

# Real-time use of instantaneous wave-free ratio: Results of the ADVISE *in-practice*: An international, multicenter evaluation of instantaneous wave-free ratio in clinical practice

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**Objectives** To evaluate the first experience of real-time instantaneous wave-free ratio (iFR) measurement by clinicians.

**Background** The iFR is a new vasodilator-free index of coronary stenosis severity, calculated as a trans-lesion pressure ratio during a specific period of baseline diastole, when distal resistance is lowest and stable. Because all previous studies have calculated iFR offline, the feasibility of real-time iFR measurement has never been assessed.

**Methods** Three hundred ninety-two stenoses with angiographically intermediate stenoses were included in this multicenter international analysis. Instantaneous wave-free ratio and fractional flow reserve (FFR) were performed in real time on commercially available consoles. The classification agreement of coronary stenoses between iFR and FFR was calculated.

**Results** Instantaneous wave-free ratio and FFR maintain a close level of diagnostic agreement when both are measured by clinicians in real time (for a clinical 0.80 FFR cutoff: area under the receiver operating characteristic curve [ROC<sub>AUC</sub>] 0.87, classification match 80%, and optimal iFR cutoff 0.90; for a ischemic 0.75 FFR cutoff: iFR ROC<sub>AUC</sub> 0.90, classification match 88%, and optimal iFR cutoff 0.85; if the FFR 0.75-0.80 gray zone is accounted for: ROC<sub>AUC</sub> 0.93, classification match 92%). When iFR and FFR are evaluated together in a hybrid decision-making strategy, 61% of the population is spared from vasodilator while maintaining a 94% overall agreement with FFR lesion classification.

**Conclusion** When measured in real time, iFR maintains the close relationship to FFR reported in offline studies. These findings confirm the feasibility and reliability of real-time iFR calculation by clinicians. (*Am Heart J* 2014;168:739-48.)

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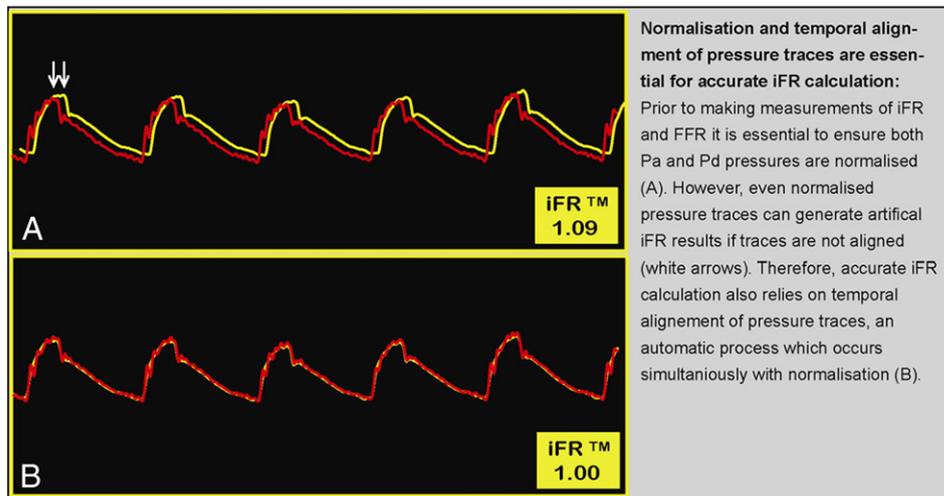
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The instantaneous wave-free ratio (iFR) is a recently proposed index of coronary disease severity, which uses a trans-lesional pressure ratio as a measure of functional stenosis severity. It can be calculated using conventional pressure guide wires and differs fundamentally from fractional flow reserve (FFR)<sup>1</sup> because it does not require vasodilators such as adenosine for its calculation.

The relationship between iFR and FFR has been extensively evaluated in more than 2,000 stenoses,<sup>1-4</sup> and their agreement in lesion classification ranges from 80% to 90%, depending on whether the comparison is made in clinical populations, with predominantly intermediate lesions, or in samples with more severe stenoses.<sup>2</sup> When compared with independent arbiters of stenosis severity, iFR and FFR have demonstrated equal diagnostic agreement

Figure 1



Pressure normalization, temporal alignment, and iFR calculation using the hemodynamic console.

against invasive flow<sup>5,6</sup> and myocardial perfusion imaging.<sup>7</sup> Also, offline studies consistently demonstrated 0.89 to 0.90 as the optimal iFR cutoff to match an FFR of 0.80.<sup>2,3,8</sup>

To date, however, in all iFR-FFR studies, pressure data and iFR calculation have been processed offline in a core laboratory, after procedural termination and appropriate data extraction. Although necessary for any new technology during its early development, this methodology does not reflect the future application of iFR in clinical practice, which will be performed by clinicians, using appropriate software installed in hemodynamic consoles. It is not known whether these practical aspects could affect the performance of iFR.

