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Editorial

Plaque erosion: Towards precision medicine in acute coronary syndromes

Filippo Crea [a,b,*], Rocco Vergallo [a]

[a] Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico A. Gemelli IRCCS, Roma, Italy
[b] Università Cattolica del Sacro Cuore, Rome, Roma, Italy

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"*Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. […] What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?*"
[– President Barack Obama, January 30, 2015. The Precision Medicine Initiative.]

For many years, we have known from pathology studies that the proximate cause of most acute coronary syndromes (ACS) is obstructive thrombosis triggered by plaque fissure or, less frequently, erosion [1,2]. Evidence supporting the notion that these two plaque complications represent distinct entities, with different pathogenesis and divergent prognosis, is becoming robust [1,3–5]. Yet, when a patient with ACS comes to our attention, we still triage him exclusively on the basis of the presence or absence of ST-segment elevation, assess him by coronary angiography, and treat him almost invariably by stenting of the culprit vessel and by a potent antithrombotic treatment. During the past two decades, the advent of optical coherence tomography (OCT) imaging allowed us to gain new insights into the pathogenesis of acute coronary thrombosis in vivo, and to get a more contemporary snapshot of the relative proportion of these two mechanisms of instability in patients with ACS [4,5]. Recent studies suggest that culprit plaques with intact fibrous cap, namely erosion, are responsible of more than one third of ACS [5]. Plaque erosion seems to be on the rise as cause of coronary thrombosis, probably due to the changing of the cardiovascular risk profile and demographics of patients with ACS and to the success of the current preventive measures, which are actively changing atherosclerotic disease phenotype [1,2]. Aggressive lipid-lowering therapies, anti-hypertensive treatments, and smoking cessation, are modifying human atherosclerosis by reducing lipid accumulation, increasing fibrous cap thickness, and suppressing inflammation. This might determine a further reduction of the prevalence of fissure as a cause of ACS, with a relative expansion of the proportion of ACS due to plaque erosion [1,2]. Why is the precise identification of patients with ACS caused by plaque erosion or fissure becoming so important? These two groups of patients appear sharply distinct in pathophysiology, atherosclerotic phenotype, and clinical outcome [4–6]. Our group recently demonstrated an alteration of hyaluronan metabolism in patients with ACS caused by plaque erosion [4]. In particular, gene expression of hyaluronidase 2, an enzyme degrading high-molecular-weight hyaluronan into its proinflammatory 20-kDa isoform, and of CD44v6 splicing variant of hyaluronan receptor were significantly higher in patients with plaque erosion than in those with plaque fissure [4]. These observations, for the first time, seem to pave the way toward novel targets in ACS that might promote the use of specific circulating biomarkers for plaque erosion and the development of personalized therapeutic strategies.

In this issue of the Journal, Kim et al. [7] add another important piece to this complex puzzle by suggesting the presence of an angiographic signature in patients with plaque erosion. Using data from an international multicenter registry, the authors assessed the angiographic features of 494 patients with non-ST-segment elevation (NSTE)-ACS after dividing them into plaque fissure and erosion based on the culprit lesion morphology at OCT imaging. The frequent observation of plaque erosion in this study (i.e., almost 50% of cases) supported, once again, the notion of its possibly rising prevalence in the current era of aggressive lipid-lowering therapies. One of the main findings of the study was that patients with plaque erosion had a lower overall atherosclerotic disease burden compared to patients with plaque fissure. These findings are in keeping with the observations of a lower pancoronary vulnerability in

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* Corresponding author at: Department of Cardiovascular and Thoracic Sciences, Policlinico Universitario A Gemelli IRCCS, Catholic University of the Sacred Heart, Largo Agostino Gemelli, 8, 00168 Rome, Italy.
E-mail address: filippo.crea@unicatt.it (F. Crea).

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patients with plaque erosion in previous three-vessel OCT studies [6,8], and may explain the better prognosis at long-term follow up in these patients as compared to those with plaque fissure [5]. Furthermore, the study by Kim et al. [7] demonstrated that plaque erosion had smaller reference diameter, less complex morphology, and lower prevalence of calcification and thrombus as compared with rupture.

Taken together, these observations bring to the fore the need to establish whether the strategies that we have refined and validated for treating ACS are equally applicable to both patients caused by plaque erosion or plaque fissure. The EROSION study demonstrated that plaque erosions causing a non-significant lumen stenosis (i.e., <70% diameter stenosis by coronary angiography) might be stabilized by potent antithrombotic therapy without the need for stent implantation in the setting of ST-segment elevation myocardial infarction (STEMI) [9]. Yet, an arm of prompt coronary stenting, that would have provided a comparison with current standard of care, was not included in that study. Randomized trials are therefore required to determine whether a conservative management of patients with erosion is at least non-inferior to coronary stenting in the setting of ACS.

Another interesting finding observed by Kim et al. [7] was the preferential localization of plaque erosion in the mid left anterior descending artery (LAD). This feature may be related to local hemodynamic factors, including altered shear stress, acting in a vessel with several emerging side branches, such as mid LAD with its septal and diagonal branches. Recent studies suggest that high endothelial shear stress may contribute to the onset of plaque erosion thus promoting endothelial detachment, platelet aggregation and thrombogenicity [1,2].

