

## ONLINE FIRST

# Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

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**C**ORONARY COMPUTED TOMOGRAPHIC (CT) angiography is a noninvasive test that enables direct visualization of coronary artery disease (CAD) and correlates favorably with invasive coronary angiography (ICA) for measures of stenosis severity.<sup>1</sup> However, CT cannot determine the hemodynamic significance of CAD, and even among CT-identified obstructive stenoses confirmed by ICA, fewer than half are ischemia-causing.<sup>2,3</sup> These findings underscore an unreliable relationship of stenosis severity to ischemia and have raised concerns that use of CT may pre-

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**Context** Coronary computed tomographic (CT) angiography is a noninvasive anatomic test for diagnosis of coronary stenosis that does not determine whether a stenosis causes ischemia. In contrast, fractional flow reserve (FFR) is a physiologic measure of coronary stenosis expressing the amount of coronary flow still attainable despite the presence of a stenosis, but it requires an invasive procedure. Noninvasive FFR computed from CT (FFR<sub>CT</sub>) is a novel method for determining the physiologic significance of coronary artery disease (CAD), but its ability to identify patients with ischemia has not been adequately examined to date.

**Objective** To assess the diagnostic performance of FFR<sub>CT</sub> plus CT for diagnosis of hemodynamically significant coronary stenosis.

**Design, Setting, and Patients** Multicenter diagnostic performance study involving 252 stable patients with suspected or known CAD from 17 centers in 5 countries who underwent CT, invasive coronary angiography (ICA), FFR, and FFR<sub>CT</sub> between October 2010 and October 2011. Computed tomography, ICA, FFR, and FFR<sub>CT</sub> were interpreted in blinded fashion by independent core laboratories. Accuracy of FFR<sub>CT</sub> and CT for diagnosis of ischemia was compared with an invasive FFR reference standard. Ischemia was defined by an FFR or FFR<sub>CT</sub> of 0.80 or less, while anatomically obstructive CAD was defined by a stenosis of 50% or larger on CT and ICA.

**Main Outcome Measures** The primary study outcome assessed whether FFR<sub>CT</sub> plus CT could improve the per-patient diagnostic accuracy such that the lower boundary of the 1-sided 95% confidence interval of this estimate exceeded 70%.

**Results** Among study participants, 137 (54.4%) had an abnormal FFR. On a per-patient basis, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of FFR<sub>CT</sub> were 73% (95% CI, 67%-78%), 90% (95% CI, 84%-95%), 54% (95% CI, 46%-83%), 67% (95% CI, 60%-74%), and 84% (95% CI, 74%-90%), respectively. Compared with obstructive CAD diagnosed by CT alone (area under the receiver operating characteristic curve [AUC], 0.68; 95% CI, 0.62-0.74), FFR<sub>CT</sub> was associated with improved discrimination (AUC, 0.81; 95% CI, 0.75-0.86;  $P < .001$ ).

**Conclusion** Although the study did not achieve its prespecified primary outcome goal for the level of per-patient diagnostic accuracy, use of noninvasive FFR<sub>CT</sub> plus CT among stable patients with suspected or known CAD was associated with improved diagnostic accuracy and discrimination vs CT alone for the diagnosis of hemodynamically significant CAD when FFR determined at the time of ICA was the reference standard.

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cipitate unnecessary ICA and coronary revascularization for patients who do not have ischemia.<sup>4,5</sup>

These concerns stem from recent randomized trials that have identified no survival benefit for patients who undergo angiographically based coronary revascularization.<sup>6,7</sup> As an ad-

junct to ICA, fractional flow reserve (FFR) has served as a useful tool to determine the likelihood that a coronary

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stenosis hinders the delivery of oxygen to the heart muscle or causes myocardial ischemia. As the currently accepted reference standard for determining lesion-specific ischemia, FFR is an invasive procedure performed at the time of ICA and represents the ratio of the mean coronary pressure distal to a coronary stenosis to the mean aortic pressure during maximal coronary blood flow.<sup>8</sup> This ratio expresses the coronary flow still attainable despite the presence of a coronary stenosis. The addition of physiologic measures of coronary flow by FFR to anatomic-based assessment of stenosis severity by ICA to guide decisions of coronary revascularization improves event-free survival in a manner that is long-lived and cost-effective.<sup>9-11</sup> To date, however, this integrated anatomic-physiologic approach has not been available through noninvasive methods.

Noninvasive calculation of FFR from CT ( $FFR_{CT}$ ) is a novel method that applies computational fluid dynamics to determine the physiologic significance of CAD.<sup>12</sup> Fractional flow reserve from CT enables calculation of rest and hyperemic pressure fields in coronary arteries without additional imaging, modification of CT acquisition protocols, or administration of medications.<sup>13</sup> In this multicenter international study, we evaluated the performance of noninvasive  $FFR_{CT}$  compared with an invasive FFR reference standard for diagnosis of ischemia.

