wide spectrum of clinical presentations as well as imaging and pathology findings.[1] While coronary thrombi had traditionally been thought to arise from plaque rupture in most cases,[2–4] patients presenting with ACS exhibit a range of culprit lesion morphologies. Recognition of the second most common pathophysiological mechanism, plaque erosion, emerged initially from pathology reviews of patients with sudden cardiac death (SCD), or fatal acute myocardial infarction (AMI),[2,5–7] a concept confirmed more recently by *in vivo* intravascular imaging studies.

While understanding of the pathophysiology of plaque rupture has become well established, the mechanisms leading to plaque erosion have remained less well understood.[8] As medical therapy has proven effective for 'stabilization' of lipid-rich atheromatous plaques, further understanding of the mechanisms underlying plaque erosion and the development of targeted treatments has gained interest in recent years.

Three principal mechanisms for ACS have been proposed: (i) Plaque erosion, the focus of this article, involves the formation of thrombus in an area of endothelial denudation adjacent to an atherosclerotic plaque without disruption of the fibrous cap overlying a superficial lipid-rich necrotic core; (ii) Plaque rupture, the most common mechanism, commonly complicates lipid-rich atherosclerotic plaques with thin fibrous cap (*Figure 1*). Metalloproteinases contribute to fibrous cap rupture and exposure of the necrotic core to the vessel lumen leading to platelet activation and thrombus formation. In a small subset, plaque disruption occurs at the site of a calcified nodule.[9,10] Plaques can rupture with or without signs of systemic inflammation[1]; and (iii) In some cases, ACS can also occur without apparent thrombus.

An early study by van der Wal *et al.*[5] reported pathology findings of 20 patients who had died of AMI: 12 patients had features consistent with plaque rupture, while the other eight had evidence of superficial erosion without rupture. A subsequent series of 50 patients similarly showed a prevalence of plaque erosion in 44% and plaque rupture in 56% of patients with SCD.[6] One of the largest studies, by Arbustini *et al.*,[7] sought to evaluate the prevalence of plaque erosion by examining pathological specimens of almost 300 consecutive patients with AMI at a single institution. This study found an acute thrombus in nearly all patients (98%), and identified plaque erosion in 25% of cases, with a higher predominance in women (37.4%) than in

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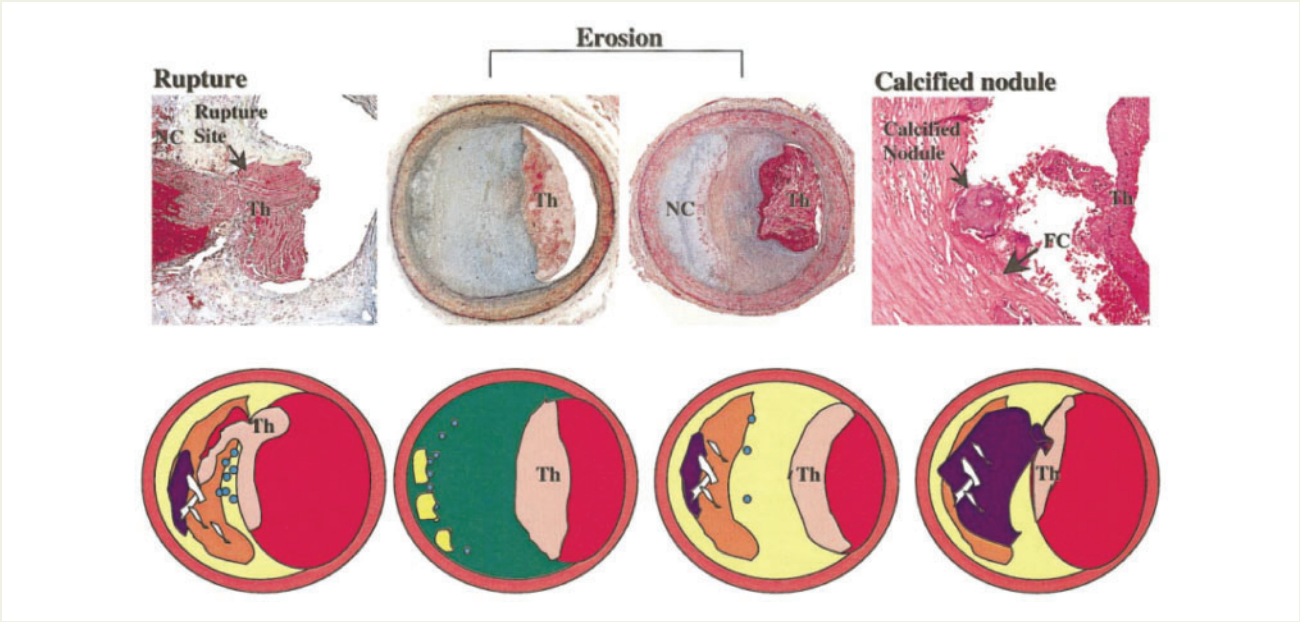

