Non-invasive Fractional Flow Reserve Derived from CT Angiography (FFR_CT) for Coronary Lesions of Intermediate Stenosis Severity: Results from the DeFACTO Study

Nakazato et al: FFR_CT for Intermediate Stenosis

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DOI: 10.1161/CIRCIMAGING.113.000297

Journal Subject Codes: Diagnostic testing:[124] Cardiovascular imaging agents/techniques, Atherosclerosis:[150] Imaging, Diagnostic testing:[30] CT and MRI, Diagnostic testing:[29] Coronary imaging: angiography/ultrasound/Doppler/CC
Abstract

Background—Fractional flow reserve derived from coronary CT angiography (FFR_{CT}) is a non-invasive method for diagnosis of ischemic coronary lesions. To date, the diagnostic performance of FFR_{CT} for lesions of intermediate stenosis severity remains unexamined.

Methods and Results—Among 407 vessels from 252 patients at 17 centers who underwent CT, FFR_{CT}, invasive coronary angiography (ICA) and invasive FFR, we identified 150 vessels of intermediate stenosis by CT, defined as 30-69% stenosis. FFR_{CT}, FFR and CT were interpreted in blinded fashion by independent core laboratories. FFR_{CT} and FFR \leq 0.80 were considered hemodynamically significant, while CT stenosis \geq 50% was considered obstructive. Diagnostic performance of FFR_{CT} versus CT was assessed for accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV). Area under the receiver-operating-characteristics curve (AUC) and net reclassification improvement (NRI) were evaluated. For lesions of intermediate stenosis severity, FFR_{CT} accuracy, sensitivity, specificity, PPV and NPV was 71%, 74%, 67%, 41% and 90%; and CT stenosis accuracy, sensitivity, specificity, PPV and NPV was 63%, 34%, 72%, 27% and 78%. FFR_{CT} demonstrated superior discrimination compared to CT stenosis on per-patient (AUC: 0.81 vs. 0.50, \( P = 0.0001 \)) and per-vessel basis (AUC: 0.79 vs. 0.53, \( P <0.0001 \)). FFR_{CT} demonstrated significant reclassification of CT stenosis for lesion-specific ischemia (NRI 0.45, 95% CI 0.25-0.65, \( P = 0.01 \)).

Conclusions—FFR_{CT} possesses high diagnostic performance for diagnosis of ischemic for lesions of intermediate stenosis severity. Notably, the high sensitivity and NPV suggests the ability of FFR_{CT} to effectively rule out intermediate lesions that cause ischemia.

Key Words: computed tomography angiography, intermediate coronary lesion, computational flow dynamics, fractional flow reserve; noninvasive imaging
Abbreviations list

CAD = coronary artery disease

CCTA = coronary computed tomographic angiography

DeFACTO = Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography

FFR = fractional flow reserve

FFR_CT = FFR from CT

ICA = invasive coronary angiography

LAD = left anterior descending artery

LCX = left circumflex artery

NPV = negative predictive value

PCI = percutaneous coronary interventions

PPV = positive predictive value

QCA = quantitative coronary angiography

RCA = right coronary artery
Coronary CT angiography (CCTA) is a non-invasive test that enables direct visualization of coronary artery disease (CAD) and correlates favorably with invasive coronary angiography (ICA) for measures of luminal diameter stenosis severity. Yet, the accuracy of CCTA in comparison to ICA in clinical practice CCTA tends towards overestimation of stenosis severity, which may lead to increase in downstream testing, radiation dose and cost. Although current generation CCTA exhibits high negative predictive value (NPV) to exclude ≥50% obstructive coronary artery stenosis, CCTA cannot determine physiologic significance of lesions and even among CCTA-identified obstructive stenoses confirmed by ICA, fewer than half are ischemia-causing. Importantly, ischemia is present in an important minority of patients with stenoses of intermediate severity who experience reductions in coronary blood flow and myocardial ischemia beyond traditional angiographic definitions of obstructive stenoses.

Fractional flow reserve (FFR) is a lesion-specific technique to determine the functional importance of a coronary stenosis. FFR is often employed for determination of the physiologic significance of coronary lesions of intermediate stenosis severity. Its use as a guide to revascularization has been demonstrated to improved outcomes and reduces health care costs.

