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Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting P_d/P_a with Fractional Flow Reserve: The RESOLVE Study

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Brief Title: Comparison of iFR and P_d/P_a vs. FFR

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DISCLOSURES

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ABSTRACT

Objectives: We sought to examine the diagnostic accuracy between the instantaneous wave-free ratio (iFR) and resting P_d/P_a with respect to hyperemic fractional flow reserve (FFR) in a core laboratory-based multicenter collaborative study.

Background: FFR is an index of coronary stenosis severity that has been clinically validated in 3 prospective randomized trials. iFR and P_d/P_a are non-hyperemic pressure-derived indices of stenosis severity with discordant reports regarding their accuracy with respect to FFR.

Methods: iFR, resting P_d/P_a and FFR were measured in 1,768 patients from 15 clinical sites. An independent physiology core laboratory performed blinded offline analysis of all raw data. The primary objectives were to determine specific iFR and P_d/P_a thresholds with ≥90% accuracy in predicting ischemic vs. non-ischemic FFR (based on an FFR cut-point of 0.80), and the proportion of patients falling beyond those thresholds.

Results: Of 1,974 submitted lesions, 381 (19.6%) were excluded because of suboptimal acquisition, leaving 1,593 for final analysis. By ROC analysis, the optimal iFR cut-point for FFR ≤0.80 was 0.90 (c-statistic 0.81 [95%CI 0.79-0.83], overall accuracy 80.4%), and the optimal cut-point for P_d/P_a was 0.92 (c-statistic 0.82 [0.80-0.84], overall accuracy 81.5%), with no significant difference between these resting measures. iFR and P_d/P_a had ≥90% accuracy to predict a positive or negative FFR in 64.9% (62.6-67.3%) and 48.3% (45.6-50.5%) of lesions, respectively.

Conclusions: This comprehensive, core laboratory analysis comparing iFR and P_d/P_a to FFR demonstrates an overall accuracy of ~80% for both non-hyperemic indices, which can be improved to ≥90% in a subset of lesions. Clinical outcome studies are required to determine whether the use of iFR or P_d/P_a might obviate the need for hyperemia in selected patients.

Key words: Fractional Flow Reserve, Coronary Physiology, Myocardial Ischemia

ABBREVIATIONS

FFR = Fractional flow reserve (hyperemic by definition)
iFR = Instantaneous wave-free ratio (non-hyperemic)
P_d/P_a = Distal coronary artery pressure / aortic pressure (non-hyperemic)
PCI = percutaneous coronary intervention
ROC = Receiver-operating characteristic
PPV = Positive predictive value
NPV = negative predictive value

INTRODUCTION

Fractional flow reserve (FFR) is an index of the hemodynamic significance of a coronary stenosis, calculated directly from hyperemic pressure measurements (1,2). The physiologic basis of FFR has been extensively validated in animal and human studies and FFR shows good correlation to non-invasive ischemia testing with perfusion scintigraphy (3) and positron emission tomography (4). FFR has been shown in 3 randomized trials to identify coronary stenoses which will benefit from early revascularization (those with a positive FFR) (5), and conversely those lesions with a negative FFR for which revascularization may be safely deferred (6,7). To measure FFR, a vasodilator (most commonly intravenous or intracoronary adenosine) is administered to minimize microvascular resistance and the effect of resting hemodynamics, such that coronary pressure becomes proportional to myocardial flow.

Interest has recently emerged as to whether 2 non-hyperemic measures of pressure might be useful to assess coronary stenosis severity. P_d/P_a is the ratio of distal coronary artery pressure to aortic pressure over the entire cardiac cycle. Conversely, the instantaneous wave-free ratio (iFR) measures coronary pressure during a specific period of diastole, when resting resistance is the lowest (8). By reducing procedural time and cost, avoiding patient-related discomfort from pharmacologic hyperemia, and allowing continuous on-line measurements (thereby facilitating multivessel interrogation), assessment of coronary stenosis severity without induction of hyperemia is intuitively appealing, provided diagnostic accuracy is preserved. However, in prior reports the diagnostic accuracy of iFR compared to FFR has ranged widely from 60% to 91% (8-11), and its relative accuracy compared to P_d/P_a has been debated. Previous comparative studies to date have been limited by different study methodologies, modest sample sizes, and the use of different algorithms to calculate iFR. Given these conflicting reports, we formed a collaborative

group of investigators to perform a large-scale, physiology core laboratory-based analysis with standardized methods to compare the diagnostic accuracy of iFR and P_d/P_a with respect to FFR as the reference standard, and to determine the proportion of patients in which the accuracy of iFR and P_d/P_a is at least 90%.

METHODS

Patient population and study inclusion criteria. The present investigation was an international, multicenter, non-randomized, retrospective, core laboratory-based analysis in patients with coronary artery disease undergoing physiologic lesion assessment by FFR, iFR and P_d/P_a. The principal investigators representing all of the published iFR/FFR comparative studies agreed to collaboratively participate in this effort, including the ADenosine Vasodilator Independent Stenosis Evaluation (ADVISE) study and registry (8,11), VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice (VERIFY) (9), and Johnson et al. (10). In addition, 6 other study sites contributed unpublished data to the analysis. All studies included in this analysis were approved by the individual sites' institutional review boards. Original raw phasic pressure waveforms from each patient were submitted digitally to the Physiology Core Laboratory at the Cardiovascular Research Foundation (New York, NY) for independent offline analysis. In addition, selected baseline patient demographic and procedural data were supplied to the core laboratory. This study was an investigator-sponsored study by the Cardiovascular Research Foundation, and was supported by funding from Volcano Corporation (San Diego, CA). The funding source was uninvolved with the design of the protocol, the analysis and interpretation of the study results.

