

Computed Tomography-Derived Fractional Flow Reserve in the Detection of Lesion-Specific Ischemia

An Integrated Analysis of 3 Pivotal Trials

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Abstract: Invasive fractional flow reserve (FFR) is the gold standard for the determination of physiologic stenosis severity and the need for revascularization. FFR computed from standard acquired coronary computed tomographic angiography datasets (FFR_{CT}) is an emerging technology which allows calculation of FFR using resting image data from coronary computed tomographic angiography (CCTA). However, the diagnostic accuracy of FFR_{CT} in the evaluation of lesion-specific myocardial ischemia remains to be confirmed, especially in patients with intermediate coronary stenosis. We performed an integrated analysis of data from 3 prospective, international, and multicenter trials, which assessed the diagnostic performance of FFR_{CT} using invasive FFR as a reference standard. Three studies evaluating 609 patients and 1050 vessels were included. The total calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FFR_{CT} were 82.8%, 77.7%, 60.8%, 91.6%, and 79.2%, respectively, for the per-vessel analysis, and 89.4%, 70.5%, 69.7%, 89.7%, and 78.7%, respectively, for the per-patient analysis. Compared with CCTA alone, FFR_{CT} demonstrated significantly improved accuracy ($P < 0.001$) in detecting lesion-specific ischemia. In patients with intermediate coronary stenosis, FFR_{CT} remained both highly sensitive and specific with respect to the diagnosis of ischemia. In conclusion, FFR_{CT} appears to be a reliable noninvasive alternative to invasive FFR, as it demonstrates high accuracy in the determination of anatomy and lesion-specific ischemia, which justifies the performance of additional randomized controlled trials to evaluate both the clinical benefits and the cost-effectiveness of FFR_{CT}-guided coronary revascularization.

(*Medicine* 94(46):e1963)

Abbreviations: CAD = coronary artery disease, CCTA = coronary computed tomographic angiography, CI = confidence interval, FFR = fractional flow reserve, FFR_{CT} = fractional flow reserve computed from standard acquired coronary computed tomographic angiography dataset, ICA = invasive coronary angiography, NPV = negative predictive value, PPV = positive predictive value.

Editor: Hoefler Imo.

Received: July 26, 2015; revised: October 9, 2015; accepted: October 13, 2015.

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The authors have no funding and conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001963

INTRODUCTION

Invasive coronary angiography (ICA) has served as the gold standard for the diagnosis of coronary artery disease (CAD).¹ However, ICA provides only anatomic information and cannot assess physiological severity. Fractional flow reserve (FFR), an invasive index measured using a coronary pressure wire at the time of ICA, is commonly used in clinical practice to determine the hemodynamic significance of coronary stenosis.^{2,3} Compared with angiographic guidance, FFR-guided revascularization improves event-free survival and decreases medical costs.^{4–6} However, the routine use of ICA and FFR is not easy, nor is it without risk, as such usage increases case complexity and may also increase the risk of catheter-related complications, including bleeding, arrhythmia, stroke, coronary artery perforation, and dissection.⁷

Given its high sensitivity and negative predictive value (NPV), coronary computed tomographic angiography (CCTA) has become a useful noninvasive alternative to ICA and has been increasingly utilized in the clinic to diagnose and rule-out CAD.⁸ However, CCTA tends to overestimate the severity of coronary artery stenosis, as only a minority of lesions identified by CCTA have been found to cause cardiac ischemia. Moreover, the presence of motion artifacts, calcified plaque, stents, and limited spatial resolution may severely compromise anatomical evaluations performed using CCTA.⁹ The suboptimal specificity and positive predictive value (PPV) of CCTA in diagnosing CAD may encourage the unnecessary use of ICA and coronary revascularization. FFR computed from standard acquired CCTA datasets (FFR_{CT}) is a novel noninvasive method of assessing lesion-specific ischemia, as it utilizes the computational fluid dynamics of CCTA and has enabled the calculation of FFR values without the use of additional medication, image acquisition techniques, or radiation exposure.^{10,11} The diagnostic accuracy of noninvasive FFR_{CT} has been evaluated in recent 3 prospective, multicenter studies.^{12–14} However, the diagnostic performance of FFR_{CT} in the identification or exclusion of functionally significant coronary stenosis using measured FFR as the reference standard remains controversial, especially in patients with intermediate coronary stenosis, wherein the clinical utility of FFR_{CT} would be most commonly expected for use. The aim of this integrated analysis of the 3 studies was to further investigate the diagnostic efficacy of FFR_{CT}, particularly on in subgroup with intermediate stenosis.