Recently, computation of FFR from CT (FFR_{CT}) has emerged as a novel non-invasive method that demonstrates high diagnostic performance for identification and exclusion of patients and coronary lesions that cause ischemia. To date, the diagnostic performance of FFR_{CT} for lesions of intermediate stenosis severity remains unexamined. To address this, we examined the performance of FFR_{CT} for assessment of coronary
lesions of intermediate stenosis severity by CCTA within a subset of individuals enrolled in the prospective multicenter international Determination of Fractional Flow Reserve by Anatomic Computed TOmographic Angiography, or DeFACTO, study.\textsuperscript{15,16}

Methods

Study design and patients

The rationale, design, and overall study results of the DeFACTO study have been reported previously.\textsuperscript{15,16} Briefly, DeFACTO was designed to evaluate the accuracy of FFR\textsubscript{CT} to diagnose hemodynamically-significant CAD, as defined by an invasive FFR reference standard, with a targeted population of subjects with suspected CAD who were referred for clinically-indicated non-emergent ICA within 60 days of performance of CT. Patients with prior coronary artery bypass graft surgery and suspected in-stent restenosis on the basis of CCTA were excluded, and final population consisted of 252 patients with 407 vessels. The DeFACTO study was conducted at 17 centers in five countries (Belgium [n=1], Canada [n=1], Latvia [n=1], South Korea [n=2], 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. The study was consistent with the principles of the Declaration of Helsinki.
Image acquisition and analysis for CCTA

CCTA was performed on ≥64 detector row CT scanners by prospective or retrospective electrocardiographic gating.\(^{17,18}\) CCTAs were transferred to a central core laboratory (Harbor UCLA Medical Center, Los Angeles, California) for blinded interpretation using an 18-segment coronary model. CCTAs were evaluated for maximal patient-, vessel-, and segment-based diameter stenosis, which was categorized as 0%, 1% to 29%, 30% to 49%, 50% to 69% or 70% or larger. Lesions of ≥50% were categorized as angiographically obstructive. Per-patient stenosis was defined as the greatest stenosis within any coronary segment, while per-vessel stenosis was defined by a maximal stenosis in any segment within each major epicardial vessel distribution. Vessel distributions were categorized as: left anterior descending artery (LAD, distribution including the first and second diagonal branches), left circumflex artery (LCX, distribution including the ramus intermedius, first and second obtuse marginal branches, and left posterolateral branch), and right coronary artery (RCA, distribution including the right posterolateral branch and posterior descending artery). The posterior descending artery was included in the LCX distribution for left-dominant coronary systems. Stenoses of intermediate severity were defined as 30-69% diameter stenosis.

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.\(^{19}\) Invasive coronary
angiograms were transferred to a central angiographic core laboratory (University of British Columbia, Vancouver, Canada) for blinded quantitative coronary angiography (QCA) of all vessels using commercially available software (Discovery Quinton).

**Fractional flow reserve**

FFR was performed at the time of ICA (PressureWire Certus, St Jude Medical Systems; ComboWire, Volcano Corp). Investigators performed FFR in vessels demonstrating an ICA stenosis and with clinical indication for FFR evaluation. After administration of nitroglycerin, a pressure-monitoring guide wire was advanced distal to a stenosis. Hyperemia was induced by intravenous or intracoronary administration of adenosine at a rate of 140 μg/kg/min. FFR 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 ≤0.80.5

**Computation of FFR\textsubscript{CT}**

Computation of FFR\textsubscript{CT} was performed in blinded fashion by the FFR\textsubscript{CT} core laboratory (HeartFlow Inc, Redwood City, California). Calculations of FFR\textsubscript{CT} were performed by computational fluid dynamic modeling after semiautomated segmentation of coronary arteries and left ventricular mass. 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.\textsuperscript{20} 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\textsubscript{CT} ratio was obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure.

**Blinded integration of FFR and CCTA**

In order to enable direct comparison of FFR\textsubscript{CT} to FFR at the precise location where the FFR was measured, a blinded core laboratory (Minneapolis Heart Institute, Minneapolis, MN) performed an integration step. This integration step involved matching the location on the CCTA to the location on the invasive angiogram where the distal FFR wire tip was placed, and communication of this point to the FFR\textsubscript{CT} core laboratory by an arrow on a 3-dimensional volume-rendered CT image of the coronary arteries.

