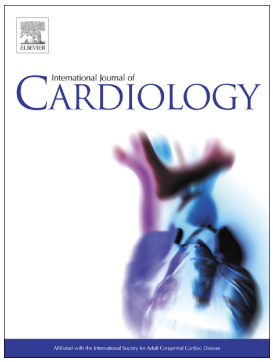


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# Adenosine-Free Indexes vs. Fractional Flow Reserve for Functional Assessment of Coronary Stenoses: Systematic Review and Meta-Analysis.

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**KEYWORDS**

Fractional flow reserve, adenosine-free indexes, instantaneous wave-free ratio, contrast-FFR, diagnostic accuracy.

**STRUCTURED ABSTRACT**

**Background:** Adenosine-free indexes (AFIs), including resting Pd/Pa, instantaneous wave-free ratio (iFR) and contrast-FFR (cFFR), have been proposed to circumvent the use of vasodilators, in order to simplify the functional evaluation of coronary stenoses. Aims of this study were to analyze the correlation between AFIs and Fractional Flow Reserve (FFR) and to compare their diagnostic accuracy when FFR is used as reference.

**Methods:** We conducted a systematic review and meta-analysis of observational studies in which AFIs were compared to FFR. We produced paired forest plots to show the variation of the sensitivity and specificity estimates. We used a hierarchical summary ROC model (HSROC) to summarize the sensitivity and specificity of AFIs in detecting the concordance with FFR assessment.

**Results:** Eighteen studies were included in this meta-analysis. Overall, 4424, 4822 and 2021 coronary lesions in 4410, 4472 and 1898 patients, respectively, were evaluated by Pd/Pa, iFR and cFFR, respectively. The overall Pearson's correlations were 0.81 (95% CI 0.78-0.83), 0.80 (95% CI 0.78-0.81) and 0.92 (95% CI 0.90-0.94) for Pd/Pa, iFR and cFFR, respectively. cFFR showed a significantly higher correlation with FFR compared to Pd/Pa and iFR ($p<0.0001$). The area under the HSROC estimating the discriminating accuracy of cFFR was 0.95 (95% CI 0.94-0.96) and it was significantly higher compared to Pd/Pa (0.86, 95% CI 0.80-0.93) and iFR (0.89, 95% CI 0.84-0.94) ($p<0.0001$).

**Conclusions**: AFIs show a good correlation with the gold standard FFR. Among AFIs, cFFR shows the highest correlation with FFR and the best diagnostic accuracy.

**ABBREVIATIONS LIST**

AFI: adenosine free index

AUC: area under the curve

cFFR: contrast-fractional flow reserve

DOR: diagnostic odds ratio

FFR:fractional flow reserve

iFR: instantaneous wave-free ratio

HSROC: hierarchical summary receiver operating characteristic model

LR: likelihood ratio

SD: standard deviation

## INTRODUCTION

Fractional flow reserve (FFR) is the ratio between the maximal myocardial flow measured in the stenotic territory and the theoretical maximal blood flow in the same territory in the absence of the stenosis. Despite FFR being a ratio of two flows, it can be easily calculated from the ratio of two pressures (the distal and the aortic, Pd/Pa) during maximal hyperemia, when resistance in the coronary circulation is constant and minimal (1). The achievement of maximal hyperemia is therefore the crucial prerequisite to assess correctly FFR. Adenosine is currently considered the gold standard for FFR evaluation (2). Although opinions are not concordant, intravenous adenosine infusion is perceived as time-consuming and costly, and it can be associated with side effects which in most cases are temporary and well-tolerated by the patient (3,4). Of note, the intracoronary administration of adenosine or other vasodilator agents, such as sodium nitroprusside or papaverine, also is limited by side effects (5-8). For these reasons, adenosine-free pressure-derived indexes (AFIs) have been proposed in order to obviate the need for administration of vasodilator agents and to facilitate the dissemination of the functional evaluation of coronary stenoses. The main available AFIs are: resting Pd/Pa, instantaneous wave-free ratio (iFR) and contrast-FFR (cFFR). Resting Pd/Pa is the simple ratio between the distal pressure and aortic pressure in resting conditions (9). Instantaneous wave-free ratio is calculated as the ratio of distal coronary pressure and aortic pressure during a specific period in late diastole, the 'so-called' wave-free period, during which intracoronary resistance would be purportedly constant and minimal (10). Contrast-FFR is the Pd/Pa ratio measured after coronary injection of contrast medium, taking advantage of the moderate hyperaemic effect of the common angiographic contrast medium (11). Aim of the present study was to analyse the correlation between resting Pd/Pa, iFR, cFFR and FFR and to compare their diagnostic accuracy when FFR is used as reference.

## METHODS

This study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement (12-14). Institutional review board approval and informed consent was not required for this systematic review and meta-analysis. The protocol for this study was previously published on an international prospective register for systematic reviews (PROSPERO) with the number: CRD42018107912.

### Search strategy

A computerized search of PUBMED, Biomed Central and Cochrane library databases up to February 28, 2018 was performed to find English-language publications that were relevant to our study. Our searched terms were as follows: ((fractional flow reserve) OR (FFR)) AND (((resting indexes)) OR ((instantaneous wave-free ratio) OR (iFR)) OR ((contrast FFR) OR (cFFR)) OR ((resting Pd/Pa) OR (Pd/Pa))). The eligibility of the articles, the data extraction, and quality assessment were independently evaluated by two reviewers (FG, RP) and a third review author (GC) was consulted to resolve disagreements. Articles considered to have original material were obtained and assessed in detail and the references cited in these publications were searched to identify further publications (Supplemental Figure 1).

