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Editorial

The role of angiography-derived physiological assessment techniques in the post-FAVOR III Europe era?

Técnicas de evaluación fisiológica derivadas de la angiografía: ¿todavía tienen cabida después de la publicación del ensayo FAVOR III Europe?

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Currently, invasive coronary angiography is still the main technique to identify obstructive coronary artery disease. However, its diagnostic yield is limited by its inability to assess the functional relevance of intermediate stenoses.[1] The introduction of pressure guidewire-based physiological assessment was first enabled by the development of fractional flow reserve (FFR).[2] Within the following decade, a large body of evidence supported the benefit of FFR in revascularization decision-making, leading to its endorsement by clinical practice guidelines.[3-5] Still, a low penetrance of FFR was observed, due to scepticism in coronary physiology, the need for coronary instrumentation, adenosine infusion, and increased procedural time and costs.[6] These challenges led to the development of several non-hyperemic indices, avoiding the need for hyperemic agents, as well as angiography-derived physiological assessment techniques (ADPAT), which avoid both the use of adenosine and coronary guidewires. Over the past few years, several ADPAT modalities have emerged with the objective of estimating FFR by combining fluid dynamic equations, 3D models of the coronary tree and certain predefined boundary flow conditions.[7]

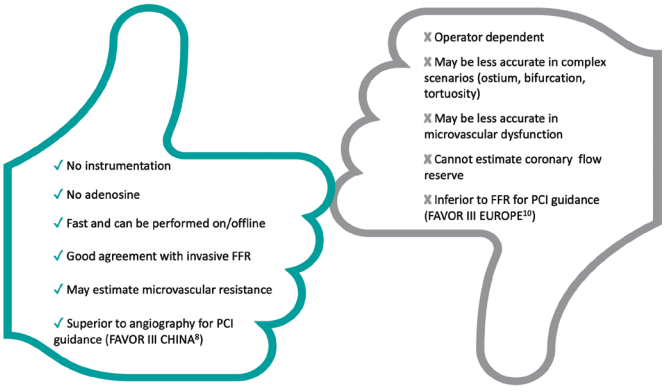

Figure 1. Advantages and disadvantages of ADPAT. ADPAT, angiography-derived physiological assessment techniques; FFR, fractional flow reserve; PCI, percutaneous coronary intervention.

Most ADPAT have pivotal validation studies that compare them to FFR showing good diagnostic accuracy. Among these methods, quantitative flow ratio (QFR) has been evaluated in the largest number of studies and, importantly, the main clinical trials powered for cardiovascular events. In the randomized FAVOR III China trial, the QFR-guided revascularization of intermediate stenoses was superior to angiography-guided revascularization,[8] prompting a 1B recommendation for the use of QFR by the European clinical practice guidelines on the management of chronic coronary syndromes.[9] However, when QFR was compared with FFR for clinical events in the randomized FAVOR III Europe trial it not only failed to show non-inferiority, but also had a significantly worse rate of adverse events, with a hazard ratio of 1.67 for the composite primary endpoint and 1.84 for myocardial infarction (MI).[10] This has raised concerns about the reliability of QFR and its applicability as a substitute for FFR in the routine clinical practice. Figure 1 illustrates the known advantages and disadvantages of ADPAT.

In a recent article published in *REC: Interventional Cardiology*, Ruiz-Ruiz et al. provide a meta-analysis on the combined and individual accuracy of the most frequently used ADPAT software in the setting of functional interrogation of intermediate stenoses.[11] After applying eligibility criteria, a total of 27 papers were finally selected, including more than 4800 patients and more than 5400 vessel analysis. Although stable angina was the most prevalent indication, roughly a third of the patients exhibited acute coronary syndromes, mostly unstable angina. In more than half of the cases, the target vessel was the left anterior descending coronary artery. The ADPAT modalities included primarily QFR; 42.6% of vessels), angiography-derived FFR (15.5%), and vessel FFR (12.0%).