Figure 1 Left: a thin cap fibroatheroma with ruptured fibrous cap and luminal thrombi is shown. A large necrotic core communicates with the lumen. Middle: erosion occurs over lesions rich in proteoglycans and smooth muscle cells. Thrombus is attached in an area that lacks endothelium. These lesions have few inflammatory cells, in particular of mononuclear leukocytes. Right: a calcified nodule is protruding into the lumen through a disrupted thin fibrous cap (adapted from Virmani *et al.*[10]). NC, necrotic core; Th, thrombi.

men (18.5%), and no significant difference in location or distribution of infarction and thrombus.[7] Overall, 11 autopsy studies to date have described plaque erosion (*Table 1*). Taken together, they have demonstrated that, on average, the prevalence of plaque erosion associated with coronary thrombosis is 31%.[14]

Pathobiology of plaque erosion

As mentioned above, unlike plaque rupture, plaque erosion remains poorly characterized.[14] In general, plaque erosion occurs over lesions rich in proteoglycans and smooth muscle cells with local absence of intimal endothelial cells.[6,15] Breaches in endothelial integrity, probably related to local flow perturbation, implicate the exposure of the underlying collagen as one nidus for thrombus formation. Further pathology studies by Durand *et al.*[15] support this mechanism for thrombus formation by demonstrating thrombus formation at sites of experimental endothelial loss provoked by induction of apoptosis with intravascular staurosporin. Cellular expression of the histocompatibility antigen HLA-DR indicates immunological activation typically stimulated by the T cell cytokine interferon gamma.[16] Early observations showed numerous T cells and macrophages with strong HLA-DR antigen expression at the site of erosion as well as strong HLA-DR expression on smooth muscle cells in adjacent tissues.[5,6,10,11,14] Subsequent work by Sugiyama *et al.*[17] provided mechanistic insight into endothelial cell desquamation at areas of plaque erosion by demonstrating that endothelial cell death and desquamation via apoptosis or oncosis pathways could result from exposure hypochlorous acid, an oxidant species elaborated by myeloperoxidase. Macrophages within the atherosclerotic plaque sub-endothelial region can express this enzyme.[17] Subsequent studies also showed that thrombus overlying plaque erosion had higher concentrations of myeloperoxidase-positive cells than that observed in ruptured plaques.[18,19] Polymorphonuclear leukocytes contain abundant myeloperoxidase. Co-culture of endothelial cells with polymorphonuclear leukocytes can induce endothelial cell injury and death.[18,20,21] Eroded plaques have a higher concentration of extracellular matrix molecules, such as hyaluronan and versican, with considerably less decorin and biglycan typically seen in plaques that exhibit morphological characteristics associated with stability. Furthermore, a cell surface receptor for hyaluronan, CD44, localizes prominently in eroded vs. ruptured or stable plaques, pointing again to a distinct mechanistic pathway for erosion.[5,6,11,14] These findings contrast sharply with the pathobiology of plaque rupture which associates with local and systemic inflammation, activation of both innate and adaptive immunity, and thrombosis triggered by tissue factor. Plaque rupture involves macrophages much more than granulocytes. Hence, the inflammatory cell types in ruptured vs. eroded plaques differ diametrically.