### Selection criteria

Studies investigating diagnostic performance of AFIs vs the gold standard FFR were considered eligible for our study if they satisfied the following criteria: i) inclusion of patients undergoing coronary angiography for ischemic heart disease; ii) investigation of at least one coronary lesion with intracoronary physiology; iii) intracoronary physiology performed with fully hyperemic FFR and at least one of the AFIs; iv) the outcomes of the studies included sufficient details to be able to obtain correlation value and the number of true-positive, false-positive, false-negative, and true-

negative patients. Studies meeting any of the following criteria were excluded: i) studies that included <50 patients; ii) reviews, editorials, letters, comments, or conference abstracts; iii) studies focusing on topics other than diagnostic accuracy of AFIs vs FFR; iv) studies with partially overlapping patients or data. All the authors agreed on the final number of studies included.

**Data abstraction, endpoints, subgroup analyses**

We predefined tables for data extraction, which were piloted in 5 articles. The information extracted included author, journal, year of publication, country, study design, baseline characteristics of the study population, AFIs, FFR, cut-offs of intracoronary physiology. We extracted the correlation value and the absolute numbers of true-positive, false-positive, false-negative and true-negative test results from the paper or through (re)calculations of the sensitivity and specificity based on the authors' diagnostic classification of the participants and sample size of the study. If a study presented multiple AFIs, the analyses were performed for each single AFI. We prespecified the analyses according three different subgroups: i) Pd/Pa vs. FFR; ii) iFR vs. FFR; iii) cFFR vs FFR.

**Internal validity and quality appraisal**

Two unblinded reviewers (FG, RP) independently evaluated the quality of the included studies using pre-specified electronic forms of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Supplemental Figure 2) (15). Discrepancies between reviewers were solved by consensus. No study was excluded based on this analysis.

**Statistical analysis**

Demographics and other baseline characteristics were summarized in terms of mean ± standard deviation (SD) if with continuous distribution, otherwise as median [interquartile range]. Categorical variables were expressed as number and percentage (%). Correlation data expressed as

Pearson's correlation, Kendall's Tau or Spearman's Rho were extracted from individual studies and then pooled using a random effect model as Pearson's correlation, with 95% confidence intervals (16,17). Sensitivity analysis was also performed repeating the meta-analysis removing one study at a time. Sensitivity, specificity, negative predictive value and positive predictive value were used as reported by the authors or (re)calculated from the data presented. The estimates of sensitivity and specificity and their 95% confidence interval were plotted in paired forest plots. We used a hierarchical summary ROC model (HSROC) to pool the sensitivity and specificity of AFIs in detecting the concordance with FFR result (coronary lesion flow-limiting vs. not flow-limiting) (18). We included all studies in each pairwise comparison to evaluate the diagnostic accuracy of AFIs using FFR as reference We used forest plots to show the results of the studies which directly compared different indexes. We pooled sensitivities and specificities of the compared different indexes by using bivariate random effects models. The model's parameters were used to plot the ROC curve in RevMan. Random effect meta-regression analysis was performed to assess the effect of some potential confounding factors (e.g. cardiovascular risk factors, clinical presentation, number of lesions, number of patients, location of the lesion on left main and/or left anterior descending) on the correlation between AFI and FFR. We defined overall accuracy of AFI as the ratio in percentage between the sum of true positives and true negatives divided for the number of measurements and negative predictive value (NPV) as the ratio in percentage between true negatives and the sum of true negatives and false negatives).

Considering the high likelihood of between-study variance, a random effect model was used. Statistical heterogeneity was assessed using Cochran's Q test. This statistic was complemented with the $I^2$ statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of $I^2$ of 0 to 24.9% represents insignificant heterogeneity, 25 to 49.9% low heterogeneity, 50 to 74.9% moderate heterogeneity, and >75 % high heterogeneity (17). The ANOVA Q-Test was used to compare the correlations between FFR and different AFI. Publication bias was appraised by graphical valuation of funnel plots and through Begg and

Mazumdar rank correlation, Egger's regression intercept, and Duval and Tweedie trim and fill (16-18). For all analyses two-sided p <0.05 values were considered statistically significant. Statistical analyses were performed using the R statistical programming language (version 2.10.13; R Core Team, 2013), STATA (version 14; Stata Corp LP) and Prometa software (Internovi, Cesena, Italy).

## RESULTS

### Literature search

The process of study selection is summarized in Supplemental Figure 1. In total, 314 studies were identified. Shortlisted citations were retrieved and checked at the title/abstract level excluding 277 studies (n=24 duplicates, n=4 lack of comparison between AFI and FFR, n=249 not in the field of our interest). Complete articles for the remaining 37 studies were checked for compliance to inclusion/exclusion criteria excluding other 12 studies with reasons (n=1 copy of another study, n=5 letters, n=4 meta-analysis, n=2 only abstract available). Finally, we identified 25 eligible studies, of which 7 were excluded because patients were included in bigger studies selected for the present meta-analysis. A total of 18 studies were included in qualitative and quantitative meta-analysis (19-36) (Supplemental Figure 1).