Patients with stable angina, unstable angina, or non-ST segment-elevation myocardial infarction (NSTEMI), undergoing coronary angiography with or without percutaneous coronary intervention (PCI) in whom FFR of a single stenosis in a major epicardial coronary artery was performed during the procedure were considered for study inclusion. Two or more lesions could be present in a single patient if in different epicardial vessels. Exclusion criteria included left main disease, heart failure as defined by New York Heart Association class III or IV, respiratory failure requiring intubation or supplementary oxygen, cardiogenic shock, significant arrhythmia precluding wave form analysis (e.g. excessive premature ventricular contractions or atrial fibrillation), and tachycardia with a heart rate >120 beats per minute.

Pressure measurements and analysis. Physiologic measurements of coronary stenoses were performed according to existing study protocols. The RadiAnalyzer Xpress instrument with the Certus coronary pressure wire (St. Jude Medical, Upsala, Sweden), the Volcano s5 imaging system with the PrimeWire (Volcano Corp., Rancho Cordova, CA), or earlier generation equipment from these manufacturers was used for coronary pressure measurements. After the pressure sensor was zeroed and equalized to aortic pressure, it was positioned at least 5 mm distal to the stenosis and a recording of the baseline distal coronary and aortic pressures was obtained. After the administration of intracoronary nitroglycerine as per the operators' discretion, hyperemia was induced by the administration of either intravenous adenosine at a dose of 140 mcg/Kg/min or intracoronary adenosine at various doses and FFR was calculated. All pressure tracings were submitted directly to the Cardiovascular Research Foundation physiology core laboratory for analysis.

FFR is the ratio of mean distal coronary pressure (P_d) to mean aortic pressure (P_a) during maximum hyperemia. The P_d signal is obtained from a guidewire with a piezoresistive pressure

transducer, and the P_a signal is obtained from a fluid-filled guiding or diagnostic catheter. FFR is taken as the lowest stable value of the P_d/P_a ratio during maximal hyperemia. In order to ensure accuracy of the analysis, waveform analysis of all pressure tracings was performed to confirm that none of the following exclusion criteria were present: significant arrhythmia that may preclude appropriate wave form analysis; loss of P_a or P_d pressure signal at any point during the run apart from intracoronary vasodilator administration; inappropriate recording of P_a or P_d (e.g. only a flat signal is present at some point during the recording); dampened P_a or P_d waveform; reversed gradient during hyperemia (i.e. P_d pressure signal elevated above P_a, resulting in FFR > 1.00); or sensor drift defined as FFR $\leq$0.97 or $\geq$1.03 after pullback of the pressure wire transducer into the guiding catheter. In addition to the waveform analysis, the FFR recording had to have an adequate baseline tracing prior to the administration of adenosine. Specifically, a minimum of 5 waveforms of uninterrupted recording adequate for analysis without significant artifact of the tracing was required. FFR was calculated independently from the original readout as the lowest, artifact-free P_d/P_a during maximal hyperemia.

iFR is the ratio of P_d/P_a measured during a pre-specified period in mid to late diastole of the cardiac cycle, without hyperemia (8). The onset of diastole was identified from the dicrotic notch, and the diastolic window was calculated beginning 25% into diastole and ending 5 ms before end diastole. iFR was calculated offline in the core laboratory using the Volcano Harvest software package which contains the iFR computational algorithm developed at the Imperial College of London (8). All analyses were performed in a fully automated manner, eliminating the need for manual selection of data time points. This automated analysis is based on a synchronized ECG signal to determine the appropriate diastolic intervals for pressure measurements. If the ECG signal was missing, the core laboratory manually inserted R-wave

markings based on the pressure waveform into the baseline tracing from which iFR was calculated.

Resting P_d/P_a was calculated in similar fashion to iFR except that P_d/P_a was time-averaged over the entire cardiac cycle, thus including both systole and diastole. In addition to the exclusion criteria for FFR measurements, iFR and P_d/P_a recordings with any of the following characteristics were also excluded from the analysis: insufficient baseline recording prior to the administration of adenosine (recording had to contain at least 5 cardiac cycles from the start of the recording until the onset of hyperemia); significant arrhythmias including supraventricular tachycardia or premature ventricular contractions within the baseline tracing; or heart rate <50 or >120 beats per minute.

Core laboratory analyses were performed in a blinded fashion at 3 separate work stations by different technicians in sequential, independent phases. First, a thorough waveform analysis was performed of all baseline and hyperemic tracings, and pressure recordings meeting any of the above outlined exclusion criteria were removed from the analysis. Second, an independent calculation of FFR was performed blinded to the original FFR readout. Third, fully automated, computerized calculations of P_d/P_a and iFR were performed by a physician unaware of the waveform analysis and FFR computation. All tracings were over-read by a physician experienced in physiology measurements (AM, PG, or AJ) to ensure data quality. FFR, iFR and P_d/P_a data were recorded on separate case report forms that were not merged until the completion of the blinded analyses.

Study Endpoints. The primary objective of this study was to evaluate the level of diagnostic accuracy of iFR and P_d/P_a compared with FFR in a variety of clinical settings in the largest population studied to date, using rigorous, pre-specified core laboratory-based processes. Using

FFR as the reference standard, the primary study endpoint was to identify the iFR thresholds which most strongly correlated with an FFR cut-point of 0.80, and to determine the proportion of lesions for which these thresholds apply. Thresholds with ≥90% diagnostic accuracy were calculated (pre-specified as representing the minimal thresholds required for potential clinical utility of iFR), and the proportion of lesions which fell beyond those thresholds were determined (defined as the adenosine free zone).