## METHODS

### Study Design

The rationale and design of the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study has been previously described.<sup>14</sup> Briefly, DeFACTO was designed to evaluate the accuracy of  $FFR_{CT}$  to diagnose hemodynamically significant CAD, as defined by an invasive FFR reference standard, with a targeted population of patients with suspected native CAD who were referred for clinically indicated nonemergent ICA within 60 days

of performance of CT. Patients with prior coronary artery bypass graft (CABG) surgery and suspected in-stent restenosis on the basis of CT were excluded. The DeFACTO study was conducted at 17 centers in 5 countries (Belgium [n=1], Canada [n=1], Latvia [n=1], South Korea [n=2], and United States [n=12]). The DeFACTO study protocol was designed by the steering committee and approved by the institutional review board at each site. All patients provided written informed consent.

### Study Population

Enrolled patients were adults with suspected CAD who underwent clinically indicated ICA after CT with no intervening coronary event. Patients were not eligible if they had a history of CABG surgery; prior percutaneous coronary intervention (PCI) with suspected in-stent restenosis; contraindication to adenosine; suspicion of or recent acute coronary syndrome; complex congenital heart disease; prior pacemaker or defibrillator; prosthetic heart valve; significant arrhythmia; serum creatinine level greater than 1.5 mg/dL; allergy to iodinated contrast; pregnant state; body mass index greater than 35 (calculated as weight in kilograms divided by height in meters squared); evidence of active clinical instability or life-threatening disease; or inability to adhere to study procedures.

### Image Acquisition and Analysis for CT

Computed tomographic angiography was performed on 64- or higher detector row scanners with prospective or retrospective electrocardiographic gating in accordance with Society of Cardiovascular Computed Tomography guidelines.<sup>15,16</sup> Computed tomographic angiograms were transferred to a central core laboratory (Harbor UCLA Medical Center, Los Angeles, California) for blinded interpretation using an 18-segment coronary model. Investigators evaluated CTs for maximal patient-, vessel-, and segment-based diameter stenosis, which was categorized

as 0%, 1% to 29%, 30% to 49%, or 50% or larger. Lesions of 50% or larger were categorized as subtotal ( $\geq 90\%$ ) or totally (100%) occluded. Per-patient and per-vessel CAD stenosis were the maximal stenoses identified in all segments or in all segments within a vessel distribution, respectively. Vessel distributions were categorized for the left anterior descending (distribution including the first and second diagonal branches), left circumflex (distribution including the ramus intermedia, first and second obtuse marginal branches, and left posterolateral branch), and right coronary artery (distribution including the right posterolateral branch and posterior descending artery). Computed tomographic angiograms were judged as excellent, good, adequate, or nondiagnostic, as previously described.<sup>17</sup>

### Image Acquisition and Analysis for ICA

Selective ICA was performed by standard protocol, with a minimum of 2 projections obtained per vessel distribution and with angles of projection optimized based on the cardiac position.<sup>18</sup> Invasive coronary angiograms were transferred to a central angiographic core laboratory (University of British Columbia, Vancouver, Canada) for blinded quantitative coronary angiography of all vessels using commercially available software (Discovery Quinton).

### Fractional Flow Reserve

Fractional flow reserve was performed at the time of ICA (PressureWire Certus, St Jude Medical Systems; ComboWire, Volcano Corp). Investigators performed FFR in vessels deemed clinically indicated for evaluation and demonstrating an ICA stenosis between 30% and 90%. Vessels deemed not clinically indicated for FFR were not interrogated. After administration of nitroglycerin, a pressure-monitoring guide wire was advanced distal to a stenosis. Hyperemia was induced by administration of intravenous adenosine at a rate of 140

µg/kg per minute. Fractional flow reserve was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during hyperemia. Fractional flow reserve was considered diagnostic of ischemia at a threshold of 0.80 or less.<sup>9</sup>

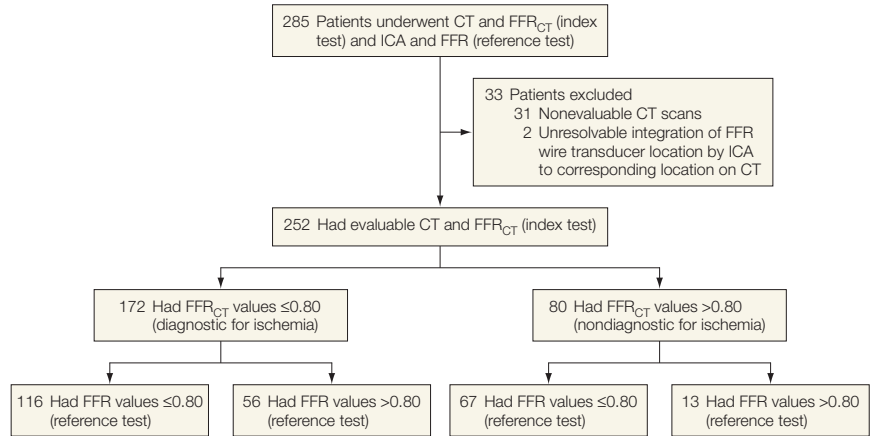
**Blinded Integration of FFR and CT**

Direct comparison of FFR<sub>CT</sub> with FFR necessitated FFR<sub>CT</sub> calculation at the precise location of the wire transducer at the time of FFR. To maintain blinding of the FFR<sub>CT</sub> core laboratory to CT, ICA, and FFR findings, an integration core laboratory (Minneapolis Heart Institute, Minneapolis, Minnesota) was used. The integration core laboratory identified the location on CT that corresponded to the point where the FFR was measured. The location was communicated to the FFR<sub>CT</sub> core laboratory by an arrow on a 3-dimensional volume-rendered CT image of the coronary arteries.