Recent *in vitro* experiments by Quillard *et al.*[21] demonstrated that Toll-like receptor-2 (TLR-2) activation can drive endothelial cell damage and may contribute to denudation in areas of superficial plaque erosion (*Figure 2*). Understanding of the key role of neutrophils in erosion continues to evolve. Eroded plaques commonly contain neutrophil extracellular traps (NETs). Further, NETs can potentiate endothelial cell stress and stimulate apoptosis, and denudation of the endothelial monolayer. Neutrophil and NETs accumulation, and levels of TLR-2 correlate with apoptotic endothelial cells seen in eroded plaques in contrast with traditional 'vulnerable' or ruptured plaques.

Table 1 Pathology studies of plaque erosion and patient clinical characteristics (adapted from White et al.[14])

Study	Number of cases	Female	Average age (years)	Rupture (%)	Erosion (%)
van der Wal et al.[5]	20 thrombus	n/r	63	60	40
Farb et al.[6]	96 SCD/50 thrombus	32%	Rupture: 53 Erosion: 44	56	44
Burke et al.[22]	113 SCD/59 thrombus	0%	50	69	31
Burke et al.[23]	51 SCD/26 thrombus	100%	Rupture: 58 Erosion: 45	31	69
Arbustini et al.[7]	298 MI/291 thrombus	37%	Rupture: 68 Erosion: 70	75	25
Kolodgie et al.[11]	49 culprit plaques	0% (Rupture) 45% (Erosion) 28% (Stable)	Rupture: 46 Erosion: 41 Stable: 47	22	41
Burke et al.[24]	457 SCD/224 thrombus	n/r	n/r	69	31
Sato et al.[12]	31 MI/23 thrombus	13%	Rupture: 70 Erosion: 68	78	22
Schwartz et al.[13]	44 SCD	14%	51	57	43
Kramer et al.[25]	345 SCD/181 thrombus	11% (Rupture) 26% (Erosion)	Rupture: 52 Erosion: 43	71	29
Tavora et al.[26]	314 SCD/170 thrombus	19%	≈50	70	30

MI, myocardial infarction; n/r, not reported; SCD, sudden cardiac death.

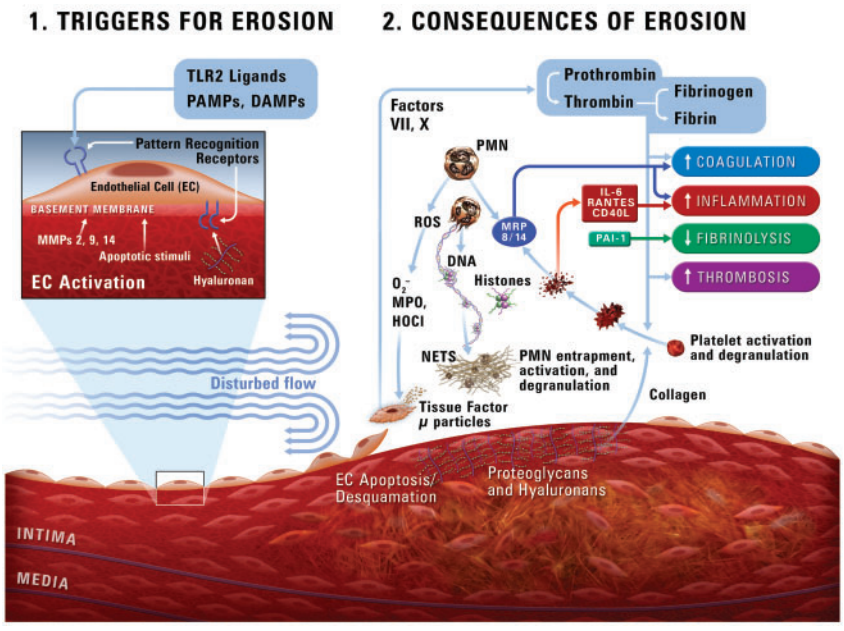

Figure 2 A schema of a potential pathophysiological pathway to superficial erosion (adapted from Quillard et al.[21]). PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns; TLR2, Toll-like receptor-2; MMP, matrix metalloproteinase; HOCl, hypochlorous acid; MPO, myeloperoxidase; NETs, neutrophil extracellular traps.

