JAMA Cardiology | Review

Diagnostic Accuracy of Computed Tomography–Derived Fractional Flow Reserve
A Systematic Review

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IMPORTANCE Computed tomography–derived fractional flow reserve (FFR-CT) is a novel, noninvasive test for myocardial ischemia. Clinicians using FFR-CT must be able to interpret individual FFR-CT results to determine subsequent patient care.

OBJECTIVE To provide clinicians a means of interpreting individual FFR-CT results with respect to the range of invasive FFRs that this interpretation might likely represent.

EVIDENCE REVIEW We performed a systematic review in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A systematic search of MEDLINE (January 1, 2011, to 2016, week 2) and EMBASE (January 1, 2011, to 2016, week 2) was performed for studies assessing the diagnostic accuracy of FFR-CT. Title words used were *computed tomography* or *computed tomographic* and *fractional flow reserve* or *FFR*. Results were limited to publications in peer-reviewed journals. Duplicate studies and abstracts from scientific meetings were removed. All of the retrieved studies, including references, were reviewed.

FINDINGS There were 908 vessels from 536 patients in 5 studies included in the analysis. A total of 365 (68.1%) were male, and the mean (SD) age was 63.2 (9.5) years. The overall per-vessel diagnostic accuracy of FFR-CT was 81.9% (95% CI, 79.4%-84.4%). For vessels with FFR-CT values below 0.60, 0.60 to 0.70, 0.70 to 0.80, 0.80 to 0.90, and above 0.90, diagnostic accuracy of FFR-CT was 86.4% (95% CI, 78.0%-94.0%), 74.7% (95% CI, 71.9%-77.5%), 46.1% (95% CI, 42.9%-49.3%), 87.3% (95% CI, 85.1%-89.5%), and 97.9% (95% CI, 97.9%-98.8%), respectively. The 82% (overall) diagnostic accuracy threshold was met for FFR-CT values lower than 0.63 or above 0.83. More stringent 95% and 98% diagnostic accuracy thresholds were met for FFR-CT values lower than 0.53 or above 0.93 and lower than 0.47 or above 0.99, respectively.

CONCLUSIONS AND RELEVANCE The diagnostic accuracy of FFR-CT varies markedly across the spectrum of disease. This analysis allows clinicians to interpret the diagnostic accuracy of individual FFR-CT results. In combination with patient-specific factors, clinicians can use FFR-CT to judge when the cost and risk of an invasive angiogram may safely be avoided.

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N oninvasive computed tomography–derived fractional flow reserve (FFR-CT) is a novel technique for determining the physiologic significance of coronary artery stenoses.[1] Computational fluid dynamics modeling permits per-vessel estimation of functional data (FFR) from a purely anatomic data set (CT coronary angiogram images).[2]

Computed tomography–derived fractional flow reserve has rapidly progressed past the proof-of-concept stage and was recently approved for clinical use by the US Food and Drug Administration and the European Medicines Agency based on its overall diagnostic accuracy compared with invasive FFR measurement.[3] The technique has even been extended to virtual stenting and treatment planning to determine optimal revascularization strategies before invasive procedures.[4]

Therefore, FFR-CT represents a powerful new diagnostic tool, and it is widely considered to be of potential great importance in the field.[5] However, a clinician reading the diagnostic accuracy results of the landmark FFR-CT studies does not immediately gain an appreciation of how to interpret an individual FFR-CT result that is received in clinical practice during clinical decision making.[6] Although knowing the overall diagnostic accuracy of FFR-CT is reassuring, in fact, the clinician knows not only whether the FFR-CT is positive or negative but also its specific value.

In this study, we set out to provide clinicians with a means of interpreting individual FFR-CT results with respect to the range of invasive FFRs that these values might likely represent and how confident the clinician can be that the findings are on a particular side of a clinical decision-making threshold.

Methods

Search Strategy

We performed a systematic review in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[7] A systematic search of MEDLINE (2011-2016, week 2) and EMBASE (2011-2016, week 2) was performed for studies assessing the diagnostic accuracy of FFR-CT. Title words used were *computed tomography* or *computed tomographic* and *fractional flow reserve* or *FFR*. Results were limited to publications in peer-reviewed journals. Duplicate studies and abstracts from scientific meetings were removed. Two independent investigators (C.M.C. and Y.A.) reviewed all of the retrieved studies, including references. Inclusion criteria were (1) assessment of the diagnostic performance of FFR-CT compared with invasive FFR as the standard procedure, (2) blinded analyses, and (3) per-vessel data displayed in either a scatterplot or Bland-Altman plot of agreement between FFR-CT and invasive FFR values.