METHODS

Search Strategy and Eligibility Criteria

A literature search was performed using the Cochrane Library, PubMed, OVID, and EMBASE to identify articles published through October 2014. Complex search strategies were formulated using the following MESH terms and text

words: fractional flow reserve, FFR, computed tomography, CT, coronary computed tomographic angiography, CCTA, coronary CTA, CTA, noninvasive FFR and FFR_{CT}. To identify any studies missed by the literature searches, we hand-searched reference lists of eligible studies and relevant review articles. We included studies where the following criteria were met: the study population included ≥ 10 patients with either suspected or known CAD; the diagnostic performance of FFR_{CT} was evaluated using invasive FFR as the reference standard; and the study allowed for sensitivity, specificity, NPV, and PPV calculations. Trials were excluded if they did not conform to the above criteria, or if there were overlapping study subjects. Finally, The DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve), DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography), and NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) studies were included.^{12–14}

Study Design

The DISCOVER-FLOW, DeFACTO, and NXT studies were prospective, international, multicenter trials designed to investigate the diagnostic accuracy of FFR_{CT} for the discrimination of hemodynamically significant CAD, when compared to invasive FFR as the reference standard.^{12–14} These studies were registered with ClinicalTrials.gov (identifiers NCT01189331, NCT01233518, and NCT01757678). The methodological characteristics of the selected studies are shown in Table 1. The DISCOVER-FLOW was conducted at 4 centers in 3 countries (South Korea [2], Latvia [1], and the United States [1]). The DeFACTO was conducted at 17 centers in 5 countries (Belgium [n = 1], Canada [n = 1], Latvia [n = 1], South Korea [n = 2], and the United States [n = 12]). The NXT was conducted at 10 centers at 8 countries (Japan [3], Australia [1], England [1], Germany [1], South Korea [1], Scotland [1], Latvia [1], and Denmark [1]). The studies were approved by the institutional review board at each site and all patients provided written informed consent.

FFR_{CT} and FFR Measurement and Integration

In all of the 3 included trials, CCTA was performed by following guidelines with 64- or higher detector row scanners.¹⁵

CCTA images were transmitted to the central cores laboratory for further blinded analysis. Investigators evaluated evaluate luminal diameter stenosis in each segment of the coronary tree with an 18-segment coronary model. CCTA images were also transferred to the FFR_{CT} core laboratory for the computation of FFR_{CT} in blinded fashion. In NXT trials, a predefined image quality score was applied to select cases suitable for FFR_{CT} analysis. Similarly, selective ICA was also performed according to guidelines or standard practice.^{16,17} FFR was measured during ICA. In DISCOVER-FLOW and DeFACTO studies, FFR procedure was performed as clinically indicated, and in NXT study measurement of FFR was performed for each stenosis $\geq 30\%$ in a vessel segment with diameter ≥ 2 mm. Finally, the blinded integration core laboratory identified the location on CCTA that corresponded to the point where the FFR was measured.

Diagnostic Efficacy Analysis

Diagnostic performance of FFR_{CT} was evaluated on a per-vessel as well as per-patient basis. For FFR and FFR_{CT}, hemodynamically significant coronary stenosis was defined as a value ≤ 0.80 . Significant obstruction on CCTA was recorded with stenosis $\geq 50\%$. Diagnostic measures included accuracy, sensitivity, specificity, PPV, NPV, positive likelihood ratio, and negative likelihood ratio. Discrimination was quantified using the area under the receiver operating characteristic curve of FFR_{CT} and CCTA.

