The ability of contemporary cardiologists to judge the ischemic impact of a coronary lesion visually

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ABSTRACT

Background: Landmark trials showed that invasive pressure measurement (Fractional Flow Reserve, FFR) was a better guide to coronary stenting than visual assessment. However, present-day interventionists have benefited from extensive research and personal experience of mapping anatomy to hemodynamics.

Aims: To determine if visual assessment of the angiogram performs as well as invasive measurement of coronary physiology.

Methods: 25 interventional cardiologists independently visually assessed the single vessel coronary disease of 200 randomized participants in The Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina trial (ORBITA). They gave a visual prediction of the FFR and Instantaneous Wave-free Ratio (iFR), denoted vFFR and viFR respectively. Each judged each lesion on 2 occasions, so that every lesion had 50 vFFR, and 50 viFR assessments. The group consensus visual estimates (vFFR-group and viFR-group) and individual cardiologists' visual estimates (vFFR-individual and viFR-individual) were tested alongside invasively measured FFR and iFR for their ability to predict the placebo-controlled reduction in stress echo ischemia with stenting.

Results: Placebo-controlled ischemia improvement with stenting was predicted by vFFR-group ($p < 0.0001$) and viFR-group ($p < 0.0001$), vFFR-individual ($p < 0.0001$) and viFR-individual ($p < 0.0001$). There were no significant differences between the predictive performance of the group visual estimates and their invasive counterparts: $p = 0.53$ for vFFR vs FFR and $p = 0.56$ for viFR vs iFR.

Conclusion: Visual assessment of the angiogram by contemporary experts, provides significant additional information on the amount of ischaemia which can be relieved by placebo-controlled stenting in single vessel coronary artery disease.

1. Introduction

Fractional Flow Reserve (FFR) and Instantaneous Wave-Free Ratio (iFR) are recommended as tools for coronary stenting because studies indicate that they are more informative than angiographic appearance in selecting the patients who will benefit [1]. While trials such as International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) suggest little if any survival benefit from stenting, there is no doubt that stenting reduces ischemia [2]. A recent clear example of this was the near complete eradication of blinded stress echo ischemia by PCI in The Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial, even though the exercise time and angina endpoints were not significantly improved [3].

FFR and iFR are related to the baseline ischemia as assessed by stress echo, nuclear scans, and perfusion cardiac magnetic resonance, and ischemia is powerfully relieved by percutaneous coronary intervention (PCI) [4–6]. Guidelines recommend judging lesions with FFR and iFR rather than visual inspection, because the hemodynamic approach outperformed the visual approach in the landmark Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial conducted from 2006 to 2007 [1]. Having gained more experience with invasive hemodynamics, the visual judgement of interventionists no longer seemed to be worse than hemodynamics in later trials, including Functional Testing Underlying coronary Revascularization (FUTURE) and Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain? (RIPCORD2) [7,8].

The case for measuring FFR and iFR is that they directly assess pressure drop and therefore can access information on ischemia which is unavailable to visual inspection alone [1,9]. This case has never been tested in a placebo-controlled trial. The ORBITA trial was designed to make this hypothesis testable, by having an independent measure of tissue ischemia measured before randomization and at follow-up in both arms. In this study, we test the hypothesis that invasive hemodynamics contain more information than is accessible to visual inspection of the angiogram.

2. Methods

2.1. Study design

The design of the ORBITA trial has been described previously [3]. In brief, ORBITA was a randomized, placebo-controlled trial of PCI in patients with angina and single vessel coronary disease referred for clinical PCI. At least 94 % had one or more positive ischemia tests at randomization. They underwent a pre-specified 6-week period of intensive medication uptitration [10]. Exercise time on a treadmill (smoothed modified Bruce protocol), patient reported symptoms (Seattle Angina Questionnaire, SAQ), physician assessed symptoms (Canadian Cardiovascular Society class), dobutamine stress echo, FFR and iFR were recorded prior to randomization to PCI or placebo.

The London Central Research Ethics Committee (reference 13/LO/1340) approved the ORBITA study and written consent was obtained from all patients before their enrolment.

2.2. Blinding and randomization

Participants were randomized 1:1 to PCI or placebo using computer software. Patients and the medical team outside the cardiac catheterization laboratory were blinded using a methodology previously described [3].

