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Guideline recommendations for QFR should be revisited: pros and cons

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Quantitative flow ratio (QFR) has emerged as an angiography-derived tool for the assessment of the functional significance of intermediate coronary stenoses without the need for a pressure wire or hyperaemic agent. While its diagnostic accuracy and clinical impact have been demonstrated over angiography alone, concerns remain regarding its performance compared to established invasive physiology methods, such as fractional flow reserve (FFR). In particular, recent evidence have shown a higher incidence of adverse events with QFR guidance compared to FFR guidance. In this context, the 2024 European guidelines on chronic coronary syndromes (CCS) granted a solid recommendation (Class of Recommendation I, Level of Evidence [LoE] B) for QFR in the evaluation of intermediate stenoses. However, methodological issues and conflicting findings from randomised trials are currently questioning such a strong endorsement. Whether current guideline recommendations should be revised or whether QFR should remain a first-line tool alongside FFR remains a subject of debate.

Pros

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Based on numerous multicentre, randomised trials and large observational registries demonstrating improved clinical outcomes in a variety of patient populations, coronary pressure wire-derived physiological assessment of moderate coronary stenoses to guide revascularisation has a Class I, LoE A indication both in European and American guidelines[1,2]. Despite this, the utilisation of pressure wire-based physiology has been lower than expected, for multiple reasons, including frustration with various aspects of the coronary pressure wire and the need for hyperaemia, if measuring FFR. To facilitate the application of coronary physiology in the catheterisation laboratory, a number of companies have developed distinct angiography-derived methods for assessing coronary physiology, without the need for a pressure wire or hyperaemic agent. One such system calculates the QFR, which has been shown to correlate with pressure wire-derived FFR, and in a large randomised trial performed in China demonstrated decreased adverse cardiac events in comparison with coronary angiography alone, when used to guide revascularisation decisions[3]. Based on these data, the most recent European Society of Cardiology guidelines for the management of chronic coronary syndromes gave QFR a Class I, LoE B recommendation for assessing the functional severity of intermediate stenoses[1].

This recommendation is surprising and needs to be revised for two main reasons. The first is that pressure wire-derived physiology is the reference standard for assessing intermediate stenoses, and QFR, at the time of this recommendation, had not been shown to be equivalent. Moreover, just recently the FAVOR III Europe Trial, which randomised 2,000 patients with at least one intermediate stenosis to either pressure wire-derived FFR-guided assessment or QFR-guided assessment, was published, demonstrating a significantly higher rate of the composite of death, myocardial infarction or ischaemia-driven revascularisation at one year in the QFR-guided arm[4]. Based on these inferior results for QFR, there is no longer evidence or general agreement that QFR is beneficial, useful and effective in this particular setting (the definition of a Class I indication). One might argue that QFR should be recommended if a pressure wire system is not available in a particular catheterisation laboratory, given its proven benefit over angiography alone; however, why would one

not have access to a pressure wire, but have access only to the presumably similarly expensive QFR?

A second reason the guidelines need to be revised is related to the usage of a proprietary name, like QFR, instead of a more generic term, like angiography-derived physiology. Throughout these same guidelines, the generic term drug-eluting stent (DES) is used, despite the fact that there are many brands of DES, with varying degrees of data supporting their use. When there is a specific and significant difference in outcomes with a certain type of DES, the guidelines distinguish them by calling them first-, second- or newer-generation DES, not by their specific brand names. Granted, the differences between the various angiography-derived physiology systems may be greater than the differences between newer-generation DES, but the guidelines could identify the particular method by which angiography-derived physiology is performed, without highlighting the system's brand name. In fact, this policy could apply to other areas of the guidelines as well. For example, many believe other non-hyperaemic pressure ratios (NHPR) are interchangeable with the instantaneous wave-free ratio (iFR) because they have such an extremely high correlation[5]. Since iFR is a proprietary name, NHPR could be used, similar to DES. Other guidelines have adopted this strategy[2].

Until we have more data (and fortunately, we will soon, as other system's outcomes studies are ongoing; ClinicalTrials.gov: NCT05893498), angiography-derived physiology, particularly QFR, should not have a Class I recommendation.

Conflict of interest statement

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Cons

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Recent European guidelines provided a strong suggestion (Class I, LoE B) to utilise QFR in the discrimination of flow-limiting lesions in CCS patients with intermediate stenosis[1]. The recent Comparison of Quantitative Flow Ratio and Conventional Pressure-wire Based Functional Evaluation for Guiding Coronary Intervention (FAVOR III Europe Japan) trial challenged this indication by failing to demonstrate QFR non-inferiority with regard to FFR in patients with intermediate lesions[4]. The rate of the composite of death, myocardial infarction, and unplanned revascularisation at 12 months was significantly higher in the QFR arm compared to the FFR arm.

The guideline recommendation is based on the findings of the Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous InterVention in Patients With cORonary Artery Disease (FAVOR III China) trial, where QFR was found to be superior to angiography-guided percutaneous coronary intervention by significantly reducing the rate of the composite of death from any cause, myocardial infarction, or ischaemia-driven revascularisation[3].

Taking into account both studies, QFR performance seems to be better than angiography but worse than FFR in terms of clinical outcomes.

However, while the superiority of angiography-derived FFR in comparison to angiography is undisputed and confirmed by longer follow-up, caution is needed before declaring its inferiority to FFR. First, many randomised studies similar to FAVOR III Europe Japan are ongoing (ClinicalTrials.gov: NCT04931771; NCT05893498) and will soon provide new data able to confirm or refute the present evidence. In the event of concordant results, we will be able to definitively rule out the use of angiography-derived FFR in CCS patients. Otherwise, the results of FAVOR III Europe Japan should be considered outliers and not easily attributable to the tool, since recent independent data suggest that the performance of different tools is overall similar[6]. Secondly, some results of the study seem counterintuitive: QFR is associated with a higher percentage of positive results, but, at the same time, a lower number of vessels with negative QFR were associated with a higher rate of events, especially myocardial infarction. Thirdly, whereas the expected rate of events in the QFR arm was consistent with the observed one (expected 6.7%, observed 6.7%), the FFR arm was significantly lower (expected 6.7%, observed 4.2%) and represented an outlier compared to other trials comparing FFR with different technologies.

However, there is an important, inherent and shared limitation of all the current versions of angiography-derived FFR systems, namely the need for operator interaction and consequent possible alteration of the results. An indirect demonstration could be represented by the higher percentage of positive QFR results in non-left anterior descending arteries, especially the left circumflex artery (LCx)[4]. Anyone with some experience with invasive physiology knows that, due to limited distribution and subtended mass, a positive FFR in the LCx is anecdotal. The implementation of these technologies in clinical practice is subordinate to the availability of fully automatic analysis.

Finally, it must be acknowledged that the best setting for angiography-derived FFR application is probably represented by stratification of non-culprit lesions in ST-segment elevation myocardial infarction. Its application may maximise the benefit of physiology in this setting by avoiding unnecessary staged procedures to invasively measure physiology and guiding the eventual treatment through the longitudinal vessel analysis based on physiology pullback. A dedicated trial has recently finished enrolment and will soon provide new insights on this matter[7].

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