Quality Assessment of Diagnostic Accuracy Studies

Included studies were analyzed using the Quality Assessment of Diagnostic Studies–2 tool.[8] This tool is designed specifically to assess diagnostic accuracy studies. Risk of bias and applicability of findings are evaluated across 4 domains: patient selection, index test, reference standard, and flow and timing. Risk of bias or concerns regarding applicability are rated as low, high, or unclear. This assessment was performed and checked by 2 authors (C.M.C. and Y.A.).

Key Points

Question How should clinicians interpret individual computed tomography–derived fractional flow reserve results received in clinical practice?

Findings In this systematic review that included 908 vessels in 536 patients, the overall diagnostic accuracy of computed tomography–derived fractional flow reserve was 81.9%. However, over narrower ranges of disease severity, diagnostic accuracy of computed tomography–derived fractional flow reserve was lower in the middle ranges of the values.

Meaning The diagnostic accuracy of computed tomography–derived fractional flow reserve is high at extremes of disease severity but is considerably weaker in the more intermediate forms of disease that form most of real-world clinical cases.

Vessel-Level Systematic Review

From the included studies, to permit a vessel-level systematic review, data were digitized from scatterplot and Bland-Altman plot using semiautomatic bitmap-to-digital software (Matlab, version 6.0; MathWorks Inc). Digitized FFR-CT and FFR values were rounded to 2 decimal places. The FFR-CT and invasive FFR values were dichotomized using 0.80 or less as the cut point for ischemia for both methods. Invasive FFR was used as the reference standard. Diagnostic accuracy was determined as a percentage value by binary FFR-CT predicting binary invasive FFR.

Tool for Interpreting Noninvasive FFR-CT Values

A clinician receiving a noninvasive FFR-CT result may be interested to know the distribution of likely invasive FFRs that the finding may represent. We calculated this distribution as a histogram of the invasive FFRs corresponding to bands of FFR-CT values, such as 0.60 to 0.69, 0.70 to 0.79, and 0.80 to 0.89. Values of 0.60 or lower were infrequent and therefore merged into a single band.

To determine the dichotomous accuracy (above vs below the cut point), we also calculated the diagnostic accuracy for each FFR-CT value across the clinical spectrum of FFR-CT values. This calculation was achieved by performing 2 logistical regressions superimposed on a single plot to ascertain the probability that both FFR-CT and invasive FFR agreed on the functional classification of a stenosis for any given individual FFR-CT value.

Assessing the Influence of FFR-CT Algorithm Versions

To determine whether the FFR-CT software algorithm versions influenced diagnostic performance, we compared FFR-CT diagnostic accuracy in subgroups using the oldest (HeartFlow, version 1.0; HeartFlow Inc) and newest (HeartFlow, version 1.4) FFR-CT software algorithms.

Statistical Analysis

Categorical variables are presented as frequency, and percentage and continuous variables are reported as mean (SD). Tests of normality were first performed using the Shapiro-Wilk test. Continuous variables were compared with paired, 2-tailed *t* tests or Mann-Whitney tests and categorical variables with χ^2 or Fisher exact tests, as appropriate. Pearson correlation and linear regression analysis

were conducted to determine the association between FFR-CT and FFR values. Bland-Altman analysis was performed to assess the degree of agreement between FFR-CT and FFR. Reproducibility of the digitization method was assessed by calculating the SD of difference between values extracted with repeat, independent digitizations. Statistical analyses were performed using the statistical environment R, version 0.98.1091 (R Foundation) with the *ggplot2* package. For all tests, $P < .05$ was considered significant.

Results

Study and Patient Characteristics
Our search strategy is outlined in **Figure 1**. A total of 5 studies consisting of 908 vessels in 536 patients met the inclusion criteria, including the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps study by Nørgaard et al[9] that used the most up-to-date computational fluid dynamics software (HeartFlow, version 1.4) for FFR-CT. Regarding the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (De-FACTO) study population, because Min et al[10] did not display any data in the form of either scatterplot or Bland-Altman plot, the De-FACTO substudy by Nakazato et al 2013[11] was used instead (**Table**). The mean (SD) age was 63.2 (9.5) years, 68.1% of the patients were male, 67.9% (364 of 536) had hypertension, and 24.4% (131 of 536) had diabetes.