### Baseline characteristics of the study population

Overall, 6127 patients and 6610 lesions were included in the meta-analysis (Table 1). Resting Pd/Pa value was measured in 4424 coronary lesions from 4410 patients. iFR measurement was performed in 4822 coronary lesions from 4472 patients. Finally, cFFR value was assessed in 2021 coronary lesions from 1898 patients. Mean age was 66.4 (±1,2); 2321 (54,6%) patients were affected by arterial hypertension; 2071 (67 %) had dyslipidaemia, 1828 (30.4%) diabetes mellitus and 2261 (37,9 %) were currently or former smokers. 1392 (28.3%) had a previous myocardial infarction and 1296 (41.2%) received a previous revascularization (including PCI or CABG). Stable coronary artery disease was the clinical indication for coronary angiography in the majority of cases (69%) (Table 1).

**Resting Pd/Pa vs. FFR**

The overall Pearson's correlation between resting Pd/Pa and FFR was 0.81 (95%CI 078-0.83, $I^2$ 83%) (Figure 1). The coupled forest plot of sensitivity and specificity of Pd/Pa vs. FFR is shown in Figure 3. The pooled sensitivity was 82% (95%CI 77–86%), the specificity was 83% (95%CI 78–87%), the diagnostic odds ratio (DOR) was 22 (95%CI 18–27), the positive likelihood ratio (LR) was 4.7 (95%CI 3.8-5.9) and the negative LR was 0.22 (95%CI 0.17–0.27) (Table 2). Green lines of the Supplemental Figure 3 show the accuracy estimates of the 5 studies comparing Pd/Pa vs. FFR (additional details in the supplemental Figure 4). The estimated area under the HSROC curve was 0.86 (95%CI 0.80-0.93). The overall accuracy of Pd/Pa was 81% with a NPV of 82% and discordance was 19%.

**iFR vs. FFR**

The overall correlation between iFR and FFR was 0.80 (95%CI, 0.78-0.81, $I^2$ 63%) similar to that of resting Pd/Pa vs. FFR (p=0.8) (Figure 1). The main results for the pooled analysis of the 12 studies comparing iFR vs FFR are reported in Table 2 and Figure 2. The HSROC curve analysis indicated a sensitivity of 83% (95%CI 77-88%) and specificity of 82% (95%CI 78-85%) resulting in an area under the curve (AUC) of 0.89 (95%CI 0.84-0.94) (Table 2). These findings were summarized in the red lines of Supplemental Figure 3 (additional details in the supplemental Figure 5) and did not significantly differ from those of resting Pd/Pa. The overall accuracy of iFR was 78%, with a NPV of 84% and discordance was 19%.

**cFFR vs. FFR**

At the pooled analysis of the 4 studies comparing cFFR vs. FFR, correlation was 0.92 (95%CI 0.90-0.94, $I^2$ 81%) (Figure 1) which was significantly higher as compared to that of resting Pd/Pa or iFR

(p<0.0001). As well as for the other AFI, the coupled forest plot of sensitivity and specificity of cFFR is shown in Figure 2. As shown in Table 2, the pooled sensitivity was 88% (95%CI 75-95%), the pooled specificity was 93% (95%CI 87-96%), the positive LR was 12.4 (95%CI 7.6-20.5) and the pooled negative LR was 0.12 (95%CI 0.005-0.28). The area under the HSROC estimating the discriminating accuracy of cFFR was 0.95 (95%CI 0.94-0.96) (black lines in Supplemental Figure 3 and additional detail in supplemental Figure 6) and it was significantly higher compared to that of resting Pd/Pa and iFR (p<0.0001). The overall accuracy of cFFR was 89%, with a NPV of 90% and discordance was 11%.

**Meta-regression, sensitivity analysis and publication bias analyses**

At meta-regression analysis, we did not find any baseline characteristics able to affect the correlation between AFIs and FFR (Supplemental Table 1). Data of the meta-analysis of correlation between cFFR and FFR, iFR and FFR and Pd/Pa and FFR were confirmed also with sensitivity analysis with the with the "leave-one-out approach" (Supplemental material Figure 8). Similarly, we did not observe evidence of publication bias (Supplemental Table 2 and Supplemental Figure 7).

**DISCUSSION**

The results of our analysis demonstrate that, taking FFR as the reference standard, among iFR, Pd/Pa and cFFR, the latter is the adenosine-free index showing the highest correlation, predictivity and accuracy.

Furthermore, in the present meta-analysis, we found that both resting Pd/Pa and iFR, have similar accuracy, predictivity and correlation to FFR. Consistently with our results, Hennigan et al. in the VERIFY 2 study (27) reported a similar diagnostic accuracy between resting Pd/Pa and iFR (in comparison with FFR) using binary cut-offs (0.92 and 0.90 respectively). Furthermore, in the RESOLVE study (36) Jeremias et al. found that the overall linear correlation between both resting indexes with FFR was moderate with an overall diagnostic accuracy of 80% for both non-