Neutrophil extracellular traps may thus contribute to the pathogenesis of plaque erosion.[21] These web-like structures consist of neutrophilic proteins (nuclear, cytoplasmic, and granular) and decondensed chromatin that entrap platelets, fibrin strands, and promote thrombosis.[21,27–29]

In summary, eroded plaques have an irregular surface with a discontinuity in the endothelial cell monolayer without fibrous cap rupture and generally lack a necrotic core. These features differ distinctly from the morphological characteristics of ruptured plaques.[10,14]

Plaque erosion appears to associate primarily with platelet-rich 'white' thrombi.[12,13] In contrast, plaque rupture exposes various thrombogenic substrates including tissue factor that stimulate the coagulation cascade and fibrillar collagens that activate platelets, yielding mixed fibrin/erythrocyte-rich ('red') and platelet-rich ('white') thrombi. Indeed, *in vivo* study after successful thrombolysis showed that the predominant component of residual thrombus was platelets in erosion and erythrocytes in rupture.[30]

In vivo diagnosis and intravascular imaging

The advent of intravascular imaging permits more detailed evaluation and better understanding of the morphological aspects discussed above, as well as the ability to diagnose these findings *in vivo* and correlate them with clinical presentations. Optical coherence tomography (OCT), with a resolution of 10–20 μm, made it possible to visualize directly microscopic features of a plaque including fibrous cap, microvessels, thrombus, inflammatory cells, and cholesterol crystals in addition to macroscopic plaque morphology. Occasionally thrombus, particularly red thrombus, at the culprit lesion interferes with evaluation of underlying plaque morphology. In such cases, repeated aspiration thrombectomy or several days of antithrombotic treatment may improve visualization of the underlying plaque.

In vivo prevalence of plaque erosion

In 2005, Hayashi *et al.*[31] reported that 39% of patients with AMI had erosion identified by coronary angioscopy (*Table 2*). Patients with erosion, as opposed to those with rupture, more frequently presented with 'pre-infarction' angina and had smaller infarct size. Kubo *et al.*[32] studied 30 patients presenting with ACS and reported superficial erosion in 23% of cases by OCT. Kusama *et al.*[33] reported that 37% of patients with acute anterior myocardial infarction lacked signs of culprit plaque rupture by intravascular ultrasound. Those studies, however, did not use clear diagnostic criteria for erosion. Visualization of the endothelial monolayer (1–5 μm) is below the resolution of OCT (10–15 μm). This recognition spurred the development of new criteria for the OCT diagnosis of plaque erosion (*Figure 3*).[34] The presence of an intact fibrous cap at the culprit site differentiates erosion from rupture. Unlike autopsy studies, the *in vivo* diagnosis of erosion requires consideration of other factors such as the effects of antithrombotic therapy and limitations of OCT. Optical coherence tomography usually shows fibrous cap fracture in ruptured plaques unambiguously (*Figure 4*). Plaque erosion is a diagnosis of exclusion. The absence of fibrous cap rupture and a cavity in a patient with ACS suggests the diagnosis of plaque erosion, especially if accompanied by thrombus or an irregular intimal surface. Some groups have consequently proposed to refer to this imaging finding as 'intact fibrous cap' rather than as erosion. A Supplementary material online, *Figure S1* includes additional OCT images of erosion.