Statistical Analysis

We pooled the diagnostic accuracy data of both FFR_{CT} and CCTA from the 3 studies on both a per-vessel and a per-patient basis. In the per-patient analysis, vessels with the most adverse clinical status were selected to represent a given patient. The reported percentages were recalculated and confirmed according to the patient numbers provided in the original publication, using standard formulas.¹⁸ Potential heterogeneity, meaning variation between studies, was evaluated by calculating the I^2 statistic, with a value of 50% or more indicating a substantial level inconsistency. Data with $I^2 \geq 50\%$ were pooled using the DerSimonian–Laird model, whereas data with $I^2 < 50\%$ were pooled using the Mantel Haenszel model. Comparison of

TABLE 1. Characteristics of the Prospective Studies

	DISCOVER-FLOW	DeFACTO	NTX
Study duration	October 2009 to January 2011	October 2010 to October 2011	September 2012 to August 2013
Investigative sites	3 countries (4 centers)	5 countries (17 centers)	8 countries (10 centers)
Sample size, n	102	252	253
CCTA scanner type	64- or 256-detector CT	64- or higher detector CT	64- or higher detector CT
Radiation dose range, mSv	3.0–15.0	3.0–14.0	3.0–15.0
CCTA prequalification and quality control	No	No	Yes
Blinded integration and computation of FFR, CCTA, and FFR _{CT}	Yes	Yes	Yes
FFR _{CT} software version	V1.2	V1.2	V1.4
Definition of intermediate coronary stenosis	40–69% stenosis	30–70% stenosis	30–70% stenosis

CCTA = coronary computed tomographic angiography, CT = computed tomography, FFR = fractional flow reserve, FFR_{CT} = fractional flow reserve computed from standard acquired coronary computed tomographic angiography datasets.

the diagnostic performances of FFR_{CT} and CCTA was completed using a chi-squared test. The results were considered statistically significant at $P < 0.05$. The integrated analyses were conducted using Stata, version 12 (Stata Corp, College Station, TX). The aggregate results from the studies were summarized as weighted means (95% confidence intervals [CI] reported in the tables and figures). A subgroup analysis was conducted involving patients with intermediate coronary stenosis. In the DISCOVER-FLOW study, intermediate stenosis was defined as a coronary lesion with diameter stenosis ranging from 40% to 69% as determined via CCTA,¹⁹ whereas the range was 30% to 70% in the DeFACTO and NXT studies.^{13,14}

RESULTS

Study Population

A total of 609 subjects (mean age 63.3 ± 9.2 years, male 68%) who underwent CCTA, FFR_{CT}, ICA, and FFR were involved across the 3 studies. The demographic and baseline characteristics of the patients are detailed in Table 2. In DeFACTO and NXT studies, approximately 78% of the patients had experienced angina within the past month. The mean interval between CCTA and ICA plus invasive FFR was 2.3 to 18.0 days. Coronary dissection requiring percutaneous coronary intervention occurred in 2 patients in DeFACTO trial and 1 patient in NXT trial during FFR measurement. Following FFR measurement, 1 patient in DeFACTO trial suffered from retroperitoneal bleeding, and 2 patients in NXT experienced transient cerebral ischemia. No serious adverse complications were observed during examination in DISCOVER-FLOW study.

Diagnostic Accuracy of FFR_{CT} for Detecting Ischemia

A total of 421 vessels and 337 patients were found to have functionally significant coronary stenosis as determined via FFR, or prevalence of 40.1% and 55.3%. Heterogeneities for relative statistics were evaluated in Tables 3 and 4. The per-vessel performances of FFR_{CT} and CCTA are included in Table 3. FFR_{CT} and CCTA demonstrated similar sensitivities (82.8% vs 86.1%, $P = 0.369$) and NPVs (91.6% vs 92.5%, $P = 0.645$). However, there were significant improvements in

specificity (77.7% vs 55.7%, $P < 0.001$), PPV (60.8% vs 38.7%, $P < 0.001$), and accuracy (79.2% vs 63.1%, $P < 0.001$) with the utilization of FFR_{CT}. On a patient-specific basis, the total calculated sensitivities, specificities, PPVs, NPVs, and accuracies for FFR_{CT} and CCTA are included in Table 4. Additional between-group analyses demonstrated that FFR_{CT} exhibited a high per-patient sensitivity compared with CCTA ($P = 0.888$) but also demonstrated significantly increased diagnostic specificity ($P < 0.001$), PPV ($P < 0.001$), NPV ($P = 0.010$), and accuracy ($P < 0.001$) (Fig. 1A–E).