hyperemic indexes (using the optimal ROC determined cut-off points of 0.92 for resting Pd/Pa and 0.90 for iFR to predict an FFR ≤0.80). In addition, there was no difference in sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy between the two methods in the prediction of FFR (37-38). Similar results were obtained in other registries and, not surprisingly, confirmed in the present meta-analysis, which includes all of them (9,25,27,30-32). Despite the suboptimal accuracy of all non-hyperemic indexes using FFR as reference, head-to-head comparisons with non-invasive imaging techniques have shown a similar diagnostic power of non-hyperemic resting indexes and FFR in detecting ischemia (39, 40). Based on the equivalence between non-hyperemic indexes, clinical recommendations for iFR could be extended to all resting indexes (41). Recently, the DEFINE-FLAIR (42) and SWEDE-HEART (43) clinical trials randomized patients with angiographically intermediate stenoses to an iFR-guided versus a FFR-guided strategy. Both studies found that in 80% of stenosis iFR and FFR were concordant and that iFR guidance was not inferior to FFR on clinical outcomes and no significant difference was observed in the MACE rate at 12 months. On these basis current European guidelines on myocardial revascularization recommend the use of FFR or iFR for functional evaluation of intermediate stenosis when evidence of ischemia is not available (44). However, the globality of evidence supports the notion that a hyperemia-based approach, even if submaximal, is more accurate in predicting FFR than non-hyperemic approaches (19,28,29,35,45,46). In addition, cFFR shows some practical advantages: contrast medium is readily available for injection in the Cath Lab during FFR assessment and virtually free of side effects at the doses normally used for cFFR assessment (single coronary injection). Importantly, reliability of cFFR is independent from the choice of the pressure wire and marginally affected by the choice and the amount of contrast medium used (47). From the original RINASCI study (45) which first tested the accuracy of cFFR in predicting FFR, through the multicenter CONTRAST study (35) to the largest MEMENTO registry (28) as some other small studies included in the present meta-analysis (19,25,29), a strong correlation between cFFR and FFR (ranging from 0.90 to 0.93) was documented in all cases. In the

CONTRAST study (35) the cut-off of 0.83 for cFFR was more accurate in predicting FFR in 763 consecutive patients than Pd/Pa (with a cut-off of 0.92) and of iFR (with the cut-off of 0.90) in predicting FFR, while resting Pd/Pa and iFR, again, provided equivalent diagnostic accuracy (AUC 0.93 for cFFR; 0.88 for iFR and resting Pd/Pa; diagnostic accuracy 86% for cFFR vs 80% for iFR and resting Pd/Pa).

Our analysis showed that contrast-FFR has the highest NPV e the lower rate of discordance among AFI in comparison with FFR, with the lower likelihood ratio for negative results. These findings lead to relevant implications from a clinical point of view, making the systematic use of the cFFR reliable for an operator performing a pressure-wire assessment in excluding the hemodynamic significance of lesions found to be negative with cFFR.

With regard to cFFR, no randomized studies investigating clinical end-points have hitherto been performed. Despite from a methodological point of view this could be considered a potential limitation, it is very unlikely that a clinically meaningful difference could be demonstrated between cFFR and FFR with a such relevant agreement between these two indexes. However, a better standardization of cFFR is needed to extend its use in clinical practice.

Finally, we think that cFFR could respond pragmatically to the need to simplify as much as possible the evaluation of angiographically intermediate coronary stenoses, without walking far away from the principles of conventional FFR.

**Limits of the study**

This is a study-level meta-analysis therefore there are some intrinsic limit for further analysis. For instance, we cannot perform a sub-analysis focused only on patients with acute coronary syndromes. Secondly, heterogeneity degree was moderate to high, ranging between 63 and 83%. Meta-regression analysis was negative for the main population characteristics, but this is an analysis considering each single factor and not all the variables together. For this reason, we should formally

consider the results of this analysis only hypothesis generating and thus a prospective trial would be needed to confirm these data.

**Conclusion**

In conclusion, with the aim of simplifying invasive functional assessement of intermediate coronary lesions several Adenosine-Free indexes have been proposed. All these indexes have been shown accurate in predicting FFR and, more importantly, safe and effective in guiding revascularization in clinical practice. Among Adenosine-Free indexes, cFFR is the best surrogate of FFR and could be the ideal alternative for those operators who prefer to rely on the solid background of FFR (48).

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## FIGURE TITLES AND LEGENDS

**Figure 1. Forest plots presenting the correlation values**

iFR: instantaneous free-wave ratio. FFR: fractional flow reserve.

**Figure 2. Forest plots presenting the punctual estimates of sensitivity and specificity and 95% credibility intervals of each study across three AFI.**

FN: false negative. FP: false positive. TN: true negative. TP: true positive. iFR: instantaneous free-wave ratio. FFR: fractional flow reserve.