2.3. Stress echo, iFR and FFR

Patients underwent a dobutamine stress echo at pre-randomization and follow-up. Each case was reviewed independently, and blinded to treatment arm and order, by 6 imaging consultants, on two separate occasions, as previously described. For ease of interpretation, a stress echo score was constructed, designed to be 0 when all 12 opinions agreed there was no ischemia, 1.0 when the opinions averaged 1 segment of hypokinesia, and so on [4].

In ORBITA, FFR and iFR were measured immediately prior to randomization. The operator undertaking the case was blinded to the coronary physiology display in order to ensure that patients with a broad, representative range of physiological values were randomized.

2.4. Multiple independent visual assessments of angiograms

After trial completion, 25 interventional cardiologists, from several centres in the UK, Brazil, Australia and Japan, independently assessed each angiogram, twice. These cardiologists thus assessed 400 angiograms, which were presented in a random sequence. We hypothesised that an expert assessment, incorporating the entire visual appearance of the angiogram, would perform better than simple quantitative coronary angiography (QCA). As such, we asked the cardiologists to predict the values of FFR and iFR using their experience and judgement, based on visual appearance alone (multiple views were available for each angiogram). The 200 angiograms therefore received 50 independent evaluations. For each angiogram, we composed group estimates for FFR and iFR, defined as the mean of the 50 independent evaluations, denoted vFFR-group and viFR-group respectively. The assessors were blinded to all other clinical data.

To assess the utility of a single operator's visual assessment we additionally assessed the performance of each individual operator's prediction of FFR and iFR. For comparison with the other metrics, we have chosen the vFFR and viFR estimates of the individual who had the median predictive performance for stress echo ischemia improvement with PCI, termed vFFR-individual and viFR-individual respectively.

2.5. Statistical analysis

The normally distributed data are presented as mean and standard deviation. The non-normally distributed data are presented as median and interquartile range (IQR). Categorical variables are presented as counts with percentages. The relationship between the invasive metrics and their visual equivalents was assessed using Spearman's rank correlation.

2.6. Assessing the predictive power of FFR, iFR and the visual estimates

The predictive power of FFR, vFFR-group, vFFR-individual, iFR, viFR-group and viFR-individual for placebo-corrected changes in stress echo ischemia were assessed using regression modelling by measuring the increment in predictive power when that individual variable was added. In each case, the same baseline model was used. It predicted final stress echo ischemia from only pre-randomization stress echo ischemia and study arm. The model used restricted cubic splines with 3 knots.

For each variable, we created a new model which additionally used that variable. For example, for FFR, we created a model like the baseline model but additionally using FFR, to predict final stress echo ischemia. We defined the contribution of FFR as the increment in predictive power between these models. We calculated the information content contributed by FFR as the Chi Squared of the model using FFR minus the Chi Squared of the baseline model. Once this had been done for all 6 variables in turn, the information contents could be displayed on a stacked bar chart, with the baseline information content equal in all 6 cases and the different incremental contributions of each variable highlighted as the top element. The above process was repeated for each outcome variable: stress echo ischemia, SAQ angina frequency and SAQ "freedom from angina".

We tested whether the contribution of the predictor (e.g. FFR) was significant beyond what could be predicted using only the pre-randomization measurement and the randomization arm. To compare pairs of predictors, we bootstrapped the difference in Chi squared between models containing both predictors and separate models containing one predictor each [12]. Analyses were performed using the open-source statistical environment R (version 4.0.2) with the "rms" regression modelling package.

3. Results

Of the 200 patients randomized in ORBITA, FFR is available in 194 and iFR in 196. Among the remaining 6: in 3 the wire would not cross; in 1 intimal disruption required immediate PCI; in 2 a hyperaemic response could not be elicited. Stress echo score was measured in 183 patients, with 17 patients not undergoing stress echo for reasons previously described [4]. The baseline characteristics of the cohort are in Table 1; the coronary physiology data are in Table 2. The mean experience with coronary physiology of the assessors was 6.8 ± 4.9 years.

3.1. Relationship between FFR/iFR and visual estimates

Visual assessments of FFR were more narrowly distributed than measured FFR, with IQRs of 0.70 to 0.79 and 0.58 to 0.81 respectively (Fig. 1). Similarly, visual assessments of iFR were more narrowly distributed than measured iFR, with IQRs of 0.79 to 0.88 and 0.68 to 0.90 respectively.