Secondary study objectives included determining the iFR thresholds necessary to achieve >90% to 99% diagnostic accuracy, construction of receiver operator characteristic (ROC) curves for iFR to assess the optimal cut-off point with respect to the clinical threshold of FFR ≤0.80; assessment of the overall correlation between iFR and FFR using regression techniques; and assessment of the sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and overall diagnostic accuracy at that cut-off point. All of the above analyses were also performed with the cycle-averaged resting pressure ratio P_d/P_a, and iFR and P_d/P_a were directly compared with respect to their diagnostic accuracy. In addition, subgroup analyses were performed for both iFR and P_d/P_a with respect to coronary vessel (left anterior descending coronary artery [LAD] vs. non-LAD), route of adenosine administration (intravenous vs. intracoronary), and study site (to assess center variability).

Statistical analysis. Data were summarized by descriptive statistics. Pearson's correlation and linear regression analysis were performed to examine the relationship between iFR and FFR and P_d/P_a and FFR, respectively. ROC curves were constructed to identify the concordance between FFR, iFR and P_d/P_a. Agreement between the methods was assessed by Bland-Altman plots with corresponding 95% limits of agreement. Sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of iFR and P_d/P_a measurement relative to an FFR cut-off of ≤0.80 were

determined, c-statistics were generated, and optimal cut-off values for iFR and P_d/P_a were computed based on maximizing the sum of sensitivity plus specificity. Binary variables were compared using Chi-Square testing. From the raw data examining the relationship between iFR (or P_d/P_a) and FFR, separate iFR (P_d/P_a) thresholds were determined for which the PPV and NPV were each ≥90% (corresponding to an FFR of ≤0.80 and >0.80, respectively), and the proportion of lesions meeting these criteria was determined. Similar analyses were performed using different thresholds from ≥90% to ≥99%. SAS software, version 9.1 (SAS Institute, Cary, North Carolina) was used for all analyses, and a two-tailed p-value of <0.05 was regarded as statistically significant.

RESULTS

Patient demographics and procedural data. A total of 1,768 patients with 1,974 lesions from 15 clinical sites were submitted for analysis. Of these lesions, 381 (19.6%) met at least 1 of the pre-defined core laboratory exclusion criteria, leaving 1,593 lesions for final analysis. The most common reasons for exclusion were insufficient baseline recording or artifact during recording (n=227), lesions not meeting study entry criteria (n=56), pressure drift or incorrect calibration (n=42), and other technical factors (n=56).

The mean age of the population was 63.4±10.3 years and 74.9% were male. There were 21.2% with prior myocardial infarction, 28.1% with diabetes mellitus, and 29.4% were current smokers. A small fraction had prior coronary artery bypass grafting (3.4%), chronic kidney disease (8.3%), and congestive heart failure (6.3%). The clinical presentation was most commonly chronic stable angina (68.6%), with 14.4% having unstable angina and 8.4% non-ST-elevation myocardial infarction. More than half of the population had multivessel coronary artery disease (53.8%) with the LAD being the most commonly interrogated target lesion (63%),

followed by the right coronary artery (20%) and the left circumflex artery (17%). FFR studies were performed with intravenous adenosine in 80.1% of cases, with intracoronary adenosine administered in the remainder.

Relationships between FFR, iFR, and P_d/P_a. Among the study population, the median [interquartile range (IQR)] for FFR, iFR and P_d/P_a were 0.79 [0.70, 0.86], 0.90 [0.83, 0.95], and 0.93 [0.86, 0.96], respectively. A scatterplot between iFR and FFR is shown in Figure 1A, demonstrating moderate overall linear correlation between the two measures (R^2 (95% confidence interval [CI]) = 0.66 (0.64-0.70), p<0.001). Similarly, the correlation of resting P_d/P_a and FFR demonstrated an R^2 (95%CI) of 0.69 (0.67-0.72), p<0.001 (Figure 1B). While the overall correlations between P_d/P_a vs. FFR and iFR vs. FFR were similar, the data points were more clustered around the regression line with a flatter slope and greater intercept for the P_d/P_a vs. FFR relationship. The area under the ROC curve (c-statistic) to predict FFR ≤0.80 was 0.81 (95%CI 0.79-0.83) for iFR and 0.82 (95%CI 0.80-0.84) for P_d/P_a, indicating moderate to good discrimination for both (Figure 2). The optimal cutoff value for FFR ≤0.80 derived from ROC analyses was 0.90 for iFR and 0.92 for P_d/P_a.

Bland-Altman plots for iFR and P_d/P_a are shown in Figure 3A and 3B, respectively. On average, iFR exceeded FFR by +0.10 (95%CI -0.06, +0.26) and P_d/P_a exceeded FFR by +0.14 (-0.01, +0.29). However, both iFR and P_d/P_a demonstrated a substantial degree of scatter, particularly below the threshold of 0.80.

The correlation between iFR and P_d/P_a is shown in Figure 4A. There was a strong correlation between these 2 parameters (R^2 = 0.95; p<0.001), demonstrating that 95% of the variation in iFR was accounted for by P_d/P_a. However, Bland-Altman analysis demonstrated that

P_d/P_a overestimates iFR on average by 0.04, and substantially more when iFR is <0.80 (Figure 4B).