In this study we explored important aspects of the relationship between iFR and FFR, when both indices are measured in real time by clinicians. First, using a *clinical* FFR cutoff of 0.80 as a reference, we evaluated whether the diagnostic performance and optimal cutoff of iFR are maintained, when compared with offline studies. Second, we extended the analysis to the original 0.75 *ischemic* FFR cutoff and explored the performance of real-time iFR to match such classification of stenoses. Finally, we aimed to validate with real-time measurements the previously reported iFR-FFR hybrid strategy, using a predefined deferral iFR cutoff of >0.93 and a predefined treatment iFR cutoff of <0.86.<sup>9</sup>

## Methods

### Study population

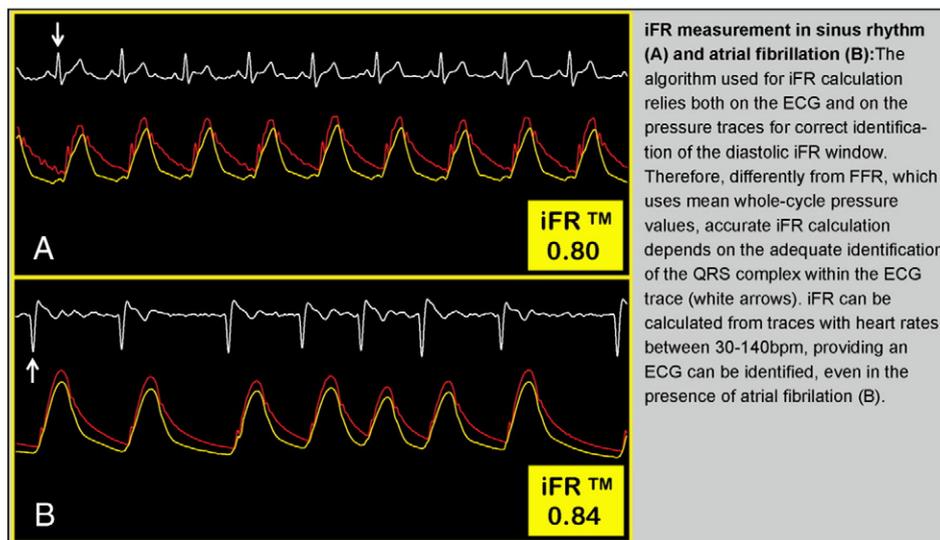
Instantaneous wave-free ratio and FFR were measured from hemodynamic consoles in 16 centers in Europe, Asia, and Africa. The study included 392 stenoses from 313 consecutive patients who, as part of clinical

investigation, required functional intracoronary assessment with pressure guide wires.

### Hemodynamic data collection and analysis

Cardiac catheterization was performed according to standard practice. Unfractionated intravenous heparin (5000 IU) and 300 to 600  $\mu\text{g}$  intracoronary nitrates were given at the start of the procedure. Acquisition of physiological data for FFR calculation was performed according to conventional practice<sup>10</sup> using commercially available FFR systems (S5i and Prestige pressure guide wire; Volcano Corporation, San Diego, California). The method to induce pharmacologic hyperemia varied according to conventional clinical practice at each center. Adenosine (or adenosine triphosphate) was used for induction of hyperemia: in 39% of the cases, it was administered via a central line, with doses ranging from 140 to 180  $\mu\text{g kg}^{-1} \text{min}^{-1}$  (median 140  $\mu\text{g kg}^{-1} \text{min}^{-1}$ ); in 61% of the cases, the intracoronary route was used with a median dose of 60  $\mu\text{g}$  (interquartile range 36-240  $\mu\text{g}$ ). Each reported iFR value and its FFR counterpart were obtained directly from the hardware console. Instantaneous wave-free ratio was calculated using software embedded onto the hemodynamic consoles, which uses proprietary iFR algorithms acting on electrocardiogram (ECG)-gated, time-aligned pressure traces, as previously described.<sup>1</sup> Instantaneous wave-free ratio was automatically calculated as a ratio of distal (Pd) to proximal (Pa) coronary pressures at the baseline iFR window. Fractional flow reserve was automatically calculated as the ratio of whole-cycle Pd/Pa during hyperemia. Anatomical severity of coronary stenoses was measured using quantitative coronary angiography.

**Figure 2**



Importance of ECG detection for accurate iFR measurement.

Prior to iFR and FFR measurements, hemodynamic consoles ensure that the pressure data are appropriately calibrated. These include steps required for both FFR and iFR calculation, such as ensuring that catheter (Pa) and wire (Pd) pressures are equal or *normalized* before wire insertion. In addition, a specific step is needed before iFR measurement, which is the adjustment of temporal delays between Pa and Pd signals. This essential process occurs automatically and simultaneously with pressure normalization (Figure 1). Figure 2 demonstrates the importance of ECG identification and the reliability of iFR calculation in sinus rhythm and atrial fibrillation.

