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Weekly Journal Scan

Vulnerable non-culprit coronary plaques: are they worth treating?

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Comment on "Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study", which has been published in *The Lancet*. doi:10.1016/S0140-6736(21)00249-X.

Key Points

- PROSPECT II was an investigator-initiated, multicentre, prospective natural history study with grant funding from Abbott Vascular, Infraredx, and The Medicines Company aimed to assess whether combined near-infrared spectroscopy (NIRS) and intravascular ultrasound (IVUS) can identify high-risk coronary plaques and patients at risk for future major adverse cardiac events (MACEs).¹
- The primary outcome was the adjudicated occurrence of MACEs [the composite of cardiac death, myocardial infarction (MI), unstable angina, or progressive angina] arising from untreated non-culprit lesions during follow-up. The relations between plaques with high lipid content, large plaque burden, small lumen area, and patient-level and lesion-level events were analysed.
- A total of 3629 non-culprit lesions were characterized in 898 patients (83% men; median age 63 years) with recent (within the past 4 weeks) MI who were enrolled after successful percutaneous coronary intervention on all flow-limiting culprit lesions. Three-vessel imaging was performed with a combined NIRS and IVUS catheter. Non-culprit lesions were identified by IVUS, and their lipid content was assessed by NIRS. Contemporary drug-eluting stents were used to treat 97% of the culprit lesions. Pressure wire assessment was used to evaluate borderline lesions in 35% of patients.
- At 4-year follow-up, 66 events (8.0%; 95% confidence interval (CI), 6.2–10.0) were attributed to untreated non-culprit lesions, whereas 36 events (4.2%; 95% CI, 3.0–5.8) were attributed to culprit lesions previously treated by stenting. Notably, since the adjudication of events as culprit- or non-culprit-related was dependent on the availability of coronary angiography at follow-up, this was not possible for all 7 cardiac deaths and 14 of 54 MIs, which remained indeterminate in origin.
- In a multivariable model, high lipid content (adjusted odds ratio (OR), 3.80; 95% CI, 1.87–7.70; $P = 0.0002$) and large plaque burden (OR, 5.37; 95% CI, 2.42–11.89; $P < 0.0001$) were independent predictors of non-culprit lesion-related events. Patients with high-risk plaques (lesions with both large plaque burden by IVUS and large lipid-rich cores by NIRS) had a 4-year non-culprit lesion-related MACE rate of 13.2% (95% CI, 9.4–17.6).

Comment

The PROSPECT II study combined for the first time prospective IVUS characterization of coronary arteries with automatically co-registered detection of lipid-rich plaques by NIRS to investigate the relationship between lipid-rich plaques and future non-culprit lesion-related MACEs. The authors suggest that the main findings provide immediate prognostic use and lay the foundation for focal treatments to improve the long-term outcomes of patients with coronary atherosclerosis. However, some important limitations of this study should be underlined.

According to the study protocol, NIRS output was electronically masked and not visible, whereas the operator could use IVUS to

optimize stent implantation on treated lesions, and this procedure could potentially influence the risk of MACEs during follow-up. Moreover, the PROSPECT II study enrolled selected patients with recent MI and excluded subjects with chronic coronary syndromes (CCS), who represent the majority of patients with coronary artery disease. Therefore, the PROSPECT II results may not be applicable to the CCS population, composed of less 'vulnerable patients' with less 'vulnerable plaques'.

Another important issue is represented by the lower rate of MACEs in the PROSPECT II compared to previous similar studies, such as the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree)² and LRP (Lipid-Rich

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Plaque).³ Beside novel stent technology (reduced strut thickness and thrombogenicity), more effective pharmacotherapy, and use of IVUS guidance for stent placement, the exclusion of patients with high-grade anatomical complexity of coronary lesions (left main involvement, total occlusion, severe tortuosity causing difficulties in NIRS procedure) may have played a role in the reduction of MACE incidence.

In the PROSPECT study,² plaque burden and minimal lumen area were already recognized as IVUS-related predictors of cardiovascular events, in addition to thin-cap fibroatheromas identified by virtual histology. Although in PROSPECT II the high lipid content of plaques detected by NIRS was shown to independently predict MACEs,¹ thereby potentially improving the accuracy of plaque evaluation, it should be emphasized that the incidence of both non-culprit lesion- and culprit lesion-related events was lower compared to previous trials.^{2,3} Moreover, the heterogeneous nature of events included in the composite outcome, with progressive angina outnumbering MI, precludes unequivocal mechanistic interpretation of the main findings.

On the basis of these results, the clinical advantages of performing NIRS appear marginal, whereas this technique implies increased procedural complexity and costs, and it is not routinely feasible in most laboratories. In such a context, other non-invasive techniques, such as cardiac computed tomography with myocardial perfusion imaging, transluminal attenuation gradients and corrected coronary opacification indexes, computed fractional flow reserve, and extrapolation from atherosclerotic plaque characteristics, may represent more feasible choices with a more favourable cost/benefit profile.⁴

From a clinical standpoint, greater benefits may derive from more intensive secondary prevention measures, such as low-density cholesterol (LDL) reduction to target and longer-term dual antiplatelet therapy, than from focal intervention on high-risk plaques. In PROSPECT II, the median LDL value was 127 mg/dL and most patients received only statins as lipid-lowering treatment (only 1% was treated with ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors were not used). Although this information is not available, it is unlikely that many patients achieved the LDL target <55 mg/dL recommended for subjects at very-high cardiovascular risk, such as those included in the study.

Additional trials, preferably including also subjects with CCS, are needed to compare the efficacy, safety, and cost-effectiveness of improved pharmacological strategies, plaque treatment, or both. At this time, however, planning interventional management of high-risk plaques is not supported by convincing evidence.

Supplementary material

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

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