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EDITORIAL

The quiescent volcanoes that don't harm anymore

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Cardiologists examine the coronary vessels much like geologists study volcanoes – by observing their continuous structural evolution and confronting similar questions: is the volcano a dormant Mauna Kea or an active Etna?

Plaque ulceration is a traumatic event in the course of atherosclerosis that most often progresses silently[1]. A long-standing question has been whether these dangerous phases of plaque destabilisation are associated with worse clinical prognosis. Several earlier studies – although not supported by robust evidence regarding the risk associated with these signs of prior plaque ulceration – have used non-culprit plaque rupture (NCPR) as a marker of high risk and investigated its prognostic significance without being able to reach definitive conclusions[2,3].

In this issue of EuroIntervention, Zhao et al[4] assess the prognostic impact of NCPR in an optical coherence tomography (OCT) study of the three major coronary vessels, for which their efforts should be commended. The authors examined, with 3-vessel OCT, a total of 930 ST-segment elevation myocardial infarction patients with 3,660 non-culprit lesions. NCPR was detected in 165 patients (18% of cases). During a median 4.1-year follow-up, non-culprit lesion-related coronary events (cardiac death, non-fatal myocardial infarction, and unplanned ischaemia-driven revascularisation) occurred more frequently in patients with versus without NCPR (hazard ratio [HR] 2.25, 95% confidence interval [CI]: 1.13-4.49; p=0.021). However, after adjusting for non-ruptured thin-cap fibroatheroma (TCFA), non-ruptured TCFA (HR 2.72, 95% CI: 1.37-5.40; p=0.004), but not plaque rupture (HR 1.48, 95% CI: 0.70-3.14; p=0.304), at the non-culprit site was significantly associated with non-culprit lesion-related coronary events.

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The reported prevalence of approximately 18% aligns with previous intravascular ultrasound studies of the major epicardial vessels[5]. This is an important observation, as it helps estimate the frequency of this potentially life-threatening pathophysiological phenomenon. The prevalence of NCPR, in fact, is relatively modest and argues against the hypothesis that plaque rupture is a particularly common event. It must also be remembered, however, that plaque ulcerations – when studied over months or years – undergo reparative processes that may evolve into morphologies recognisable on OCT as multilayer plaque[6,7]. A second major finding of the study concerns the relative stability of NCPR, which, in the multivariable analysis, was not found to be associated with an increased incidence of cardiovascular events. This suggests that the ulcerated cavity may undergo reparative histopathological processes, including re-endothelialisation, which protects it from further destabilisation. The appearance of plaque ulceration on OCT is instinctively perceived by interventional cardiologists as a dangerous factor requiring immediate pre-emptive treatment even if located at sites considered non-culprit. The conclusions of the present study are certainly not in favour of this approach. Instead, they are consistent with the few clinical observations that support the stability of these lesions over time[8]. Although *ad hoc* imaging studies are warranted in this regard, it seems reasonable to assume that, unless there is significant luminal

narrowing at the site of NCPR, proceeding with local invasive treatment should be avoided.

Nevertheless, in the presence of NCPR, operators should extensively evaluate other plaque characteristics, keeping in mind that NCPR should be interpreted as a marker of more aggressive coronary artery disease. According to Zhao et al, NCPR is more likely to occur in more advanced atherosclerotic plaques characterised by a large lipid core, a thin fibrous cap, and a more abundant macrophage infiltration. The authors reported a higher proportion of vulnerable plaque characteristics in patients with versus without plaque rupture (all p<0.001), with non-ruptured TCFA being detected in 33.3% of patients with non-culprit plaque rupture versus 20.8% of patients without (p=0.001).

This paper adds another piece to the complex puzzle of high-risk coronary plaque detection. Several prior studies have highlighted the importance of combining multiple high-risk morphological features[9]. Recently, the long-term follow-up of the CLIMA study reported on the prognostic impact of the simultaneous presence in the same lesion of four vulnerability criteria (thin fibrous cap <75 µm, minimal lumen area <3.5 mm^2, lipid arc >180°, presence of macrophages) up to 5 years[10]. The PECTUS study[2] considered other criteria, including NCPR together with a thin fibrous cap <65 µm and a large lipid arc >90°. Once a thin fibrous cap undergoes rupture, causing local thrombosis, other morphological elements such as a reduced lumen or a large lipid plaque can transform the event into a complete vessel occlusion. The work of Zhao et al[4] is certainly instrumental in this regard, offering the conclusion that NCPR does not work as an independent marker of plaque vulnerability.

The paper, although interesting and original, has some limitations that should be acknowledged. Apart from its retrospective nature, a major limitation resides in its design and in the choice of a primary endpoint including unplanned revascularisations. The adoption of invasive imaging modalities for tackling cardiovascular events should aim at reducing hard endpoints, including cardiac death and myocardial infarction. Additionally, the study was underpowered for assessing hard events, as only 10 non-fatal target vessel myocardial infarctions were included. Lastly, despite the choice of a 65-micron threshold to detect thin fibrous caps, which is a validated histological cutoff for identifying vulnerable lesions, it remains uncertain whether the use of less restrictive thresholds (e.g., 75 microns) would have yielded different results.

In conclusion, the message of the present paper is rather reassuring. NCPR is a sign of past plaque destabilisation that should not cause harm anymore. They are like old volcanoes that, after eruptive periods, geologists would consider dormant.

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Conflict of interest statement

F.G. Biccirè reports consulting or lecturing fees from Abbott, Ultragenyx, and Sanofi, outside the submitted work. F. Prati has no conflicts of interest to declare.

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