### Statistical analysis

The classification agreement (and sensitivity, specificity, negative predictive value, and positive predictive value) between iFR and FFR as well the area under the receiver operating characteristic curves (ROC<sub>AUC</sub>) were calculated for 2 different FFR cutoffs. First, a 0.80 *clinical* FFR cutoff (as per FAME, FAME II trials, and current clinical guidelines) was used (FFR or iFR ≤0.8 as a reference test to define significant stenoses). For this clinical FFR cutoff, we established a prespecified iFR cutoff of 0.90 and evaluated whether it would also represent the optimal cutoff by ROC analysis (defined as the best sum of sensitivity and specificity). Second, the diagnostic performance of iFR was evaluated for a 0.75 *ischemic* FFR cutoff, as per original validation studies and DEFER<sup>11,12</sup> (FFR or iFR ≤0.75 as a reference test to define significant stenoses). Finally, the diagnostic performance of iFR was explored when allowing for the 0.75 to 0.80 FFR gray zone (zone of values which,

according to DEFER and FAME/FAME II studies, is *both* safe to defer and treat stenoses). Comparisons between proportions (classification agreement between iFR and FFR) observed in this study with previous offline data sets were made with the  $\chi^2$  test for homogeneity of proportions. Areas under the receiver operating characteristic curve were compared using the method described by DeLong et al<sup>13</sup> in STATA, version 11 (StataCorp, College Station, Texas). Data are expressed as mean ± SD. A *P* value of <.05 was considered statistically significant.

### Hybrid iFR-FFR analysis

The real-time iFR and FFR values reported in this sample were evaluated in a hybrid decision-making strategy, according to the methodology previously described.<sup>9</sup> We aimed to prospectively apply the following decision-making arms into this sample: when iFR >0.93, stenoses would be deferred; when iFR <0.86, stenoses would be treated; when iFR would fall between 0.86 and 0.93, FFR would be calculated. For such strategy, we evaluated the overall agreement in stenoses classification with an FFR-only strategy and the proportion of stenoses spared from vasodilator administration.

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**Table.** Demographic and angiographic data

No. of stenoses (patients)	392 (313)
Age (y), mean $\pm$ SD	67 $\pm$ 11
Male %	79
Comorbidities (%)	
Hypertension	74
Hypercholesterolemia	67
Smoking history	51
Diabetes	30
Ejection fraction, mean $\pm$ SD	58 $\pm$ 12
Clinical presentation (%)	
Stable angina	73
Unstable angina (nonculprit vessel)	27
Coronary anatomy (%)	
Single-vessel CAD	36
Multivessel CAD	63
LAD	66
LCx	10
RCA	14
Other	10
Diameter stenosis (%), men $\pm$ SD	56 $\pm$ 13
Adenosine route (%)	
Intravenous	39
Intracoronary	61

Abbreviations: CAD, Coronary artery disease; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

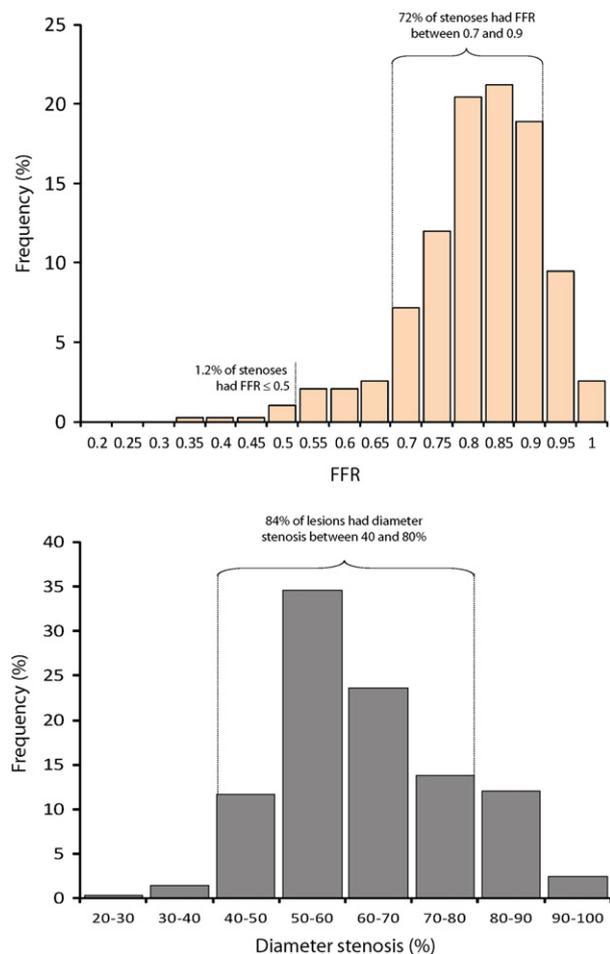
## Results

### Sample characteristics

The 392 stenoses (from 313 patients) included in this study demonstrated a unimodal distribution of FFR and diameter stenosis values. Population demographic and angiographic data are presented in [Table](#). Fractional flow reserve and iFR were measured in all attempted cases. Mean FFR was  $0.82 \pm 0.10$ , and mean iFR was  $0.89 \pm 0.11$ . This sample was formed predominantly by physiologically intermediate lesions, with 71% of stenoses falling between FFR 0.70 and 0.90. The proportion of stenoses with FFR values lower than 0.80, 0.75, 0.60, and 0.50, respectively, was 39%, 18%, 4.6%, and 1.3%. Mean percentage diameter stenosis was  $56\% \pm 13\%$ , with 84% of lesions falling within the 40% to 80% group. [Figure 3](#) presents a histogram of FFR and diameter stenosis values.

