

The pressure wire holds its ground: the debacle of QFR

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In patients with stable coronary artery disease, percutaneous coronary intervention (PCI) has demonstrated clinical benefit when epicardial stenosis limits blood flow¹. Physiological assessment with a pressure wire has emerged as the cornerstone for decision-making about the need for revascularisation². One of the key elements driving the value of invasive physiological evaluation is its ability to identify lesions that can be effectively managed medically, thus avoiding unnecessary interventions³. Furthermore, physiology has been recently expanded to the prediction of angina relief after PCI, positioning physiology as a more clinically relevant tool than ever before^{4,5}.

Fractional flow reserve (FFR) has long been the gold standard of physiological assessment. Quantitative flow ratio (QFR) is an alternative method that simulates FFR from angiograms. QFR aims to “simplify” functional assessment and replace pressure wires with an estimation of epicardial resistance based on quantitative coronary angiography (QCA)⁶. An independent evaluation has determined that the accuracy of angiography-derived FFR software (e.g., QFR, vessel FFR [vFFR], and others) is approximately 75%⁷. Despite its moderate diagnostic performance, questions about its clinical performance for decision-making compared to invasive FFR remained unanswered.

The FAVOR III Europe trial was the first adequately powered study to evaluate the clinical applicability of QFR in practice. It was a multicentre, randomised, open-label, non-inferiority trial comparing QFR with FFR diagnostic strategies for patients with intermediate coronary stenosis. The study, led by an independent academic group, showed that the primary endpoint – a composite of death, myocardial infarction, and unplanned revascularisation at 12 months – occurred 40% less often with invasive FFR compared to QFR. Importantly, QFR failed to meet non-inferiority to FFR⁶. These findings raise concerns about the reliability and safety of QFR in guiding revascularisation. Two trial features are particularly notable. First, the population had a low-risk profile, with a third of patients being asymptomatic and a median FFR of 0.84, in contrast

with trials like FAME (mean FFR 0.71)⁸. Second, the lesion severity criterion (40-90% stenosis) mandated physiological assessment for almost all lesions, resulting in >98% of the lesions being assessed by physiology – higher than trials like DEFINE-FLAIR in which only 50% of the lesions were assessed by physiology⁹.

In this issue of EuroIntervention, Andersen et al offer an insight into the FAVOR III Europe trial, evaluating the deferred lesions, i.e., lesions with QFR or FFR >0.80. Among 1,122 deferred patients, QFR deferral was associated with a higher 1-year major adverse cardiac events rate (5.6%) versus FFR (2.8%; adjusted hazard ratio [HR] 2.07, 95% confidence interval: 1.07-4.03; $p=0.03$)¹⁰. Target vessel failure was also higher with QFR (3.7% vs 1.8%; HR 2.27; $p=0.049$). Outcomes were primarily driven by unplanned revascularisations in the QFR group. While invasive FFR demonstrated low 1-year event rates (<3%), the performance of QFR challenges its reliability as a substitute for FFR in PCI deferral decisions.

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Integrating lesion-specific factors that affect coronary physiology is complex. Coronary geometry, lesion length, and microcirculatory function interact to determine flow, creating pressure drop patterns that are challenging to model. Additionally, QFR is fundamentally based on QCA, a two-dimensional method that is limited because of factors such as vessel foreshortening and overlap, which can impede proper lesion evaluation. Furthermore, the flow conditions are estimated from contrast injections or are assumed based on vessel characteristics, ignoring patient-specific physiology. QFR disregards microvascular variability, which modulates epicardial flow¹¹. These intricacies partly explain the moderate accuracy of angiography-based systems in estimating FFR. From a user perspective, QFR depends on operator expertise for image acquisition and manual vessel contour adjustments, which can introduce variability in the final results¹². All these factors may have led to inadequate lesion severity evaluation, inappropriate lesion deferral, and worse clinical outcomes.

The FAVOR III subanalysis extends the previous report, highlighting the need for caution when implementing QFR. However, it does not address the reasons behind the failure of QFR to identify lesions that could be safely deferred. A core laboratory analysis is underway to compare lesions that progressed to events between core lab and site evaluations to determine whether variability in QFR assessments contributed to these discrepancies. Based on these findings, the current European Society of Cardiology guidelines endorsing QFR should be reconsidered, acknowledging the limitations of QFR and emphasising patient selection criteria. QFR should not be regarded as equivalent to FFR for clinical decision-making, especially in deferral strategies, as shown by the present FAVOR III subanalysis.

Angiography-derived FFR software is aimed to broaden physiological assessment adoption. Two ongoing non-inferiority trials (FAST III [ClinicalTrials.gov: NCT04931771] and ALL-RISE [ClinicalTrials.gov: NCT05893498]) are evaluating vFFR and FFR_{angio} versus FFR. These studies may confirm or challenge the inferiority of angiography-derived FFR compared to FFR. While FAVOR III tempers enthusiasm for integrating QFR into clinical practice, QCA-based FFR systems remain promising. Further refinement of algorithms – integrating microvascular and plaque metrics – could improve accuracy and clinical utility. Hybrid strategies and real-time “clickless” automation may streamline workflow and enhance reliability.

The FAVOR III Europe analysis highlights the risks of adopting new technologies without thorough validation. While QFR initially showed promise, its demonstrated inferiority to FFR raises concerns about its clinical utility. Until more robust evidence supports its reliability, invasive FFR holds its ground as the preferred method for physiology-guided PCI.

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Conflict of interest statement

C. Collet reports receiving research grants from Biosensors, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott; consultancy fees from HeartFlow, OpSens Medical, Abbott, and Philips/Volcano; and has patents pending on diagnostic methods for coronary artery disease. T. Mizukami reports receiving research grants from Boston Scientific; and speaker fees from Abbott, CathWorks, and Boston Scientific. K. Ikeda has no conflicts of interest to disclose.

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