The quality assessment as per the Quality Assessment of Diagnostic Studies–2 tool is represented in eFigure 1 in the Supplement. Generally, there was low risk of bias and low concerns regarding applicability of all included studies.

### Distribution of FFR-CT and Invasive FFR Values
The distributions of FFR-CT and FFR values are shown in eFigure 2 in the Supplement. Median and interquartile range of FFR-CT and FFR were 0.86 (0.76-0.91) and 0.88 (0.79-0.94), respectively, in-

dicating a predominantly mild cohort of disease severities. A significant difference in median FFR values was noted between FFR-CT and invasive FFR modalities ($P < .001$). Among the 908 vessels assessed, 320 (35.2%) were classified ischemic by FFR-CT, whereas 244 (26.9%) were classified ischemic by FFR.

Overall Measures of FFR-CT Diagnostic Performance
Using the invasive FFR threshold of 0.80 or less, the overall diagnostic accuracy of FFR-CT was 81.9% (95% CI, 79.4%-84.4%). For vessels with FFR-CT values below 0.60, 0.60 to 0.70, 0.70 to 0.80, 0.80 to 0.90, and above 0.90, diagnostic accuracy of FFR-CT was 86.4% (95% CI, 78.0%-94.0%), 74.7% (95% CI, 71.9%-77.5%), 46.1% (95% CI, 42.9%-49.3%), 87.3% (95% CI, 85.1%-89.5%), and

Figure 1. Diagram of the Review Process
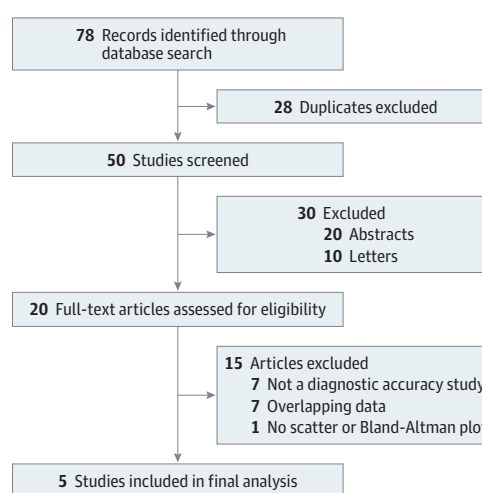
Of the 78 records identified, 5 studies were included for analysis.

Table. Included Study Characteristics

Characteristic	Study[a]				
	Koo et al[12,b]	Nakazato et al[11,c]	Kim et al[4]	Renker et al[13]	Nørgaard et al[9,d]
Study					
Year	2011	2013	2014	2014	2014
Design	Prospective, multicenter	Prospective, multicenter	Prospective, multicenter	Retrospective, single center	Prospective, multicenter
Patients, No.	103	82	44	53	254
Vessels, No.	159	150	48	67	484
CFD software	HeartFlow, version 1.0	HeartFlow, version 1.2	HeartFlow, version 1.0	Siemens cFFR, version 1.4	HeartFlow, version 1.4
Patient Baseline					
Age, mean (SD), y	62.7 (8.5)	63 (8)	65 (9.1)	61.2 (12)	64 (10)
Male, No. (%)	74 (72)	60 (73)	35 (80)	34 (64)	162 (64)
HTN, No. (%)	67 (65)	56 (68)	36 (81)	31 (54)	174 (69)
Smoking, No. (%)	24 (36)	12 (15)	NR	8 (14)	16 (18)
Diabetes, No. (%)	26 (26)	16 (20)	13 (29)	18 (32)	58 (23)
Previous MI, No. (%)	17 (17)	5 (6)	5 (10)	NR	5 (2)
BMI, mean (SD)	25.8 (3.5)	NR	24.4 (2.6)	28.9 (6.5)	26 (3)
Previous PCI, No. (%)	16 (16)	8 (10)	NR	9 (16)	NR

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CFD, computational fluid dynamics; FFR, fractional flow reserve; HTN, hypertension; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention.

[a] Percentages reported as in original studies.

[b] Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve.

[c] Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography substudy.

[d] Analysis of Coronary Blood Flow Using CT Angiography: Next Steps.