### Classification agreement between iFR and FFR

**Using a clinical FFR cutoff of 0.80.** In this sample, the predefined iFR cutoff of 0.90 was also identified as the ROC-derived optimal cutoff, yielding a classification agreement with FFR of 80%. The  $\text{ROC}_{\text{AUC}}$  for iFR to was 0.87 (CI 0.84-0.91). The diagnostic agreement between iFR and FFR when measured in real time (80%) was not different from previously reported offline studies performed in clinical samples (RESOLVE study<sup>8</sup> 80%,

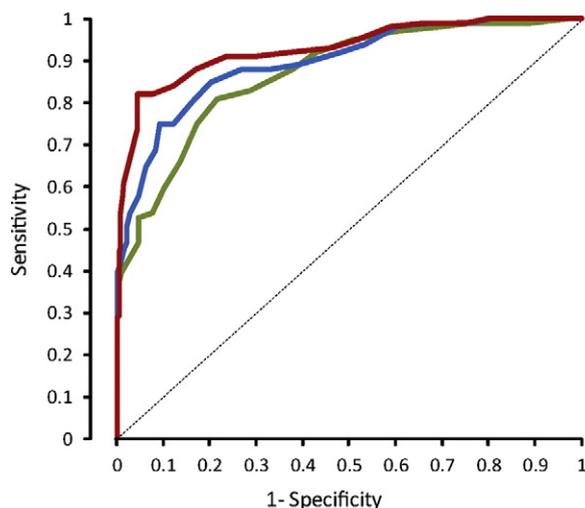
**Figure 3**

Frequency distribution of FFR and percentage diameter stenosis values in the study.

$N = 1,593$ ; ADVISE Registry<sup>2</sup> study 80%,  $N = 339$ ; and by Park et al<sup>3</sup> 82%,  $N = 238$ ;  $P = .95$  for all comparisons). The detailed diagnostic performance of iFR is summarized in [Figure 4](#). For this clinical FFR cutoff, the diagnostic relationship between iFR and FFR remained close within the intermediate anatomical lesion range (iFR-FFR  $\text{ROC}_{\text{AUC}}$  within 40%-80% diameter stenosis = 0.86 [0.83-0.90]).

**Using a ischemic FFR cutoff of 0.75.** For the ischemic FFR cutoff, classification match between iFR and FFR was 88% with an  $\text{ROC}_{\text{AUC}}$  of 0.90 (CI 0.86-0.94). To match an FFR of 0.75, the ROC-derived optimal iFR cutoff was 0.85 ([Figure 4](#)). For this ischemic FFR cutoff, the diagnostic relationship between iFR and FFR also remained unchanged within the intermediate anatomical lesion range (iFR-FFR  $\text{ROC}_{\text{AUC}}$  within 40%-80% diameter stenosis = 0.88 [0.85-0.91]).

**Figure 4**



**Classification agreement between iFR and FFR**

	FFR 0.8	FFR 0.75	FFR gray zone*
<b>iFR cut-off</b>	0.9	0.85	0.85
<b>ROC AUC</b>	0.87	0.90	0.93
<b>Classification match</b>	80%	88%	92%
<b>Sensitivity</b>	81%	75%	82%
<b>Specificity</b>	79%	91%	96%
<b>PPV</b>	71%	70%	86%
<b>NPV</b>	87%	93%	95%

\* Accounting for the 0.75 - 0.8 FFR gray zone

Diagnostic agreement between iFR and FFR.

When the FFR values falling into the 0.75 to 0.80 gray zone were considered equally safe to be classified as *normal or abnormal*, the  $ROC_{AUC}$  increased to 0.93 (CI 0.90-0.96) and the classification agreement between iFR and FFR to 92%. Both  $ROC_{AUC}$  and classification agreement were significantly higher when accounting for the FFR gray zone, when compared with single FFR cutoffs ( $P < .001$  for comparisons against FFR 0.75 and FFR 0.80).

### Hybrid iFR-FFR decision-making analysis

The previously reported iFR cutoffs of a hybrid iFR-FFR approach<sup>9</sup> were also validated in this real-time iFR sample. Using a predefined deferral iFR cutoff of  $>0.93$  and a predefined treatment iFR cutoff of  $<0.86$  (and measuring FFR only in those lesions with iFR between 0.86 and 0.93) would generate a 94% overall agreement with an FFR classification of lesions, while sparing 61% of patients from adenosine, proportions that are not different from the previous offline report (Petraco et al,<sup>9</sup>  $N = 577$ ;  $P = .92$ ). Figure 5 summarizes other possible iFR-FFR diagnostic strategies.