**Table 1. Study population characteristics: cardiovascular risk factors**

| | Patients | Lesions | Age | Hypertension | Smokers | Dyslipidemia | Diabetes | SHID | NSTEACS | STEMI | Other Diagnosis | AFI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Mamas 2010* | 483 | 528 | 61.5±1.1 | 293 (60.6) | 300 (62) | NA | 128 (26) | 311 (64) | 172 (36) | 0 (0) | 0 (0) | Pd/Pa |
| *Park 2013* | 238 | 238 | 62.8±0.6 | 133(56) | 148 (63) | 64 (27) | 66 (28) | 151 (63) | 84 (36) | 0 (0) | 0 (0) | iFR |
| *Escaned 2015* | 598 | 690 | 63.6±10.8 | 471(78.8) | 135 (23) | NA | 209 (35) | 398 (67) | 185 (31) | 15 (2) | 77 (13)** | iFR |
| *Fede 2015* | 54 | 89 | 67±11 | 44 (81) | NA | 49 (91) | 14 (26) | 36 (66) | 18 (34) | 0 (0) | 0 (0) | iFR |
| *Harle 2015* | 108 | 151 | 67±11 | NA | NA | NA | NA | NA | NA | NA | NA | iFR |
| *Indolfi 2015* | 82 | 123 | 63.5±9 | 65 (79.1) | 49 (60) | NA | 16 (14) | 29 (34) | 53 (66) | 0 (0) | 0 (0) | iFR |
| *Jeremias 2014* | 1768 | 1593 | 63,4±10,3 | NA | 520 (29) | NA | 497 (28) | 1213 (68) | 403 (23) | 0 (0) | 152 (9)¶ | Pd/Pa; iFR |
| *Johnson 2016* | 763 | 763 | 60±10 | 542 (71) | 511 (67) | 366 (48) | 221 (29) | 595 (78) | 160 (21) | 8 (1) | 0 (0) | Pd/Pa; iFR; cFFR |
| *Henningan 2016* | 197 | 257 | NA | 123(62.4) | 133 (67) | 48 (24) | 31 (16) | 99 (50) | 74 (38) | 6 (3) | 18 (9)¥ | Pd/Pa; iFR |
| *Kanaji 2016* | 97 | 132 | 66.6±10.3 | 80(63.8) | 66 (55) | 83 (69) | 49 (41) | 97 (100) | 0 (0) | 0 (0) | 0 (0) | iFR; cFFR |
| *Israeli 2017* | 134 | 134 | 65±10.2 | 96 (71.7) | 100 (74) | 51 (38) | 35 (26) | 84 (62) | 32 (24) | 9 (7) | 9 (7)† | Pd/Pa |
| *Leone 2017* | 962 | 1026 | 68±3.8 | 788(82) | 619 (64) | 387 (40) | 322 (33) | 634 (66) | 328 (34) | 0 (0) | 0 (0) | Pd/Pa; cFFR |
| *Morioka 2017* | 141 | 186 | 68.7±10.6 | 101(71.6) | 91 (64) | 52 (37) | 80 (57) | 141 (100) | 0 (0) | 0 (0) | 0 (0) | iFR |
| *Musto 2017* | 50 | 66 | 68±11 | 31 (62) | 24 (48) | 19 (38) | 13 (26) | 0 (0) | 0 (0) | 50 (100) | 0 (0) | iFR |
| *Rivero 2017* | 106 | 121 | 67±10 | 89 (84) | 83 (78) | 39 (37) | 35 (33) | 59 (56) | 35 (33) | 0 (0) | 12 (11) ¶ | iFR |
| *Scarsini 2017* | 167 | 290 | 79.8±9.5 | 144 (86.3) | 142 (85) | 114 (68) | 60 (36) | 167 (100) | 0 (0) | 0 (0) | 0 (0) | iFR |
| *Shiode 2017* | 103 | 123 | 70.4±8.7 | 82(79.6) | 61 (59) | 28 (27) | 40 (39) | 92 (89.3) | 11 (10,7) | 0 (0) | 0 (0) | Pd/Pa; iFR |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Van Wyk 2017* | 76 | 100 | 65.6 | 40 (51.3) | 44 (58) | 7 (9) | 12 (16) | 40 (53) | 36 (47) | 0 (0) | 0 (0) | cFFR |

SHID: stable ischemic heart disease. NSTEACS: no ST-segment elevation acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. LM: left main. LAD: left anterior descending. AFI: adenosine free indexes. iFR: instantaneous free-wave ratio. cFFR: contrast fractional flow reserve. NA: not available. * Percentage is calculated on the lesion's number. **: silent ischemia; ¶: not specified; ¥: 5% atypical chest pain, 2% chronic heart failure, 1 % arrhythmia, 1 % valvular disease (surgical); †: 2%: congestive heart failure; 5%: syncope, arrhythmia, positive stress test, valvular heart disease.

**Table 2. Bivariate summary estimates for each AFI in the comparison with FFR**

| AFIs | No. of studies | Summary estimates (95%CI) | | Likelihood ratio (95%CI) | | DOR | Area under HSROC curve (95%CI) |
|---|---|---|---|---|---|---|---|
| | | Sensibility | Specificity | LR+ | LR- | | |
| Pd/Pa | 7 | 82 (77-86) | 83 (78-87) | 4.7 (3.8-5.9) | 0.22 (0.17-0.27) | 22 (18-27) | 0.86 (0.80-0.93) |
| iFR | 14 | 83 (77-88) | 82 (78-85) | 4.6 (4-5.4) | 0.2 (0.15-0.27) | 23 (17-32) | 0.89 (0.84-0.94) |
| cFFR | 4 | 88 (75-95) | 93 (87-96) | 12.4 (7.6-20.5) | 0.12 (0.05-0.28) | 99 (33-293) | 0.95 (0.94-0.96) |

AFI: adenosine free indexes. NO: number. LR: likelihood ratio. DOR: diagnostic odds ratio. HSROC: hierarchical summary receiver operating characteristic. iFR: instantaneous free-wave ratio. cFFR: contrast fractional flow reserve.