Figure 2. Scatterplot Showing the Overall Association Between Computed Tomography–Derived Fractional Flow Reserve (FFR-CT) and FFR
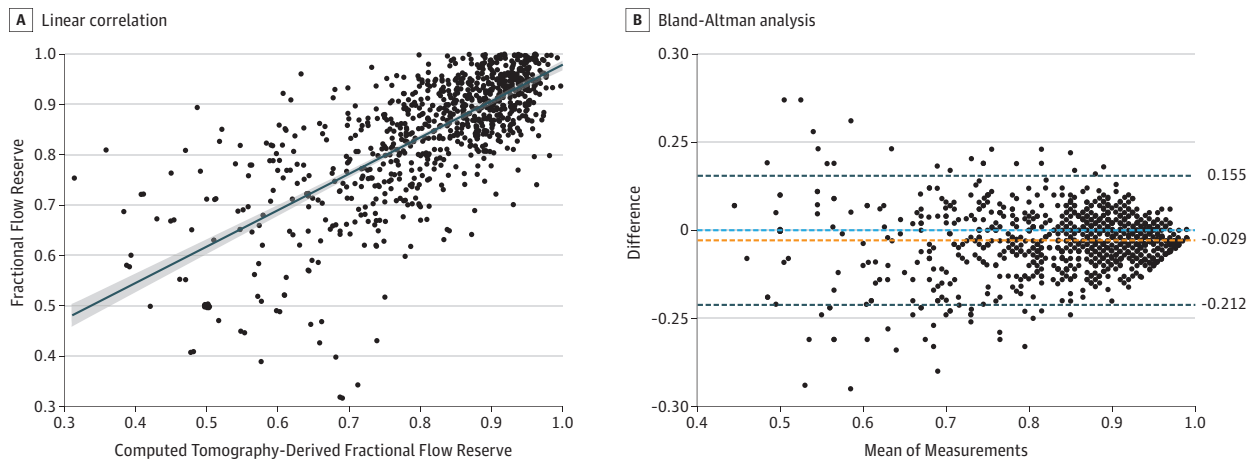
A, The solid blue line represents the line of best fit between FFR-CT and FFR. The gray shaded area represents the 95% CI for the line of best fit; $r^2 = 0.54$; 95% CI, 0.50-0.58; $P < .001$. B, Bland-Altman plot of differences against the means for FFR. The zero line is displayed in red. The mean bias is represented by the solid blue line (with the 95% CI represented by the dashed blue lines).

97.9% (95% CI, 97.0%-98.8%), respectively. The linear correlation between the FFR-CT and FFR was 0.73 ($r^2 = 0.54$; 95% CI, 0.50-0.58; $P < .001$) (**Figure 2**A).

The scatterplot demonstrated significant heteroscedasticity, with significantly greater scatter between FFR-CT and invasive FFR values below 0.80 ($P < .001$). Bland-Altman analysis demonstrated a small bias toward underestimation of invasive FFR by FFR-CT (bias, −0.029 [0.09]; $P < .001$), with 95% limits of agreement ranging from −0.212 to 0.155 (**Figure 2**B).

Interpreting FFR-CT Values in Terms of Corresponding Invasive FFR Values

The distribution of likely invasive FFR values per 0.1-U FFR-CT value range is displayed in **Figure 3**. The preponderance of functionally mild stenoses is illustrated by the greatest frequency of values within the FFR-CT 0.9 to 1.0 range.

The histogram bars are colored according to the invasive FFR of 0.80 or lower cut point for functional significance. However, because the entire distribution of invasive FFR values is displayed, clinicians may apply any alternative invasive FFR threshold that they believe to be clinically appropriate (eg, FFR<0.75).

Interpreting the Diagnostic Accuracy of Individual FFR-CT Values in Clinical Practice

The diagnostic accuracy of FFR-CT per each 0.1-U FFR-CT value range is listed in the eTable in the Supplement. Very mild FFR-CT values (>0.90) provided almost complete certainty that the invasive FFR was negative for ischemia (264 of 270 [97.8%]). Similarly, very severe FFR-CT values (≤0.60) provided a high degree of certainty that the invasive FFR was positive for ischemia (63 of 72 [87.5%]), albeit with fewer data points available for analysis at low FFR-CT values. However, nearer the cut point, there was less certainty, with classification agreement between invasive FFR and FFR-CT at its lowest in the FFR-CT 0.7 to 0.8 range.

