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EDITORIAL

Seeing is believing

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Risk scores are essential tools in cardiovascular medicine for stratifying patients' risk of recurrent events and guiding secondary prevention strategies. One of the well-validated scores in large cohorts of patients after myocardial infarction (MI) is the Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention (TRS-2P)[1].

Intravascular imaging has become a cornerstone in assessing coronary plaque morphology. Among the available modalities, optical coherence tomography (OCT) enables the precise visualisation of features associated with plaque vulnerability, such as thin-cap fibroatheroma (TCFA), a large lipid core, or plaque rupture[2]. Previous studies demonstrated that OCT identified the presence of high-risk plaque (HRP) in up to 48% of non-culprit arteries in patients presenting with acute coronary syndrome (ACS)[3-5]. Conversely, physiological lesion assessment using either conventional or angiography-based physiology appeared to only have a limited negative predictive value as HRP was determined in up to 31% of fractional flow reserve (FFR)-negative non-culprit lesions[4,6].

Despite the clear benefits of OCT, its use in routine clinical practice remains limited, primarily due to factors such as challenges in reimbursement and lack of specialised operator expertise. As a result, validating current clinical risk scores in their predictive ability to identify HRP is a reasonable and pertinent question as the relationship between the presence of HRP and adverse clinical events is well established.

In this issue of EuroIntervention, Volleberg et al present a non-predefined patient-level data meta-analysis from the COMBINE (OCT-FFR) and PECTUS-obs studies aimed at determining whether stratification according to a modified TRS-2P clinical risk score can identify patients with HRP[7]. Subsequent analyses were performed to assess the impact of HRP on clinical outcomes across different risk profiles.

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The study includes a total of 810 patients – 390 from the COMBINE study and 420 from the PECTUS-obs study. Using the modified TRS-2P score, patients were stratified into low- (38.4%), intermediate- (32.7%), and high-risk (28.9%) groups. The prevalence of OCT-detected HRP was consistent across all clinical risk categories: 32.8% in low-risk patients, 32.1% in intermediate-risk and 35.9% in high-risk. Moreover, no significant interaction between risk strata and HRP-associated outcomes was observed. TRS-2P shows no discriminative ability for detecting HRP (area under the curve 0.51). Importantly, even patients classified as low risk had increased event rates in the presence of HRP, whereas high-risk patients without HRP exhibited comparatively lower event rates. Nevertheless, patients with both high clinical risk and an OCT-defined HRP exhibited the highest absolute event rates across groups.

This analysis reinforces growing evidence that plaque morphology, with OCT-detected HRP in particular, offers prognostic information beyond traditional risk scores and physiological lesion assessment[8,9]. While these findings are of clear interest, several limitations need to be addressed in this attempt to answer the question why traditional risk factors fail to predict HRP and whether the TRS-2P was given a fair chance to perform.

First, the incidence of HRP within the present meta-analyses should be interpreted within the context of the respective

study designs and may have been underestimated for the following reasons: (1) patients included already had another treated culprit vessel, which likely may have had vulnerable plaque features; (2) assessed lesions were FFR-negative, again decreasing the number of lesions at risk of having HRP features (not even mentioning that the use of physiology in an ACS setting is not common practice); (3) incidences of HRP reported within the PREVENT and a subanalysis of COMPLETE were 45% and 48% respectively, partly driven by using different definitions and or imaging modalities. For instance, next to minimal lumen area (<4 mm^2), PREVENT also included plaque burden (>70%), a parameter that has been repeatedly demonstrated to have the strongest predictive value for future events[10].

Second, as the authors rightfully acknowledged, this was a *post hoc* analysis, and the TRS-2P score – originally developed for long-term risk stratification after MI – was applied outside its intended context (40% of patients in the present population had not presented with MI) and modified by removing 2 out of 9 important components (congestive heart failure and other vascular disease). Finally, multiple imputations were used for missing baseline values, further hampering the calculation of a validated TRS-2P score (e.g., creatinine was imputed in 67 patients).

Third, the study failed to link any of the traditional risk factors to the presence of HRP. Whereas this finding is consistent with previous studies on the topic, it should be acknowledged that the included patient sample was not a random sample of patients with known coronary artery disease. Instead, next to the studied non-culprit vessels, all included patients within the present study had significant coronary artery disease at the time of enrolment, warranting revascularisation, and as many as 56% of patients had diabetes mellitus. This may question the rationale and clinical relevance of validating a risk score in the studied patient population. Future studies within validated frameworks, including those leveraging artificial intelligence-driven risk prediction models, may help refine their role in contemporary risk stratification.

In conclusion, Volleberg et al demonstrate that traditional clinical risk scores fail to predict the presence of OCT-defined high-risk plaques in this specific clinical scenario and underscore the independent value of high-resolution invasive imaging in identifying HRP in vessels that would not have qualified for revascularisation based on current guidelines. The latter should challenge the field to further study the potential protective effect of innovative pharmacological and interventional treatment options to further improve the outcome of patients at the highest risk.

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Conflict of interest statement

J. Daemen received institutional grant/research support from Abbott, Boston Scientific, ACIST Medical, Medtronic, Pie Medical Imaging, and Recor Medical; and consultancy and speaker fees from Abbott, ACIST Medical, Boston Scientific, Cardialysis BV, CardiacBooster, Kaminari Medical, Recor Medical Imaging, Pie Medical, Sanofi, Siemens Healthineers, and Medtronic. K. Sadowski has no conflicts of interest to declare.

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