## Discussion

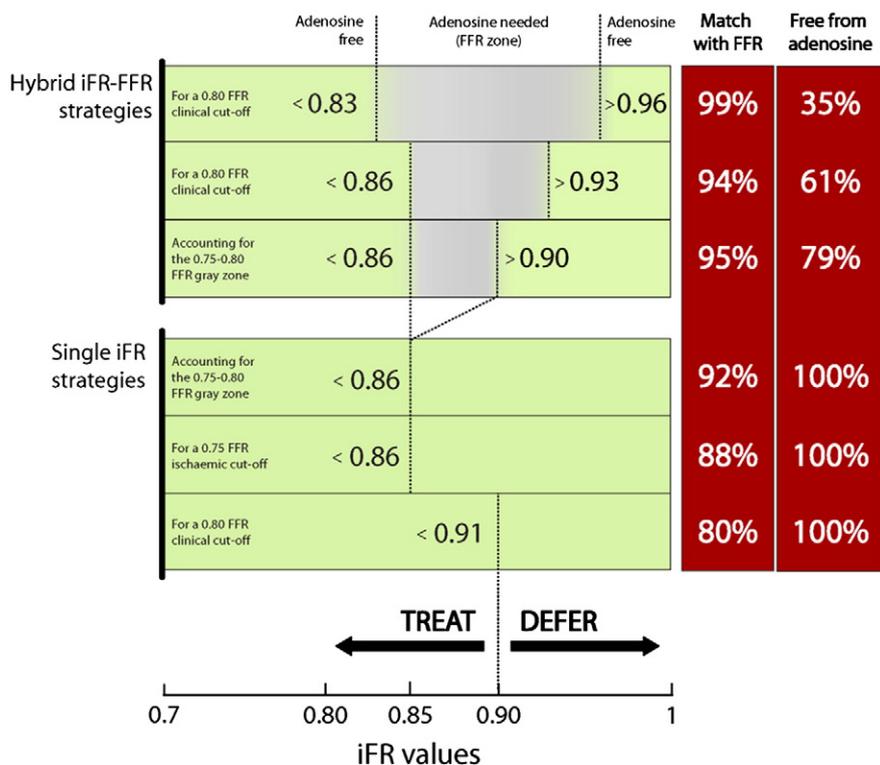
In this study, we present the results of the first clinical application of real-time iFR measurements in patients undergoing invasive functional assessment of intermediate coronary stenoses. We found that (1) for a clinical FFR cutoff of 0.80, a predefined iFR value of 0.90 provides the optimal cutoff, with a classification match of 80%, similar to what has been reported in previous offline studies;

(2) when the originally validated 0.75 ischemic FFR cutoff is used as a reference comparison, the agreement between iFR and FFR increases to 88% with the optimal iFR cutoff being 0.85; (3) when accounting for the known 0.75 to 0.80 FFR gray zone, the classification match between iFR and FFR increases to 93%; and (4) confirming previous reports,<sup>8,9</sup> a hybrid decision-making strategy with iFR and FFR could spare 61% of patients from vasodilator, while maintaining 94% overall agreement with FFR classification of lesions.

### Real-time iFR measurement in the catheterization laboratory is feasible

One potential limitation applicable to all studies that so far evaluated the relationship between iFR and FFR is the fact that all hemodynamic analyses were performed offline. This inevitable stage in the development of a new technology creates the theoretical possibility of *expertise bias* where only operators specifically trained in the offline analysis of hemodynamic traces, such as in a core laboratory, perform the analysis. We have found that when iFR is implemented in catheter laboratories around Europe, Africa, and Asia and the measurements are performed by clinicians who routinely perform functional assessment using pressure guide wires, the close agreement between iFR and FFR is maintained. Our results, therefore, demonstrate the feasibility of iFR use by the clinical community and the applicability of earlier offline core laboratory reports to clinical practice. Figure 6 shows 2 examples of lesion interrogation by iFR and FFR.

Figure 5



Decision-making strategies of revascularization, using iFR only (bottom panel) and a hybrid iFR-FFR approach (top panel). FFR gray zone (0.75-0.80) refers to a region within which is known to be safe to defer and treat stenoses with equivalent clinical outcomes.

### Validation of the clinical iFR cutoff and match with FFR classification

In this study, when a clinical FFR cutoff of 0.80 was used as a reference comparison, a prespecified iFR value of 0.90 was also found to be the optimal cutoff identified by ROC, yielding a classification agreement of 80%, with an  $ROC_{AUC}$  of 0.87. This comparison with an FFR of 0.80 is important because it reflects current clinical guidelines,<sup>14</sup> is in line with FAME<sup>15</sup> and FAME II studies,<sup>16</sup> and validates with real-time measurements the results of all previous iFR-FFR studies in clinical populations.<sup>2,3,8</sup>