**Figure 1**

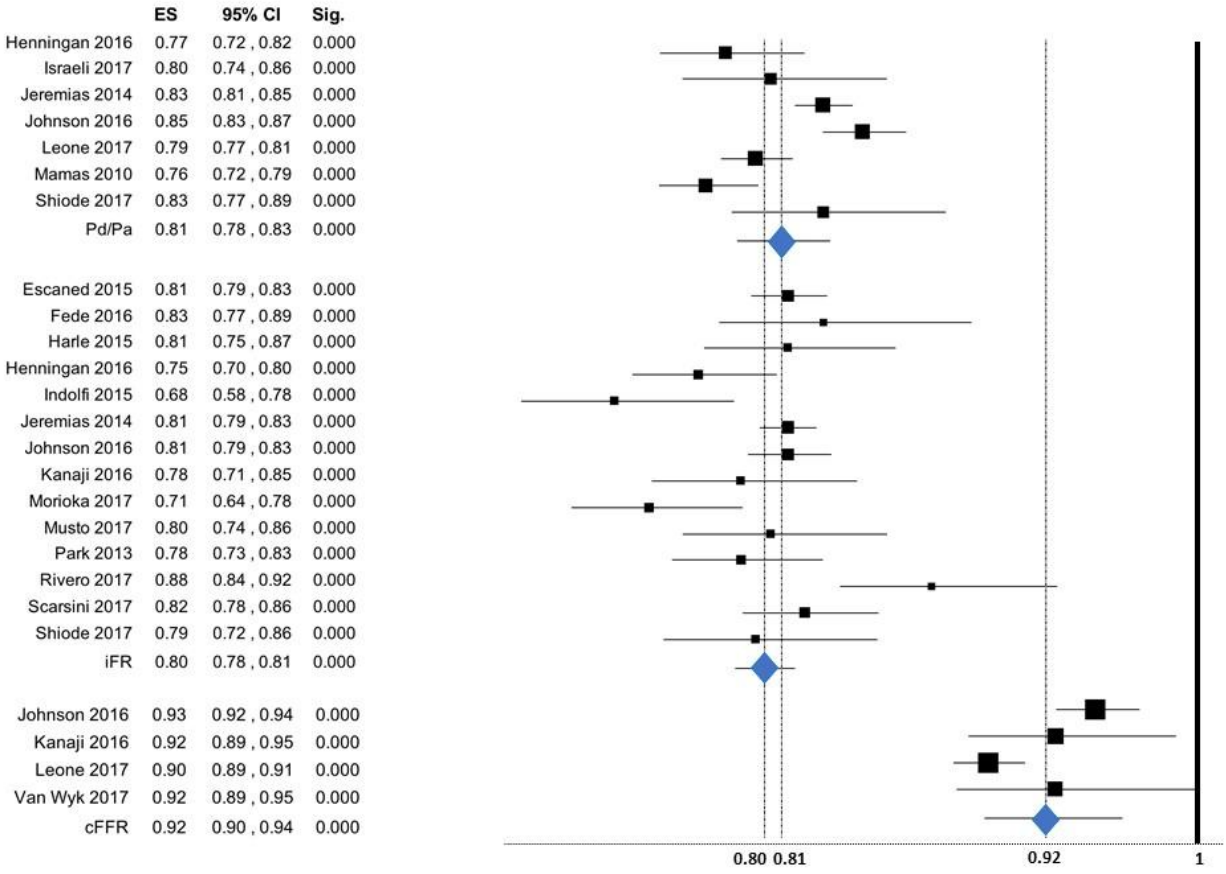
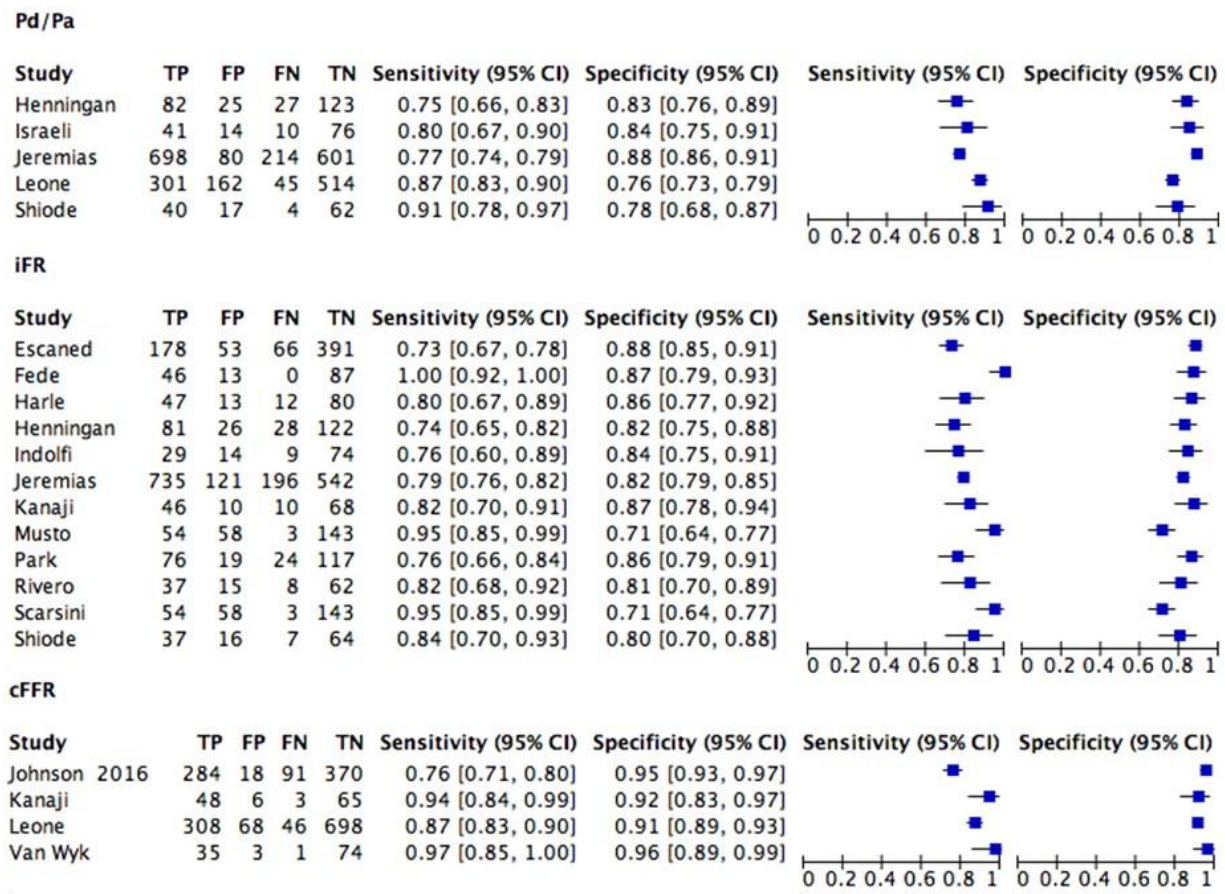