Compared with both the DISCOVER-FLOW and the DeFACTO trials, the FFR_{CT} technology used in the NXT trial was refined.²⁰ Therefore, additional analyses were conducted to determine whether the improvements in FFR_{CT} technology influenced its diagnostic performance. Although there were no significant differences noted in per-patient sensitivity (90.7% vs 86.3%, $P = 0.281$), PPV (71.9% vs 65.1%, $P = 0.209$), NPV (86.3% vs 92.6%, $P = 0.090$), or accuracy (76.9% vs 81.1%, $P = 0.212$) between the integrated results from the DISCOVER-FLOW and the DeFACTO trials compared with the data from the NXT trial, there was a significant increase noted in specificity (62.2% vs 78.7%, $P < 0.001$) with the use of the upgraded FFR_{CT} technology (Figure 1F).

Diagnostic Accuracy of FFR_{CT} for Patients With Intermediate Coronary Stenosis

Of the 609 patients enrolled in the 3 included studies, 378 patients (62.1%) were found to have intermediate coronary stenosis by CCTA. In the DISCOVER-FLOW study, only the per-lesion diagnostic performances of FFR_{CT} and CCTA were reported for the patients with intermediate stenosis. In light of the similar numbers of patients ($n = 60$) and lesions ($n = 66$) with intermediate stenosis in the DISCOVER-FLOW trial, we used the per-lesion diagnostic value instead of the per-patient value for the integrated analysis. When the patient-based analysis was restricted to patients with intermediate stenosis, the combined sensitivity, specificity, PPV, NPV, and accuracy for FFR_{CT} were 85.3% (95% CI: 78.0–90.9), 76.5% (95% CI: 70.8–81.5), 64.7% (95% CI: 57.0–71.9), 91.1% (95% CI: 86.5–94.6), and 79.4% (95% CI: 75.0–83.4), respectively. Consistent with the findings in the general patient population,

TABLE 2. Baseline Demographics and Clinical Characteristics

	DISCOVER-FLOW (n = 103)	DeFACTO (n = 252)	NXT (n = 254)
Mean age (SD), yr	62.7 (8.5)	62.9 (8.7)	64 (10)
Male	74 (72)	178 (70.6)	162 (64)
Hypertension	67 (65)	179 (71.2)	174 (69)
Hyperlipidemia	67 (65)	201 (79.8)	200 (79)
Diabetes	26 (26)	53 (21.2)	58 (23)
Current smoker	24 (23)	44 (17.5)	46 (18)
Patients with intermediate stenosis	60 (58.3)	83 (32.9)	235 (92.5)
Family history of coronary artery diseases	NR	50 (19.9)	NR
Prior myocardial infarction	17 (17)	15 (6.0)	5 (2)
Prior percutaneous coronary intervention	16 (16)	16 (6.3)	0 (0)
Angina within the past month	NR	195 (77.2)	198 (78)
Left ventricular ejection fraction (SD), %	62.3 (5.7)	NR	62 (7)
Creatinine (SD), mg/dL	0.97 (0.18)	NR	0.9 (0.2)
Mean body mass index (SD), kg/m ²	25.8 (3.5)	NR	28 (3)

Values are reported as N (%) unless otherwise indicated. NR = not reported, SD = standard deviation.

TABLE 3. Diagnostic Performance of FFR_{CT} and CCTA for Detection of Lesion-Specific Ischemia on Per-Vessel Basis