**Statistical analyses**

Analyses were conducted for FFR\textsubscript{CT} on an intention-to-diagnose sample, defined as all patients with interpretable CCTAs as determined by the CT core laboratory with invasive FFR, which served as the reference standard. Categorical variables are presented as frequency and percentage and continuous variables as mean ± SD. FFR and FFR\textsubscript{CT} measurements were recorded on a continuous scale and dichotomized at the 0.80 threshold.
(values ≤0.80 considered ischemia). Stenosis on CCTA was recorded on an ordinal scale and dichotomized at the 50% threshold, with stenosis of ≥50% considered obstructive. Intermediate stenosis lesions (30-69%) by CCTA were further evaluated by sub-category with 30-49% and 50-69% stenosis.

Analyses were performed on per-patient and per-vessel basis. In per-patient analysis, vessels with the most adverse clinical status were selected to represent a given patient (minimum FFR, minimum FFR<sub>CT</sub>, highest CT stenosis category). In per-patient analysis, the diagnostic performance of CT stenosis alone vs. FFR<sub>CT</sub> alone was evaluated for accuracy, sensitivity, specificity, positive predictive value (PPV) and NPV. Diagnostic measures of accuracy were obtained for binary FFR<sub>CT</sub> predicting binary FFR (gold standard), both using the 0.80 threshold, stratified over low, intermediate, or high levels of pretest CADENZA likelihood of CAD.<sup>21</sup>

In order to account for the correlation of coronary artery segments within patients in an unbalanced design, a random effects logit model for binary data was applied, where the outcome (FFR ≤0.80) was modeled using a binomial distribution and a logit link function, with patient ID the random component.<sup>22</sup> All diagnostic performance analyses were reported using this method. Bland–Altman analysis was performed using FFR as the reference standard. Additionally, a per-vessel analysis was done in intermediate-stenosis vessels grouped by proximal, mid, or distal location.

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>23</sup> Further, we evaluated net reclassification improvement (NRI) of FFR<sub>CT</sub> compared to CT stenosis on per-patient basis for the intermediate stenosis group.
In order to calculate the intermediate NRI, clinical cut points for low, intermediate and high were defined by stenoses <30%, 30-69%, and ≥70% for CT stenosis; and by >0.80, 0.75-0.80, and ≤0.75 for FFR<sub>CT</sub>. For NRI calculations, cases were defined as patients having lesion-specific ischemia (FFR ≤0.80) while controls were defined as those without lesion specific ischemia (FFR >0.80). Associations and differences were identified, with p values <0.05 were considered significant. Statistical analyses were performed using STATA software (version 11, StataCorp LP, College Station, TX).

Results

Patient characteristics

Of the 252 patients in the DeFACTO study, 82 patients (33%) had 150 vessels with CCTA confirmed maximal diameter stenosis 30% to 69%, which differed by 1 patient from our original report. In the current study, we restricted the patients for whom the maximal CT stenosis was intermediate in severity, thus resulting in the exclusion of a single patient with a high-grade lesion. Baseline characteristics of this study population are presented in Table 1 and were not different from the overall DeFACTO study population. Among the 150 vessels of intermediate stenosis severity interrogated by FFR, 35 (23%) were considered ischemic by FFR while 64 (43%) were considered ischemic by FFR<sub>CT</sub>. Prevalence of lesions with 30% to 49% and 50% to 69% stenosis were 71% (106/150) and 29% (44/150), respectively. Prevalence of lesion-specific ischemia was 22% (23/106) in 30-49% stenosis and 27% (12/44) in 50-69% stenosis. Distributions of FFR by CT stenosis category are
shown in Supplemental Figure 1.

**FFR\textsubscript{CT} and FFR**

The correlation was moderate between FFR and QCA (\(r=0.42, p<0.0001\)), between FFR and FFR\textsubscript{CT} (\(r=0.50, p<0.0001\)) (Figure 1A). In overall, Bland-Altman limits of agreement for FFR value ranged from -0.3 to 0.1 with slight underestimation of FFR\textsubscript{CT} compared with FFR (bias -0.05) (Figure 1B). Bland-Altman plots in each vessel are shown in Figure 1C-E. A difference in mean values between FFR and FFR\textsubscript{CT} was observed (0.85 ± 0.08 vs. 0.80 ± 0.11, \(P<0.0001\)).