**Computation of FFR<sub>CT</sub>**

Computation of FFR<sub>CT</sub> was performed in blinded fashion by the FFR<sub>CT</sub> core laboratory (HeartFlow Inc, Redwood City, California). Calculations of FFR<sub>CT</sub> were performed by computational fluid dynamic modeling after semiautomated segmentation of coronary arteries and left ventricular mass. This process required approximately 6 hours per case. Three-dimensional blood flow simulations of the coronary arteries were performed, with blood modeled as a Newtonian fluid using incompressible Navier-Stokes equations, and solved subject to appropriate initial and boundary conditions using a finite element method on a parallel supercomputer.<sup>13</sup> Since coronary flow and pressure were unknown a priori, a method to couple lumped parameter models of the microcirculation to the outflow boundaries of the 3-dimensional model was used. Coronary blood flow was simulated under conditions modeling adenosine-mediated coronary hyperemia. The FFR<sub>CT</sub> ratio was obtained by dividing the mean pres-

**Figure 1. Study Enrollment**



CT indicates computed tomographic angiography; FFR, fractional flow reserve; FFR<sub>CT</sub>, fractional flow reserve calculated from CT; ICA, invasive coronary angiography.

sure distal to the coronary stenosis by the mean aortic pressure. Similar to invasive FFR, default FFR<sub>CT</sub> values of 0.50 and 0.90 were assigned to subtotally and totally occluded arteries or nonstenotic coronary arteries, respectively.

**Statistical Analyses**

The primary study end point was the diagnostic accuracy of FFR<sub>CT</sub> plus CT for diagnosis of per-patient ischemia compared with an FFR reference standard. The study was powered based on the protocol-specified primary analysis, in which diagnostic accuracy of FFR<sub>CT</sub> dichotomized at the 0.80 threshold was to be significantly greater than 70% using a 1-sided test at the .05 level of significance. Assuming a 0.35 proportion of patients with ischemia by FFR, a total of 219 evaluable patients were required to achieve 85% power. A total of 252 patients were enrolled, which provided greater than 90% power to answer the primary study hypothesis. Primary analyses were conducted for FFR<sub>CT</sub> on an intention-to-diagnose sample, defined as all patients with interpretable CTs (as determined by the CT core laboratory prior to and independent of the FFR<sub>CT</sub> core laboratory) and with invasive FFR, which served as the reference standard.

**Table 1. Baseline Characteristics of the Study Population**

Characteristics	No. (%) of Patients (N = 252) <sup>a</sup>
Age, mean (SD), y	62.9 (8.7)
Male	178 (70.6)
Hispanic or Latino	12 (4.8)
Race/ethnicity	
White	169 (67.1)
Asian	78 (31.0)
Black or African American	4 (1.6)
American Indian or Alaska Native	1 (0.4)
Diabetes mellitus	53 (21.2)
Hypertension	179 (71.2)
Hyperlipidemia	201 (79.8)
Family history of coronary artery disease	50 (19.9)
Current smoker	44 (17.5)
Prior myocardial infarction	15 (6.0)
Prior percutaneous coronary intervention	16 (6.3)
Angina within the past month <sup>b</sup>	195 (77.2)
Angina type (worst type) <sup>c</sup>	
Stable	201 (79.7)
Worsening	43 (17.2)
Silent ischemia	1 (0.5)
Other	7 (2.6)

<sup>a</sup>Data are reported as No. (%) unless otherwise indicated.  
<sup>b</sup>Available in 250 patients.  
<sup>c</sup>Available in 192 patients.

Analyses were performed on a per-patient as well as per-vessel basis. In the per-patient analysis, vessels with the most adverse clinical status were se-

**Table 2.** Patient and Vessel Characteristics by ICA, FFR, CT, and FFR<sub>CT</sub>

Characteristics	No. (%) of Vessels <sup>a</sup>
ICA and FFR characteristics (n = 408 vessels from 252 patients)	
Obstructive CAD (≥50% stenosis) <sup>b</sup>	190 (46.5)
Average diameter stenosis, mean (SD), % <sup>b</sup>	46.8 (15.7)
Lesion location	
LAD	223 (54.6)
LCx	95 (23.3)
RCA	90 (22.1)
FFR ≤0.80 <sup>b</sup>	151 (37.1)
CT and FFR <sub>CT</sub> characteristics (n = 406 vessels from 252 patients)	
Obstructive CAD (≥50% stenosis) <sup>c</sup>	216 (53.2)
>90% Stenosis	79 (19.5)
Coronary calcium score, mean (SD), Agatston units <sup>d</sup>	381.5 (401.0)
Scan quality	
Excellent	309 (76.2)
Good	86 (21.0)
Satisfactory	11 (2.8)
Poor	0
FFR <sub>CT</sub> ≤0.80 <sup>b</sup>	216 (53.3)

Abbreviations: CAD, coronary artery disease; CT, computed tomographic angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery.