To determine the diagnostic accuracy for any given FFR-CT result received in clinical practice, logistical regressions were per-formed to ascertain the probability that both FFR-CT and invasive FFR agreed on the functional classification of a stenosis for any given individual FFR-CT value (**Figure 4**A). Using this approach, the overall 81.9% diagnostic accuracy threshold was met for FFR-CT values lower than 0.63 or higher than 0.83 (Figure 4B). The application of more stringent 95% and 98% diagnostic accuracy thresholds, which some clinicians may wish to apply, was met for FFR-CT values lower than 0.53 or higher than 0.93 and lower than 0.47 or higher than 0.99, respectively.

The Influence of Software Algorithm Versions on the Diagnostic Accuracy of FFR-CT

The FFR-CT values were calculated in a total of 207 vessels (147 patients) using the earliest FFR-CT software algorithm (HeartFlow, version 1.0) and 484 vessels (254 patients) using the most recent FFR-CT software algorithm (HeartFlow, version 1.4). Overall diagnostic accuracy was numerically higher with the most recent software (86.2% vs 80.7%; $P = .07$). The comparative diagnostic performance of earliest and latest FFR-CT algorithm versions is displayed in eFigure 3 in the Supplement.

Discussion

In the present study, we performed a systematic review of the diagnostic performance of FFR-CT for the identification and exclusion of ischemia-causing lesions compared with invasive FFR as the reference standard. The individual vessel data from 908 vessels show the situations in which FFR-CT is helpful to clinicians in determining noninvasively whether invasive FFR results would be positive.

### Practical Information of FFR-CT Value for Clinicians

The number of noninvasive tests with direct comparison with invasive FFR is limited, and the FFR-CT data within this systematic review represent a large experience. In this study, for vessels with

Figure 3. Likely Invasive Fractional Flow Reserve (FFR) Values in Terms of Noninvasive Computed Tomography–Derived FFR (FFR-CT)
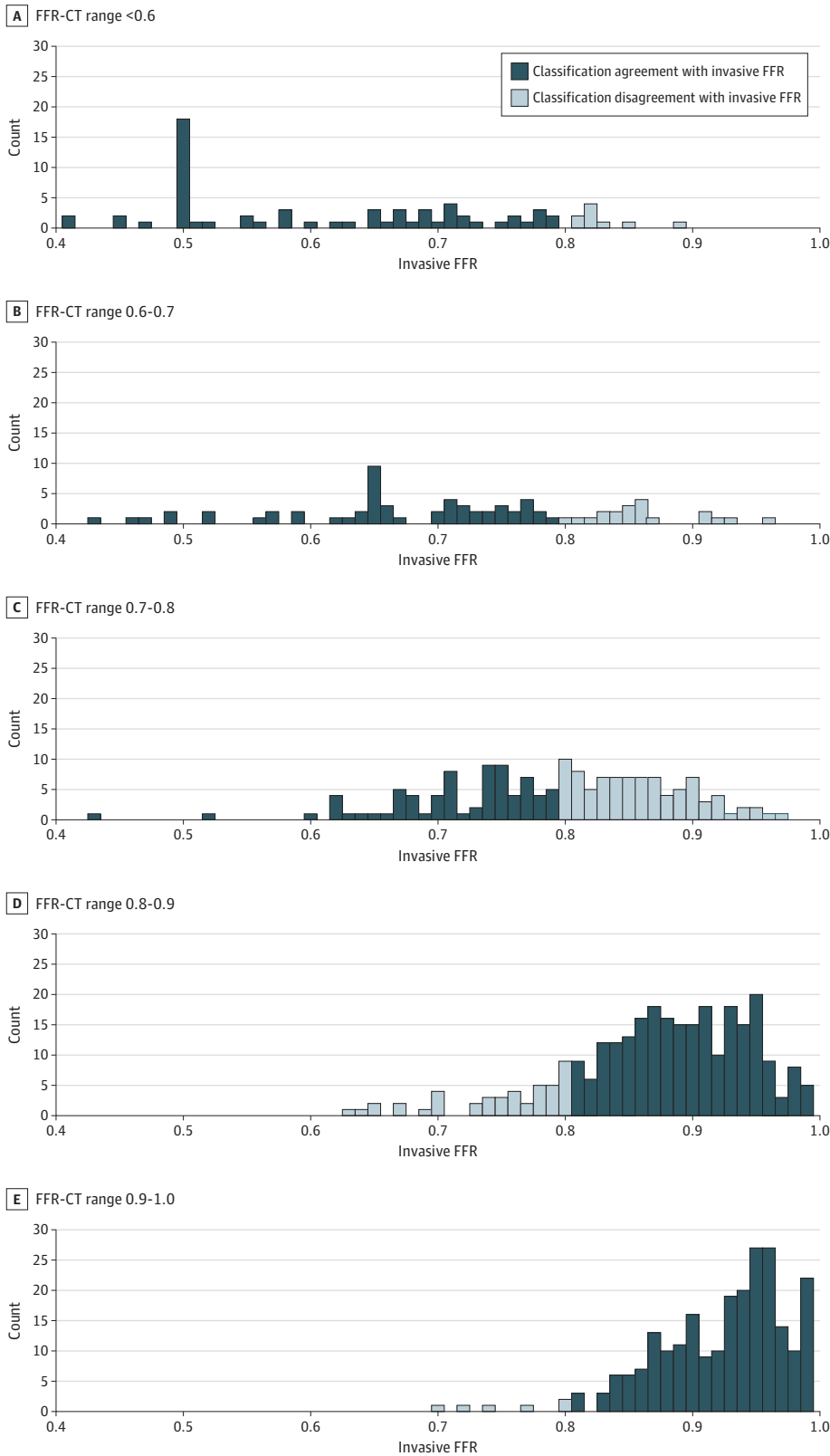
Distributions of the invasive FFRs corresponding to bands of FFR-CT values. Diagnostic accuracy (above vs below the FFR≤0.80 cut point) is displayed for these bands of FFR-CT values.