There was a moderate correlation between vFFR-group and invasive FFR (Rho = 0.69, $p < 0.0001$) and between viFR-group and invasive iFR (Rho = 0.62, $p < 0.0001$) (Fig. 2). Individual experts' visual assessments also correlated with the invasive measures: range from 0.21 to 0.67 for FFR, and 0.15 to 0.62 for iFR. The distribution of the induvial predictions for each assessed lesion can be seen in Fig. 3.

3.2. Relationship between vFFR/viFR and pre-randomization stress echo ischemia

There was a significant relationship between the consensus visual estimates, vFFR-group and viFR-group, with pre-randomization stress echo ischemia: Rho = −0.47, ($p < 0.0001$) and Rho = −0.48 ($p < 0.0001$) (Fig. 4).

3.3. Predictive power of invasive and visually assessed FFR and iFR

For predicting final stress echo score, each of the 6 potential predictive variables (FFR, vFFR-group, vFFR-individual, iFR, viFR-group and viFR-individual) made significant contributions beyond the baseline model that had only pre-randomization stress echo score and randomization arm ($p < 0.0001$ for each, Fig. 5). There were no significant differences between the sizes of these 6 incremental contributions. Additionally, there was no significant difference between the size of these contributions and the contribution from Quantitative Coronary Angiography (QCA). For SAQ Angina Frequency and SAQ Angina Freedom, none of the potential predictor variables made a significant contribution ($p \geq 0.05$ for each, Supplementary Appendix Figs. S1 and S2 respectively).

4. Discussion

All 6 assessed coronary physiology metrics in this analysis (FFR, vFFR-group, vFFR-individual, iFR, viFR-group and viFR-individual) provided significant additional information beyond the base model. Interestingly, we have found that visually estimated FFR and iFR performed as well as invasively measured physiology, in predicting placebo-controlled improvement in stress echo ischemia with PCI. The average of the visual assessments of all 25 operators in this study, "vFFR-group" and "viFR-group", numerically, but not statistically significantly, outperformed the median individual operator.
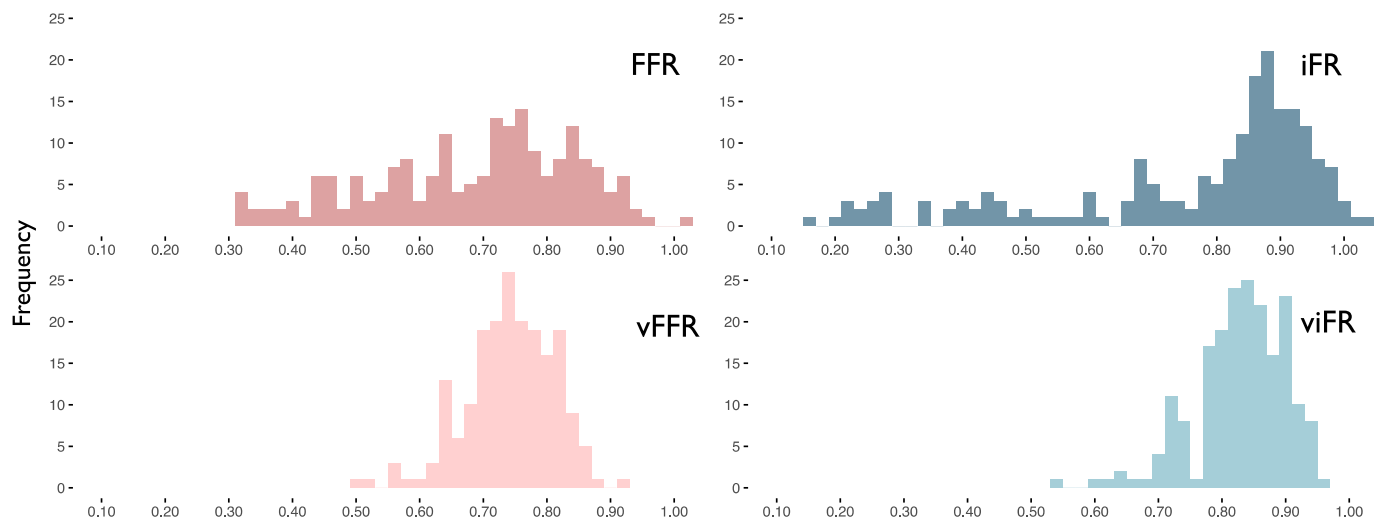
While the visual metrics correlated with their invasive equivalents, there were differences in their distributions. The median vFFR and viFR were lower than their invasive counterparts and more tightly clustered around clinically used cut points for significance. No matter how angiographically severe the lesion, operators rarely gave vFFR values <0.60 (3.5 % of vFFR estimates), yet the measured FFR value was <0.60 in 28.9 % of cases. Similarly, operators very rarely suggested viFR values <0.60 (0.5 % of viFR estimates), yet the measured iFR value was <0.60 in 20.4 % of cases (Fig. 1).