<sup>a</sup>Data are reported as No. (%) unless otherwise indicated.

<sup>b</sup>By quantitative coronary angiography in vessels directly interrogated by FFR and FFR<sub>CT</sub> (n=407).

<sup>c</sup>Computed tomographic interpretation was missing in 2 patients.

<sup>d</sup>Available in 218 patients.

lected to represent a given patient (minimum FFR, minimum FFR<sub>CT</sub>, highest CT stenosis category). Fractional flow reserve and FFR<sub>CT</sub> measurements were recorded on a continuous scale and dichotomized at the 0.80 threshold (values ≤0.80 considered diseased). Stenosis on CT was recorded on an ordinal scale and dichotomized at the 50% threshold, with stenoses of 50% or larger considered obstructive. In patient-based analysis, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated as simple proportions with corresponding 95% confidence intervals. In vessel-based analyses, these values were computed using generalized estimating equations to ac-

count for within-patient correlation. Discrimination was quantified using the area under the receiver operating characteristic curve (AUC), and AUCs were compared using the method of DeLong et al<sup>19</sup> in the per-patient analysis and percentile bootstrap with 999 resamples in the per-vessel analysis. Pearson correlation coefficients were calculated to determine the relationship between FFR<sub>CT</sub> and FFR.

One vessel had missing FFR<sub>CT</sub> and 2 had missing CT data. Missing data were handled by exclusion of these vessels as well as by the worst-case imputation. Because the results based on both of these methods did not differ materially, we present the analyses excluding the single vessel with missing FFR<sub>CT</sub>. Because FFR and FFR<sub>CT</sub> were not available for vessels not clinically indicated for FFR, we evaluated performance in keeping with prior multicenter trials, wherein a value of 0.50 was imputed for both FFR and FFR<sub>CT</sub> in vessels with stenosis on CT of 90% or larger and a value of 0.90 was imputed when maximal stenosis severity by CT was 30% or smaller, to define FFR<sub>CT</sub> test characteristics that would be expected across the full range of vessels analyzed by CT within the study. As a secondary analysis, we evaluated the diagnostic performance of FFR<sub>CT</sub> among patients with intermediate CT stenosis severity wherein the clinical utility of FFR<sub>CT</sub> would be most commonly expected for use. We restricted this analysis to patients in the clinically equivocal range of CT, with at least 1 stenosis on CT between 30% and 70% and no stenoses larger than 70%.<sup>2</sup> All analyses were performed using SAS software, version 9.1 or higher (SAS Institute Inc).

**RESULTS**

Among 285 patients who underwent CT, ICA, FFR, and FFR<sub>CT</sub> between October 2010 and October 2011, 31 patients were excluded by the CT core laboratory for nonevaluable CTs and 2 patients were excluded for unresolvable integration of the FFR wire transducer location by ICA to its correspond-

ing location on CT, resulting in 252 patients included in the analyses (FIGURE 1). Baseline demographic and clinical characteristics of the study population are listed in TABLE 1. About 77% of patients had experienced angina within the last month. The median duration between CT and ICA plus FFR was 15.5 days (interquartile range, 5-33 days).

The per-patient prevalence of obstructive CAD of 50% or greater by CT and ICA and prevalence of ischemia by FFR and FFR<sub>CT</sub> are presented in TABLE 2. Among 615 study vessels, 271 had less than 30% stenosis and 101 had at least 90% stenosis. Four hundred seven vessels were directly interrogated by both FFR and FFR<sub>CT</sub> (FIGURE 2). The numbers of patients within the intention-to-diagnose sample with FFR<sub>CT</sub> and FFR values above and below the 0.80 threshold are listed in TABLE 3.

Two enrolled patients experienced coronary dissection during FFR wire crossing that required PCI, and 1 patient experienced a retroperitoneal bleed requiring blood transfusion and corrective surgery. No untoward events were identified following CT, with no episodes of serious contrast reactions or contrast-induced nephropathy noted. The median radiation dose of CT was 6.4 mSv (interquartile range, 4.4-15.0 mSv).

**Diagnostic Accuracy of FFR<sub>CT</sub> for Diagnosis of Ischemia**

Per-patient performance of FFR<sub>CT</sub> and CT is listed in TABLE 4. Diagnostic accuracy for FFR<sub>CT</sub> plus CT was 73% (95% CI, 67%-78%), which did not meet the prespecified primary end point of greater than 70% of the lower bound of the 95% confidence interval. By comparison, diagnostic accuracy of CT alone was 64% (95% CI 58%-70%). When comparing FFR<sub>CT</sub> alone with CT stenosis of 50% or greater alone, FFR<sub>CT</sub> demonstrated superior discrimination (AUC, 0.81 [95% CI, 0.75-0.86] vs 0.68 [95% CI, 0.62-0.74]; difference, 0.13 [95% CI, 0.06-0.20]; P < .001) (FIGURE 3A).