Diagnostic accuracy of iFR. Overall sensitivity, specificity, PPV and NPV for iFR ≤0.90 vs. FFR ≤0.80 were 78.9%, 82.4%, 85.2%, and 73.3%, respectively, with an overall diagnostic accuracy of 80.4%. To achieve ≥90% diagnostic accuracy at each extreme, the overall iFR range had to be restricted to ≤0.88 (to predict an FFR ≤0.80) and ≥0.97 (to predict an FFR >0.80), comprising 1034/1593 (64.9%) of the study lesions. In other words, if a ≥90% diagnostic accuracy compared with FFR is deemed sufficient for therapeutic interchangeability, 64.9% (95%CI 62.6-67.3%) of the study lesions would fall within the adenosine free zone and not require hyperemia for the diagnosis of ischemia. Figure 5 demonstrates the association between the adenosine free zone and diagnostic accuracy. The adenosine free zone narrows as increasing diagnostic accuracy of iFR is required, such that only 28.6% (26.4-30.8%) and 18.0% (16.1-19.8%) of lesions would achieve ≥95% and ≥99% diagnostic accuracy, respectively.

Diagnostic accuracy of P_d/P_a. Sensitivity, specificity, PPV and NPV for P_d/P_a ≤0.92 for FFR ≤0.80 were 76.3%, 88.1%, 89.2%, and 74.4%, respectively, resulting in an overall diagnostic accuracy of 81.5%. A diagnostic accuracy of ≥90% was achieved when the P_d/P_a range was restricted to ≤0.92, with 769/1593 (48.3%, 45.6-50.5%) of the lesions falling in that range. However, in contrast to iFR, there was no upper boundary of P_d/P_a which predicted with ≥90% accuracy a negative FFR value; i.e. >10% of lesions with a P_d/P_a of 1.00 had an FFR ≤0.80. Figure 5 demonstrates the association between the adenosine free zone and diagnostic accuracy for P_d/P_a. Similar to iFR, there was a tradeoff between diagnostic accuracy and the size of the adenosine free zone. Only 36.0% (33.7-38.4%) and 19.5% (17.5-21.4%) of lesions would achieve a diagnostic accuracy of ≥95% and ≥99%, respectively.

Subgroup analyses. There was no significant difference in diagnostic accuracy of iFR compared to FFR with intravenous vs. intracoronary adenosine administration (81.5% vs. 78.2%, p=0.07) nor among patients presenting with stable vs. unstable angina (80.4% vs. 80.2%, p=0.97). Similarly, no significant differences in diagnostic accuracy were noted when LAD stenoses were compared with non-LAD stenoses (79.9% vs. 81.9%, p=0.34), nor for tracings with vs. without an embedded ECG signal (83.7% vs. 80.2%, p=0.39). Finally, the variation in overall accuracy between iFR and FFR at individual study sites ranged from 78.6% to 82.7%, and the correlation varied from R^2=0.54 to R^2=0.72 (Table 1). For P_d/P_a the overall accuracy ranged from 72.6% to 89.5% with a correlation of R^2=0.61 to R^2=0.75.

DISCUSSION

In this large, core laboratory-based analysis the overall linear correlation between both iFR and P_d/P_a with FFR was moderate (R^2=0.66 and 0.69, respectively), with an overall diagnostic accuracy of ~80% for both non-hyperemic indices (using the optimal ROC-determined cut-off points of 0.90 and 0.92 to predict an FFR ≤0.80). The diagnostic accuracy was independent of vessel, embedded vs. core lab generated ECG gating signal, use of intravenous vs. intracoronary adenosine to induce hyperemia, and clinical site. Accepting FFR as the reference method (in the absence of outcome studies with iFR or P_d/P_a), this level of accuracy is insufficient to use either parameter for procedural guidance in all cases as ~20% of therapeutic decisions would be discordant from FFR.

While iFR and P_d/P_a are imperfect surrogates of FFR close to the clinically utilized cut-off value of 0.80 (11), they may still provide acceptable accuracy at greater or lesser degrees of functional stenosis severity. The fundamental principle of FFR, justifying pressure-derived estimation of coronary flow impairment is that the translesional pressure ratio approximates flow

when microvascular resistance is minimized (12,13), requiring the use of a potent vasodilator. However, microvascular resistance is influenced by many factors including capacitive, inertial and resistive forces as well as the complex effects of systolic contraction. Non-hyperemic pressure ratios may theoretically have adequate concordance with hyperemic pressure measurements when there is a large baseline gradient (i.e. obvious impairment of coronary flow) or no gradient at all (i.e. absence of any resting flow disturbance). In this regard a recent retrospective analysis of almost 500 patients demonstrated a good correlation between P_d/P_a and FFR with an AUC of 0.86 (14). When only trans-lesional resting pressure ratios of <0.88 and >0.95 were considered, the PPV and NPV increased to >95%, with more than half of the study population falling in these categories. The present larger, multicenter, core laboratory based analysis demonstrates that if 90% accuracy compared to the FFR reference standard is accepted at the margins (the pre-specified precision limit for therapeutic interchangeability in the present study), use of iFR and P_d/P_a might avoid hyperemia in 65% and 48% of lesions, respectively. If 95% accuracy is required, however, use of iFR and P_d/P_a might avoid hyperemia in only 29% and 36% of lesions, respectively. In addition, the percentage of lesions falling into the adenosine free zone will vary based on the spectrum of lesions being studied. If only intermediate lesions are investigated (i.e. with FFR near 0.80 in a greater proportion of patients), the adenosine free zone may be smaller compared to the findings of the current study.

A secondary goal of the present study was to compare and contrast iFR and P_d/P_a. By restricting measurements to a specific segment of diastole in which the maximum achievable coronary flow occurs during resting conditions, iFR has a theoretical advantage compared to P_d/P_a. However, using FFR as the reference standard, we found no significant differences between iFR and P_d/P_a with respect to sensitivity, specificity, PPV, NPV or diagnostic accuracy.

Although modest differences were noted between the iFR and P_d/P_a vs. FFR regression patterns, the overall similar results are consistent with a prior retrospective analysis by Johnson et al. (10). Prospective studies are required to determine whether the differences between iFR and P_d/P_a are practically or clinically relevant.