The distribution of individual visual estimates is wide at all levels of measured FFR or iFR and many of these individual estimates are not closely correlated with the invasive measurement (Fig. 3). The relationship between the group mean vFFR and viFR and the measured value is closer than on an individual basis (Fig. 2). We should be cautious, therefore, in expecting every operator to be able to generate an accurate estimation of FFR or iFR on a visual basis alone. However, the group mean visual predictions, and the predictions of the median performing operator in our cohort of assessors, were able to predict ischaemia improvement with placebo-controlled PCI, as effectively as the invasively measured value.

4.1. Clinical implications

Measurement of invasive physiology is widely recommended to guide PCI, because it was reported to perform better than visual assessment, in the era in which FFR was being developed [13]. A decade ago, addition of FFR information would frequently cause cardiologists to change their management plan [14]. Importantly, guidelines would tell us that invasive physiology predicts ischaemia more than angiography alone in a stenosis ≤ 90 %. This analysis shows us that even in the range of ≥ 70 %, angiography can be used to predict ischaemia.

Contemporary cardiologists are, of course, much more familiar with the coronary physiology impact of lesions than their predecessors were in the era of the conduct of the landmark FFR trials. In the United Kingdom, pressure wire utilisation has increased 5-fold between 2008 and 2021 from 3979 cases to 20,382 cases annually [15]. The results of our study suggest that contemporary cardiologists, who have benefited from these years of experience with coronary physiology, have developed substantial skill in predicting the ischemic impact of a coronary stenosis. For example, it is now widely understood that the tightest anatomical severity is by no means the sole determinant of the physiological impact of a lesion. This is reflected in this analysis, where the quantification of luminal stenosis by

Table 1
Baseline demographics.

	PCI (n = 103)	Placebo (n = 93)	Complete group (n = 196)
Age (y)	65.7 ± 9.5	66.1 ± 8.3	65.9 ± 9.0
Male	72 (69.9)	71 (76.3)	143 (73.0)
Hypertension	70 (68.0)	65 (69.9)	135 (68.9)
Hypercholesterolemia	79 (77.0)	61 (65.6)	140 (71.4)
Diabetes mellitus	15 (14.6)	21 (22.6)	36 (18.4)
Previous myocardial infarction	4 (3.9)	7 (7.5)	11 (5.6)
Previous percutaneous coronary intervention	10 (9.7)	14 (14.1)	24 (12.2)
Diameter stenosis by QCA	64.1 ± 13.7	63.7 ± 13.6	63.9 ± 13.6
Area stenosis by QCA	84.4 ± 10.1	84.0 ± 10.2	84.2 ± 10.1
Canadian Cardiovascular Society Angina Class			
I	2 (1.9)	3 (3.2)	5 (2.5)
II	62 (60.2)	53 (57.0)	115 (58.7)
III	39 (37.9)	37 (39.8)	76 (38.8)
Angina duration (months)	9.5 ± 15.8	8.5 ± 7.6	9.0 ± 12.6

PCI = percutaneous coronary intervention, QCA = quantitative coronary angiography.

Table 2
Visual and invasive FFR and iFR.

Measure	Median (IQR)	Correlation between measured and visually estimated
FFR	0.72 (0.58–0.81)	Rho 0.69, $p < 0.0001$
vFFR-group	0.74 (0.70–0.79)	
iFR	0.85 (0.68–0.90)	Rho 0.62, $p < 0.0001$
viFR-group	0.83 (0.79–0.88)	

IQR = interquartile range, FFR = fractional flow reserve, iFR = instantaneous wave-free ratio, vFFR = visual-FFR, viFR = visual iFR.