Using the newly established OCT diagnostic criteria, Jia *et al.*[34] reported erosion in 31% of patients with ACS. Subsequent studies by Higuma *et al.*,[35] Saia *et al.*,[36] and Kajander *et al.*[39] showed that the prevalence of erosion was 27%, 33%, and 44% in patients with AMI, respectively. Niccoli *et al.*,[40] Yonetsu *et al.*,[39] and Kwon *et al.*[41]

Table 2 ***In vivo*** **prevalence of plaque rupture and plaque erosion in patients with acute coronary syndromes and acute myocardial infarction**

Author	Presentation	Number	Modality	Plaque with rupture (%)	Plaque without rupture (%)	Others
Hayashi *et al.*[31]	AMI	107 (72)	Angioscopy	61	39	
Kubo *et al.*[32]	AMI	30	OCT	73	23	
Kusama *et al.*[33]	Anterior MI	91	IVUS	59	41	
Ozaki 2011	ACS	57 (35)	CT	71	29	
Jia *et al.*[34]	ACS	126 (104)	OCT	44	31	8% (CN)
Higuma *et al.*[35]	AMI	112	OCT	64	27	8% (CN)
Saia *et al.*[36]	AMI	140 (97)	OCT	65	33	2% (SCAD)
Niccoli *et al.*[37]	ACS	139	OCT	59	41	
Yonetsu *et al.*[38]	ACS	318	OCT	44	41	15%[a]
Kajander *et al.*[39]	AMI	93	OCT	49	44	7% (CN)
Kwon *et al.*[41]	ACS	133	OCT	68	32	

Number: a total number of patients enrolled in the study. The number in parenthesis is the number of patients included in analysis.
ACS, acute coronary syndromes; AMI, acute myocardial infarction; CN, calcified nodule; IVUS, intravascular ultrasound; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection.
[a]Massive thrombus.

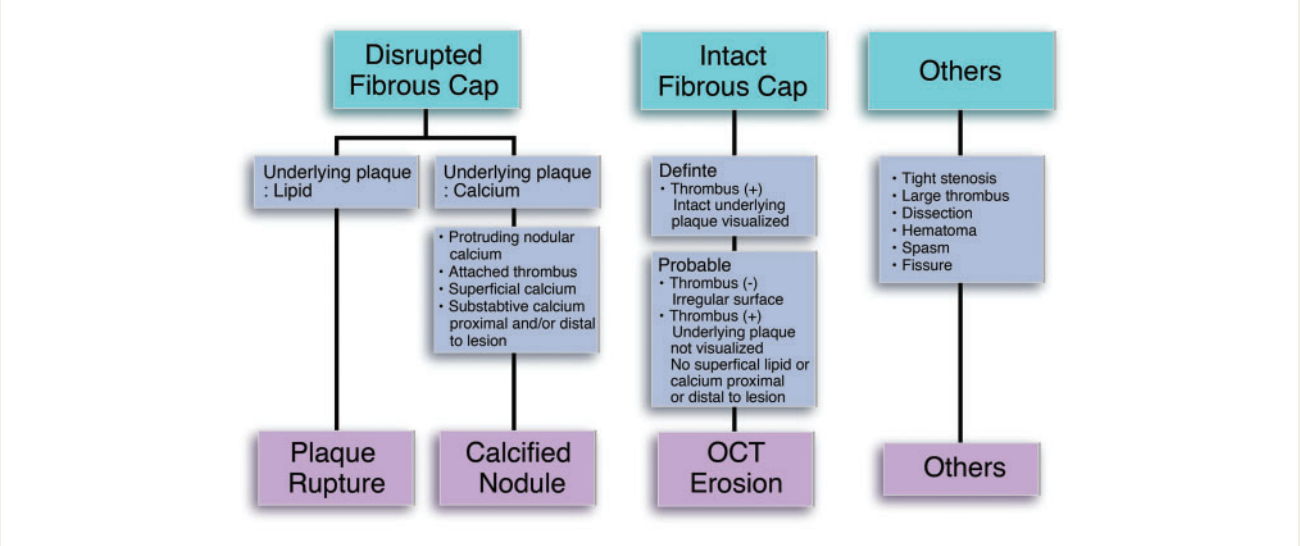

Figure 3 An intact fibrous cap separates erosion from rupture or calcified nodule. In lesions without an intact fibrous cap, other characteristics of the underlying plaque further categorize the atheroma disruption as due to rupture or to penetration by a calcified nodule (adapted from Jia *et al.*[34]). OCT, optical coherence tomography.