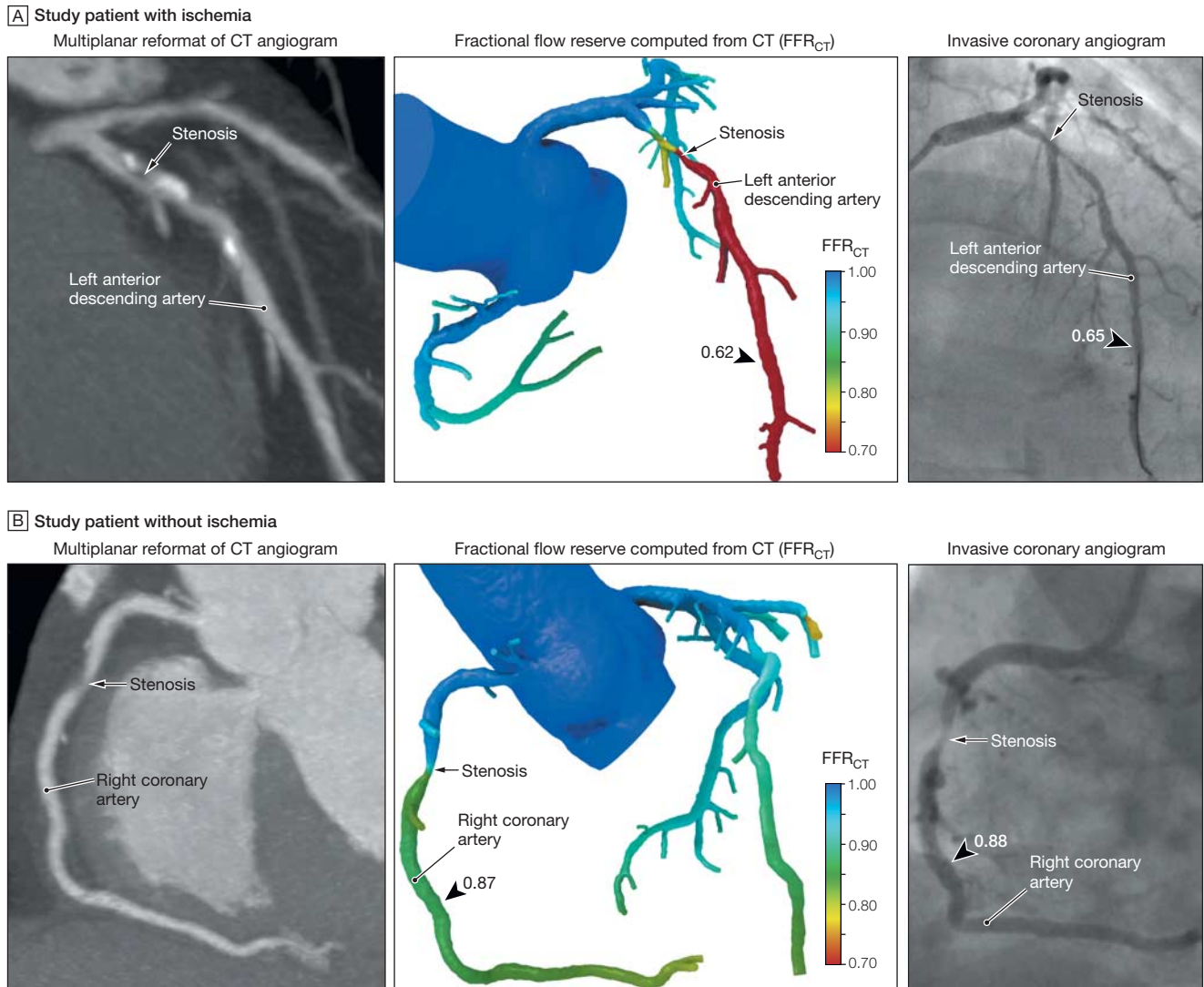
For vessels directly interrogated by FFR,  $FFR_{CT}$  also demonstrated higher discriminatory power than CT stenosis alone (Figure 3B). For these vessels, the diagnostic sensitivity and specificity of  $FFR_{CT}$  alone were 80% (95% CI, 73%-86%) and 61% (95% CI, 54%-67%), respectively. When FFR and  $FFR_{CT}$  values were imputed in cases of greater than 90% or less than 30% ste-

nosis, the diagnostic sensitivity and specificity of  $FFR_{CT}$  alone were 83% (95% CI, 76%-88%) and 78% (95% CI, 73%-82%), respectively. Direct per-vessel correlation of  $FFR_{CT}$  to FFR was good (Pearson correlation coefficient, 0.63; 95% CI, 0.56-0.68), with underestimation of  $FFR_{CT}$  compared with FFR (mean difference, 0.058; 95% CI, 0.05-0.07).

**Diagnostic Performance of  $FFR_{CT}$  for Patients With Intermediate Stenosis Severity by CT**

In patient-based analysis restricted to those with an intermediate stenosis ranging from 30% to 70%, diagnostic accuracy, sensitivity, positive predictive value, and negative predictive value were higher for  $FFR_{CT}$  than for CT, with similar specificity (TABLE 5).