**Diagnostic performance of FFR\textsubscript{CT} for diagnosis of ischemia**

Among individuals with intermediate lesions, the per-patient diagnostic accuracy, sensitivity, specificity, PPV and NPV were 73\% (95\% CI 62\%-82\%), 82\% (95\% CI 62\%-94\%), 69\% (95\% CI 55\%-81\%), 56\% (95\% CI 40\%-72\%) and 88\% (95\% CI 75\%-96\%) for FFR\textsubscript{CT}; 55\% (95\% CI 43\%-66\%), 37\% (95\% CI 19\%-58\%), 64\% (95\% CI 50\%-76\%), 33\% (95\% CI 17\%-53\%) and 67\% (95\% CI 53\%-80\%) for CT stenosis. Per-vessel diagnostic performance of FFR\textsubscript{CT} and CT stenosis for diagnosis of lesion-specific ischemia in lesions of intermediate severity is listed in Figure 2. For lesions of intermediate severity, FFR\textsubscript{CT} demonstrated accuracy, sensitivity, specificity, PPV and NPV of 69\% (95\% CI 61\%-76\%), 74\% (95\% CI 57\%-88\%), 67\% (95\% CI 58\%-75\%), 41\% (95\% CI 29\%-54\%) and 90\% (95\% CI 81\%-95\%); while CT stenosis demonstrated accuracy,
sensitivity, specificity, PPV and NPV of 63% (95% CI 55%-71%), 34% (95% CI 19%-52%), 72% (95% CI 63%-80%), 27% (95% CI 15%-43%) and 78% (95% CI 69%-86%).

Agreement of stenosis grade between CCTA and QCA was 58% for 30-49% CCTA stenosis and 57% for 50-69% CCTA stenosis. The diagnostic performance in subgroup with concordant lesions and discordant lesions are listed in Table 2.

In per-patient diagnostic performance as a function of pretest likelihood of CAD, NPV was high in both low-intermediate (<70%) as well as high (≥70%) pretest likelihood of CAD (Supplemental Table 1). Diagnostic performance of lesion location for diagnosis of lesion-specific ischemia is shown in Table 3. NPV of FFR\textsubscript{CT} was higher than CT stenosis for coronary lesions in proximal or mid segments (88%) as well as distal segments (100%).

**Discrimination of ischemia for coronary lesions of intermediate stenosis by FFR\textsubscript{CT} and CCTA**

On a per-patient basis FFR\textsubscript{CT} demonstrated superior discrimination over CT stenosis (AUC, 0.81 [95% CI, 0.72-0.90] vs 0.50 [95% CI, 0.39-0.61]; difference, 0.31; \(P = 0.0001\)) in predicting abnormal FFR ≤0.80 (Figure 3A).

Similarly, on a per-vessel basis FFR\textsubscript{CT} also demonstrated superior discrimination over CT stenosis (AUC, 0.79 [95% CI, 0.72-0.87] vs 0.53 [95% CI, 0.44-0.62]; difference, 0.26; \(P <0.0001\)) (Figure 3B). Greater discriminatory power was demonstrated in FFR\textsubscript{CT} compared to CCTA both in per-patient and per-vessel basis.

FFR\textsubscript{CT} demonstrated accuracy, sensitivity, specificity, PPV and NPV of 81% (95% CI 72%-88%), 74%
(95% CI 52%-90%), 83% (95% CI 73%-91%), 55% (95% CI 36%-73%), 92% (95% CI 83%-97%) for lesions of 31-49% stenosis and 66% (95% CI 50%-80%), 42% (95% CI 15%-72%), 75% (95% CI 57%-89%), 39% (95% CI 14%-68%), 77% (95% CI 59%-90%) for lesions of 50-69% stenosis. ROC curves of FFR\textsubscript{CT} for lesion specific ischemia are depicted in Figure 2C and 2D for vessels with CT stenosis 31-49% and 50-69%, respectively.

**Net reclassification improvement of ischemic lesions**

Among total 82 patients of intermediate stenosis severity interrogated by FFR, 55 (67%) were considered non-ischemic by FFR >0.80, while 27 (33%) were considered ischemic by FFR \(\leq 0.80\). Thirty nine patients were correctly reclassified by FFR\textsubscript{CT} over CT stenosis, while only 7 patients were incorrectly reclassified by FFR\textsubscript{CT} over CT stenosis. FFR\textsubscript{CT} enabled effective reclassification in the study population over CT stenosis (NRI 0.45, 95% CI 0.25-0.65, \(P = 0.003\)). Representative examples of stenoses of intermediate severity that did versus did not cause ischemia are shown in Figures 4 and 5.