Study	Number of Vessels	Sensitivity	Specificity	PPV	NPV	Accuracy
DISCOVER-FLOW	159	51/58 (0.879)	83/101 (0.822)	51/69 (0.739)	83/90 (0.922)	134/159 (0.843)
DeFACTO	407	121/151 (0.801)	160/256 (0.625)	121/217 (0.558)	160/190 (0.842)	281/407 (0.690)
NXT	484	84/100 (0.840)	333/384 (0.867)	84/135 (0.622)	333/349 (0.954)	417/484 (0.862)
Total (95% CI)	1050	0.828 (0.782–0.869)	0.777 (0.746–0.807)	0.608 (0.560–0.655)	0.916 (0.891–0.936)	0.792 (0.767–0.817)
I ² , %	N/A	0.00	96.10	73.90	89.40	66.10
DISCOVER-FLOW	159	53/58 (0.914)	40/101 (0.396)	53/114 (0.465)	40/45 (0.889)	93/159 (0.585)
NXT	484	83/100 (0.830)	230/384 (0.599)	83/237 (0.350)	230/247 (0.931)	313/484 (0.647)
Total (95% CI)	643	0.861 (0.797–0.911)	0.557 (0.511–0.601)	0.387 (0.336–0.441)	0.925 (0.888–0.952)	0.631 (0.593–0.669)
I ² , %	N/A	59.00	92.50	78.50	0.00	0.00

CI = confidence intervals, FFR = fractional flow reserve, FFR_{CT} = fractional flow reserve computed from standard acquired coronary computed tomographic angiography datasets, NPV = negative predictive value, PPV = positive predictive value; other abbreviation as in Table 1.

TABLE 4. Diagnostic Performance of FFR_{CT} and CCTA for Detection of Lesion-Specific Ischemia on Per-Patient Basis

Study	Number of Patients	Sensitivity	Specificity	PPV	NPV	Accuracy
DISCOVER-FLOW	103	50/54 (0.926)	40/49 (0.816)	50/59 (0.847)	40/44 (0.909)	90/103 (0.874)
DeFACTO	252	116/129 (0.899)	67/123 (0.545)	116/172 (0.674)	67/80 (0.838)	183/252 (0.726)
NXT	254	69/80 (0.863)	137/174 (0.787)	69/106 (0.651)	137/148 (0.926)	206/254 (0.811)
Total (95% CI)	609	0.894 (0.850–0.928)	0.705 (0.654–0.753)	0.697 (0.645–0.746)	0.897 (0.855–0.930)	0.787 (0.752–0.818)
I ² , %	N/A	0.00	91.40	76.80	52.10	66.10
DISCOVER-FLOW	103	51/54 (0.944)	12/49 (0.245)	51/88 (0.580)	12/15 (0.800)	63/103 (0.612)
DeFACTO	252	108/129 (0.837)	51/123 (0.415)	108/180 (0.600)	51/72 (0.708)	159/252 (0.631)
NXT	254	75/80 (0.938)	59/174 (0.339)	75/190 (0.395)	59/64 (0.922)	134/254 (0.528)
Total (95% CI)	609	0.890 (0.845–0.925)	0.353 (0.302–0.405)	0.511 (0.464–0.558)	0.808 (0.736–0.867)	0.585 (0.544–0.624)
I ² , %	N/A	71.00	60.80	90.00	81.80	0.00

Abbreviation as in Table 2.