**Figure 2.** Representative Examples of 2 Patients From the DeFACTO Study



Although both patients have obstructive coronary artery disease by computed tomographic angiography (CT), one patient (A) has ischemia and the other patient (B) does not have ischemia. A, Multiplanar reformat of a CT angiogram demonstrating obstructive stenosis of the proximal portion of the left anterior descending artery (LAD) and a computed fractional flow reserve ( $FFR_{CT}$ ) value of 0.62, indicating vessel ischemia. Invasive coronary angiogram demonstrates obstructive stenosis of the proximal portion of the LAD and measured fractional flow reserve (FFR) values of 0.65, indicating vessel ischemia. B, CT angiogram demonstrating obstructive stenosis of the mid portion of the right coronary artery (RCA) and a computed  $FFR_{CT}$  value of 0.87, indicating no vessel ischemia. Invasive coronary angiogram demonstrates obstructive stenosis of the mid portion of the RCA and a measured FFR value of 0.88, indicating no vessel ischemia.

**COMMENT**

In this multicenter international study of stable patients with suspected or known CAD, we observed that FFR<sub>CT</sub>—a novel method that applies computational fluid dynamics to derive physiologic data from CT—demonstrated improved diagnostic accuracy vs CT alone for diagnosis of ischemia, although this study did not satisfy its prespecified primary end

point of diagnostic accuracy of greater than 70% of the lower bound of the 1-sided 95% confidence interval. Taken together, these study results suggest the potential of FFR<sub>CT</sub> as a promising non-invasive method for identification of individuals with ischemia. The present study findings can be considered proof of concept of the feasibility of this novel technology and, to our knowledge, represent the first large-scale prospective

demonstration of the use of computational models to calculate rest and hyperemic coronary pressure fields from typically acquired CT images.

At the patient level, FFR<sub>CT</sub>, when added to CT, improved diagnostic accuracy vs CT alone, driven by improvements in sensitivity as well as specificity. These results suggest that FFR<sub>CT</sub> can impart considerable discriminatory power to identify and exclude ischemia in patients with suspected CAD. These findings are supported by the receiver operating characteristics curves—which are generally considered to be independent of disease prevalence—wherein enhanced diagnostic performance of FFR<sub>CT</sub> vs CT alone was reflected by greater discrimination on both a per-patient and per-vessel basis. Importantly, the sensitivity and negative predictive value of FFR<sub>CT</sub> were high, indicating a low rate of false-negative studies. These diagnostic features of FFR<sub>CT</sub> may encourage a greater sense of diagnostic certainty that patients who undergo CT who have ischemia are not overlooked, such that clinicians may be confident in not proceeding to invasive angiography in patients with stenoses on CT when FFR<sub>CT</sub> results are normal. Nevertheless, de-

**Table 3.** No. of Patients With FFR<sub>CT</sub> and FFR Above and Below the 0.80 Threshold in the Intention-to-Diagnose Sample

	Per-Vessel Performance		Per-Patient Performance	
	FFR <sub>CT</sub> ≤ 0.80	FFR <sub>CT</sub> > 0.80	FFR <sub>CT</sub> ≤ 0.80	FFR <sub>CT</sub> > 0.80
FFR ≤ 0.80	121	30	116	13
FFR > 0.80	96	160	56	67

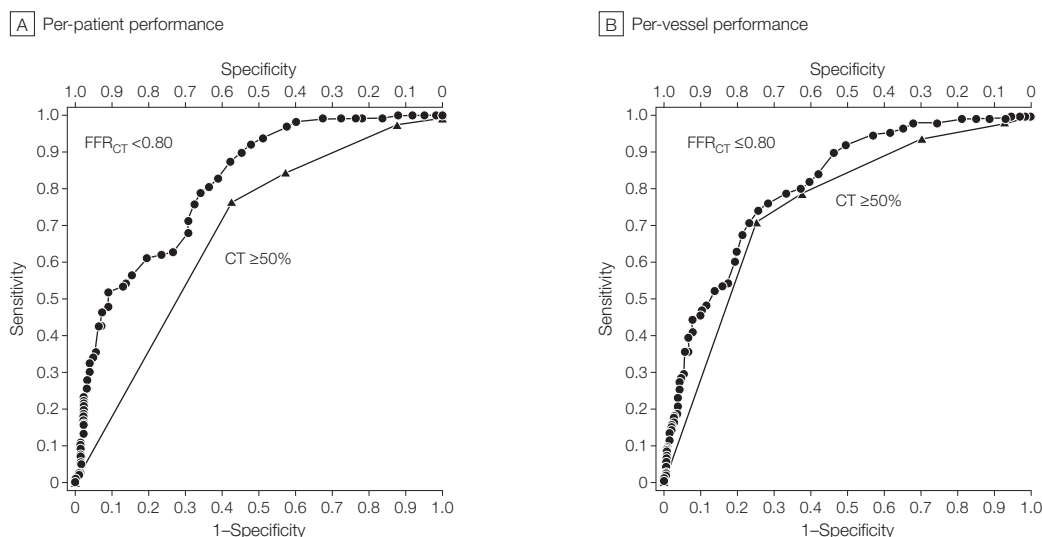
Abbreviations: FFR, fractional flow reserve; FFR<sub>CT</sub>, fractional flow reserve calculated from computed tomography.