The main results from the meta-analysis suggest a good diagnostic performance of the different ADPAT tools considered vs FFR. Overall sensitivity and positive predictive value were around 85%, whereas total specificity and negative predictive value exceeded 90%, highlighting a potential value of these techniques to identify functionally non-significant stenoses and defer revascularization. The area under the curve for predicting a significant FFR was remarkable (0.947). However, evidence quality on every ADPAT software was uneven and a large proportion of pivotal studies was included in the meta-analysis, precluding the results to properly represent a real-world patients' population. Furthermore, there were several exclusion criteria, such as > 10% prevalence of

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previous surgical revascularization, > 25% prevalence of atrial fibrillation, or > 30% of the patients exhibiting MI if time from the event to physiological evaluation was not specified, which means the studies included are highly selected and may not accurately reflect our routine clinical practice.

In any case, taken at face, these data of diagnostic accuracy for ADPAT seem encouraging. The pressure wire-based instantaneous wave-free ratio (iFR) demonstrated an area under the curve, as well as positive and negative predictive values very similar to those reported in this meta-analysis for ADPAT.[12] This would be indicative of a similar clinical value, which is why the negative results of the FAVOR III Europe trial came as such a shock. It is well established for FFR and iFR that much of the clinical benefit of physiology-based revascularisation derives from deferral of unneeded coronary interventions.[13] Similarly, the advantage of QFR over angiography in the FAVOR III China trial was associated with a lower number of lesions treated in the QFR arm.[8] However, data from the FAVOR III Europe trial questioned the ability of QFR to defer as many revascularizations as FFR. In this trial, median QFR values were lower than those of FFR, leading to more than 20% additional patients undergoing revascularization in the QFR group.[10] On the other hand, it could be that the inaccuracy goes both ways: a *post hoc* subanalysis of the trial revealed that QFR-based intervention deferral was associated with worse outcomes, especially in terms of unplanned revascularizations.[14] This suggests that excess events in the QFR arm of FAVOR III Europe trial might be attributed to both false positive and false negative measurements. For reproducibility, a pre-specified sub-study of the trial compared investigator-performed QFR measurements with repeated assessments by the core laboratory. Almost 30% disagreement was documented, including both significant and non-significant QFR values.[15] Of note, the study included a rigorous training and certification protocol for all the investigators involved in QFR assessment.

Clearly, the final word on these techniques has not yet been written. If we aim to predict and reduce the risk of adverse cardiovascular events, both microvascular dysfunction and plaque vulnerability are 2 factors that we should taken into consideration. The former, not only modifies the risk of cardiovascular events, but affects the accuracy of ADPAT measurements.[16] The latter is a major driver of adverse coronary events, may prompt percutaneous revascularization even in physiologically non-significant lesions,[17,18] and cannot be accurately estimated by any angiographic technique. In this regard, the use of intravascular imaging to assess both plaque vulnerability and physiological significance by means of dedicated algorithms seems promising.[19,20] Another important unsolved issue is the performance of physiology –of any kind– in clinical scenarios other than chronic coronary syndrome. Current clinical practice guidelines from the European Society of Cardiology do not support the use of FFR in ST-segment elevation MI due to conflicting evidence, and all other physiological indexes are lacking clinical trials in this setting. Of note, MI with and without ST-segment elevation accounts for more than half of revascularization procedures in most centers with a primary percutaneous coronary intervention program in our setting. The ongoing VULNERABLE trial[18] should shed light on this issue of whether physiology is sufficient to safely defer non-culprit lesions in ST-segment elevation MI, or rather a more proactive approach is needed to detect and treat vulnerable plaques. As we wait for the results of this and other trials, integrative efforts such as the meta-analysis conducted by Ruiz-Ruiz et al.[11] may contribute to expand knowledge and expertise on ADPAT.

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CONFLICTS OF INTEREST

None declared.

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