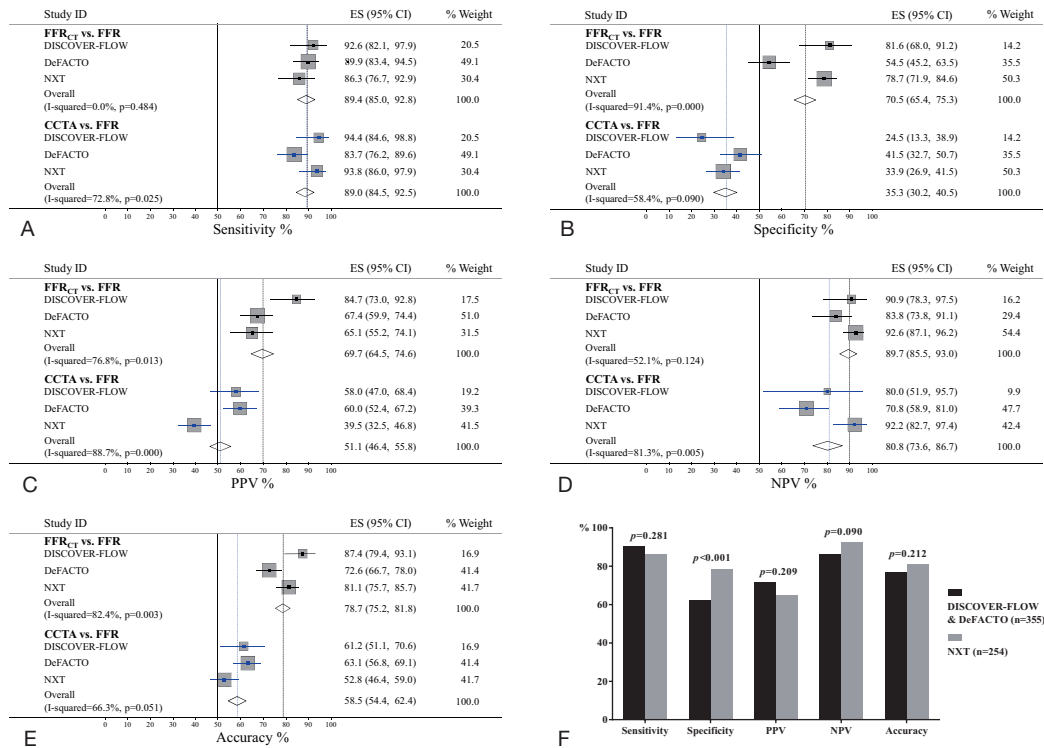


FIGURE 1. Diagnostic accuracies of fractional flow reserve computed from standard acquired coronary computed tomographic angiography datasets (FFR_{CT}) and coronary computed tomography angiography (CCTA) in the detection of hemodynamically significant coronary stenosis using a patient-based analysis and invasive FFR as a reference standard. (A–E) Forest plots of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FFR_{CT} and CCTA. (F) A comparison between the integrated diagnostic values of the DISCOVER-FLOW and DeFACTO trials and the data from the NXT trial. FFR = fractional flow reserve.

per-patient diagnostic specificity ($P < 0.001$), PPV ($P < 0.001$), NPV ($P = 0.003$), and accuracy ($P < 0.001$) were each significantly higher for FFR_{CT} than for CT, with similar sensitivities ($P = 0.321$) among the patients with intermediate coronary stenosis (Fig. 2A–E). However, there was no significant difference between the combined results from the DISCOVER-FLOW and the DeFACTO trials compared with the data from the NXT trial (Figure 2F).

DISCUSSION

This integrated analysis of 3 prospective, multicenter trials involving 609 patients with either suspected or known CAD was characterized by the high diagnostic accuracy of FFR_{CT} in the detection of hemodynamically significant coronary stenosis, using invasive FFR as standard reference. We observed that FFR_{CT} exhibited comparable sensitivity to CCTA but was superior with respect to all other evaluated parameters compared with CCTA among patients with CAD, both on a per-vessel and a per-patient basis, which was also consistent with a recent review about FFR_{CT}.²¹ Importantly, we confirmed that FFR_{CT} maintained a high sensitivity and specificity for the diagnosis of ischemia in patients with intermediate coronary stenosis, who are particularly challenging for clinicians to manage due to the poor relationship between angiographic severity and ischemia.²² Compared with CCTA, the number of false-positive findings was significantly lower for FFR_{CT}. These results are germane, particularly for individuals whose coronary stenosis fall below conventional definitions of

angiographically severe, yet confer hemodynamic importance that may explain symptoms of angina. Diffuse mild luminal narrowing has been demonstrated to be associated with decreased stress-induced myocardial blood flow and abnormal epicardial coronary artery resistance even before a high-grade segmental stenosis is apparent.²³

The DISCOVER-FLOW trial was the first study to compare the diagnostic performances of CCTA and FFR_{CT} with invasive FFR. Although the DISCOVER-FLOW study confirmed that FFR_{CT} correlated well with invasive FFR, the study was not powered on a per-patient level. Therefore, the DeFACTO trial was subsequently conducted to evaluate the diagnostic accuracy of FFR_{CT}; invasive FFR served as a reference standard in the diagnosis of per-patient ischemia; the primary analysis was performed to determine whether the per-patient diagnostic accuracy of FFR_{CT} exceeded 70% using a 1-sided test at the 0.05 level of significance, with a power calculation based on the DISCOVER-FLOW findings.²⁴ FFR_{CT} demonstrated improved diagnostic accuracy compared with CCTA alone in the DeFACTO trial. However, the study did not achieve its prespecified primary end point regarding the diagnostic accuracy of FFR_{CT} compared with FFR. Actually, the DISCOVER-FLOW and DeFACTO trials had almost identical study designs. When we combined the results of these 2 trials, we observed that the integrated per-patient diagnostic accuracy was 76.9% (95% CI: 72.2–81.2), with a lower 95% CI border >70%, which indicated that an insufficient number of study subjects may have been one of the reasons why the DeFACTO trial failed to meet the prospective primary