The present study has several strengths, but also some limitations. Prior studies examining the relationship between iFR, P_d/P_a and FFR demonstrated significant variability and thus reached strikingly different conclusions (8-10). In this regard, it is reassuring to note that by applying a rigorous study methodology, common inclusion and exclusion criteria, and a standardized physiology assessment methodology, the data from these prior studies showed relatively little variation with diagnostic accuracy ranging from 79-83%. We have applied linear models to our data, although the complete physiologic relationship between FFR and iFR or rest P_d/P_a may best be described by a curvilinear relationship. RESOLVE is the first coronary physiology study that employed a core laboratory for analysis of hyperemic and resting pressure derived indices of stenosis severity. Surprisingly, 20% of measurements were found to be sub-optimal and were excluded from the analysis (perhaps explaining the reduced site-to-site variability in the present report compared to previously published individual studies). Future clinical trials should consider including core laboratory analysis to assess the validity of hemodynamic measurements, as is currently the standard for quantitative coronary angiography and intravascular ultrasound. An additional strength is the size of the present study, encompassing all iFR studies published to date as well as several non-published clinical experiences, which provides incremental power to accurately locate point estimates while reducing CI width, and affording subgroup analysis. However, the present retrospective analysis is limited by non-uniform patient and lesion characteristics at each site, and varying FFR

acquisition protocols. Despite the fact that all studies underwent rigorous analysis by an independent core laboratory to eliminate potential erroneous measurements and minimize variability, we cannot fully exclude selection bias and other sources of inconsistencies. A final pullback of the pressure wire into the guiding catheter confirming the absence of pressure drift was not required and was performed in only a small minority of cases.

Clinical implications. As with any diagnostic test FFR, iFR and P_d/P_a have inherent variability (9,15,16). On the basis of 3 randomized trials demonstrating superior clinical outcomes with FFR guidance compared to angiographic guidance alone (5-7), FFR is justifiably accepted as the standard in both US and European guidelines for invasive physiologic lesion assessment and clinical decision-making (17,18). Based on the present report and consistent with prior studies (9,10), the universal adoption of iFR or P_d/P_a with use of a single cut-off point cannot be recommended (19). However, using a hybrid approach wherein P_d/P_a or iFR are accepted at the 2 outer tails of the spectrum with FFR-based decisions required in the grey area in-between (20) may be feasible and might avoid the use of hyperemia in approximately 48% to 65% of lesions, respectively, if ≥90% correlation with an FFR ≤0.80 cutoff is accepted. While there will always be a trade-off for greater diagnostic accuracy (e.g. if >99% accuracy compared to FFR is desired, the adenosine free zone would shrink to <20% of patients), a small (≤10%) degree in variability between non-hyperemic physiologic measurements and FFR in a large proportion of patients may be acceptable to many physicians in daily clinical practice given the cost, inconvenience and potential side effects associated with adenosine administration (21,22), and the relatively low major adverse cardiac event rate around the FFR 0.80 cut-point (5), where most classification errors are likely to occur. However, the iFR and P_d/P_a cut-off values identified in the present retrospective study require validation, and prospective, randomized trials are required to

determine whether a hybrid strategy results in non-inferior clinical outcomes to the routine use of FFR.

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FIGURE LEGENDS

Figure 1. Scatter plot demonstrating the relationship between iFR and FFR (A) and P_d/P_a and FFR (B). The dotted blue line represents the line of best fit. The horizontal dashed line in 1A notes the optimal iFR cut-off of 0.90 based on ROC analysis. The horizontal dashed line in 1B notes the optimal P_d/P_a cut-off of 0.92.

Figure 2. ROC curves for iFR and P*d*/P*a*. Comparisons are made with FFR at a cut-point of 0.80.

Figure 3. Bland-Altman analysis. Bland-Altman plots of differences against the means are displayed for iFR (A) and P_d/P_a (B). The zero line is displayed in red. The mean bias is represented by the solid blue line (with 95% CI in dashed blue).

Figure 4. Relationship between iFR and P_d/P_a. Scatter plot demonstrates a highly linear relationship (A). Bland-Altman plot displays differences against the mean demonstrating substantial variation between iFR and P_d/P_a (B). Lines as in Figure 3.

Figure 5. Association between adenosine use and diagnostic accuracy of iFR and P_d/P_a. An inverse relationship between adenosine use and diagnostic accuracy is demonstrated, such that with increasing accuracy the 'adenosine free zone' decreases in width for both iFR and P_d/P_a. The blue line displays this association for iFR while the red line depicts P_d/P_a.

Table 1. Individual data from included studies and individual study Sites

		iFR				P_d/P_a			
Study/ Participating Site	**No. of Lesions**	**Cutoff Point**	**AUC from ROC (c-statistic)**	**Overall Accuracy (%)**	**Correlation (R^2)**	**Cutoff Point**	**AUC from ROC (c-statistic)**	**Overall Accuracy (%)**	**Correlation (R^2)**
Total	1593	0.90	0.81	80.4	0.66	0.92	0.82	81.5	0.69
ADVISE*	432	0.91	0.82	81.9	0.71	0.92	0.82	81.9	0.75
VERIFY†	654	0.89	0.80	79.4	0.60	0.92	0.81	79.8	0.65
Seoul National University	179	0.92	0.83	82.7	0.68	0.93	0.82	82.1	0.70
Stony Brook University	149	0.93	0.81	79.2	0.54	0.93	0.83	83.2	0.61
Columbia University	95	0.91	0.84	82.1	0.62	0.92	0.87	89.5	0.70
AMC/VUmc/KCL	84	0.90	0.78	78.6	0.72	0.93	0.72	72.6	0.70

*Includes data from the ADVISE study and ADVISE registry; †includes data from the prospective and retrospective VERIFY cohorts.

