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Skating on thin ice: searching for vulnerable plaques

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Back in the late eighties, pathological studies by Davies et al and other groups clarified the association between plaque rupture and intracoronary thrombus formation, setting the basis for the restless search for so-called "vulnerable plaques" and, at the same time, paving the way for an endless controversy in cardiology.

In the subsequent three decades, cardiologists have struggled in the search for vulnerable lesions, mainly relying on suboptimal intravascular methodologies[1].

If we had an imaging tool capable of detailing a high-risk plaque with the sharpness of a microscope lens, would we ignore what we saw? Think of a skater on an ice-covered lake in late winter. The first question that comes to mind is whether the ice cap is thick enough to sustain the skater's weight.

The main criticisms raised by sceptics in the search for vulnerable plaques

1) Any attempt to stabilise plaques seems worthless, as plaque phenotypes are too dynamic to become a reliable target.

There is a lack of definitive data that would allow us to establish with certainty whether plaque instability is a common or rare event. Based on multivessel intravascular ultrasound (IVUS) or optical coherence tomography (OCT) studies, at least one ulceration occurs in about 30% of patients[2]. This does not seem to be a trivial number. However, anecdotal cases, based on sequential imaging studies, have shown that plaque ulcers can remain stable for months or years.

Moreover, plaques can lose their "vulnerable" characteristics in response to therapy. However, a snapshot of the characteristics of plaques at a certain point may be worth obtaining. In fact, intense lipid-lowering therapy or interventional treatment are each potentially capable of stabilising high-risk plaques prone to rupture. Of note, intensive lipid-lowering therapy leads to a significant reduction in coronary plaque burden. Furthermore, as shown recently in OCT studies, proprotein convertase subtilsin-kexin type 9 (PCSK9) inhibitors can stabilise plaques, significantly increasing the minimum fibrous cap thickness and decreasing the maximum lipid arc[3].

2) Past vulnerability studies were rather timid in their scope.

Although a great effort was devoted to the search for and quantification of lipid plaques with IVUS or OCT, past studies failed to identify patients at risk of hard events, including cardiac death and/or myocardial infarction (MI). Regardless of the adopted diagnosing modality, the search for large plaque burden as a single

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common causal feature of acute coronary syndromes (ACS) did not seem to be the ideal solution.

Only recently, intracoronary studies proved the effectiveness of a more comprehensive approach to evaluate the target plaque morphology. In the PROSPECT II study[4], the combined and complementary use of IVUS and near-infrared spectroscopy (NIRS) identified patients at a higher risk of myocardial infarction. The study stressed the incremental value of a high lipid content in mature lesions with a large plaque burden.

In the CLIMA OCT study[5], patients with high-risk lesion phenotypes in the left anterior descending coronary artery (simultaneous presence of thin fibrous cap [TFC], small minimum lumen area, large lipid arc and presence of superficial macrophage) had a 7.5-fold higher risk of cardiac death or MI at one year. The single presence of TFC (cap thickness <75 µ) was by far the most effective vulnerability feature (hazard ratio 4.65). Along the same lines, Kubo et al[6] confirmed in a large retrospective OCT study that non-culprit lipid-rich plaques with TFC identify patients at risk of subsequent ACS.

3) Physiological assessment works better than plaque morphology to predict the risk of hard events.

This statement is based on the assumption that MI is mainly caused by angiographically severe lesions, and vice versa, that the residual risk of death or MI in physiologically non-severe lesions is minimal.

Recent findings are in contrast with this assumption. The COMBINE trial[7] highlighted the prognostic role of OCT-detected thin-cap fibroatheroma (TCFA) in fractional flow reserve (FFR)-negative lesions in diabetics. The incidence of the composite endpoint (cardiac death, MI and hospitalisation for angina pectoris) was 4 times higher in lesions with TCFA.

The FLOWER-MI[8] trial randomised patients with ST-elevation MI (STEMI) and multivessel disease to receive complete revascularisation guided by either FFR or angiography. The primary endpoint (composite of death from any cause, non-fatal MI, or urgent revascularisation at 1 year) was similar between the two groups.

These recent studies are confirmatory of previous invasive studies on the search for ischaemia in the stable and, more importantly, the unstable clinical setting.

Should we target and treat vulnerable plaques?

There is still some question as to whether there is a need to test the effectiveness of different methods of treating vulnerable plaques at risk of ulceration. In this regard, OCT and NIRS-IVUS seem to be the two coronary imaging options with the greatest potential for evaluating these treatment protocols.