Figure 4. Diagnostic Accuracy of Individual Computed Tomography–Derived Fractional Flow Reserve (FFR-CT) Results Received in Clinical Practice
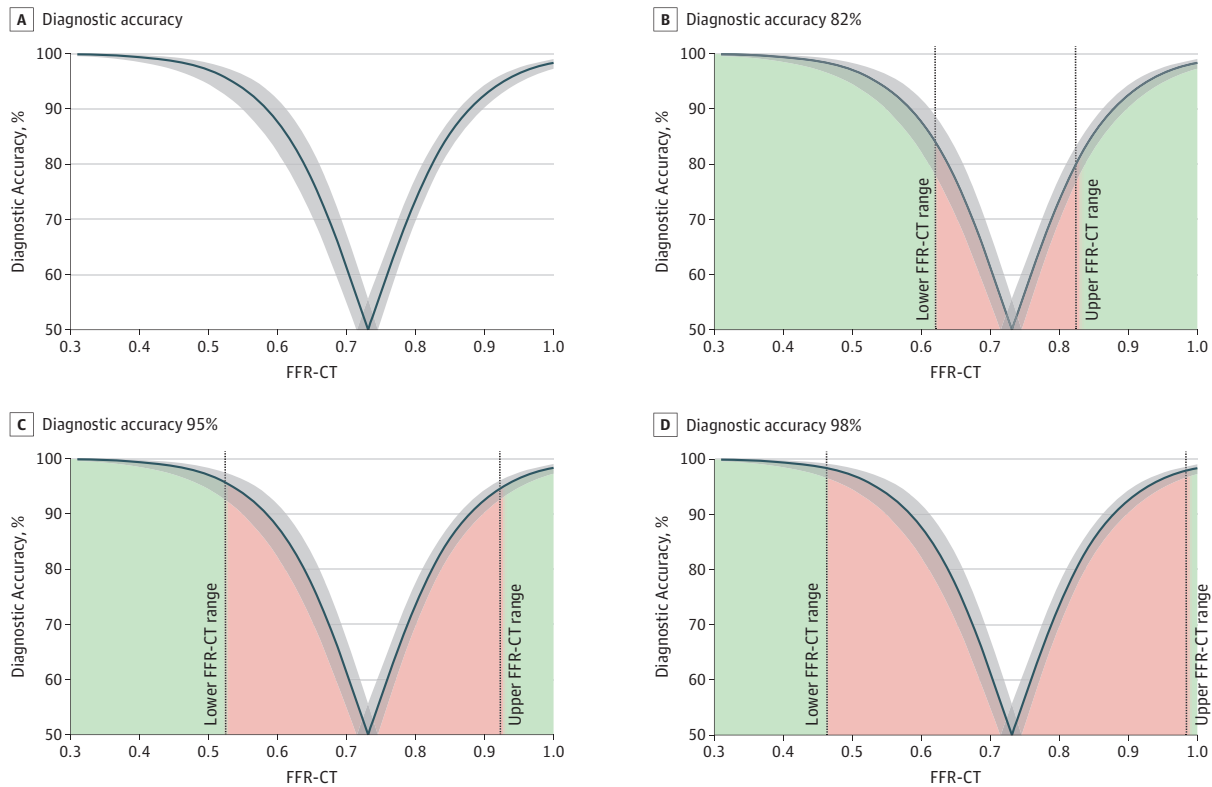
A, The solid blue line reveals the level of agreement (ie, diagnostic accuracy) between FFR-CT and invasive FFR across the clinical range of FFR-CT values. Agreement between FFR-CT and invasive FFR values was considered when both were below, equal to, or above the established cutoff value of 0.80. B, This panel demonstrates the range of FFR-CT values that meet the 82% overall diagnostic certainty threshold for agreement with invasive FFR measurement. C and D, These panels demonstrate the ranges of FFR-CT values that meet 95% and 98%, respectively, diagnostic certainty thresholds for agreement with invasive FFR measurement.

