Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

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Context Coronary computed tomographic (CT) angiography is a noninvasive 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_CT) 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_CT 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_CT between October 2010 and October 2011. Computed tomography, ICA, FFR, and FFR_CT were interpreted in blinded fashion by independent core laboratories. Accuracy of FFR_CT and CT for diagnosis of ischemia was compared with an invasive FFR reference standard. Ischemia was defined by an FFR or FFR_CT 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_CT 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_CT 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_CT 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_CT 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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steno sis 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. 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. 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. 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. 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. 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 instantaneous 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. 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 subtotally (≥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 intermediate, 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.

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. 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.9

**Blinded Integration of FFR and CT**

Direct comparison of FFRCT with FFR necessitated FFRCT calculation at the precise location of the wire transducer at the time of FFR. To maintain blinding of the FFRCT 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 FFRCT core laboratory by an arrow on a 3-dimensional volume-rendered CT image of the coronary arteries.

**Computation of FFRCT**

Computation of FFRCT was performed in blinded fashion by the FFRCT core laboratory (HeartFlow Inc, Redwood City, California). Calculations of coronary blood flow 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.13 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 FFRCT ratio was obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure. Similar to invasive FFR, default FFRCT 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 FFRCT 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 FFRCT 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 0.33 proportion of patients with ischemia by FFR, a total of 219 evaluable patients were required to achieve greater than 70% 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 FFRCT 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 FFRCT core laboratory) and with invasive FFR, which served as the reference standard.

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Table 2. Patient and Vessel Characteristics by ICA, FFR, CT, and FFRCT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of Vesselsa</th>
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<tbody>
<tr>
<td>ICA and FFR characteristics (n = 406 vessels from 252 patients)</td>
<td></td>
</tr>
<tr>
<td>Obstructive CAD (=50% stenosis)b</td>
<td>190 (46.5)</td>
</tr>
<tr>
<td>Average diameter stenosis, mean (SD), %b</td>
<td>46.8 (15.7)</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>223 (54.6)</td>
</tr>
<tr>
<td>LCx</td>
<td>95 (23.3)</td>
</tr>
<tr>
<td>RCA</td>
<td>90 (22.1)</td>
</tr>
<tr>
<td>FFR ≤ 0.80b</td>
<td>151 (37.1)</td>
</tr>
<tr>
<td>CT and FFRCT characteristics (n = 406 vessels from 252 patients)</td>
<td></td>
</tr>
<tr>
<td>Obstructive CAD (=50% stenosis)c</td>
<td>216 (53.2)</td>
</tr>
<tr>
<td>&gt;90% Stenosis</td>
<td>79 (19.5)</td>
</tr>
<tr>
<td>Coronary calcium score, mean (SD), Agatston unitsd</td>
<td>381.5 (401.0)</td>
</tr>
<tr>
<td>Scan quality</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>309 (76.2)</td>
</tr>
<tr>
<td>Good</td>
<td>86 (21.0)</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
</tr>
<tr>
<td>FFRCT ≤ 0.80b</td>
<td>216 (53.3)</td>
</tr>
</tbody>
</table>

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

aData are reported as No. (%) unless otherwise indicated.
bBy quantitative coronary angiography in vessels directly interrogated by FFR and FFRCT (n = 407).
cComputed tomographic interpretation was missing in 2 patients.
dAvailable in 218 patients.

lected to represent a given patient (minimum FFR, minimum FFRCT, highest CT stenosis category). Fractional flow reserve and FFRCT 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 account 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 al19 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 FFRCT and FFR.