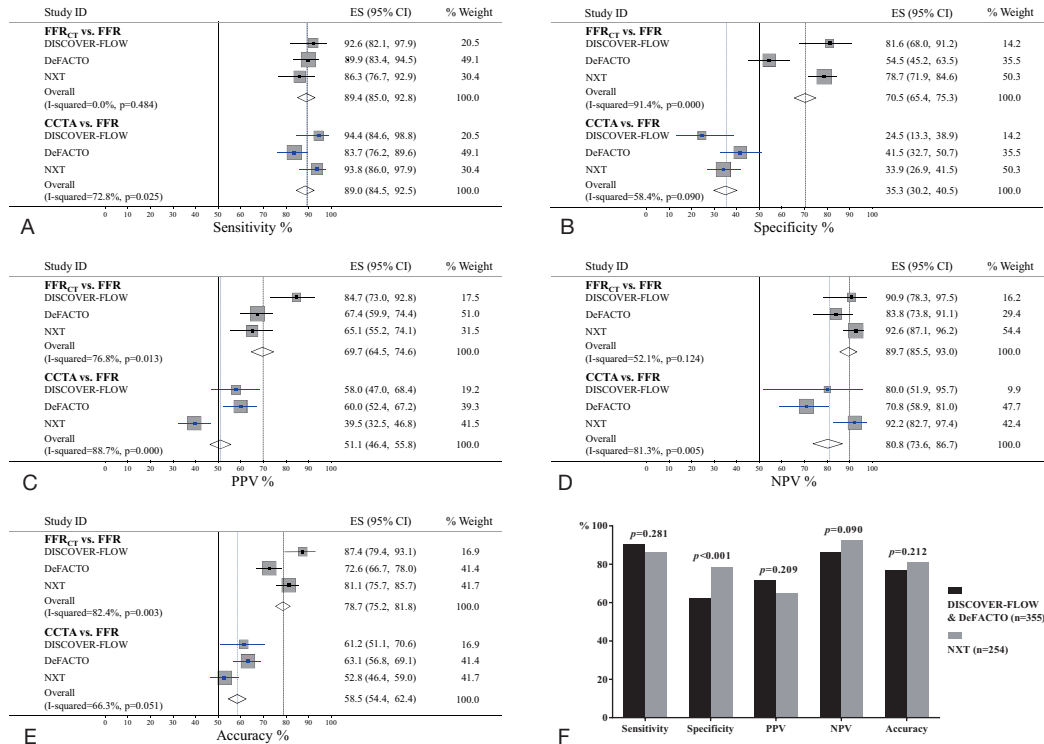


FIGURE 2. Diagnostic accuracy of FFR_{CT} and CCTA in the detection of hemodynamically significant coronary stenosis, using a patient-based analysis and invasive FFR as a reference standard, among patients with intermediate coronary stenosis. (A–E) Forest plots of the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of FFR_{CT} and CCTA. (F) A comparison between the integrated diagnostic values from the DISCOVER-FLOW and DeFACTO trials and the data from the NXT trial. The abbreviations are the same as those used in Figure 1.

endpoint. The recently published NXT trial, which used a refined version of the FFR_{CT} technology that exhibited an improved ability to identify luminal boundaries and improvements in physiological models of microcirculatory resistance, demonstrated improved results compared with both the DISCOVER-FLOW and the DeFACTO trials, particularly regarding specificity. In addition to refinements in FFR_{CT} technology, more stringent CT image quality control in the NXT trial may also have contributed to the improvements noted in diagnostic specificity.²⁵ In contrast, FFR_{CT} demonstrated both a high sensitivity and a high NPV in the diagnosis of ischemia, or 89.4% (with a lower 95% CI of 85.0%) and 89.7% (with a lower 95% CI of 85.5%) in the detection of hemodynamically significant coronary stenosis. However, missing a diagnosis of ischemia producing lesions in 1 to 2 patients out of 10 is unacceptable, as such an error may have serious consequences. Therefore, additional effort is necessary to improve the diagnostic performance of FFR_{CT}.