**Discussion**

In the present study, we examined the performance of non-invasive FFR\textsubscript{CT} for identification and exclusion of ischemia-causing lesions of intermediate stenosis severity as confirmed by a blinded CCTA core laboratory. Our study findings demonstrate improved diagnostic performance of FFR\textsubscript{CT} over CT stenosis for diagnosis of
ischemia-causing lesions.

In particular, a high NPV of $\text{FFR}_{\text{CT}}$ suggests its use as a potential method to successfully exclude ischemia possible need of revascularization in lesions of intermediate stenosis severity. These findings are particularly important, given prior reports that have demonstrated that stenosis severity is often overestimated by CCTA, which may contribute to generally high rates of referral to ICA following CCTA. The ability of $\text{FFR}_{\text{CT}}$ to exclude physiologically significant coronary stenosis may empower clinicians to avoid unnecessary invasive procedure in a manner not possible from stenosis assessment alone. Nevertheless, the high NPV of $\text{FFR}_{\text{CT}}$ must be viewed with caution, given that some patients with hemodynamically significant CAD may be missed even by this technology. Future large-scale studies will be required to determine the effect of this technology on health outcomes.

Importantly, $\text{FFR}_{\text{CT}}$ enabled improved discrimination as well as effective reclassification of individuals for intermediate ischemic lesions over measures of CT stenosis. These findings are germane, especially for individuals whose stenoses do not meet the traditional criteria of angiographically severe, yet confer hemodynamic importance that may explain symptoms of angina. In this regard, it is notable that $\text{FFR}_{\text{CT}}$ was consistently effective for proximal or mid/distal vessel segments and across all measures of pretest likelihood of CAD.

Current guidelines recommend that CAD evaluation should be differentially based on patient pretest risk assessment. Low-risk patients are recommended to receive only expectant medical management, while
intermediate-to-high risk patients are considered candidates for non-invasive testing with imaging.24 To date, these non-invasive tests have been constrained to either an anatomic approach—such as with CCTA—to identify obstructive CAD or a physiologic approach to determine ischemia by relative hypoperfusion or left ventricular wall motion via an array of available stress test types. To date, a combined anatomic-physiologic assessment by a single non-invasive test has been lacking, with either anatomic or physiologic approaches generally reliant upon the other. This sequential testing has evoked concerns of excess resource utilization, higher radiation doses and unnecessary invasive angiography.

By invasive methods, FFR is often employed for determination of the physiologic significance of coronary lesions of intermediate stenosis severity, and its performance enables guidance of PCI in a manner that results in improved event-free survival and reduced resource utilization.5, 13, 14 In the current study, we analyzed the lesions of intermediate stenosis severity as visualized by CCTA. These types of lesion are difficult for diagnostic evaluation, given that they fall below conventional definitions of angiographically “severe.” Yet these lesions are often associated with considerable rates of ischemia. Diffuse mild luminal narrowing has been demonstrated to be associated with reduced stress-induced myocardial blood flow and abnormal epicardial coronary artery resistance even before a high-grade segmental stenosis is apparent.6, 7, 25 Uren et al. assessed the relationship between the severity of stenosis in a coronary artery and the degree of impairment of myocardial blood flow using O15-water PET.25 They found that among the patients with stenoses of ≥40% of diameter stenosis myocardial blood flow during hyperemia and myocardial flow reserve progressively decreases as the
degree of stenosis increased (40-59% and 60-79%). Myocardial blood flow during hyperemia in the patients
with stenoses <40% was not significantly different from myocardial blood flow in patients with no stenosis, in
keeping with the present study results.