FFR-CT values above 0.90, 97.9% met the invasive FFR guideline criterion for deferral (FFR>0.80). At the other end of the spectrum, for vessels with FFR-CT values below 0.60, 86.4% met the invasive FFR guideline criterion for stenting (FFR≤0.80). In between, FFR-CT gave less certainty as to whether the invasive FFR will meet the stenting criterion (Figure 3). Figure 4A presents the diagnostic accuracy for any individual FFR-CT result that may be received in clinical practice if more fidelity is required. Clinicians and patients alike can balance the degree of uncertainty against the need for invasive confirmation of ischemia as well as determine the range of FFR-CT values in which acceptable levels of diagnostic accuracy are met (Figures 4B-4D).

From the Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME)[14] and FAME II[15] studies, the combined prevalence of angiographically intermediate lesions (50%-70% stenosis) was 46.8%. From the DEFER study[16] and the clinical ADVISE Registry,[17] the respective prevalence of physiologically intermediate lesions (FFR, 0.70-0.80) was 46.3% and 71.2%. However, in the studies of FFR-CT eligible for our analysis, median invasive FFR was 0.88, and the prevalence of physiologically intermediate stenoses was just 12.8% (116 of 908). This low prevalence indicates a substantially milder disease population than that of the pioneering studies of visually moderate lesions of uncertain ischemia significance,

in which the mean FFR values were 0.71[14] and 0.64.[15] Therefore, the clinical FFR-CT trials happened to have focused on patients who, having milder disease, have a greater chance to benefit from a reliable noninvasive screening test.

The Clinical Impact of FFR-CT

Our analysis is consistent with the findings of the 2015 Prospective Longitudinal Trial of FFR(CT): Outcome and Resource Impacts study,[18] which compared an FFR-CT–based strategy with a usual-care strategy in patients with suspected coronary artery disease. The FFR-CT strategy allowed more than half of patients who would otherwise have had invasive coronary angiography to avoid the procedure and showed that these individuals did not later develop complications. Clinicians seeking to replicate this valuable utility in day-to-day practice should focus on applying FFR-CT in patients whose coronary arteries are likely to be minimally diseased or normal.

Using FFR-CT to Guide Clinical Decisions

The results of this study assist the clinician in practice because the FFR-CT test provides a numeric value and not just a dichotomous status. Across 908 vessels included in this systematic review, we now have a more complete picture of what different levels of FFR-CT mean in terms of invasive FFR. There need not be a single cutoff level

in FFR-CT in deciding whether invasive coronary angiography is needed because individual patients present with different clinical scenarios. If a patient is asymptomatic, the patient and clinician might be willing to stop investigations at an FFR-CT that left a substantial possibility of positive results of an invasive FFR. However, if the patient is symptomatic, the patient and clinician would likely pursue invasive angiography unless the possibility of a positive FFR is very remote. Viewing the histogram of invasive FFRs corresponding to the observed FFR-CT (Figure 2) and the diagnostic accuracy of individual FFR-CT values (Figure 3) may be helpful to patient and clinician alike.