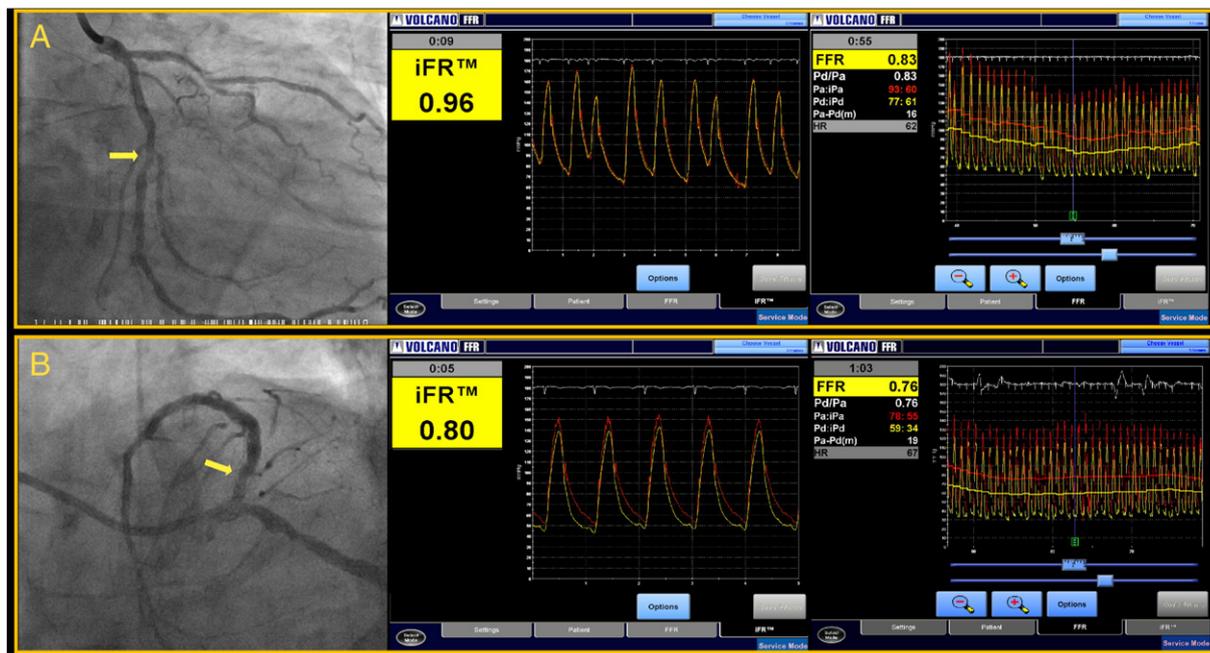
### Performance of iFR to identify FFR-ischemic stenoses

Despite its clinical use for decision making, it must be remembered that FFR 0.80 is not an ischemia-derived FFR optimal cutoff. Studies that evaluated FFR against measures of myocardial perfusion more consistently identified FFR 0.74 to 0.75 as the optimal FFR cutoff.<sup>11</sup> The change from FFR 0.75 to 0.80 was subsequently implemented in large clinical trials<sup>15,16</sup> and was aimed to increase the negative predictive value of FFR-based decisions and avoid significant lesions being missed by a lower cutoff of FFR 0.75. Therefore, the original and

extensively validated *ischemic* 0.75 FFR cutoff<sup>12,13</sup> is also essential for new indices to be validated against, as it has been shown to provide the best match to previous perfusion modalities.<sup>11,14,15</sup> Indeed, in ADVISE *in-practice* when such a comparison was made, the agreement between iFR and FFR increased to 88% when an iFR cutoff of 0.85 was used. In addition, the finding of an iFR cutoff of 0.85 being equivalent to an FFR of 0.75 is very supportive to the ischemic iFR cutoff found in the CLARIFY study (iFR 0.86), which used invasive flow as a reference discriminator.<sup>5</sup> Also, similarly to what has been observed with FFR, a higher iFR value of  $>0.90$  increases the negative predictive value of iFR to 95% to exclude ischemic stenoses ( $FFR \leq 0.75$ ).

Therefore, across studies reported so far, in more than 2,000 patients, there appears to be a consistent ischemic iFR cutoff of 0.85 to 0.86, which matches an FFR 0.75, and a clinical iFR cutoff of iFR 0.89 to 0.90, which provides the best agreement with the clinically used FFR of 0.80. Reassuringly, similar to FFR, our findings confirm the presence of these 2 distinct iFR cutoffs (ischemic and clinical) when measurements are performed in real time, by interventionalists in the catheter laboratory.

**Figure 6**



Screenshots of measurements of iFR and FFR. **A**, An example of interrogation in the left circumflex artery (horizontal arrow), in which both iFR and FFR were negative, above their respective cutoffs of 0.90 and 0.80; revascularization was deferred. **B**, An example in which both iFR and FFR revealed a functionally significant stenosis in the proximal segment of the left anterior descending artery (oblique arrow); percutaneous revascularization was performed. Because iFR is performed without the need for vasodilator administration, the time of lesion interrogation is typically reduced to around 5 to 10 seconds, from 60 to 120 seconds for FFR.