Treatment can encompass both interventional and medical solutions. In pursuing an interventional treatment strategy for vulnerable lesions, the net clinical benefit of coronary stenting must be measured against optimal medical therapy. The COMPLETE Trial OCT Substudy[9] showed a high prevalence of patients with at least one TFC lesion (47%) in patients with STEMI, providing the rationale for the interventional solution to vulnerable lesions.

The PROSPECT ABSORB trial[10] compared the treatment of vulnerable plaques by NIRS-IVUS by means of a bioresorbable vascular scaffold versus optimal medical therapy only. Major adverse cardiovascular events (MACE) at 24 months occurred at similar rates.

Stenting an FFR-positive lesion is, however, a one-size-fits-all solution. Plaques with a high lipid content and TFC may deserve a different treatment as compared to plaques with different features of vulnerability, such as those with signs of ulceration, calcified nodules or OCT-identified signs of plaque healing. This latter finding seems to identify patients at a lower risk of ACS.

Future randomised studies will provide new answers for the treatment of intermediate non-culprit lesions in ACS patients. The INTERCLIMA study (ClinicalTrials.gov: NCT050227984) will compare a functional versus OCT-guided stenting strategy. Similarly, the COMBINE INTERVENE and PREVENT trials (ClinicalTrials.gov: NCT05333068 and NCT02316886, respectively) will focus on non-ischaemic (FFR >0.75) vulnerable plaques to compare revascularisation versus medical treatment.

In conclusion, invasive imaging modalities can detect high-risk features of coronary atherosclerosis. Further studies are needed to determine whether the adoption of a comprehensive plaque imaging strategy that is able to address multiple features of vulnerability, including fibrous cap thickness, is capable of guiding prophylactic percutaneous coronary intervention to prevent adverse hard cardiac events.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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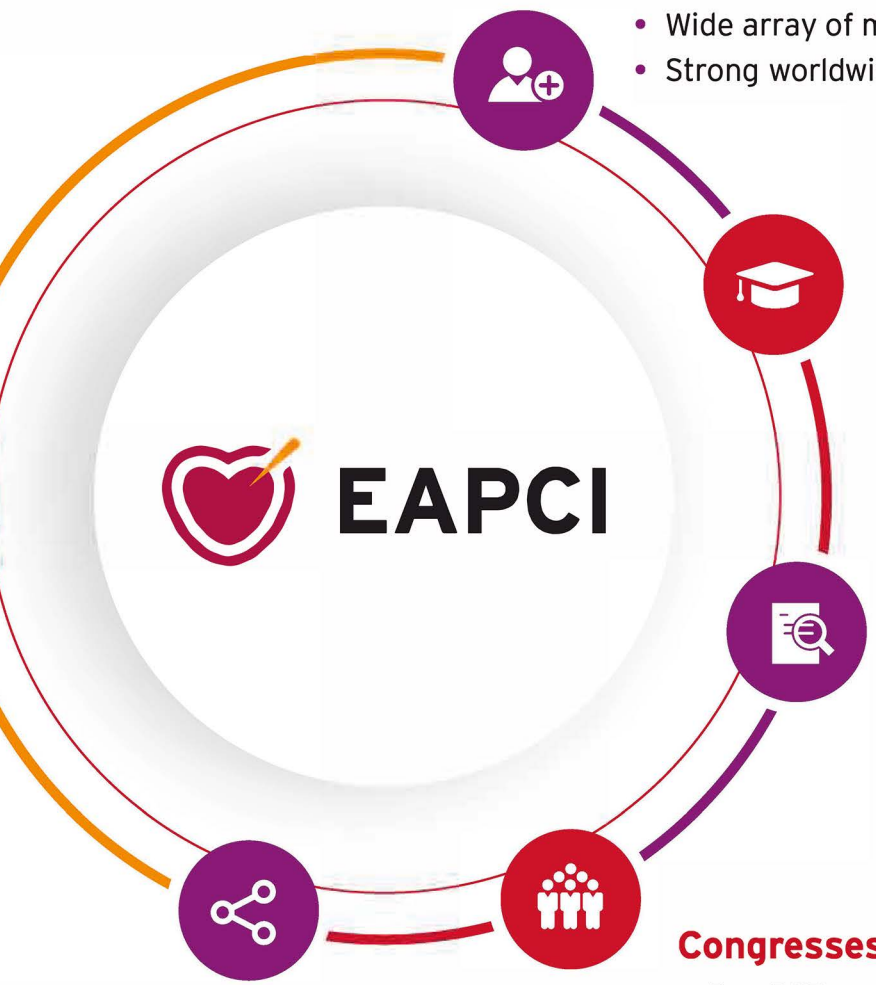

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