Pathophysiologically, the totality of atherosclerosis proximal to a coronary lesion has been
demonstrated as vital to the contribution of ischemia. De Bruyne et al. reported that early stage coronary
atherosclerosis with mild coronary stenoses are often associated with abnormal resistance of the epicardial
coronary arteries before a high-grade segmental stenosis is apparent at angiography by ICA. In addition to the
resistance caused by focal stenosis or by arteriolar vasomotor dysfunction, diffusely atherosclerotic epicardial
coronary arteries without high-grade segmental stenoses often manifest a continuous pressure decline along their
length, reduced coronary flow reserve, as well as induce myocardial ischemia. These findings suggest the
importance of measuring the atherosclerotic plaque in high-grade stenotic lesions as well as the angiographically
less severe lesions that may include diffuse atherosclerosis. This issue is underscored by the almost one-quarter
of intermediate lesions in the current study which were associated with ischemia, a finding that mirrors prior
 multicenter studies. In particular, in the present study, despite an angiographically milder appearance of 30% to
49% stenosis, 22% of such lesions were nevertheless causal of ischemia. The converse was also observed in that
lesions between 50-69% luminal narrowing manifested ischemia only 27% of the time. These findings
emphasize the need for functional assessment of the hemodynamic significance of intermediate coronary artery
lesions, given that measurements of stenosis demonstrate an unreliability to ischemia presence. In this regard,
FFR_{CT} may serve to advance the non-invasive diagnostic approach by providing a “one-stop-shop” for integrated anatomic-physiologic assessment of CAD. Importantly, in contradistinction to physiologic stress testing methods, FFR_{CT} provides an index of epicardial stenosis-related ischemia and thus, may provide an added diagnostic advantage of being able to pinpoint the specific lesion that causes ischemia. These features may allow for more judicious selection of patients for ICA and of vessels for coronary revascularization than methods that can only assess myocardial hypoperfusion that may occur from an array of causes that include epicardial stenosis but also endothelial dysfunction and microvascular disease.

Our current study findings, if proven, may also contribute substantively to assessing individuals’ prognosis. Bech et al. reported in the 2-year follow-up, in patients referred for PCI of intermediate stenosis without objective proof of ischemia by noninvasive testing, approximately half of these stenoses were not hemodynamically significant.\textsuperscript{26} Compared with medical treatment, PCI in these patients did not reduce adverse cardiac events or the use of antianginal drugs, nor did it result in a better functional angina class). In contrast, in patients with intermediate stenosis and ischemic FFR, which indicates hemodynamic significance, PCI resulted in a significantly greater improvement in functional class. Subsequently, Pijls et al. reported at 5-year follow-up, in patients with intermediate stenosis without evidence of ischemia by noninvasive test, the most important prognostic factor was myocardial ischemia by FFR.\textsuperscript{27} In those patients, even when treated by PCI, clinical outcome is significantly worse than in patients with non-ischemic FFR.

Recently, a subanalysis of the Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive
Fractional Flow Reserve (DISCOVER-FLOW) trial was reported.\textsuperscript{28} In this study, high diagnostic performance of FFR\textsubscript{CT} was observed for diagnosis of ischemia for lesions of intermediate stenosis severity, as judged by QCA, as well as high discrimination of lesions that do versus do not cause ischemia. FFR\textsubscript{CT} performed robustly against an invasive FFR reference standard, with good agreement to invasive FFR and without significant mean differences. The difference between the current study and the prior report is that the present data comprises all stenoses between 30-69\% stenosis severity as judged by CCTA in individuals with a maximal stenosis severity in the intermediate range. Further, the current data were derived from a large prospective, international, multicenter study. Finally, the present study results directly extends prior investigation findings by examining the ability of FFR\textsubscript{CT} to reclassify coronary artery lesions judged by CT stenosis to be ischemic versus non-ischemic, with almost half of all lesions correctly reclassified by FFR\textsubscript{CT}.

Notably, FFR\textsubscript{CT} also offers several operational advantages in that it does not require modification of CCTA protocols, does not require administration of additional medications beyond what is typically administered for CCTA, and does not confer any additional radiation.

This study is not without limitations. This present study was small, but represents the largest to date from a prospective multicenter study. We did not interrogate lesions <30\% previous studies have identified 30\% angiographic stenosis as a threshold below which ischemia is rarely observed, and ethical considerations precluded our performing invasive FFR in vessels in whom no significant CAD was present. We identified intermediate coronary stenoses by CCTA assessment at central core laboratory. Thus, whether the present study
results can be universally applied to practitioners interpreting CCTA in clinical setting requires further study. At present, only one for-profit company possesses a computational fluid dynamic solution for the calculation of FFR_{CT}, with several other groups developing their own proprietary software. The workflow of how FFR_{CT} will be utilized in clinical practice – whether on or off site – remains to be determined, as this technology is still in its investigational stage and not approved for commercial use in the US.