AUC = area under curve; ROC = receiver operator characteristic.

Figure 1A

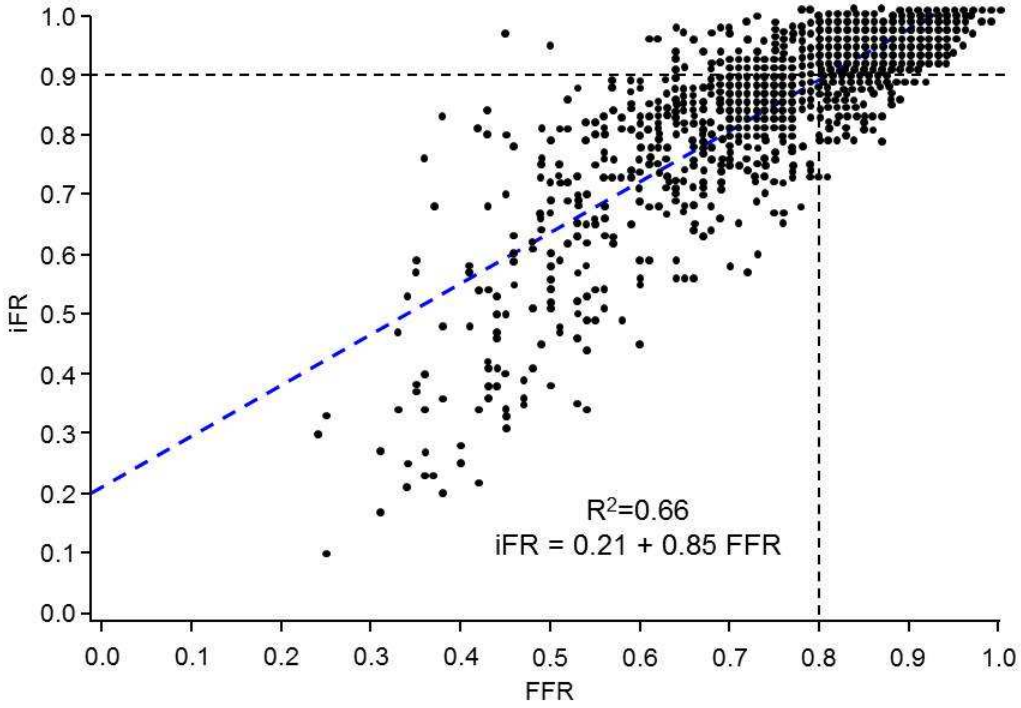


Figure 1B

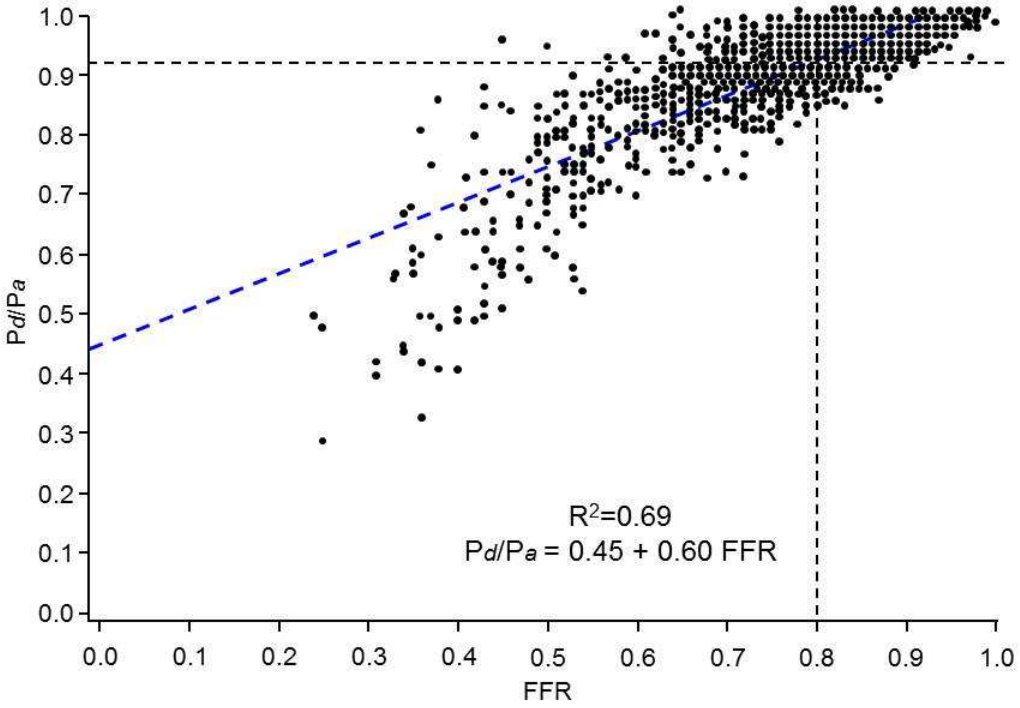
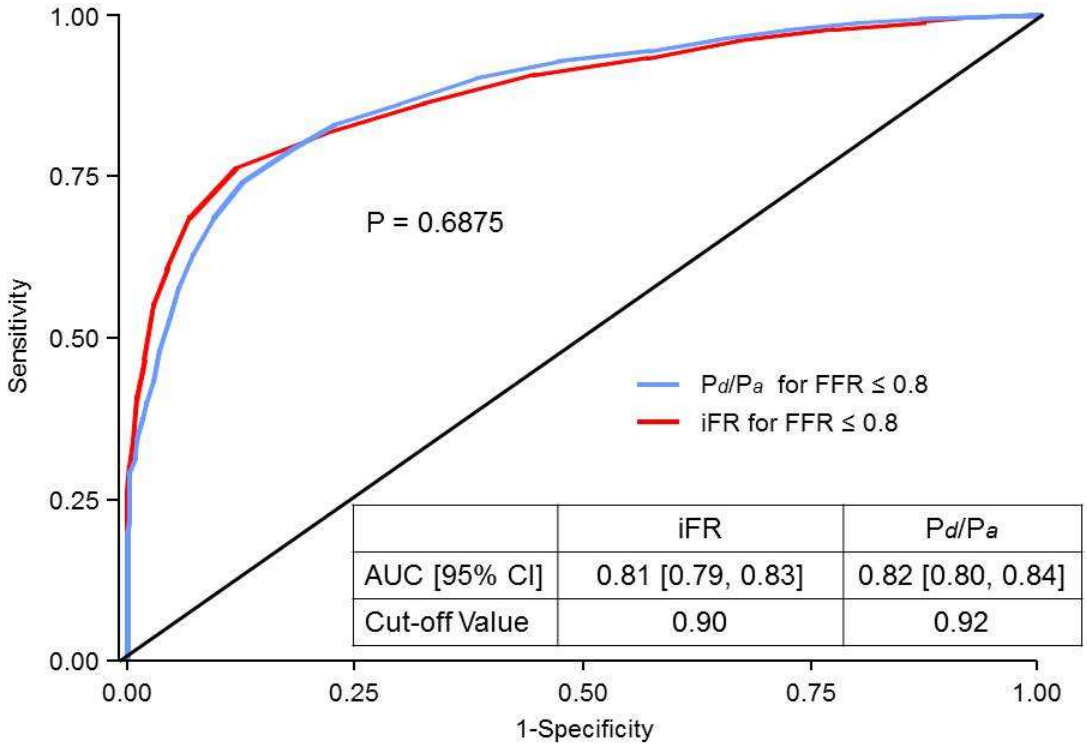