One vessel had missing FFRCT 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 FFRCT. Because FFR and FFRCT 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 FFRCT 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 FFRCT 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 FFRCT among patients with intermediate CT stenosis severity wherein the clinical utility of FFRCT 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%.2 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 FFRCT between October 2010 and October 2011, 31 patients were excluded by the CT core laboratory for nonevaluable CTS and 2 laboratories were excluded for unresolved integration of the FFR wire transducer location by ICA to its corresponding 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 FFRCT 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 FFRCT (Figure 2). The numbers of patients within the intention-to-diagnose sample with FFRCT 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 FFRCT for Diagnosis of Ischemia

Per-patient performance of FFRCT and CT is listed in Table 4. Diagnostic accuracy for FFRCT 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 FFRCT alone with CT stenosis of 50% or greater alone, FFRCT 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% stenosis, 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

**A** Study patient with ischemia
- Multiplanar reformat of CT angiogram
- Fractional flow reserve computed from CT (FFR$_{CT}$)
- Invasive coronary angiogram

**B** Study patient without ischemia
- Multiplanar reformat of CT angiogram
- Fractional flow reserve computed from CT (FFR$_{CT}$)
- Invasive coronary angiogram

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.

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COMMENT

In this multicenter international study of stable patients with suspected or known CAD, we observed that FFRCT—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 FFRCT 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, FFRCT, when added to CT, improved diagnostic accuracy vs CT alone, driven by improvements in sensitivity as well as specificity. These results suggest that FFRCT 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 FFRCT 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 FFRCT were high, indicating a low rate of false-negative studies. These diagnostic features of FFRCT 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 FFRCT results are normal. Nevertheless, de-

Table 3. No. of Patients With FFRCT and FFR Above and Below the 0.80 Threshold in the Intention-to-Diagnose Sample

<table>
<thead>
<tr>
<th>Per-Vessel Performance</th>
<th>Per-Patient Performance</th>
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<tbody>
<tr>
<td></td>
<td>FFRCT ≤ 0.80</td>
</tr>
<tr>
<td>FFR ≤ 0.80</td>
<td>121</td>
</tr>
<tr>
<td>FFR &gt; 0.80</td>
<td>96</td>
</tr>
</tbody>
</table>

Abbreviations: FFR, fractional flow reserve; FFRCT, fractional flow reserve calculated from computed tomography.

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

<table>
<thead>
<tr>
<th></th>
<th>Estimate, % (95% CI)</th>
<th>No. of Patients in Group</th>
<th>Estimate, % (95% CI)</th>
<th>No. of Patients in Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>73 (67-78)</td>
<td>252</td>
<td>64 (58-70)</td>
<td>252</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90 (84-95)</td>
<td>129</td>
<td>84 (77-90)</td>
<td>129</td>
</tr>
<tr>
<td>Specificity</td>
<td>54 (46-63)</td>
<td>123</td>
<td>42 (34-51)</td>
<td>123</td>
</tr>
<tr>
<td>PPV</td>
<td>67 (60-74)</td>
<td>172</td>
<td>61 (53-67)</td>
<td>180</td>
</tr>
<tr>
<td>NPV</td>
<td>84 (74-90)</td>
<td>80</td>
<td>72 (61-81)</td>
<td>72</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomographic angiography; FFRCT, 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 FFRCT ≤ 0.80 and CT Stenosis ≥ 50% Compared With Invasive FFR for Diagnosis of Ischemia

FFR indicates fractional flow reserve; CT, computed tomographic angiography; FFRCT, fractional flow reserve calculated from CT.
Despite its superiority to CT alone, the diagnostically specific 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 clinical and economic 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. 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. However, overestimation of stenosis severity by CT has been observed, and even among stenoses considered obstructive by CT analysis that are subsequently confirmed by ICA, only a minority cause ischemia. 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. 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. 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 retroperitoneal 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. 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-

**Table 5.** Per-Patient Diagnostic Performance of FFR_{CT} ≤0.80 and CT ≥50% vs FFR ≤0.80 Among Patients With Intermediate CT StenosisSeverity (30%-70%)

