Instantaneous wave-free ratio versus fractional flow reserve

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Instantaneous Wave-free Ratio versus Fractional Flow Reserve

TO THE EDITOR: Davies et al. (May 11 issue)[1] report on the DEFINE-FLAIR trial (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation). In the same issue, Götberg et al.[2] report on the iFR-SWEDEHEART trial (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome). The revascularization rate was lower in the instantaneous wave-free ratio (iFR) group than in the fractional flow reserve (FFR) group in both trials (47.5% and 53.4% in the DEFINE-FLAIR trial; 53.0% and 56.5% in the iFR-SWEDEHEART trial).

In the ADVISE II study (Adenosine Vasodilator Independent Stenosis Evaluation II), an iFR cutoff value of 0.89, as compared with FFR, had a specificity of 87.8% and a sensitivity of 73.0%.[3] Conceivably, revascularization of some lesions that would be warranted according to an FFR-guided strategy would be deferred with an iFR-guided strategy. Although an iFR-guided revascularization strategy was noninferior to FFR-guided revascularization in the trials reported by Davies et al. and Götberg et al., outcomes in patients with iFR-guided deferral of revascularization were not reported.

In the FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2), among patients with an FFR higher than 0.80 in all vessels who were enrolled in a registry and received the best available medical therapy, the rate of major adverse cardiovascular events was 3%; this rate was lower than that among patients who were randomly assigned to both the medical-therapy and percutaneous coronary intervention (PCI) groups in this trial.[4] It would be interesting to know whether the patients in the DEFINE-FLAIR and iFR-SWEDEHEART trials who had an FFR higher than 0.80 or an iFR higher than 0.89 and for whom intervention was deferred had similar outcomes. If indeed the clinical outcomes were similar, interventional cardiologists would have more confidence in deferring revascularization if the iFR is higher than 0.89, and these findings would help to encourage transition from a hybrid iFR–FFR approach to a pure iFR-guided strategy.[5]

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TO THE EDITOR: Götberg et al. and Davies et al. found that coronary revascularization guided by iFR was noninferior to revascularization guided by FFR with respect to the risk of major adverse cardiac events at 1 year. As stated by Götberg et al., previous studies had shown that iFR (an adenosine-free index) and FFR have diagnostic accuracy that is similar to that of independent measures of myocardial ischemia.

However, a recent study[1] showed that the diagnostic accuracy of adenosine-free indexes depends on the location of the lesion in the coronary tree. In particular, the diagnostic accuracy of iFR was significantly lower than that of FFR for lesions located in the left main or proximal left anterior descending coronary artery; this is probably related to the larger amount of myocardium supplied. This difference may have clinical relevance. As a consequence, we think that it would be important for the authors to provide data about the rates of clinical events according to lesion location.

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TO THE EDITOR: The trials conducted by Davies et al. and by Götberg et al. foster the awareness of physiological guidance of PCI. More than 20 years after we introduced FFR,[1] the iFR is a welcome companion to FFR for interventional cardiologists who prefer to avoid the administration of hyperemic agents.

The question of whether iFR is noninferior to FFR, however, cannot be answered with the data reported by Davies et al. and Götberg et al., because both trials are functionally underpowered. Indeed, in 80% of stenoses, iFR and FFR are concordant[2]; thus, since the decision regarding revascularization would be the same, no difference in outcome could be expected. Only patients who have lesions in which iFR and FFR are discordant (20% of stenoses) should be included in a randomized, noninferiority trial.

This flaw undermines the conclusions of both articles but is not even touched on in the corresponding editorial by Bhatt.[3] Although the DEFINE-FLAIR and iFR-SWEDEHEART trials are a step in the right direction, clinicians cannot conclude that iFR is noninferior to FFR.

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Dr. Pijls reports receiving consulting fees from St. Jude Medical and Opsens, owning equity in Heartflow, Philips, General Electric, and Advanced Semiconductor Materials Lithography, and that his institution receives grant support from St. Jude Medical; Dr. De Bruyne, holding shares in Siemens, General Electric, Bayer, Philips, Heartflow, Edwards Lifesciences, Sanofi, and Omega Pharma, receiving consulting fees from St. Jude Medical, Opsens, and Boston Scientific, and that his institution (Cardiovascular Center, Aalst, Belgium) receives grant support from Abbott Vascular, Boston Scientific, Biotronik, and St. Jude Medical. No other potential conflict of interest relevant to this letter was reported.

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DRS. GÖTBERG AND FRÖBERT REPLY: Aggarwal and Pavlides highlight the safety of deferring revascularization of lesions with the use of intracoronary physiological assessment — a vital aspect of an invasive test. The safety of deferral of revascularization with the use of FFR had been established in only 91 patients (in the DEFER study).[1] The merged results from the iFR-SWEDEHEART and DEFINE-FLAIR trials show that revascularization was deferred in 2130 patients on the basis of either iFR or FFR. Major adverse clinical events were similar between the iFR and FFR groups at 1 year; this confirms the safety of both methods.

