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EDITORIAL

Superficial erosion and the precision management of acute coronary syndromes: not one-size-fits-all

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This editorial refers to 'Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study)'†, by H. Jia *et al.*, on page 792.

Post-mortem evaluation of the culprit lesions associated with coronary thrombosis identified superficial erosion as a mechanism that accounts for a substantial proportion of acute coronary syndromes (ACS).[1,2] The morphological study of superficial erosion reveals sessile thrombi overlying plaques that characteristically lack the thin fibrous cap typically found in lesions complicated by plaque rupture, long considered the dominant mechanism provoking ACS. As autopsy studies require death as an entry criterion, the actual prevalence of superficial erosion as a cause of non-fatal ACS has remained unclear. The advent of optical coherence tomography (OCT) has helped to remedy this knowledge gap. OCT provides a nearly microscopic near field view of the arterial intima. This invasive intravascular imaging technique sheds new 'light' on the underlying mechanisms of acute coronary thrombosis. OCT visualizes readily ruptured fibrous caps, the hallmark of plaque rupture. Practitioners of OCT have developed criteria that allow classification of culprit lesions causing ACS as ruptured, definite erosion, and possible erosion.[3] This important advance in intracoronary imaging allows us to deepen our probing of the mechanisms underlying ACS in a broader swath of patients than permitted by post-mortem examination.

Most of our understanding of the prevalence of superficial erosion as a substrate for ACS derived from autopsy studies performed in the last century. Now, OCT enables us to obtain a more contemporary snapshot of the proportion of ACS due to superficial erosion. Recent studies suggest that a quarter to a third or more of ACS in the current era result from culprit lesions with intact fibrous caps.[2,3]

We have proposed the hypothesis that superficial erosion is on the rise as a cause of ACS due to the success of current preventive measures.[4,5] Lipid-lowering, anti-hypertensive therapy, and smoking cessation, we argue, have changed human atherosclerosis in ways that reduce lipid accumulation, quell inflammation, and render plaques less likely to rupture and provoke thrombosis.[6] A reduction in rupture could expand the proportion of ACS due to superficial erosion. Such a shift would highlight the importance of this problem as a contributor to the unacceptable burden of residual risk in ACS despite today's standard of care.[7] The possibly rising prevalence of superficial erosion and the implementation of successful therapies for the prevention and treatment of plaque rupture bring to the fore the need to determine whether the strategies that we have developed and validated for treatment of ACS apply equally to those provoked by superficial erosion or by a fissured fibrous cap. The current impetus to adopt a greater degree of precision medicine personalized management underscores the urgency of this question.[8]

Why might the optimal therapeutic approach to superficial erosion differ from ACS produced by plaque rupture? The pathophysiology of superficial erosion appears quite distinct. Rupture characteristically complicates a thin-capped, lipid-rich atheroma with abundant macrophages. In contrast, lesions associated with superficial erosion harbour relatively few inflammatory cells, but contain abundant extracellular matrix characterized by accumulations of collagen, proteoglycan, and glycosaminoglycans (*Figure 1*, right panel). In contrast to more fibrin-rich 'red' thrombi, those associated with erosion appear more platelet rich ('white' thrombi).[9] These findings could reflect differences in the mechanisms that trigger thrombosis in these two types of lesions.

Clotting provoked by plaque rupture probably results from contact of blood with tissue factor-derived primarily from macrophages, a cell type that abounds in lesions with morphology associated with fissure of the fibrous cap (*Figure 1*, left panel). Thrombi complicating plaques with intact fibrous caps, on the other hand, may result initially

