

# Quantitative flow ratio will supplant wire-based physiological indices: pros and cons

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Quantitative flow ratio (QFR) represents a physiological index derived from angiography through three-dimensional (3D) quantitative coronary analysis. When compared to coronary angiography, QFR showed better performance both for guiding percutaneous coronary intervention (PCI) in case of intermediate coronary lesions and for optimising PCI results. In addition, QFR showed good diagnostic agreement with other established physiological indices, such as fractional flow reserve (FFR), with important practical advantages (e.g., fast and offline analysis). However, data on clinical outcomes in comparisons to wire-based physiological indices as well as validation studies in complex PCI and high-risk scenarios are still lacking. Further research is needed to determine the exact field of application of QFR, and whether it can supplant wire-based physiological indices remains a matter of debate.

## Pros

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The evaluation of intermediate coronary stenosis remains a controversial topic due to multiple diagnostic pathways and numerous methods in clinical use. For patients reaching the cath lab, pressure wire-based evaluation is currently the gold standard, with some advantages over angiographic assessment. Still, the long-term outcome data supporting routine use of FFR are not overly convincing, with a neutral 5-year clinical endpoint in the F.A.M.E. trial<sup>1</sup>, the disappointing FAME 3 results<sup>2</sup>, and risk for major adverse cardiovascular events (MACE) at ~0.5% related to FFR measurement. The recent long-term data showing increased mortality in patients guided by instantaneous wave-free ratio (iFR) compared with FFR<sup>3</sup> adds to the controversy, and the Class Ia recommendation by European Society of Cardiology (ESC) guidelines<sup>4</sup> for iFR and similar methods could be in jeopardy.

QFR is a wire- and adenosine-free method for the computation of FFR that has the potential to overcome many of the inherent challenges of wire-based indices. The FAVOR III China trial (n=3,825), comparing QFR and angiography-guided lesion assessment, was rather similar to

F.A.M.E. (n=1,005) but had more power and a strong sham control design<sup>5</sup>. With a positive primary endpoint in FAVOR III China, increasing benefit up to 2 years<sup>6</sup>, and procedural advantages over FFR including lower costs, the road is paved for a much wider adoption of functional lesion evaluation.

The body of evidence supporting QFR is substantial. In more than 130 published studies, QFR continues to impress with good results and only few questions raised. A meta-analysis of prospective investigator studies showed a high accuracy of QFR in direct comparison with FFR<sup>3</sup>, confirming the findings in most of the numerous *post hoc* analyses. A repeat finding in the analysis of non-dedicated studies was only moderate feasibility of QFR, in the range of 60-70%. However, when physicians routinely performed the angiograms according to instructions for QFR, feasibility increased to >95% in indicated cases<sup>7</sup>.

The early experience with QFR identified a few obstacles, of which most have been addressed in newer versions of the application. Reproducibility across studies has been good overall, but this was questioned in the QREP study<sup>8</sup>. QREP showed that observers must follow the instructions for use to achieve high reproducibility. Suboptimal use also affects the accuracy of pressure wire-based methods. Newer versions of QFR have improved

workflow, and steps that could introduce bias have been further automated.

Both FAVOR II Europe-Japan<sup>7</sup> and FAVOR II China<sup>9</sup> showed that QFR assessment was faster than FFR in paired comparisons. Further advantages are the option for analysing QFR simultaneously while the operator continues with the PCI and that QFR can be analysed offline, e.g., the next morning in patients with secondary lesions treated during the night for a ST-segment elevation myocardial infarction (STEMI). In the randomised FAVOR III China, the overall procedure time was even shorter in the QFR-guided group compared with the standard angiography-guided group.

The present QFR application may be suitable for 85-90% of lesions, but assessment of the left main, more complex bifurcation lesions and in-stent restenosis awaits further validation and ongoing developments of QFR.

For now, the pending piece of evidence is from the FAVOR III Europe non-inferiority trial<sup>10</sup> comparing QFR and FFR,

with main results aimed for presentation in the second half of 2024.