**Figure 2**



**Highlights**

- Our meta-analysis demonstrated that Adenosine-Free indexes are accurate in predicting FFR.
- Taking FFR as reference, cFFR showed the higher correlation, predictivity and accuracy compared to iFR and resting Pd/Pa.
- Among AFIs, cFFR showed the best diagnostic performance, representing a safe e valuable diagnostic tool limiting the need for adenosine. Further studies are needed to implement its use in routine practice.

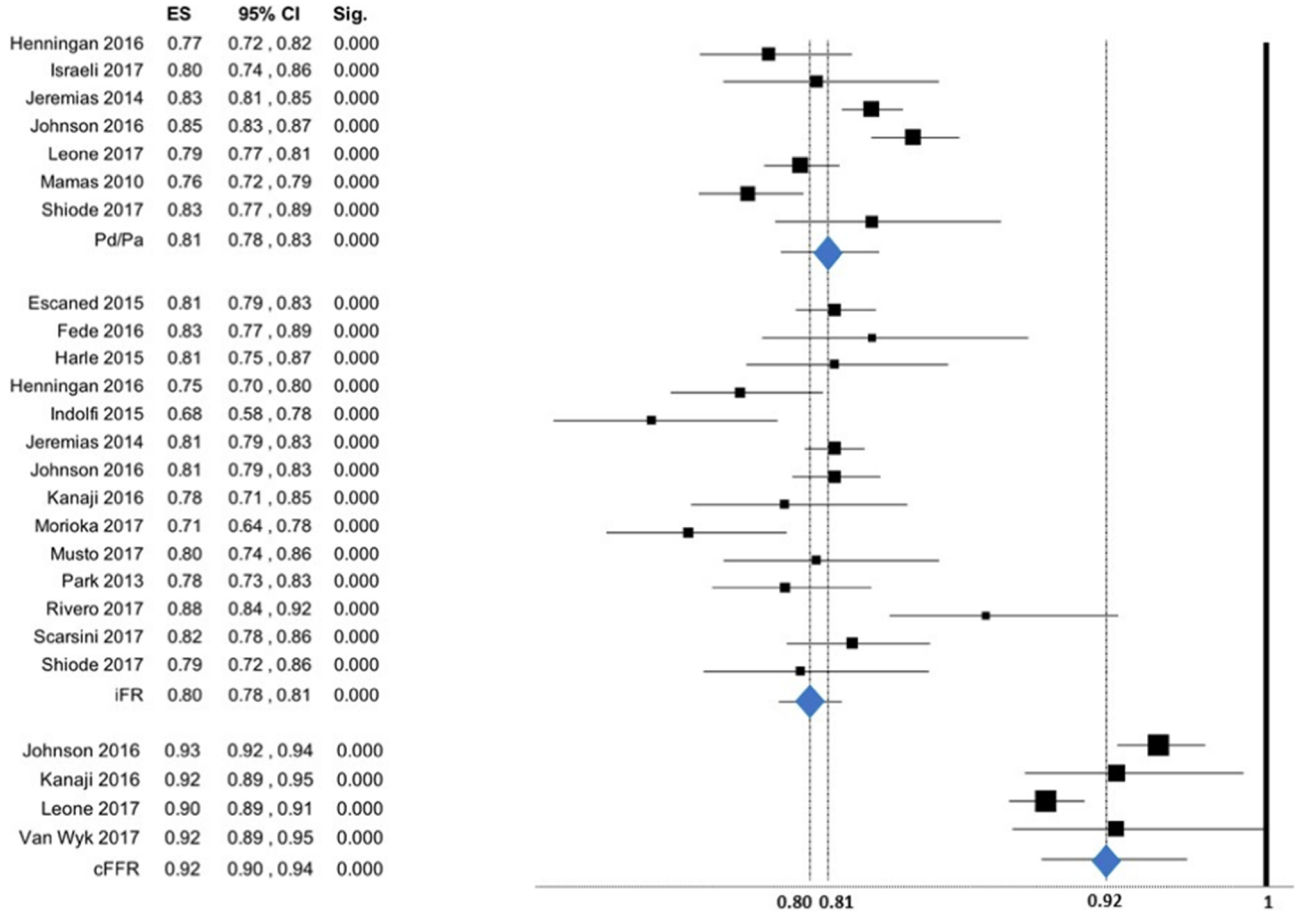
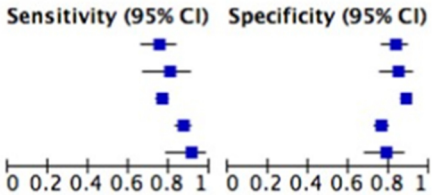