Several landmark trials have demonstrated that the clinical benefits of coronary revascularization are primarily limited to ischemia-producing lesions. It has been reported that coronary revascularization in patients with intermediate stenosis without objective proof of ischemia neither reduce adverse cardiac events nor lead to a better functional angina class compared with medical treatment.²⁶ Invasive FFR is now the gold standard for the determination of lesion-specific ischemia. However, this method is associated with complications related to coronary vessel instrumentation. In the 3 trials studied, 3 patients and 1 patient suffered from coronary dissection and retroperitoneal bleeding, respectively. FFR_{CT} allows for the

determination of anatomy and lesion-specific ischemia via noninvasive testing. Moreover, a recent published pilot research study suggested that virtual coronary stenting based on FFR_{CT} results is feasible.²⁷ Furthermore, 2 studies used the clinical data from the DISCOVER-FLOW and the NXT trials to evaluate the cost-effectiveness of FFR_{CT} and determined that treatment planning using FFR_{CT} to guide the selection of patients for ICA and virtual coronary stenting may reduce costs and improve clinical outcomes in patients with suspected CAD.^{28,29}

Although FFR_{CT} represents a promising means of non-invasively assessing the functional significance of coronary stenosis, several major points must be addressed. First, numerous CT-related artifacts and patient-related factors, including misalignment, motion, beam hardening from coronary calcification, and increased image noise, may adversely affect the image quality and subsequent diagnostic performance of FFR_{CT}.³⁰ Proper adherence to imaging protocols to ensure optimal image quality and enable the quantitative interpretation of lumen boundaries and nitroglycerin pretreatment before CCTA acquisition to ensure that the coronary arteries are dilated may improve the diagnostic accuracy of FFR_{CT}.³¹ Second, the calculation of FFR_{CT} costs several hours per examination due to both segmentation and computational processing.³² FFR_{CT} is based on computational fluid dynamics. The computational technology underlying FFR_{CT} incorporates multiple numerical methods and algorithms to solve the governing equations of fluid dynamics, which are founded in the balanced relationship between the conservations of mass and momentum.³³ The equations are known as the Navier–Stokes equations and have been known for almost 2 centuries.

However, the solving of these equations requires significant computational power which only became possible with the development of modern supercomputers and numerical methods. At present, this computational power is greater than can be made available onsite, thereby requiring said data to be transferred off-site for any subsequent calculations and analysis. Improvements in both the segmentation and the computational processing may allow for both on-site and timely integration.

Study Limitations

There were several limitations to this integrated analysis. First, all 3 of the included trials were supported by funding from HeartFlow, which also supplied the proprietary software. Second, the results of our study were limited to patients with stable (suspected) CAD. Patients with acute coronary syndromes and a history of either prior coronary intervention or bypass graft surgery were excluded from all 3 studies. Patients with cardiac arrhythmias were also excluded. Third, although each of the trials had similar study designs, there was some heterogeneity regarding CCTA prequalification, quality control, and the FFR_{CT} evaluation. Unlike the 2 prior trials, the NXT trial optimized CCTA data acquisition and utilized improved FFR_{CT} technology. Finally, in the subgroup analysis, the definition of intermediate coronary stenosis was not identical among the trials, which may have resulted in selection bias.

CONCLUSIONS

In this integrated analysis, FFR_{CT} demonstrated high accuracy in the detection of lesion-specific ischemia using invasive FFR as a reference standard. Notably, the high sensitivity and NPV suggest the ability of FFR_{CT} to effectively rule out intermediate lesions that cause ischemia. However, in light of the serious health consequences of a missed diagnosis of hemodynamically significant coronary stenosis, efforts should be undertaken to improve the diagnostic efficacy of FFR_{CT}. Additionally, randomized controlled trials evaluating both the clinical benefits and the cost-effectiveness of FFR_{CT} guided coronary revascularization are warranted.

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