### The FFR 0.75 to 0.80 gray zone: safety implications for the development of new indices

Early studies that validated FFR as a new diagnostic method identified optimal cutoffs that varied slightly from 0.66, 0.72, 0.74, to 0.75.<sup>11</sup> The validity of the 0.75 cutoff was subsequently confirmed in 2 landmark studies, which laid the foundations of FFR as a clinical tool. First, the multitesting study that compared FFR against 3 noninvasive functional methods<sup>17</sup> undoubtedly demonstrated that no ischemia was detected when FFR fell between 0.75 and 0.80 and only 1 case when between 0.74 and 0.83. This safety was later translated into clinical outcomes with the results of the DEFER study,<sup>12</sup> which documented a rate of major cardiac events of less than 0.6% per year for deferred stenoses with FFR values of  $\geq 0.75$ .<sup>18</sup> Recently, however, FAME and FAME II have also demonstrated the safety and prognostic importance of revascularizing lesions with FFR  $\leq 0.80$ .<sup>15,16</sup> Therefore, the 0.75 to 0.80 FFR zone is a region within which it is known to be equally safe to defer *and* treat stenoses, where ischemia is almost certainly absent but cannot be always excluded.

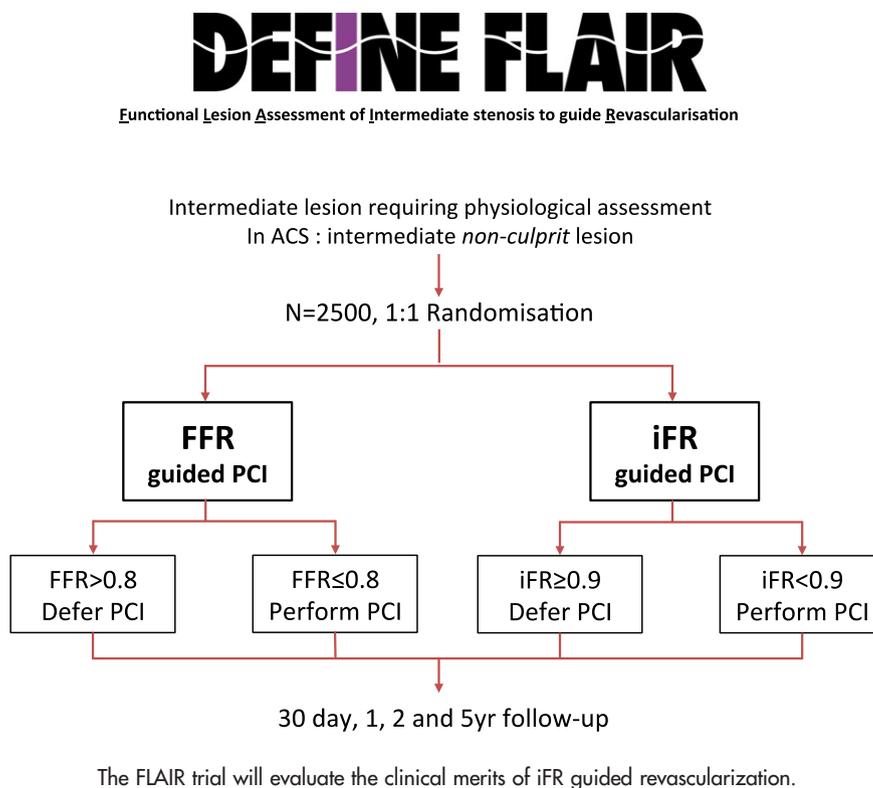
This DEFER-FAME gray zone not only is clinically relevant (as it permits clinicians to defer *or* treat stenoses

with the same confidence)<sup>19</sup> but also has implications to the development of new indices, which use the safety of FFR classification of lesions as a reference comparison. For instance, we have found that when this gray zone is taken into account, and either a DEFER or FAME approach is taken, iFR classification match with FFR increases to 92% with an ROC<sub>AUC</sub> of 0.93. This suggests that most of iFR-FFR disagreements are unlikely to be prognostic, as they predominantly fall in the FFR gray zone. Future trials with clinical outcomes will need to confirm this finding prospectively.

### Hybrid approach confirms adenosine-sparing potential of iFR application

Until clinical outcome studies judge the merits of iFR as an independent diagnostic method, clinicians might prefer to maintain a higher magnitude ( $>90\%$ ) of classification agreement with FFR, given its established role to select lesions for revascularization. For this purpose, a hybrid decision-making strategy using both iFR and FFR can be applied. A hybrid analysis on this real-time iFR data set with prespecified cutoffs has reproduced the results reported previously.<sup>9</sup> Our findings confirm the potential feasibility of using iFR and FFR

Figure 7



together in a hybrid decision-making approach, in which 61% of patients could be spared from vasodilator, while maintaining the safety of a 94% match with FFR classification of lesions (Figure 5).

Study samples of patients undergoing invasive physiological assessment in clinical practice: how do they differ from large randomized clinical trials?