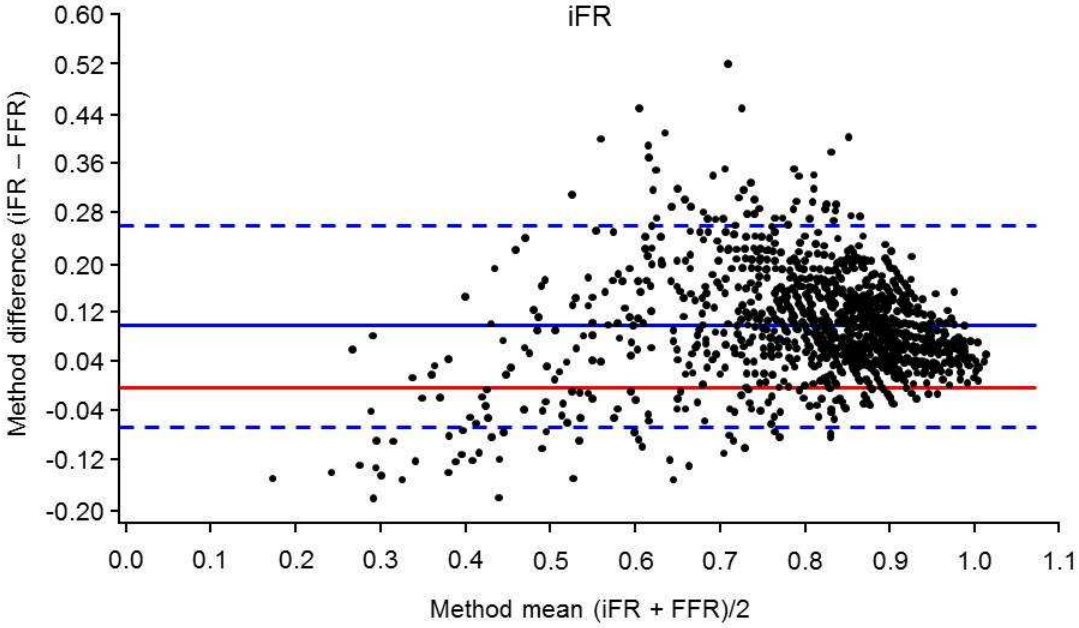


Figure 2



	iFR	Pd/Pa
AUC [95% CI]	0.81 [0.79, 0.83]	0.82 [0.80, 0.84]
Cut-off Value	0.90	0.92

Figure 3A



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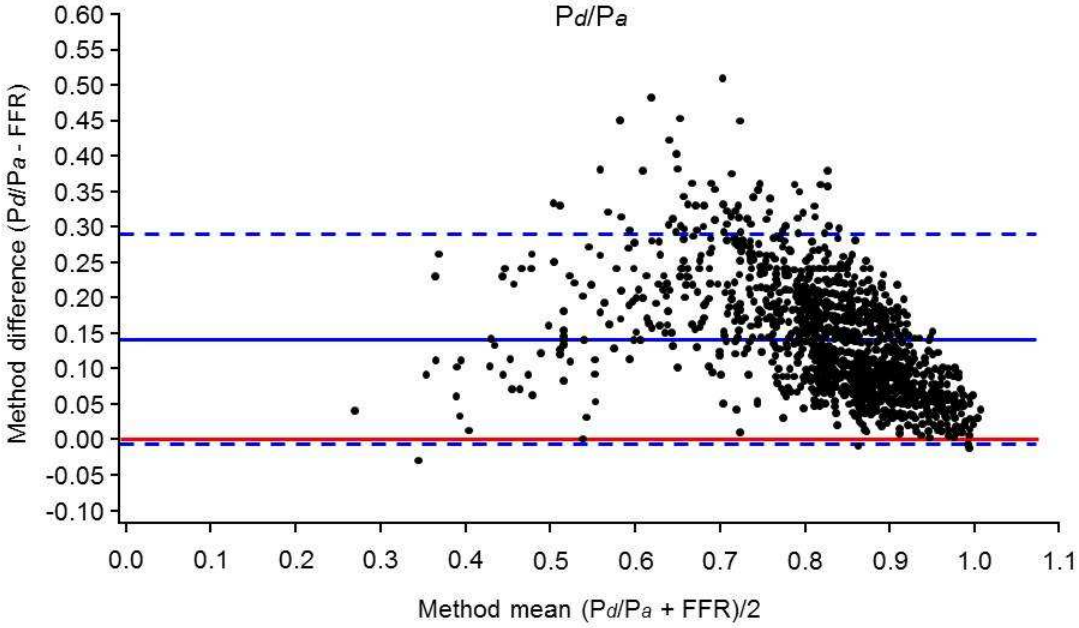