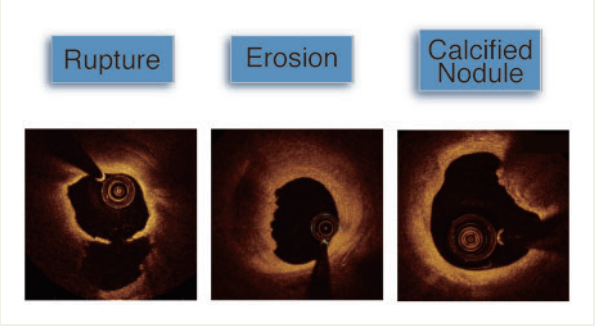

Figure 4 Optical coherence tomography imaging of a ruptured plaque shows circumferential superficial lipid and ruptured fibrous cap at 6 o'clock communicating with an empty cavity. A plaque complicated by erosion shows preserved vascular structure with larger lumen and the appearance of a platelet-rich thrombus. A calcific nodule resides at 1–3 o'clock. Such deposits are often seen in the area of substantive calcification.

reported the prevalence of erosion in 24%, 41%, and 32% of ACS patients, respectively. Taken together, the prevalence of erosion as determined by OCT ranges between 30% and 40% in patients with ACS/AMI. As patients with ACS do not undergo intravascular imaging routinely, the studies cited above may underestimate the actual incidence of plaque erosion.[42]

Type of lesion and clinical presentations

In the first systematic OCT study, of 126 patients with ACS, plaque erosion associated with non-ST-segment elevation ACS (NSTE-ACS) clinical presentation in 61.5% of patients. In contrast, plaque rupture occurred more commonly in ST-segment elevation myocardial infarction (STEMI) in 70.9% of cases, but in only 29.1% of

Table 3 Incidence of ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndromes/unstable angina pectoris in patients with plaque erosion

	STEMI (%)	NSTE-ACS/UAP (%)
Jia *et al.*[34]	38.5	61.5
Niccoli *et al.*[37]	29.8	70.2
Yonetsu *et al.*[38]	16	84
Kwon *et al.*[41]	35	65

NSTE-ACS, non-ST-segment elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

NSTE-ACS.[34] Consistent with autopsy studies, patients with the culprit plaque erosion more frequently had NSTE-ACS. With less disruption of arterial integrity and larger lumens, patients with erosion might have non-occlusive thrombus or occlusive thrombus that could easily embolize distally. Four studies that included both STEMI and NSTE-ACS patients consistently showed higher incidence of NSTE-ACS in patients with plaque erosion (*Table 3*).

Management of acute coronary syndromes due to superficial erosion and future directions

Current guidelines for the management of both STEMI and NSTE-ACS generally recommend early percutaneous coronary intervention (PCI) and stent implantation to achieve reperfusion and revascularization. Improved plaque imaging has shown the ability to distinguish the underlying pathophysiological mechanism of thrombosis, and thus offer the opportunity to tailor management.

Impact on outcome: erosion vs. rupture

Advances in culprit lesion imaging have improved understanding of the clinical features of erosion vs. rupture. A retrospective study by Higuma *et al.*[35] showed that ACS associated with plaque rupture, has higher risk of larger infarction size, no-reflow phenomenon, and subsequently lower left ventricular function. A recent study by Yonetsu *et al.*[38] showed that ACS patients with plaque erosion had better long-term prognosis than those with plaque rupture during a median follow-up of 576 days. Another study with 139 consecutive ACS patients (66% NSTE-ACS, 34% STEMI) also showed fewer major adverse cardiac events in patients with intact fibrous cap (14.0%) when compared with plaque rupture (39.0%) during up to 3 years of follow-up.[37] The mechanisms that underlie the worse outcome of plaque rupture remain speculative and require further research.