Montone and Minelli refer to a trial examining the influence of lesion location on the diagnostic accuracy of iFR as compared with FFR with the use of a 0.80 FFR cutoff value as a standard.[2] A lower agreement between the indexes was found in the left main stem and proximal left coronary artery than in other vessels. This interesting finding is based on a retrospective hypothesis-generating analysis performed under the assumption that FFR is infallible for detecting coronary ischemia. Validation trials of FFR as compared with noninvasive indexes of myocardial ischemia show an overall diagnostic accuracy with FFR of approximately 80%.[3]

A variable response to hyperemia may partly explain the observed differences between iFR and

FFR. In vessels with high coronary flow, a hemodynamically important FFR value but normal coronary flow reserve has been observed. Two recent studies showed a closer agreement between iFR and coronary flow reserve as compared with that between FFR and coronary flow reserve. Thus, the observed variation could potentially be explained by disagreement between coronary flow and FFR rather than between iFR and FFR. An analysis of vessel dependency and outcomes in the iFR-SWEDEHEART trial is planned. An ongoing trial (the DEFINE-FLOW trial [Distal Evaluation of Functional Performance with Intravascular Sensors to Assess the Narrowing Effect — Combined Pressure and Doppler FLOW Velocity Measurements]; ClinicalTrials.gov number, NCT02328820) investigating the safety of deferring revascularization of lesions in patients with normal coronary flow but pathologic FFR is under way to shed further light on this unresolved issue.

We respectfully disagree with Pijls and De Bruyne that the iFR-SWEDEHEART and DEFINE-FLAIR trials did not show noninferiority. When iFR and FFR were compared with a third ischemic test as arbiter, iFR showed equal or improved diagnostic accuracy as compared with FFR in the majority of previous studies. Also, the safety of deferral with the use of iFR has been established. In the JUSTIFY-CFR study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity–Coronary Flow Reserve), iFR was shown to have a closer correlation with coronary flow reserve than with FFR in intermediate lesions; this was a plausible explanation for the discrepancies between iFR and FFR in some lesions.[4] Thus, there is currently no scientific foundation to support the opinion that FFR provides diagnostic information that is superior to that of iFR in patients with stable angina or an acute coronary syndrome.

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Since publication of their article, the authors report no further potential conflict of interest.

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DR. DAVIES AND COLLEAGUES REPLY: We agree with Aggarwal and Pavlides that the DEFINE-FLAIR and iFR-SWEDEHEART trials encourage the transition toward an iFR-guided approach. In addition, we can confirm that a combined analysis involving 4529 patients shows that despite deferring more patients with the use of iFR, event rates were low and similar with the use of either iFR (4.12%) or FFR (4.05%).

Montone and Minelli correctly note that iFR does not match FFR in all coronary territories. Such differences are caused by mismatch between FFR and flow; this has been highlighted by investigators in the past.[1] Indeed, identification of events associated with such cases of false positive FFR (normal flow) are now the subject of a clinical trial (the DEFINE-FLOW trial) designed to show that when flow is normal, it is safe to defer revascularization in patients, irrespective of a positive FFR. Given that iFR mirrors flow more closely than FFR,[1] it is unsurprising that there is vessel-specific discordance.

We are delighted to read the positive sentiments from Pijls and De Bruyne. However, we are surprised regarding their concerns about the trial design given the limitations of the FFR evidence base before the DEFINE-FLAIR and iFR-SWEDEHEART trials.

The clinical value of FFR was established with three randomized trials (DEFER, FAME, and FAME 2). None of these trials were blinded, and none included a predominance of patients who had a profile that was similar to that of patients who are currently evaluated with FFR in clinical practice (Fig. 1). Indeed, in making their recommendations, the developers of clinical practice guidelines assumed that the results of pivotal trials on FFR guidance would be applicable to contemporary patient populations. Until the DEFINE-FLAIR and iFR-SWEDEHEART trials,

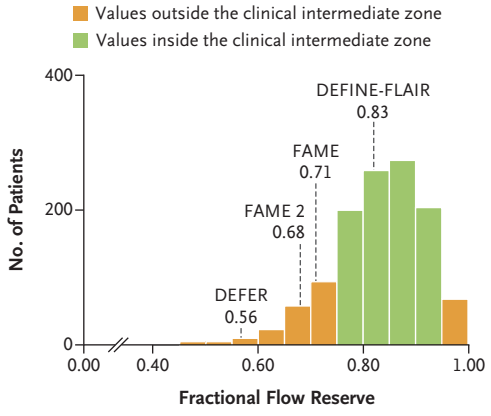

Figure 1. Results of the DEFER, FAME, and FAME 2 Trials Outside the Routine Distribution of Clinical Patients.