**Conclusion**

Compared to CCTA, FFR_{CT} provides higher diagnostic performance for lesions of intermediate stenosis severity, with a two-fold increase in sensitivity and high NPV. These data suggest a role for FFR_{CT} to non-invasively exclude ischemia with high certainty.

**Sources of Funding**

This study was funded by HeartFlow, Inc, Redwood City, California. HeartFlow, Inc. did not have involvement in the design of the study, nor were they involved in the data analysis, manuscript preparation, and review or authorization for submission.

**Disclosures**

Dr Berman reports receiving grant support from Siemens Medical Systems and Lantheus Medical Imaging. Drs
Budoff, Leipsic and Min report receiving grant support from GE Healthcare. The remaining authors have no disclosures relevant to this project.

References


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Table 1. Baseline patient characteristics in intermediate stenosis

<table>
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<tr>
<th>Variables</th>
<th>Mean ± SD or Frequency n (%)</th>
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<td>Age, years</td>
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<tr>
<td>Male gender</td>
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<td>Risk factors</td>
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<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>16 (20)</td>
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<tr>
<td>Dyslipidemia, n (%)</td>
<td>65 (79)</td>
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<tr>
<td>Family history of CAD</td>
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<td>Current smoker, n (%)</td>
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<tr>
<td>Prior myocardial infarction</td>
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<tr>
<td>Prior percutaneous coronary intervention</td>
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<td>Race/Ethnicity</td>
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<td>White</td>
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<td>Asisn</td>
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Table 2. Diagnostic performance of FFR\textsubscript{CT} and CT stenosis in concordant lesions and discordant lesions

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<th>Discordant lesions (n=64)</th>
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<td></td>
<td>Estimate, % (95% CI)</td>
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<tr>
<td></td>
<td>No. of patients in group</td>
<td>No. of patients in group</td>
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<tr>
<td>FFR\textsubscript{CT}</td>
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<tr>
<td>Accuracy</td>
<td>71 (60-80)</td>
<td>65 (53-77)</td>
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<tr>
<td></td>
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<td>64</td>
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<tr>
<td>Sensitivity</td>
<td>71 (44-90)</td>
<td>78 (52-94)</td>
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<tr>
<td>Specificity</td>
<td>71 (59-81)</td>
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<tr>
<td>PPV</td>
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<td>NPV</td>
<td>91 (80-97)</td>
<td>88 (71-97)</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>32</td>
</tr>
<tr>
<td>AUC</td>
<td>0.71 (0.58-0.83)</td>
<td>0.69 (0.57-0.82)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CT stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>65 (54-75)</td>
<td>61 (48-73)</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>64</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>35 (14-62)</td>
<td>33 (13-59)</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Specificity</td>
<td>73 (60-83)</td>
<td>72 (57-84)</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>46</td>
</tr>
<tr>
<td>PPV</td>
<td>24 (9-45)</td>
<td>32 (13-57)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>NPV</td>
<td>82 (70-91)</td>
<td>73 (58-85)</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>45</td>
</tr>
<tr>
<td>AUC</td>
<td>0.54 (0.41-0.67)</td>
<td>0.53 (0.40-0.66)</td>
</tr>
<tr>
<td></td>
<td>-</td>
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</table>
Table 3. Diagnostic performance of $\text{FFR}_{\text{CT}}$ and CT stenosis based upon lesion location within a vessel

<table>
<thead>
<tr>
<th></th>
<th>Proximal/mid (n=135)</th>
<th>Distal (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate, % (95% CI)</td>
<td>No. of patients in group</td>
</tr>
<tr>
<td>$\text{FFR}_{\text{CT}}$</td>
<td>Accuracy</td>
<td>68 (60-76) 135</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>73 (55-87) 33</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>67 (57-76) 102</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>41 (29-55) 58</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>88 (79.95) 77</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>0.70 (0.61-0.79)</td>
</tr>
<tr>
<td>CT stenosis</td>
<td>Accuracy</td>
<td>64 (55-72) 135</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>33 (18-52) 33</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>74 (64-82) 102</td>
</tr>
<tr>
<td></td>
<td>PPV</td>
<td>29 (15-46) 38</td>
</tr>
<tr>
<td></td>
<td>NPV</td>
<td>77 (68-85) 97</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>0.53 (0.44-0.63)</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1.** Correlation and Bland-Altman plot of FFR vs. FFR\textsubscript{CT} on per-vessel basis. Overall correlation between FFR and FFR\textsubscript{CT} (A). Bland-Altman plot for overall vessels (B), Left ascending coronary artery (C) Left circumflx artery (D), Right coronary artery (E). FFR\textsubscript{CT} = fractional flow reserve calculated from CT; FFR = fractional flow reserve.