Fig. 1. Title: Distributions of FFR, iFR, vFFR and viFR. Legend: Distributions of measured FFR and iFR (upper panels) and their corresponding visual estimates (lower panels). FFR = fractional flow reserve, vFFR = visual FFR, iFR = instantaneous wave-free ratio, viFR = visual iFR.
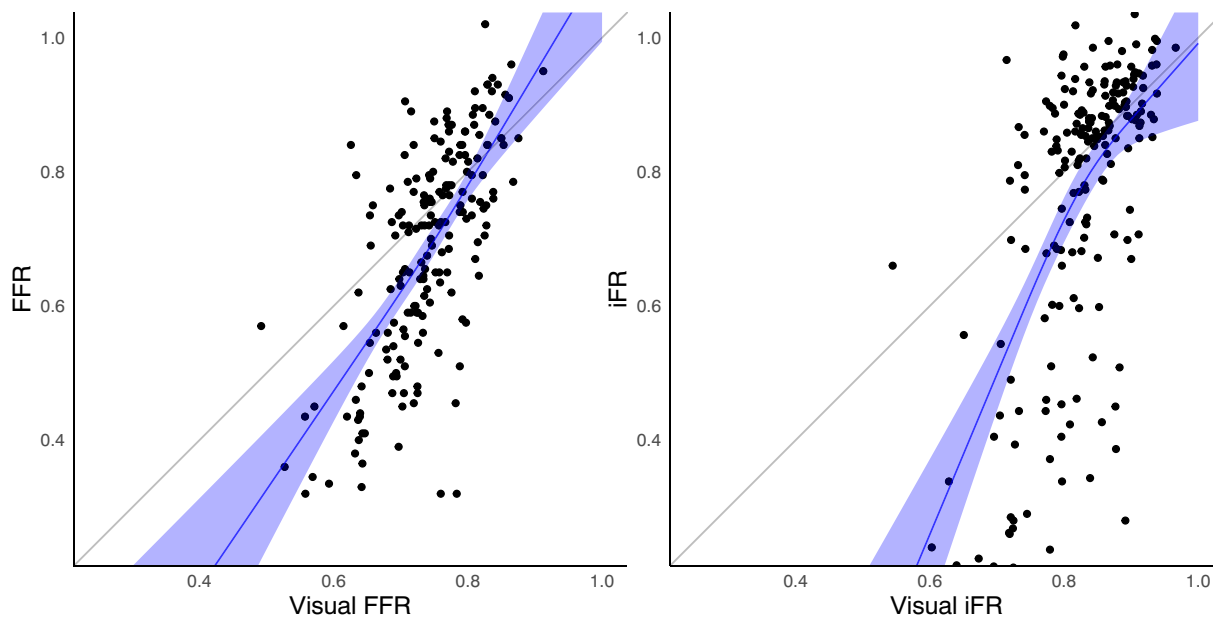
Fig. 2. Title: The relationship between visually estimated and invasive FFR and iFR. Legend: FFR = fractional flow reserve, iFR = instantaneous wave-free ratio. vFFR = visual FFR, viFR = visual iFR.

QCA did not add significantly more information about the potential for PCI to improve ischemia than FFR, iFR or their visual counterparts.

The modern cardiologist may, even subconsciously, predict the FFR or iFR of a stenosis in the cardiac catheterisation laboratory, recapitulating the experiment we have conducted. Contemporary trials suggest that with modern training, visual assessment performs similarly to FFR assessment in guiding therapy or perhaps even better [7,8]. Their visual prediction may be as good as the invasive measure and of course, is not associated with the time, expense, or risk of a pressure wire assessment.

In a cardiac catheterisation laboratory setting, the "mini-multidisciplinary team" consisting of a small number of colleagues is unlikely to replicate the vFFR-group and viFR-group used in this analysis, with fewer opinions available and estimates being influenced by the opinion of others in the group. However, this study has highlighted that even a single typical

operator is able to predict the ischemic potential of a stenosis and the placebo-controlled improvement of ischaemia with PCI.