The authors have to be congratulated for the many insights provided by this and their previous studies in this important and promising field of investigation. Yet, several questions remain unanswered. For instance, what is the predictive value of clinical and demographic findings for plaque erosion in the current era of cardiovascular prevention and aggressive lipid-lowering therapies? Historically, plaque erosion has been considered a disease of young patients, typically women, and active smokers, as suggested by seminal pathology studies [1,2]. A recent large OCT study found similar findings, but it included Chinese patients admitted for STEMI only, thus the results are not generalizable [10]. Other recent studies enrolling contemporary patient populations with

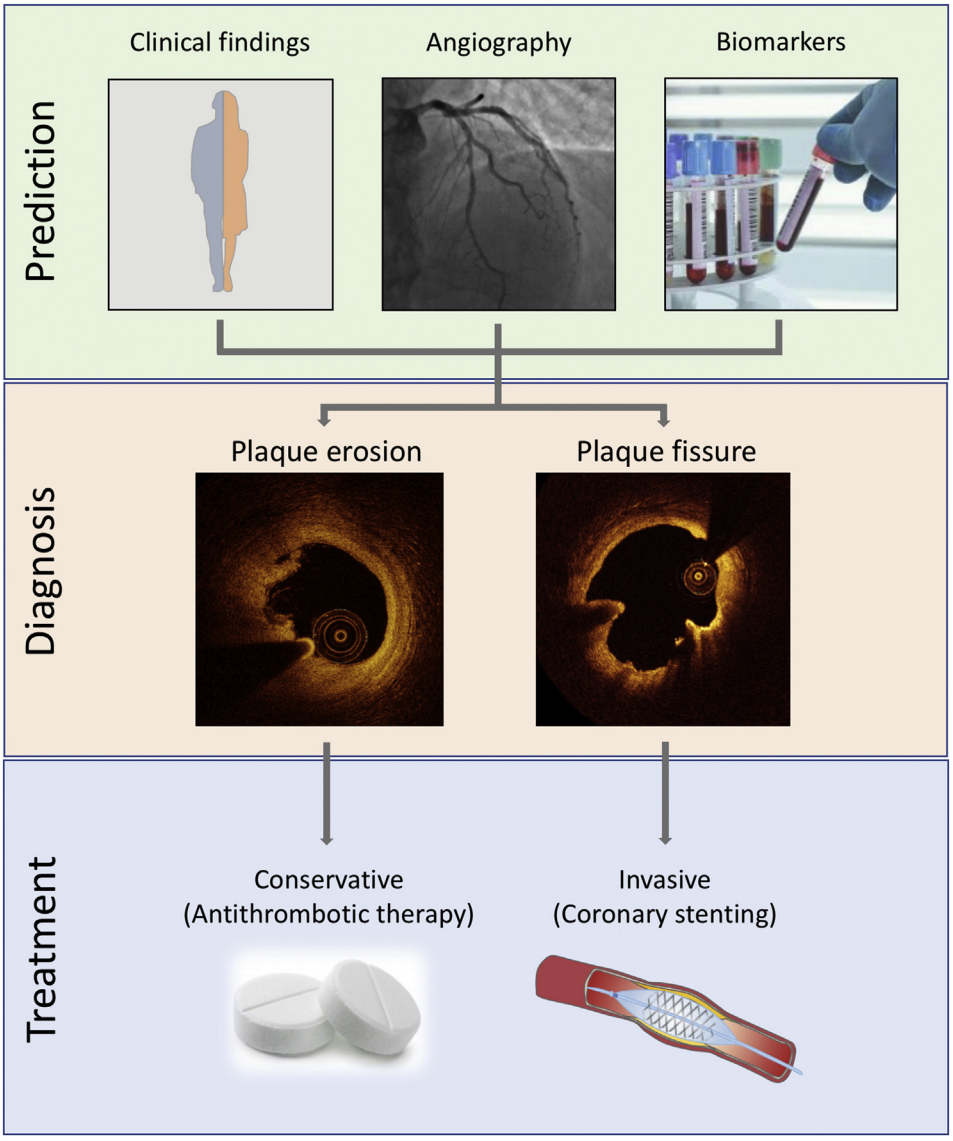

Fig. 1. Prediction, diagnosis, and treatment of plaque erosion in the era of precision medicine. Angiographic and clinical findings and, hopefully, novel circulating biomarkers will, in the near future, help identifying plaque erosion without the need for a systematic use of OCT imaging. If confirmed in future studies, patients with plaque erosion without significant stenosis might be conservatively treated with medical therapy (e.g., antithrombotic drugs, novel agents), thus avoiding stenting and its complications.

different ethnicities, including the current study by Kim et al., failed to identify significant differences in demographics and cardiovascular risk profile between patients with and without plaque erosion [5,7]. It will probably be necessary to identify novel biomarkers able to non-invasively identify plaque erosion among patients with an ACS. Myeloperoxidase and hyaluronidase-2 are potential candidate to this end [3,4].

In conclusion, this elegant study by Kim et al. provides us with new instruments for the prediction of coronary plaque erosion among patients with ACS. Angiographic and clinical findings and, hopefully, novel circulating biomarkers will, in the near future, help identifying plaque erosion without the need for a systematic use of OCT imaging (Fig. 1). If confirmed in future studies, patients with plaque erosion without significant stenosis might be conservatively treated using antithrombotic therapy or novel agents (e.g., drugs interfering with hyaluronan metabolism), thus avoiding stenting and its complications. We have a long journey ahead before the grail of precision medicine is achieved in patients with ACS, although this event horizon is now in sight.

Fundings

None.

Conflicts of interest

Nothing to disclose.

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