The present study also highlights an important feature of unselected clinical FFR cohorts: they are predominantly formed by intermediate FFR values. In the present sample, mean FFR was  $0.82 \pm 0.10$ , with 71% of stenoses falling within the 0.70 and 0.90 FFR range and only 20%  $\leq 0.75$  and 39%  $\leq 0.80$ . Importantly, physiologically severe lesions appear extremely rare in samples in which FFR is used to guide clinical decisions, with only 4.6% having an FFR  $\leq 0.6$  and 1.3%  $\leq 0.5$ . These figures are very similar to what has been previously reported in large independent clinical cohorts from Europe<sup>2</sup> and Asia<sup>3</sup> and reflect routine clinical application of FFR as recommended per guidelines.<sup>14</sup> Importantly, they differ markedly from the distribution of FFR values of previous large FFR clinical trials. For instance, mean FFR of treated lesions in DEFER<sup>12</sup> was  $0.57 \pm 0.16$ , while in FAME,<sup>15</sup> it was  $0.60 \pm 0.14$ . Notably, in the medical arm of FAME II study,<sup>16</sup> 19% and 26% of the stenoses had FFR less than 0.50 and 0.60,

respectively, which contrasts with the rarity of such severe lesions in clinical samples.

These differences between unselected clinical cohorts and studies in which patients are actively recruited by investigators are very relevant. First, they demonstrate that interventionalists have an excellent overall clinical judgement as to which stenoses require functional interrogation, as most clinically selected *anatomically* intermediate stenoses are also *physiologically* intermediate (Figure 3). Second, it appears that clinical populations such as found in this study provide the most conservative scenario with respect to the magnitude of agreement between iFR and FFR, because they are predominantly formed by intermediate FFR values, when disagreements are naturally higher.<sup>2,20</sup> In populations with more severe lesions, such as in DEFER or FAME studies, classification agreement between iFR and a clinical FFR cutoff of 0.80 is expected to be higher, around 90%, as previously demonstrated.<sup>1,21</sup>

### Clinical implications of our findings

Routine clinical application of a vasodilator-free index such as iFR could potentially expand the benefits of physiology-guided revascularization to many more patients with coronary disease, as the need for vasodilator is one of the reasons for the low adoption of FFR.<sup>22</sup> In South Africa, for example, 15 ampoules of a specific adenosine preparation are required for one intravenous

infusion, at considerable cost. Similar restrictions occur in other countries, such as Russia, Turkey, and in Latin America, where papaverine is still frequently used as a hyperemic agent with its incumbent risks of serious cardiac arrhythmias.<sup>23</sup> The costs and procedural delays associated with vasodilator administration (particularly long intravenous infusions, the recommended route for a complete vessel assessment) are particularly relevant to patients with multivessel disease, who might need 3-vessel interrogation. This group of patients is perhaps the one that benefits the most from invasive evaluation of intermediate stenoses,<sup>15,16</sup> although it appears to be the most affected by the lack of its widespread adoption.

### Future directions: the need for clinical trials

An accumulation of evidence supports iFR as an index of stenosis severity. However, clinical outcome data are required to further advance the global adoption of iFR as a single measure in clinical decision making. The DEFINE-FLAIR trial (NCT 02053038) will compare strategies of revascularization guided by iFR and FFR in 2,500 patients requiring physiological interrogation in clinical practice. The primary outcome will be the rate of major adverse cardiac events (composite of death, myocardial infarction, and unplanned revascularization) at 1 year (Figure 7). Other studies, such as the SYNTAX II, Prospect II, and iFR-SWEDEHEART will further evaluate the merits of iFR in clinical decision making.

### Limitations

The present study only performed a direct comparison between the classification of stenoses by iFR and FFR. No alternative noninvasive method was applied in this analysis, which prevents a more in-depth interpretation of iFR-FFR disagreements.

There was no active recruitment of study subjects. Patients included in this study represent the selection of clinicians based on a clinical indication for FFR measurement. Also, no formal measurement protocol for iFR or FFR was suggested, and technical aspects were left to the discretion of the interventionalist according to their routine clinical practice. Also, iFR and FFR measurements were not blinded from each other, as the clinical operator had access to both results.

Although each individual FFR value might have been different if different doses or routes of adenosine were used, it is likely that on average, across the whole study population, this would not affect the overall relationship with iFR because this variability would likely occur in both ways (more or less hyperemia). Importantly, as a retrospective analysis of the routine clinical application of FFR, our study used no fixed protocol of adenosine administration, which means that our results entirely reflect the choice of clinicians and the way FFR is used everyday around the world. This can be seen as a strength

of our study because the relationship between iFR and FFR, therefore, reflects the clinical relationship expected when iFR is used for clinical reasons. Also, the recently presented ADVISE II study,<sup>24</sup> which used a rigid protocol of central IV adenosine administration, demonstrated a level of agreement between iFR and FFR equal to our study, which again confirms the validity of our findings.

Finally, the present study cannot evaluate the impact of iFR use on clinical outcomes because we simply described its diagnostic agreement with FFR in clinical practice. This merit will be addressed by the DEFINE-FLAIR study (Figure 7) and other future trials.

### Conclusion

Real-time iFR measurement in the cardiac catheterization laboratory is feasible and accessible to clinicians, delivering the same magnitude of agreement between iFR and FFR as described in core laboratory studies. Outcome studies are needed to evaluate the clinical value of iFR as an independent decision-making tool in such population.

### Disclosures

J.E. Davies holds patents pertaining to iFR technology, which is under licence to Volcano Corporation. J.E. Davies is a consultant for Volcano Corporation. The other authors have no conflicts of interest to declare.

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