4.2. Study limitations

All the stenoses in the ORBITA study were angiographically severe (≥70 %) and operators were blinded to FFR and iFR. This was to ensure that patients with a wide range of physiological values were randomized. However, in international guidelines, FFR and iFR are recommended to guide the management of angiographically moderate stenoses [16]. The results of this study reflect this: visual predictions were clustered around cut points used in clinical practice, whereas measured values were more spread. This is likely due to cardiologists predicting values that they are used to seeing in clinical practice, with FFR and iFR values in a 'borderline'
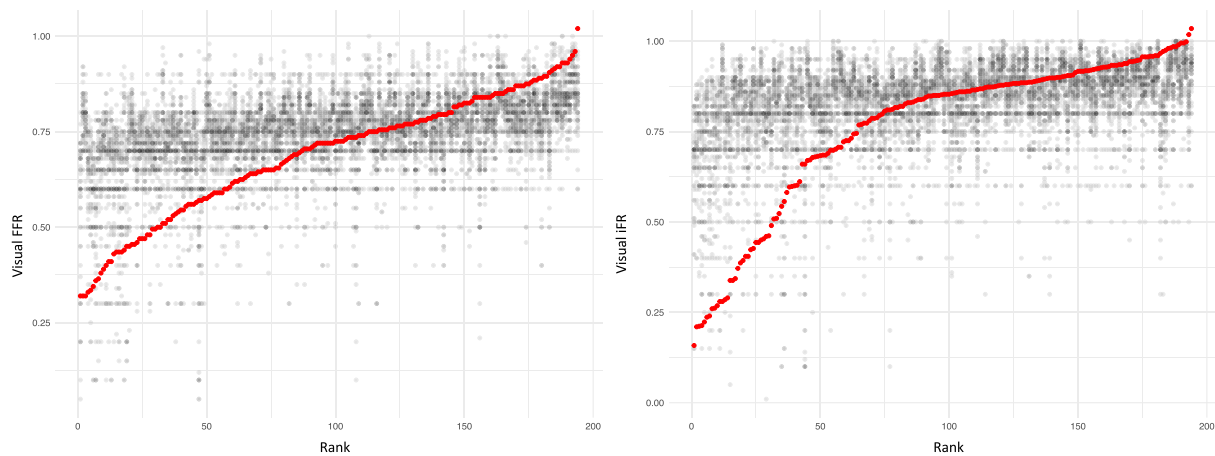
Fig. 3. Title: The distribution of individual visual estimates of FFR and iFR for each assessed lesion. Legend: Lesions are ranked from lowest to highest FFR and iFR respectively. The grey points represent an assessor's individual estimate. The red points represent the invasively measured value for that lesion. FFR = fractional flow reserve, iFR = instantaneous wave-free ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
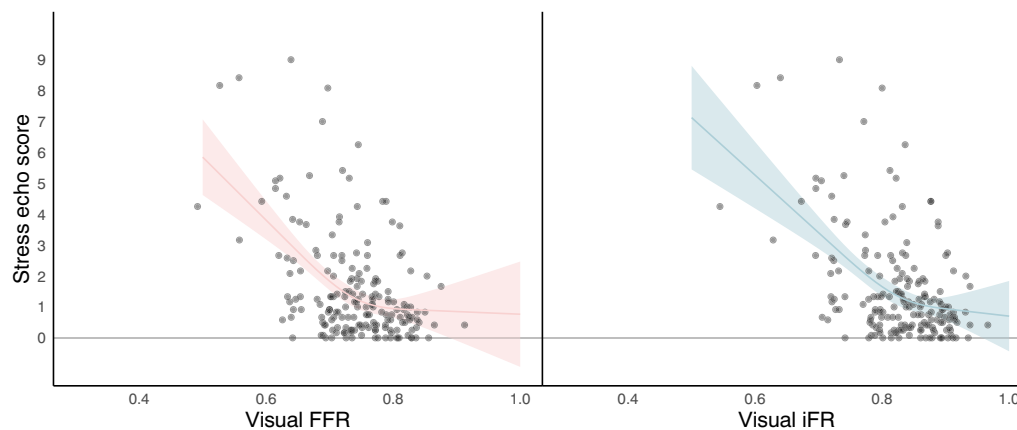
Fig. 4. Title: The relationship between visually estimated physiology and ischemia. Legend: The relationship between vFFR-group and viFR-group with stress echo ischemia. vFFR = visual FFR, viFR = visual iFR.

range. Invasive physiology for angiographically severe stenoses is not routine practice. It could be that FFR and iFR outperform visual assessments in predicting stress echo or symptom improvement in an angiographically moderate stenosis cohort, however, a placebo-controlled trial of physiology guided PCI outcomes in patients with angiographically moderate stenoses has not been undertaken.

vFFR and viFR were generated from the predictions of 25 cardiologists who were willing to input predictions into the web-based platform. This group may have been self-selecting as particularly interested or proficient with coronary physiology. As such, visually predicted FFR and iFR may be less powerful in predicting stress echo improvement in other settings. Indeed, the median performing operator in our group, whose predictions formed "vFFR-individual" and "viFR-individual" may have in fact been better than typical, when compared to an unselected group of operators. Although it has been reported that there were significant inter-observer differences in interpreting medical data, the impact of institutional volume or degree of experience on visually estimated FFR and iFR was not evaluated in the present study [17].

