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EDITORIAL

Intermediate coronary stenosis evaluation in patients with or without diabetes: are FFR and IVUS equally "sweet"?

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Current clinical practice guidelines strongly advocate the use of invasive coronary physiology as a gatekeeper to guide coronary revascularisation in patients with intermediate stenosis. In contrast, the role of intravascular ultrasound (IVUS) to guide revascularisation has been established only in specific scenarios, such as left main coronary artery disease[1]. Diabetes mellitus, one of the most common comorbidities among patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), is an independent predictor of adverse cardiac events following PCI[2]. The high-risk nature of diabetic patients characterised by more extensive and diffuse atherosclerosis with more vulnerable plaque characteristics and a tendency to progression makes them a particularly challenging subgroup[3]. Despite this, a head-to-head comparison between fractional flow reserve (FFR)- and IVUS-guided PCI in diabetic patients has not yet been thoroughly evaluated.

In this issue of EuroIntervention, Cho and colleagues report a prespecified *post hoc* analysis of diabetic and non-diabetic patients enrolled in the Fractional FLow Reserve And IVUS for Clinical OUtcomes in Patients With InteRmediate Stenosis (FLAVOUR) trial[4]. The FLAVOUR trial is a randomised, open-label, non-inferiority trial conducted across 18 sites in South Korea and China that compared FFR and IVUS guidance for PCI in patients with *de novo* intermediate coronary stenosis. Revascularisation criteria differed between the groups, with FFR-guided PCI performed for an FFR value ≤0.80, while IVUS-guided PCI was indicated for a minimal lumen area (MLA) ≤3 mm² or 3-4 mm² with a plaque burden >70%. Among the 1,682 patients enrolled, 554 (32.9%) had diabetes; these patients had higher baseline SYNTAX scores, smaller MLA and greater plaque burden, compared with non-diabetic patients. The analysis found no significant difference in the primary outcome of major adverse cardiac events (MACE; defined as a composite of death, myocardial infarction, or any revascularisation) at 24 months between the FFR and IVUS groups, regardless of diabetic status (diabetic: 9.3% vs 8.3%, hazard ratio [HR] 0.96; p=0.90; non-diabetic: 7.5% vs 8.6%, HR 1.16; p=0.50). Target vessel failure (TVF) rates were also similar between the groups for both diabetic (2.9% vs 3.6%, HR 1.35; p=0.55) and non-diabetic patients (3.4% vs 2.7%, HR 0.79; p=0.49). However, IVUS was associated with significantly higher PCI rates compared to FFR (diabetic: 69.1% vs 48.2%; p<0.001; non-diabetic: 63.3% vs 42.6%; p<0.001). Finally, among non-diabetic patients who underwent PCI, the FFR group showed a higher rate of target vessel revascularisation (TVR; 5.1% vs 2.0%, HR 0.36; p for interaction=0.07).

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This subanalysis of the FLAVOUR trial is the first to evaluate FFR and IVUS guidance in diabetic patients, directly comparing these strategies in a well-defined cohort of patients with intermediate coronary lesions with low complexity.

While both strategies demonstrated comparable efficacy in guiding PCI, some caveats warrant careful interpretation. First, this is a subanalysis of a study that had a non-inferiority design. Even though patients were stratified according to diabetic status, the original study was not powered for the comparison of IVUS and FFR in diabetic and non-diabetic patients. Second, MACE rates between diabetic and non-diabetic (8.8% vs 8.0%; p=0.72) patients showed no significant difference – a finding inconsistent with previous studies including a recent randomised trial with a similar design where diabetes nearly doubled the MACE risk[5]. This discrepancy likely reflects the low-risk profile of the FLAVOUR cohort – as evidenced by the low SYNTAX scores – and the lack of stratification by insulin-dependence status, which might have provided greater clinical

granularity. Diabetes treatment and control in both groups were not evaluated and might have influenced the results. Moreover, the study included approximately 30% of patients with acute coronary syndrome – a context where the utility of FFR remains debated.

Additionally, the exclusive enrolment of Asian patients, whose smaller body surface area (BSA) may affect the validity of IVUS-derived MLA thresholds, limits the generalisability of these findings to non-Asian populations with larger BSAs. The exclusion of left main coronary stenoses – for which IVUS has established benefits – and the inclusion of patients with low disease severity as defined by the SYNTAX score further limit the applicability of these findings to complex lesions.

Diabetic patients have atherosclerotic plaques with more features of vulnerability[3]. Detection of these high-risk plaques could be one of the potential advantages of the use of intracoronary imaging in this population. Previous studies like COMBINE OCT-FFR trial, have highlighted the prognostic importance of identifying thin-cap fibroatheromas in FFR-negative lesions, associated with higher event rates[6]. However, FLAVOUR did not evaluate features of plaque vulnerability within the IVUS arm.

Finally, some of the study findings are counterintuitive including the higher rate of TVR in the FFR group only among non-diabetic patients who underwent PCI. It is difficult to explain how the benefit of intracoronary imaging for optimisation could only apply to non-diabetic patients. The authors suggest it may be related to the superior effectiveness of imaging-guided optimisation in treating focal lesions with lower plaque burden that could be more frequent in the non-diabetic population. However, no data about plaque distribution are provided in this study. Furthermore, several studies have shown that the benefit of intracoronary imaging is larger in complex lesions, as reflected in recent clinical practice guidelines[1].

In summary, this subanalysis of the FLAVOUR trial demonstrates that FFR and IVUS offer comparable outcomes in guiding PCI for intermediate low complexity coronary lesions, irrespective of diabetic status. However, the study design with potential underpowering for the diabetic subgroup, the low-risk population, ethnic homogeneity, and absence of plaque vulnerability assessment call for further investigation in the topic. While FFR and IVUS appear equally "sweet", their complementary roles in addressing different clinical questions highlight the importance of selecting the most appropriate tool based on the specific anatomical and clinical context and reinforce the value of a tailored approach to PCI guidance.

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Conflict of interest statement

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