Figure 4A

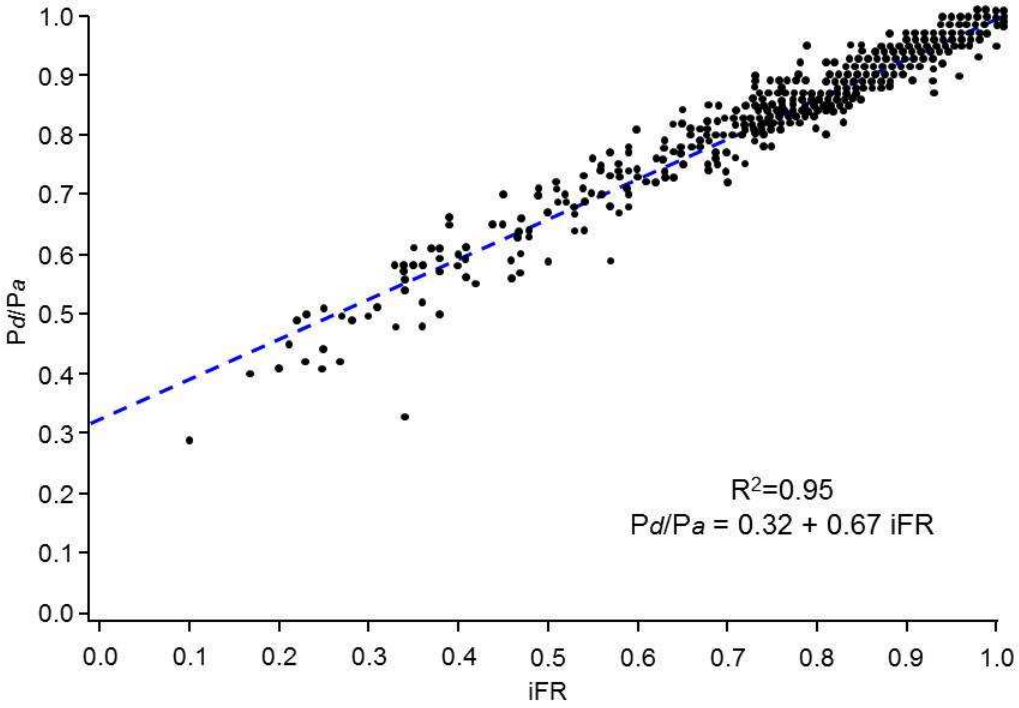

Figure 4B

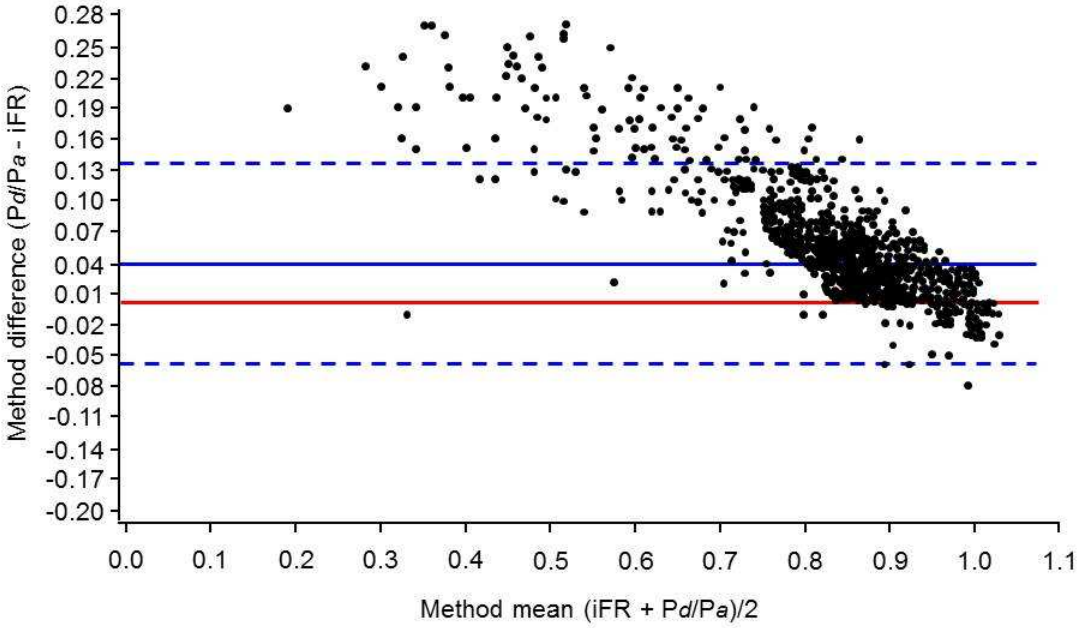

Figure 5