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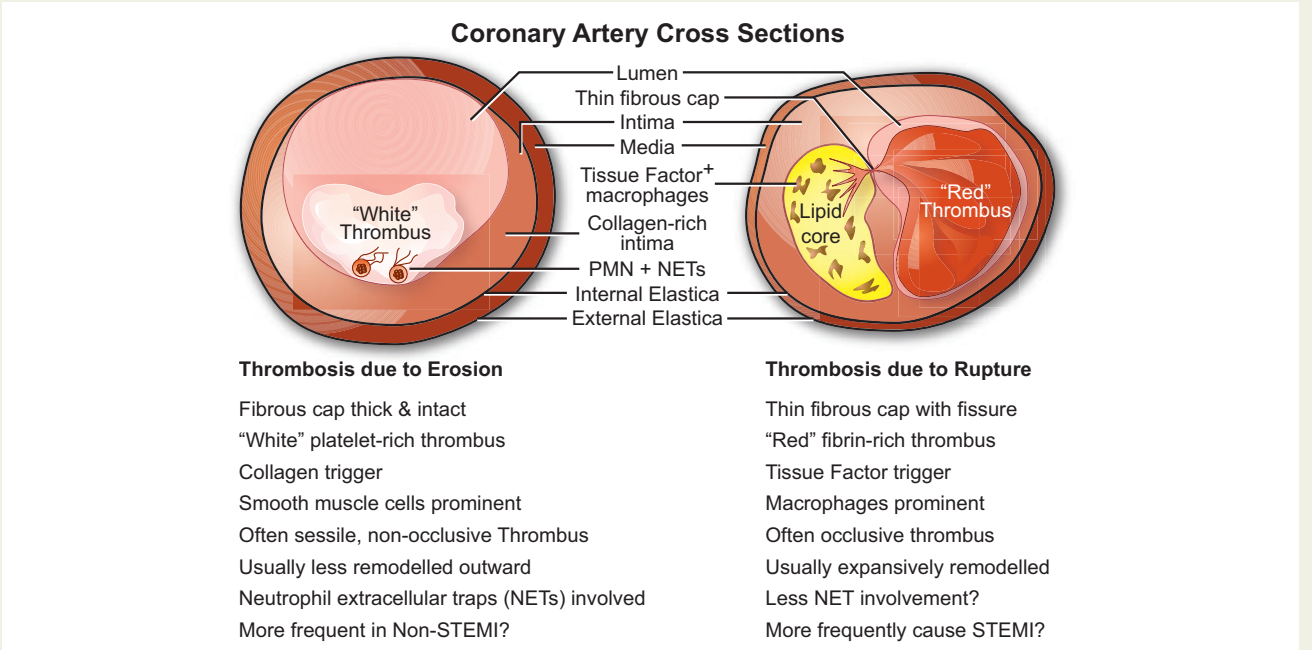

Figure 1 Distinct mechanisms may trigger coronary thrombosis due to superficial erosion vs. fibrous cap rupture. This diagram depicts cross-sections of coronary arteries. On the left, thrombosis due to erosion shows a sessile, 'white' thrombus superimposed on an extracellular matrix-rich lesion with little or no expansive remodelling. Endothelial cell sloughing or death can expose plaque collagen that can initiate such platelet-rich thrombi. Recruited polymorphonuclear leucocytes (PMN) can contribute to a second wave of thrombus amplification and propagation due to their elaboration of neutrophil extracellular traps (NETs). Further, erosion may associate more frequently with non-ST-segment elevation myocardial infarction (non-STEMI) than with STEMI.[5] The right side of this illustration depicts thrombosis due to rupture that typically results from a lesion with a fissured thin fibrous cap. Such thrombi tend to slant towards a 'red' fibrin-rich clot. Tissue factor derived from the abundant macrophages probably triggers thrombosis in plaque rupture. In thrombosis due to plaque rupture, the underlying lesions may more often exhibit expansive remodelling, and the thrombi may more often occlude the vessel and provoke a STEMI vs. a non-STEMI.

from contact of platelets with collagen, an extracellular matrix component characteristically prominent in plaques that erode and cause clot formation (*Figure 1*, right panel).