We must be cautious in the extrapolation of these data. An advantage of measured FFR is its reproducibility, removing subjectivity from the assessment of a stenosis. Though the predictions of the median performing cardiologist in this study were as informative as FFR and iFR, how effectively any given operator will visually assess any given stenosis, particularly angiographically moderate stenoses not included in ORBITA, is not currently known. This could be a focus of future research, involving large numbers of assessors.

5. Conclusion

Visual assessment of the angiogram provides significant additional information in the prediction of placebo-controlled improvement of ischaemia with PCI. In this study, the additional information provided by the mean of multiple expert assessments and the single estimate of the median performing expert, was similar to that provided by FFR or iFR.

Disclosure statement

Michael Foley, Christopher Rajkumar and Rasha Al-Lamee have received speakers honoraria from Menarini Pharmacueticals and Philips Volcano. Sayan Sen, Ricardo Petraco and Sukhjinder Nijjer have received speakers honoraria from Philips Volcano. Takayuki Warisawa has received consulting fees from Abbott Vascular Japan and Philips Japan. Hitoshi Matsuo has received speakers honoraria from Philips Japan, Abbott Medical Japan, Boston Scientific Japan, and Zeon Medical. Shingo Kuwata is a consultant for Abbott Medical Japan.
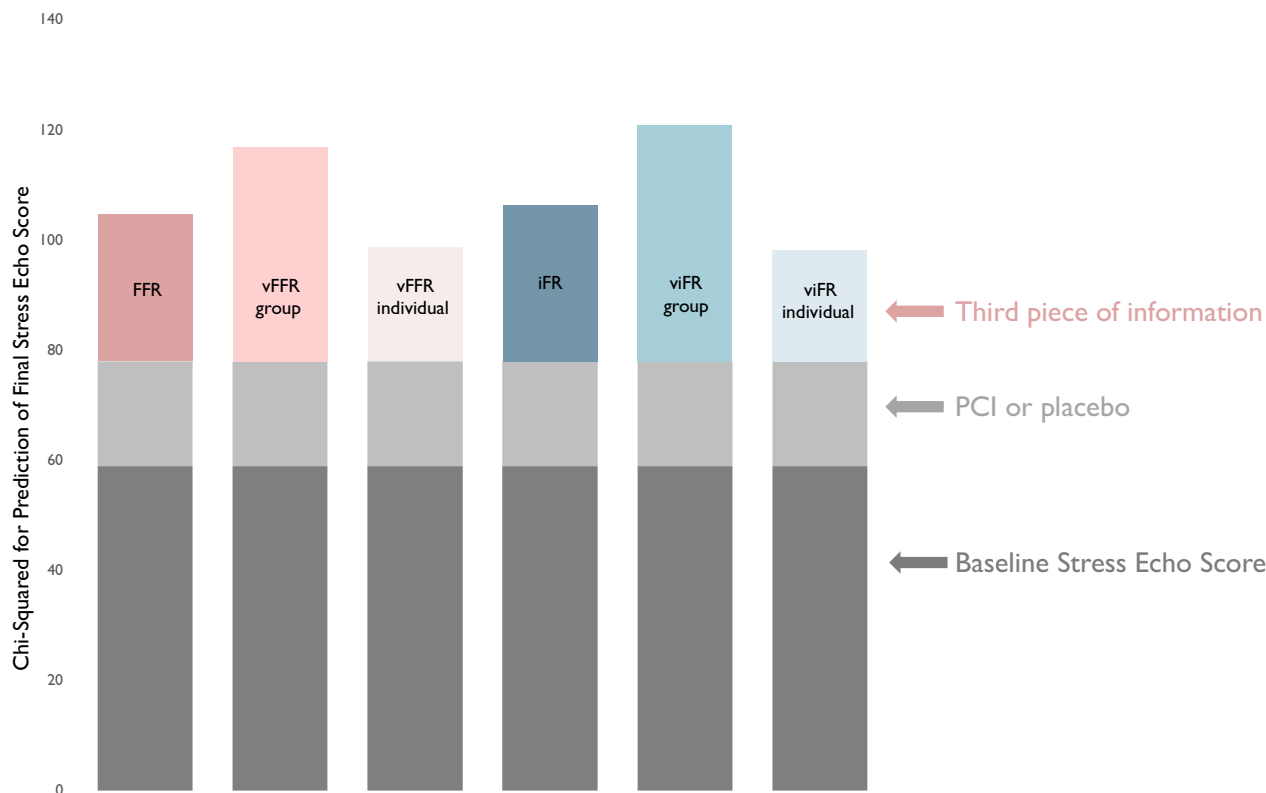
Fig. 5. Title: The incremental benefit of measured and visually estimated coronary physiology. Legend: Predictive power for final stress echo score of each of the predictors (FFR, vFFR-group, vFFR-individual, iFR, viFR-group and viFR-individual) displayed as a stacked bar chart. The additional information from each metric is added to a base model containing the baseline stress echo score and randomization arm. PCI = percutaneous coronary intervention, FFR = fractional flow reserve, vFFR = visual FFR, iFR = instantaneous wave-free ratio, viFR = visual iFR.