<table>
<thead>
<tr>
<th></th>
<th>FFR_{CT} ≤0.80</th>
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<th>CT &gt;50%</th>
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<tbody>
<tr>
<td></td>
<td>Estimate, %</td>
<td>No. of Patients in Group</td>
<td>Estimate, %</td>
<td>No. of Patients in Group</td>
</tr>
<tr>
<td>Accuracy</td>
<td>71 (61-80)</td>
<td>83</td>
<td>57 (46-67)</td>
<td>83</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>82 (63-92)</td>
<td>27</td>
<td>37 (22-56)</td>
<td>27</td>
</tr>
<tr>
<td>Specificity</td>
<td>66 (53-77)</td>
<td>56</td>
<td>66 (53-77)</td>
<td>56</td>
</tr>
<tr>
<td>PPV</td>
<td>54 (39-68)</td>
<td>41</td>
<td>34 (20-53)</td>
<td>29</td>
</tr>
<tr>
<td>NPV</td>
<td>88 (75-95)</td>
<td>42</td>
<td>68 (55-79)</td>
<td>54</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomographic angiography; FFR_{CT}, fractional flow reserve calculated from CT; NPV, negative predictive value; PPV, positive predictive value.
sions. Furthermore, this testing mis-
classifies a significant proportion of
patients as low risk and has signifi-
cant false-positive and false-negative
rates such that the proportion of pa-
tients undergoing ICA after testing in
whom no obstructive CAD is identi-
ﬁed remains substantial.25,26

Accordingly, some have advocated
for hybrid imaging with physiologic and
anatomic evaluation of CAD by stress
testing and CT, respectively.27 How-
ever, this approach requires 2 tests and
is associated with higher costs and
greater per-patient radiation burden.
The addition of FFRCT to CT may al-
low for combined anatomic-physi-
ologic assessment of CAD from perform-
ance of a single imaging test in a
manner that may promote salutary out-
comes. Future studies to assess the
clinical effectiveness and cost-
effectiveness of such an approach now
appear warranted.

Importantly, the prespeciﬁed pri-
mary end point for FFRCT was selected
on the basis of an array of prior stud-
ies that have demonstrated 70% to be
generally at the mid point of reported
diagnostic accuracies for stress imaging,
depending on test type, patient popu-
lation, and disease prevalence.28 In this
study, FFRCT demonstrated a per-
gramatic accuracy of 73%, with
conﬁdence intervals that suggest a di-
agnostic accuracy as low as 67% and
as high as 78%. These ﬁndings establish
a performance of FFRCT that is within
the range of conventional stress imaging
testing. Furthermore, considerable
added value of FFRCT exists when an
anatomic imaging test such as CT is
used as an alternative test to stress
imaging for CAD evaluation. The sig-
niﬁcant gain in discriminatory power
of FFRCT relative to anatomic CT ste-
nosis alone supports its potential ap-
lication to identify individuals with is-
chemic stenoses, and the combined
anatomic and physiologic informa-
tion imparted by these noninvasive
methods may allow for more reﬁned pa-
tient-physician discussions regarding
treatment options in a manner not pos-
sible with either stress imaging or CT
testing alone. Given this possibility,
studies to address the clinical impact
of FFRCT added to CT compared with
traditional stress imaging algorithms are
currently being designed.

This study has several limitations.
The prescribed exclusion criteria dis-
qualiﬁed individuals with prior CABG
or PCI with suspected in-stent restes-
fion from study participation. Fur-
thermore, not every vessel in study par-
ticipants was interrogated after ethical
review due to concerns regarding FFR
in very low-risk or very severe coro-
nary stenoses. Yet in this study, all ves-
sels directly interrogated by FFR and
FFRCT were ones that were deemed
clinically indicated for evaluation. Also,
remains unknown whether revascu-
larization of the ischemic lesions iden-
tiﬁed by FFRCT would achieve ther-
apeutic reduction in ischemia from
revascularization. The computational
data analysis algorithms that enable calculation of FFRCT also allow
for “virtual” revascularization, and the ability of FFRCT to predict the extent of
ischemia resolution after revascular-
ization is currently under investiga-
tion. Finally, to study patients for whom
and vessels for which FFRCT would
most likely be used in clinical prac-
tice, we examined a subset of patients
with intermediate anatomic stenosis se-
verity. This population is the most chal-
eling in which any imaging mode can
discriminate ischemia. Despite this re-
striction, FFRCT 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 ac-
curacy, use of noninvasive FFRCT plus
CT among stable patients with sus-
pected 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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