Degranulation of platelets activated by collagen on the denuded intimal surface of the eroded plaque, as in the laboratory test tube, causes release or exteriorization of pre-formed mediators including leucocyte chemoattractants (e.g. RANTES), pro-inflammatory cytokines (e.g. CD40L), as well as ADP, a purine derivative that propagates platelet activation and aggregation. Chemoattractants for polymorphonuclear leucocytes (PMN) and adhesion molecules induced by pro-inflammatory cytokines released by platelets at the site of erosion can recruit neutrophils, and further granulocytes can become enmeshed in the forming fibrin network as the clot propagates. These granulocytes that accumulate at the site of superficial erosion can elaborate structures known as neutrophil extracellular traps (NETs). These strands of DNA extruded by dying granulocytes become decorated with tissue factor, myeloperoxidase, and various proteases that may sustain and amplify thrombosis and inflammation locally.[10–12]

Given the dichotomy in these two mechanisms that give rise to ACS, in the spirit of precision or personalized medicine, should the mode of thrombosis dictate specific therapeutic approaches? Current standard of care mandates immediate stenting for ST-segment elevation myocardial infarction (STEMI), and usually an early invasive strategy with stenting for many cases of non-STEMI. Could erosion, given its distinct features, have an optimal management strategy that differs from our current one-size-fits-all approach? Prati *et al.* described 31 patients with STEMI who had culprit lesions with intact fibrous caps by OCT, thus classified as superficial erosion.[13] As the coronary thrombi in ~40% of these cases did not critically obstruct the vessel, they underwent treatment with dual anti-platelet therapy. The remaining 60% underwent stenting. After >2 years of follow-up, the type of therapy did not seem to make a difference in outcome. At follow-up, no patients in either group had ischaemic symptoms. The EROSION study, in this issue of the journal, advanced this concept in a series of patients with STEMI ACS with OCT-defined erosion who were treated with anti-coagulant/anti-platelet but no mechanical revascularization therapy.[14] The study lacked an arm of prompt stenting for STEMI ACS that would provide a comparison with current standard of care. By its very design, the study was not blind. The primary endpoint was an apparently arbitrary >50% reduction in thrombus burden. A secondary endpoint examined major adverse coronary events, although the study was underpowered in this regard. EROSION was prospective and relatively large: it enrolled 60 patients with ACS attributed to erosion at a single centre in Harbin, China. Almost 80% of the patients showed a > 50% reduction of thrombus volume after 1 month. More than a third of patients had no thrombus detectable at

the 1-month follow up. This study and that of Prati *et al.* suggest that pharmacological rather than interventional treatment may effectively manage coronary thrombosis due to superficial erosion.

In addition to lacking a control group in EROSION, there was non-randomized allocation to various anti-coagulant/anti-platelet therapies according to the discretion of the local care team. Many patients received glycoprotein IIb/IIIa inhibitors, a therapeutic approach that may currently see less use in other practice environments. The study population seems somewhat unusual, as 393 of the 405 ACS patients presented with STEMI. Contemporary trends in other countries show a growing predominance of non-STEMI compared with STEMI. Thus, the patient population studied in EROSION may not reflect practice in all environments.

Both the series reported by Prati and the EROSION study used OCT to define erosion. This invasive technique often requires clearing blood with a contrast flush. While an excellent research tool, routine OCT will probably prove impractical for widespread routine diagnostic use on the frontline of cardiology practice worldwide. Could one use soluble biomarkers to define a subset of ACS patients whose thrombosis more probably results from erosion rather than rupture? Ferrante *et al.* found that blood concentrations of myeloperoxidase, a product of granulocytes, rose in individuals with OCT-defined superficial erosion compared with patients with ACS due to plaque rupture.[15] We have presented evidence that NET formation occurs more frequently in atheromata with characteristics of 'eroded' vs. 'ruptured' lesions. Biomarkers of NET formation might thus add to the discrimination between ACS caused by erosion vs. rupture. Indeed, assays for NETs that may prove clinically practicable are under development, and patients with ACS overall have higher levels of biomarkers of NETs than patients with stable angina.[16] Ultimately, we will need randomized clinical trials, perhaps guided by such biomarkers, to put the provocative proposition of the Prati series and the EROSION study to a rigorous test. The prospect of such a trial may seem daunting. Yet, because superficial erosion currently causes up to a third of ACS, such a change in practice could change our management of an enormous number of individuals. Moreover, the expense and potential complications of stenting over and above dual anti-platelet therapy could render such a trial worthwhile. Such a strategy of a biomarker-defined allocation of specific therapies would take us a step closer to the goal of personalized, precision medicine.[17,18] This prospect promises an advance beyond our current 'one-size-fits-all' approach to invasive revascularization for most ACS.

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