**Table 4.** Per-Patient Diagnostic Performance of FFR<sub>CT</sub> ≤ 0.80 and CT ≥ 50% vs FFR ≤ 0.80 in the Intention-to-Diagnose Sample

	FFR <sub>CT</sub> ≤ 0.80		CT ≥ 50%	
	Estimate, % (95% CI)	No. of Patients in Group	Estimate, % (95% CI)	No. of Patients in Group
Accuracy	73 (67-78)	252	64 (58-70)	252
Sensitivity	90 (84-95)	129	84 (77-90)	129
Specificity	54 (46-83)	123	42 (34-51)	123
PPV	67 (60-74)	172	61 (53-67)	180
NPV	84 (74-90)	80	72 (61-81)	72

Abbreviations: CT, computed tomographic angiography; FFR<sub>CT</sub>, fractional flow reserve calculated from CT; NPV, negative predictive value; PPV, positive predictive value.

**Figure 3.** Areas Under the Receiver Operating Characteristic Curve of Per-Patient and Per-Vessel Performance of FFR<sub>CT</sub> ≤ 0.80 and CT Stenosis ≥ 50% Compared With Invasive FFR for Diagnosis of Ischemia



FFR indicates fractional flow reserve; CT, computed tomographic angiography; FFR<sub>CT</sub>, fractional flow reserve calculated from CT.

spite its superiority to CT alone, the diagnostic specificity and positive predictive value of  $FFR_{CT}$  for ischemia detection remained low, suggesting that while false-positive studies would be reduced with this approach, a substantial rate would remain. In this regard, universal application of  $FFR_{CT}$  to guide invasive assessment may result in referral of a nonnegligible number of patients without ischemia, and future studies will be needed to determine the potential clinicoeconomic effectiveness of  $FFR_{CT}$  for this particular indication.

Compared with CT alone, we also observed improvements in diagnostic accuracy of  $FFR_{CT}$  for ischemia in patients with lesions of intermediate stenosis severity, who represent a particularly challenging clinical subset among whom angiographic severity is an often ambiguous metric for ischemia diagnosis.<sup>20</sup> Notably, however, the improvements in diagnostic accuracy afforded by  $FFR_{CT}$  among patients with lesions of intermediate stenosis severity were for measures of sensitivity rather than specificity, the latter of which was identical for  $FFR_{CT}$  and CT. Similar to per-patient findings, these performance characteristics suggest a low false-negative rate if assessments by  $FFR_{CT}$  were used to identify ischemia-causing intermediate lesions, with negligible effects on reductions of false-positive results. In this regard, the use of  $FFR_{CT}$  may significantly advance clinical assessment of patients without conventional measures of anatomic high-grade coronary stenosis, largely by proper identification of a significantly greater proportion of patients with manifest ischemia rather than as a safeguard to further invasive evaluation.

In recent years, CT has emerged as a noninvasive imaging test that permits direct visualization of coronary stenoses with high performance compared with invasive angiography.<sup>1</sup> However, overestimation of stenosis severity by CT has been observed, and even among stenoses considered obstructive by CT analysis that are sub-

**Table 5.** Per-Patient Diagnostic Performance of  $FFR_{CT} \leq 0.80$  and  $CT \geq 50\%$  vs  $FFR \leq 0.80$  Among Patients With Intermediate CT Stenosis Severity (30%-70%)

	$FFR_{CT} \leq 0.80$		$CT > 50\%$	
	Estimate, % (95% CI)	No. of Patients in Group	Estimate, % (95% CI)	No. of Patients in Group
Accuracy	71 (61-80)	83	57 (46-67)	83
Sensitivity	82 (63-92)	27	37 (22-56)	27
Specificity	66 (53-77)	56	66 (53-77)	56
PPV	54 (39-68)	41	34 (20-53)	29
NPV	88 (75-95)	42	68 (55-79)	54

Abbreviations: CT, computed tomographic angiography;  $FFR_{CT}$ , fractional flow reserve calculated from CT; NPV, negative predictive value; PPV, positive predictive value.

sequently confirmed by ICA, only a minority cause ischemia.<sup>2</sup> This discordance is not restricted to CT but has been observed for ICA-determined stenosis as well and underscores the complex relationship between stenosis severity and ischemia. One contemporary example of this anatomic-physiologic incongruity was observed in the nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, wherein among patients with severe angiographic stenosis, only 32% exhibited moderate or severe ischemia and 40% manifested none or mild ischemia by single-photon emission CT.<sup>21</sup> This marked disparity suggests that even in the setting of severe coronary stenosis, other factors are operative in the regulation of ischemia.