ES 95% CI Sig.
Henningan 2016 0.77 0.72 , 0.82 0.000
Israeli 2017 0.80 0.74 , 0.86 0.000
Jeremias 2014 0.83 0.81 , 0.85 0.000
Johnson 2016 0.85 0.83 , 0.87 0.000
Leone 2017 0.79 0.77 , 0.81 0.000
Mamas 2010 0.76 0.72 , 0.79 0.000
Shiode 2017 0.83 0.77 , 0.89 0.000
Pd/Pa 0.81 0.78 , 0.83 0.000
Escaned 2015 0.81 0.79 , 0.83 0.000
Fede 2016 0.83 0.77 , 0.89 0.000
Harle 2015 0.81 0.75 , 0.87 0.000
Henningan 2016 0.75 0.70 , 0.80 0.000
Indolfi 2015 0.68 0.58 , 0.78 0.000
Jeremias 2014 0.81 0.79 , 0.83 0.000
Johnson 2016 0.81 0.79 , 0.83 0.000
Kanaji 2016 0.78 0.71 , 0.85 0.000
Morioka 2017 0.71 0.64 , 0.78 0.000
Musto 2017 0.80 0.74 , 0.86 0.000
Park 2013 0.78 0.73 , 0.83 0.000
Rivero 2017 0.88 0.84 , 0.92 0.000
Scarsini 2017 0.82 0.78 , 0.86 0.000
Shiode 2017 0.79 0.72 , 0.86 0.000
iFR 0.80 0.78 , 0.81 0.000
Johnson 2016 0.93 0.92 , 0.94 0.000
Kanaji 2016 0.92 0.89 , 0.95 0.000
Leone 2017 0.90 0.89 , 0.91 0.000
Van Wyk 2017 0.92 0.89 , 0.95 0.000
cFFR 0.92 0.90 , 0.94 0.000
0.80 0.81
0.92
1

Figure 1

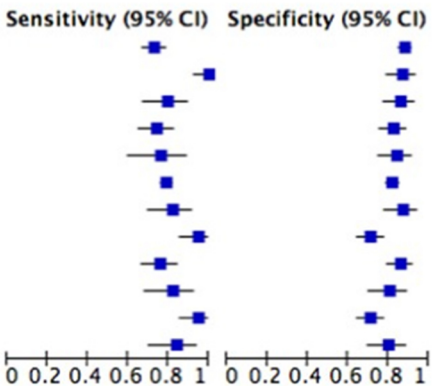
**Pd/Pa**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Henningan | 82 | 25 | 27 | 123 | 0.75 [0.66, 0.83] | 0.83 [0.76, 0.89] |
| Israeli | 41 | 14 | 10 | 76 | 0.80 [0.67, 0.90] | 0.84 [0.75, 0.91] |
| Jeremias | 698 | 80 | 214 | 601 | 0.77 [0.74, 0.79] | 0.88 [0.86, 0.91] |
| Leone | 301 | 162 | 45 | 514 | 0.87 [0.83, 0.90] | 0.76 [0.73, 0.79] |
| Shiode | 40 | 17 | 4 | 62 | 0.91 [0.78, 0.97] | 0.78 [0.68, 0.87] |




**iFR**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Escaned | 178 | 53 | 66 | 391 | 0.73 [0.67, 0.78] | 0.88 [0.85, 0.91] |
| Fede | 46 | 13 | 0 | 87 | 1.00 [0.92, 1.00] | 0.87 [0.79, 0.93] |
| Harle | 47 | 13 | 12 | 80 | 0.80 [0.67, 0.89] | 0.86 [0.77, 0.92] |
| Henningan | 81 | 26 | 28 | 122 | 0.74 [0.65, 0.82] | 0.82 [0.75, 0.88] |
| Indolfi | 29 | 14 | 9 | 74 | 0.76 [0.60, 0.89] | 0.84 [0.75, 0.91] |
| Jeremias | 735 | 121 | 196 | 542 | 0.79 [0.76, 0.82] | 0.82 [0.79, 0.85] |
| Kanaji | 46 | 10 | 10 | 68 | 0.82 [0.70, 0.91] | 0.87 [0.78, 0.94] |
| Musto | 54 | 58 | 3 | 143 | 0.95 [0.85, 0.99] | 0.71 [0.64, 0.77] |
| Park | 76 | 19 | 24 | 117 | 0.76 [0.66, 0.84] | 0.86 [0.79, 0.91] |
| Rivero | 37 | 15 | 8 | 62 | 0.82 [0.68, 0.92] | 0.81 [0.70, 0.89] |
| Scarsini | 54 | 58 | 3 | 143 | 0.95 [0.85, 0.99] | 0.71 [0.64, 0.77] |
| Shiode | 37 | 16 | 7 | 64 | 0.84 [0.70, 0.93] | 0.80 [0.70, 0.88] |




**cFFR**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Johnson 2016 | 284 | 18 | 91 | 370 | 0.76 [0.71, 0.80] | 0.95 [0.93, 0.97] |
| Kanaji | 48 | 6 | 3 | 65 | 0.94 [0.84, 0.99] | 0.92 [0.83, 0.97] |
| Leone | 308 | 68 | 46 | 698 | 0.87 [0.83, 0.90] | 0.91 [0.89, 0.93] |
| Van Wyk | 35 | 3 | 1 | 74 | 0.97 [0.85, 1.00] | 0.96 [0.89, 0.99] |

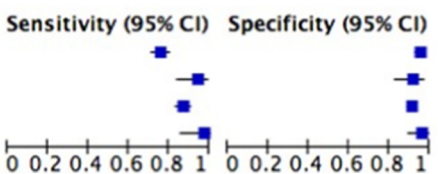



Figure 2