Vascular response to stenting: erosion vs. rupture

Possible differences in responses to PCI in rupture vs. erosion remain poorly understood. Higuma *et al.*[35] studied 112 patients with STEMI and found that those with plaque erosion had less microvascular damage and a trend towards less myocardial damage post-PCI. Saia *et al.*[36] evaluated 140 consecutive patients with STEMI who underwent OCT pre-, immediately post, and 9-month post-DES implantation. They showed no differences in plaque morphology between erosion and rupture at follow-up. Both groups had similar late lumen loss, restenosis, neointimal area, malapposition, or stent strut coverage.[36] Another study found more favourable immediate post-stent outcomes in plaque erosion than in plaque rupture in 141 patients with ACS.[44] There were lower rates of stent malapposition (7.3% vs. 37.5%, $P < 0.001$), thrombus (14.6% vs. 59.4%, $P < 0.001$), protrusion (73.2% vs. 93.8%, $P = 0.008$), no-reflow and distal embolization in erosion vs. rupture. In contrast, a recent study of 65 patients with ACS who underwent 6-month follow-up OCT showed that plaque erosion (37% of cases) less favourable vascular healing following DES implantation at 6 months when compared with plaque rupture. The degree of neointima coverage was lower and a ratio of uncovered/covered struts was higher at 6 months in the plaque erosion compared with plaque rupture.[45] While the mechanisms for these findings remain uncertain, greater release of platelet-derived growth factor from a larger thrombus burden following rupture might have contributed to better healing.

Seminal prospective trials

Given the potential differences in vascular responses to PCI between plaque rupture and erosion and the association of plaque erosion with better overall clinical prognosis, a shift in management focusing on antithrombotic therapies rather than PCI in erosion cases merits consideration.[42] Potential benefits include avoiding the risk of stent thrombosis and restenosis, and the need for prolonged dual antiplatelet therapy. An observational retrospective study showed that patients with OCT-defined plaque erosion who underwent aspiration thrombectomy remained asymptomatic for over 2 years. In this study, of 31 patients identified from four institutions, 40% were managed with dual antiplatelet therapy without PCI and 60% were managed with dual antiplatelet therapy plus PCI at the discretion of the treating clinicians. After over 2 years of follow-up, all patients remained asymptomatic regardless of stent implantation.[46]

The EROSION study was the first proof-of-concept study aimed at tailoring the treatment of ACS due to plaque erosion. This study showed the feasibility and initial safety of antithrombotic therapy without stenting in patients with plaque erosion.[47] If OCT showed plaque erosion, and the residual vessel stenosis was <70% with TIMI grade 3 flow, patients received antithrombotic therapy without stenting (heparin for 3 days with concurrent aspirin and ticagrelor). Many patients also received glycoprotein IIb/IIIa antagonists, tirofiban. Plaque erosion was found in 25.4% of all cases, and at 1-month OCT follow-up, 78.3% of patients showed >50% decrease in thrombus volume (primary endpoint), and all but two patients remained free of major adverse cardiac events. While from a small, single-centre study, these data support further evaluation of therapeutic approaches tailored to the specific underlying mechanism of ACS.[29]

Clinical implications

Taken together, these findings suggest that pharmacological rather than mechanical intervention could provide an optimal treatment for patients with plaque erosion. This proposition calls for larger, randomized studies to affirm the pilot data and evaluate longer-term outcomes to test rigorously this novel management strategy for ACS due to plaque erosion. Ultimately, larger scale trials assessing the approach by which a combination of erosion-specific biomarkers[40] and high resolution, non-invasive imaging that sharpens the ability to diagnose accurately plaque erosion, might pave the way towards practicing precision medicine based on pathophysiology of ACS. Confirmation of this concept in large-scale trials with longer follow-up could lead not only to a major shift in the management of over a million patients with ACS each year, but also to substantial saving of health care resources.

Supplementary material

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

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