On top of lesion evaluation, QFR further provides reference measurements for stent sizing and enables a validated, functional post-PCI evaluation showing a clear relation to outcomes<sup>11</sup>; an angiography-derived index of microcirculatory resistance (angio-IMR) based on QFR has recently seen promising results<sup>12</sup>.

In conclusion, angio-based functional lesion evaluation may allow for a wider uptake of functional lesion evaluation and, pending positive results, may soon supplant the vast majority of pressure wire-based assessment of intermediate coronary lesions.

## Conflict of interest statement

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## Cons

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QFR and other angiography-based indices utilise the information contained in the angiographic images to create 3D models of the coronary vessel and input contrast flow velocity, and, from that information, derive an estimation of pressure loss across a lesion. QFR has been calibrated and validated against FFR. In a small pilot study, the diagnostic agreement between QFR and FFR was 80%<sup>13</sup>. In a subsequent multicentre study including 329 patients and comparing online QFR measurement with FFR, the diagnostic agreement between the two indices was 86.8%<sup>7</sup>. FAVOR III China, a large randomised clinical trial, investigated whether QFR-guided PCI, compared with angiography-guided PCI, improved clinical outcome<sup>5</sup>. QFR was found to be associated with an improved 1-year outcome (QFR: 5.8% vs angiography: 8.8%, hazard ratio 0.65, 95% confidence interval: 0.51 to 0.83;  $p=0.0004$ ). Even when periprocedural myocardial infarction (MI) was excluded, an improved clinical outcome with QFR was still found, driven by a combination of lower rates of spontaneous MI and ischaemia-driven revascularisation.

Although QFR seems to provide some additional clinical improvement over using angiography to guide PCI, at present, it is unknown whether QFR is clinically non-inferior to FFR. This is currently being investigated in a randomised clinical study (FAVOR III Europe Japan; ClinicalTrials.gov: NCT03729739)<sup>10</sup>.

QFR could potentially have an additional benefit compared with FFR in the assessment of non-culprit lesions in STEMI patients due to the disturbed coronary physiology in the acute setting<sup>14</sup>.

There are, however, several important drawbacks and limitations of using QFR which hamper its adoption into wider clinical practice. Bifurcations and left main lesions have often been exclusion criteria in the validation studies. Additionally, the diagnostic agreement between QFR and FFR

among diabetic patients seems to be lower<sup>7</sup>. Thus, although the results so far are indeed encouraging, more validation studies are required to investigate the performance of QFR in different clinical settings, as well as in commonly occurring coronary pathologies.

Although the time to calculate QFR is quick, the process of image acquisition deviates significantly from normal cath lab practice. Currently, to perform a QFR assessment, two separate angiographic projections  $\geq 25$  degrees apart need to be acquired, using a high frame rate and longer contrast phase to optimise image quality. Furthermore, these non-standard projections often need to be adjusted further to avoid overlapping vessels. In case of multiple lesions being assessed, the process needs to be repeated. This requirement for the acquisition of high-quality images is time-consuming, puts additional strain on cath lab practice, requires more contrast, and exposes both the patient and staff to more radiation.

QFR likely provides an incremental clinical benefit compared with angiography, since it has the potential to achieve a significantly higher adoption of coronary physiology beyond that which has been achieved by wire-based indices.

However, to achieve this goal, an angiography-based technology such as QFR would likely first have to be further developed in order to be seamlessly integrated into cath lab practice. It should ideally be running as a background application during an angiography, allowing image acquisition using standard projections. The application should be able to automatically identify vessels and suspected lesions, add further diagnostic accuracy if further projections of the same lesion were performed, potentially, even suggest additional projections if needed, and finally, the calculations should be complete by the time the angiography is finished.

Although clinical trials are truly fundamental in the validation of a new technology, ease of use and integration into cath lab practice are key factors in driving the adoption of angiography-based physiology, which ultimately will improve patient outcome. The future is indeed close, but it is not here yet.

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