The bar graph shows the frequency distribution of fractional flow reserve (FFR) in the DEFINE-FLAIR trial (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation), with values inside the intermediate clinical zone, as compared with the frequency distribution of FFR in previous trials with values outside the intermediate clinical zone. The DEFER study and the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME 2 trials all tested the role of FFR in guiding therapy in a range of patients, which is not typical of routine distributions of patients. This means that until the DEFINE-FLAIR and iFR-SWEDEHEART (Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) trials, data were lacking from prospective, randomized clinical trials testing the role of FFR in clinical distributions. The authors of the DEFINE-FLAIR and iFR-SWEDEHEART trials conclude that FFR and instantaneous wave-free ratio (iFR) are associated with similar outcomes in terms of overall decision making about revascularization and the safety of the deferral of revascularization. The values shown are those reported in each trial. The mean (±SD) FFR of 0.56±0.16 in the DEFER trial is the mean FFR in the reference group. The mean FFR of 0.71±0.18 in the FAME trial is the mean cross-population FFR. The mean FFR of 0.68±0.10 in the FAME 2 trial is the mean FFR in lesions with an FFR of 0.80 or less. In comparison, in the DEFINE-FLAIR trial, the mean FFR was 0.83±0.09, and the majority of values were in the clinically intermediate zone.

this remained a subject for which the answer was pending. The results of our trial were published when the interventional community was awaiting the publication of the results of the FUTURE trial (Functional Testing Underlying Coronary Revascularisation; NCT01881555), a large randomized trial on FFR guidance in modern-day clinical populations, including those with the acute coronary syndrome. That study was discontinued prematurely because of the excess of events in the FFR group. It was therefore paramount that we included a broad population of clinically relevant patients, rather than a select group, in the DEFINE-FLAIR and iFR-SWEDEHEART trials to ensure that the trial results are applicable to clinical practice.

The DEFINE-FLAIR and iFR-SWEDEHEART trials showed that iFR had proven safety as well as a shorter procedural time and less patient discomfort than FFR. We hope that these findings will promote physiological assessment in clinical practice so that more patients can realize the benefits of physiologically guided revascularization.

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THE EDITORIALIST REPLIES: Pijls and De Bruyne have contributed immensely to the development of FFR. This diagnostic method has been studied intensively, and its use enhances the cardiovascular outcomes of PCI. The trials by Davies et al. and Götberg et al. compared iFR with FFR and showed noninferiority of iFR. The high rate of concordance between iFR and FFR noted in these and other studies provides great reassurance that the methods are quite similar. Although one can second-guess the boundaries of noninferiority chosen, the DEFINE-FLAIR and iFR-SWEDEHEART trials are far larger than typical studies involving diagnostic methods, and the fact that two separate trial groups reached the same conclusion provides further reassurance regarding the findings.

Instead of the debate between FFR and iFR, the much more important point is the underuse of hemodynamic assessment of angiographically ambiguous coronary artery lesions, which leads to both overtreatment and undertreatment with stenting.[1] Indeed, greater use of invasive and

perhaps noninvasive evaluation of lesions would further improve the effectiveness of PCI.[2]

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Since publication of his editorial, the author reports no further potential conflict of interest.

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Ventilation in Preterm Infants and Lung Function at 8 Years

TO THE EDITOR: Doyle et al. (July 27 issue)[1] found no reduction in the rate of bronchopulmonary dysplasia and an increased rate of obstructive lung disease in a cohort of infants born in 2005, as compared with a cohort born in 1997. The lower survival rate that was observed and the shorter courses of mechanical ventilation in 1991 and 1992, as compared with the later cohorts (1997 and 2005), suggest that babies who were at the highest risk for bronchopulmonary dysplasia did not survive long enough for it to develop; thus, the earlier cohort (1991–1992) cannot be compared with the 2005 cohort.

There was no significant difference between the 1997 cohort and the 2005 cohort in the rate of endotracheal ventilation, and it has been shown that even short exposure to endotracheal positive pressure ventilation is harmful.[2] There was a striking decrease in the rate of use of postnatal glucocorticoids between these two periods, from 46% in the 1997 cohort to 23% in the 2005 cohort. These differences among eras could explain the results found by Doyle et al.

The study conducted by Doyle et al. may suggest that we should try to further minimize the use of endotracheal ventilation by using noninvasive ventilation more and perhaps that we should adopt policies of using postnatal glucocorticoids, such as inhaled glucocorticoids,[3] low-dose hydrocortisone,[4] or intratracheal glucocorticoids with surfactant,[5] that do not adversely affect the neurodevelopmental outcome.

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TO THE EDITOR: Doyle and colleagues found higher rates of bronchopulmonary dysplasia and evidence of airway obstruction at 8 years of age with increasing use of nasal continuous positive airway pressure (CPAP) in preterm infants. The results are intriguing but not totally unexpected, because none of the major randomized, controlled trials comparing CPAP with mechanical ventilation in preterm infants have shown a significantly lower incidence of bronchopulmonary dysplasia with CPAP. Possible reasons for the lack of benefit of CPAP include a high failure rate of noninvasive ventilation among smaller and sicker infants (the population at highest risk for bronchopulmonary dysplasia), a possible delay in surfactant administration with aggressive use of CPAP, and a greater need for supplemental oxygen during noninvasive support than during invasive ventilation. These results should not be interpreted as if invasive ventilation is superior to noninvasive support in all infants with extremely low birth weight. The challenge is to find the right indication for invasive or noninvasive support and the right timing during the respiratory course in each infant. Let us not swing the pendulum back to invasive ventilation until more evidence becomes available.