By invasive methods, addition of physiologic assessment of CAD by  $FFR$  to ICA augments assessment of coronary stenoses in a clinically and economically efficient manner.<sup>9</sup> In the multicenter Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME) study, combined assessment of stenosis and ischemia by ICA and  $FFR$ , respectively, for decisions about revascularization resulted in improved event-free survival compared with revascularization based on anatomic stenosis alone. However, this approach is invasive and associated with potential complications related to coronary vessel instrumentation. In the present study, we observed 2 coronary dissections and 1 significant ret-

roperitoneal hemorrhage in these clinically indicated invasive studies. In contrast, calculation of  $FFR_{CT}$  can be performed noninvasively without these risks. Indeed,  $FFR_{CT}$  can be calculated from typically acquired CTs without additional imaging, added radiation, modification of image acquisition protocols, or administration of medications. In the present study, performance of  $FFR_{CT}$  was reflective of "real-world" practice, wherein vessels interrogated by site investigators were those that were deemed clinically necessary for  $FFR$  evaluation, irrespective of size and across a wide range of CT image quality. Given these study characteristics, the high number of participating centers, and the international scope, the present findings should be considered robust and widely generalizable.

The primary goal of noninvasive imaging of CAD has been to develop a single test that identifies high-grade stenosis as well as determines the hemodynamic significance of these lesions. At present, professional societies endorse the use of noninvasive stress imaging for evaluation of symptomatic patients with suspected CAD, given the large-scale observational evidence that ischemia may guide decisions of revascularization in a salutary fashion.<sup>22-24</sup> These stress imaging studies identify regional differences in coronary flow reserve or wall motion abnormalities as a surrogate for ischemia yet do not directly visualize coronary stenoses or assess the hemodynamic significance of individual coronary le-

sions. Furthermore, this testing misclassifies a significant proportion of patients as low risk and has significant false-positive and false-negative rates such that the proportion of patients undergoing ICA after testing in whom no obstructive CAD is identified remains substantial.<sup>25,26</sup>

Accordingly, some have advocated for hybrid imaging with physiologic and anatomic evaluation of CAD by stress testing and CT, respectively.<sup>27</sup> However, this approach requires 2 tests and is associated with higher costs and greater per-patient radiation burden. The addition of FFR<sub>CT</sub> to CT may allow for combined anatomic-physiologic assessment of CAD from performance of a single imaging test in a manner that may promote salutary outcomes. Future studies to assess the clinical effectiveness and cost-effectiveness of such an approach now appear warranted.

Importantly, the prespecified primary end point for FFR<sub>CT</sub> was selected on the basis of an array of prior studies that have demonstrated 70% to be generally at the mid point of reported diagnostic accuracies for stress imaging, depending on test type, patient population, and disease prevalence.<sup>28</sup> In this study, FFR<sub>CT</sub> demonstrated a per-patient diagnostic accuracy of 73%, with confidence intervals that suggest a diagnostic accuracy as low as 67% and as high as 78%. These findings establish a performance of FFR<sub>CT</sub> that is within the range of conventional stress imaging testing. Furthermore, considerable added value of FFR<sub>CT</sub> exists when an anatomic imaging test such as CT is used as an alternative test to stress imaging for CAD evaluation. The significant gain in discriminatory power of FFR<sub>CT</sub> relative to anatomic CT stenosis alone supports its potential application to identify individuals with ischemic stenoses, and the combined anatomic and physiologic information imparted by these noninvasive methods may allow for more refined patient-physician discussions regarding treatment options in a manner not possible with either stress imaging or CT

testing alone. Given this possibility, studies to address the clinical impact of FFR<sub>CT</sub> added to CT compared with traditional stress imaging algorithms are currently being designed.

This study has several limitations. The prescribed exclusion criteria disqualified individuals with prior CABG or PCI with suspected in-stent restenosis from study participation. Furthermore, not every vessel in study participants was interrogated after ethical review due to concerns regarding FFR in very low-risk or very severe coronary stenoses. Yet in this study, all vessels directly interrogated by FFR and FFR<sub>CT</sub> were ones that were deemed clinically indicated for evaluation. Also, it remains unknown whether revascularization of the ischemic lesions identified by FFR<sub>CT</sub> would achieve therapeutic reduction in ischemia from revascularization. The computational fluid dynamic-based algorithms that enable calculation of FFR<sub>CT</sub> also allow for “virtual” revascularization, and the ability of FFR<sub>CT</sub> to predict the extent of ischemia resolution after revascularization is currently under investigation. Finally, to study patients for whom and vessels for which FFR<sub>CT</sub> would most likely be used in clinical practice, we examined a subset of patients with intermediate anatomic stenosis severity. This population is the most challenging in which any imaging mode can discriminate ischemia. Despite this restriction, FFR<sub>CT</sub> compared favorably with CT stenosis alone.

## CONCLUSION

Although the study did not achieve its prespecified primary outcome goal for the level of per-patient diagnostic accuracy, use of noninvasive FFR<sub>CT</sub> plus CT among stable patients with suspected or known CAD was associated with improved diagnostic accuracy and discrimination compared with CT alone for the diagnosis of hemodynamically significant CAD when FFR at the time of ICA served as the referent standard.

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**Study concept and design:**

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