Like almost any biological variable, FFR is not absolutely reproducible. No pair of tests can agree better than the individual tests agree with themselves. The FFR-CT trials do not appear to have reported any test-retest variability data on FFR; therefore, such data could not be quantitatively built into our analysis. In place of these data, the diagnostic accuracy of FFR-CT plotted in combination with the reproducibility of invasive FFR measurements is presented in eFigure 4 in the Supplement. Finally, due to the significant scatter and poor numeric match of FFR-CT and invasive FFR values below the 0.80 treatment threshold, the proposed extended application of FFR-CT to virtual stenting and noninvasive revascularization planning currently seems implausible.

Limitations

The FFR-CT and invasive FFR data points were extracted from scatterplots from studies using digitization software. We tested for digitization error using blinded test-retest reproducibility of the digitization process. The SD of difference between repeat digitizations was 0.00 (to 2 decimal places) for both the FFR-CT and FFR values.

The 2012 DeFACTO study was excluded from our analysis because a lack of either a scatterplot or Bland-Altman plot prevented digitization and extraction of individual data points for analysis. However, we were able to include the 2013 DeFACTO substudy by Nakazato et al.[11] This analysis consisted of coronary lesions of intermediate severity—the most representative patient cohort in real-world clinical practice.

In the studies included in our analysis, some patients (eg, 10.0%[18] or 13.0%[9]) were excluded after a CT was performed because the images were judged as not suitable for FFR-CT computation. Projecting to real-world practice, the utility of an FFR-CT strategy might be a little lower than illustrated in Figure 4. Technology and clinical protocols for FFR-CT may continue to improve in years to come.

Our analysis colors the invasive FFR histogram bars in the manner specified in the guidelines[19,20] by dichotomously separating those above and below 0.80. Using the 0.80 cutoff level may not be applicable to FFR-CT technology since an entirely new cutoff level may be appropriate. Some clinicians also consider there to be a gray zone in invasive FFR values, for example, 0.75 to 0.80. Johnson et al[21] have identified an optimal composite of death, myocardial in-

farction, and revascularization threshold in FFR of 0.67. However, leaders of interventional cardiology have stated definitively that there is no gray zone,[22] and no gray zone appears in the guidelines or the individual trials.[14,19,20,23] With such a plethora of proposed thresholds, presenting the data explicitly as a histogram, as in Figure 3, allows clinicians to apply their own preferred system of interpretation.

A net reclassification analysis is an additional method of characterizing the clinical utility of FFR-CT; however, in the absence of FFR-CT value-specific patient outcomes, such an analysis is not currently possible. Future studies of the diagnostic performance of FFR-CT may wish to determine individualized outcomes (with accompanying reference to both the invasive FFR and FFR-CT values) to perform net reclassification analyses.

Our analysis of FFR-CT diagnostic accuracy was performed at the per-vessel level owing to the included studies reporting only individual data points on a per-vessel basis. Future primary trials might be better to present per-patient analyses or publish supplementary data in tabular form (ie, the most severe FFR-CT value in the patient and the most severe invasive FFR).

Our per-vessel analysis was unable to determine whether vessel type or stenosis location within the vessel influenced the diagnostic accuracy of the FFR-CT measurement. Although some of the studies reported study population vessel characteristics, none of the data points were stratified in this manner.

For clinicians mindful of the additional cost of FFR-CT above that of plain coronary CT angiography, it may be useful to depict the added diagnostic value of FFR-CT over plain CT angiography in the manner shown in Figure 4A. However, because none of the included studies reported the individual data for plain CT angiography results vs invasive FFR, such an analysis is not possible.

Finally, because the most widely used FFR-CT algorithm is proprietary and confidential, it is not apparent at which point in the vessel the estimated FFR value was measured. An important implication of this lack of information is that, if the FFR-CT was attempting to give a value so distal in the vessel that it could not be stented, the invasive FFR measurement process may not have advanced the wire that far and therefore may have reported a less severe value. As newer imaging algorithms arise and potentially become available for inspection and improvement, this problem should resolve.

Conclusions

The diagnostic accuracy of FFR-CT varies markedly across the spectrum of disease. This analysis allows clinicians to interpret the diagnostic accuracy of any individual FFR-CT result that may be received in clinical practice. With this information in combination with patient-specific factors, clinicians can use FFR-CT to judge when the cost and risk of an invasive angiogram may safely be avoided.

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