CRediT authorship contribution statement

Michael Foley: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Christopher A. Rajkumar:** Investigation, Visualization. **Fiyyaz Ahmed-Jushuf:** Methodology, Writing – review & editing. **Daniel Nour:** Methodology, Writing – original draft. **Chi Ho Fung:** Methodology, Writing – original draft. **Henry Seligman:** Investigation, Methodology. **Rachel H. Pathimagaraj:** Investigation, Visualisation. **Ricardo Petraco:** Investigation, Writing – review & editing. **Sayan Sen:** Investigation, Writing – review & editing. **Sukhjinder Nijjer:** Investigation, Writing – review & editing. **James P. Howard:** Formal analysis, Visualization. **Yousif Ahmad:** Investigation. **Usaid Allahwala:** Investigation. **Ravinay Bhindi:** Investigation. **Daniel Chamie:** Investigation. **Shunich Doi:** Investigation. **Shingo Kuwata:** Investigation. **Toshiki Kaihara:** Investigation. **Masashi Koga:** Investigation. **Yuki Ishibashi:** Investigation. **Takumi Higuma:** Investigation. **Yasuhiro Tanabe:** Investigation. **Masafumi Nakayama:** Investigation. **Yoshiaki Kawase:** Investigation. **Akifumi Watanabe:** Investigation. **Naohiro Funayama:** Investigation. **Ryo Horinaka:** Investigation. **Nobuhiro Hijikata:** Investigation. **Takamichi Takahashi:** Investigation. **Hitoshi Matsuo:** Investigation. **Peter S. Hansen:** Investigation. **Andre Manica:** Investigation. **James Weaver:** Investigation. **Karam Alzuhairi:** Investigation. **Thon-Hon Yong:** Investigation. **Takayuki Warisawa:** Investigation. **Darrel P. Francis:** Conceptualization, Writing – review & editing.

Matthew J. Shun-Shin: Methodology, Software, Visualization, Formal analysis, Supervision. **Rasha K. Al-Lamee:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rasha Al-Lamee reports a relationship with A Menarini International Pharmaceutics that includes: speaking and lecture fees. Michael Foley reports a relationship with A Menarini International Pharmaceutics that includes: speaking and lecture fees. Christopher Rajkumar reports a relationship with A Menarini International Pharmaceutics that includes: speaking and lecture fees. Rasha Al-Lamee reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Michael Foley reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Christopher Rajkumar reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Sayan Sen reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Ricardo Petraco reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Sukhjinder Nijjer reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Takayuki Warisawa reports a relationship with Abbott Vascular Japan Co Ltd. that includes: consulting or advisory. Takayuki Warisawa reports a relationship with Philips Healthcare that includes:. Hitoshi Matsuo reports a relationship with Philips Healthcare that includes: speaking and lecture fees. Hitoshi Matsuo reports a relationship with Abbott Vascular Japan Co Ltd. that includes: speaking and lecture fees. Hitoshi Matsuo reports a relationship with Boston Scientific Japan that includes: speaking and lecture fees. Hitoshi Matsuo reports a relationship with Zeon Medical that includes: speaking and lecture fees. Shingo Kuwata reports a relationship with Abbott Vascular Japan Co Ltd. that includes: consulting or advisory.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2023.08.003.

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