**Figure 2.** Per-vessel diagnostic performance of FFR\textsubscript{CT} and CT stenosis among intermediate stenosis severity (30-69%). PPV = positive predictive value; NPV = negative predictive value; other abbreviations as in Figure 1.

**Figure 3.** Performance of FFR\textsubscript{CT} and CT stenosis for detecting ischemic lesions using FFR ≤ 0.80 as gold standard. Area under the receiver operating characteristics curve (AUC) of per-patient (A) and per-vessel (B) performance of FFR\textsubscript{CT} and CT stenosis ≥50% compared with invasive FFR for discriminating ischemic lesions. AUC for discriminating ischemic lesions in vessels with CT stenosis 31-49% (C) and 50-69% (D). AUC = area under the receiver operating characteristic curve.

**Figure 4.** Representative example of patient with ischemic RCA intermediate lesion.

(A) Multiplaner reformat of CCTA demonstrating intermediate stenosis (**white arrow**, corresponding cross sectional image is magnified) in the proximal portion of RCA. (B) Invasive coronary angiogram demonstrates
intermediate stenosis (white arrow) and FFR value of 0.74 (black arrow), indicating vessel ischemia. (C) FFR<sub>CT</sub> value of 0.71 (black arrow) indicating vessel ischemia. CCTA = coronary computed tomographic angiography; RCA = right coronary artery; QCA = quantitative coronary angiography. Other abbreviations as in Figure 1.

**Figure 5.** Representative example of patient with non-ischemic RCA intermediate lesion.

(A) Multiplaner reformat of CCTA demonstrating intermediate stenosis (white arrow, corresponding cross sectional image is magnified) in the mid portion of RCA. (B) Invasive coronary angiogram demonstrates intermediate stenosis (white arrow) and FFR value of 0.88 (black arrow), indicating vessel not causing ischemia. (C) FFR<sub>CT</sub> value of 0.82 (black arrow) indicating vessel not causing ischemia. Abbreviations as in Figure 1 and 4.
**A**

![Graph A](image)

- **FFR**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.81 (95% CI 0.72-0.90)

- **CT**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.50 (95% CI 0.39-0.62)

**B**

![Graph B](image)

- **FFR**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.79 (95% CI 0.72-0.87)

- **CT**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.53 (95% CI 0.44-0.62)

**C**

![Graph C](image)

- **FFR**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.83 (95% CI 0.74-0.92)

**D**

![Graph D](image)

- **FFR**
  - Sensitivity vs. 1-Specificity
  - AUC: 0.71 (95% CI 0.56-0.86)
CT stenosis 31-49%  QCA stenosis 50-69%
CT stenosis 31-49%  QCA stenosis 50-69%
Non-invasive Fractional Flow Reserve Derived from CT Angiography (FFR_{CT}) for Coronary Lesions of Intermediate Stenosis Severity: Results from the DeFACTO study

Ryo Nakazato, Hyung-Bok Park, Daniel S. Berman, Heidi Gransar, Bon-Kwon Koo, Andrejs Erglis, Fay Y. Lin, Allison M. Dunning, Matthew J. Budoff, Jennifer Malpeso, Jonathon Leipsic and James K. Min

_Circ Cardiovasc Imaging_, published online September 30, 2013;
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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Supplemental Table 1. Performance of $\text{FFR}_{\text{CT}}$ and CT stenosis for diagnosis of ischemia based upon pre-test likelihood of anatomically obstructive coronary artery disease

<table>
<thead>
<tr>
<th></th>
<th>Pretest likelihood &lt;70% (n=51)</th>
<th>Pretest likelihood ≥70% (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate, % (95% CI)</td>
<td>No. of patients in group</td>
</tr>
<tr>
<td>Accuracy</td>
<td>75 (60-86)</td>
<td>51</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>78 (52-94)</td>
<td>18</td>
</tr>
<tr>
<td>Specificity</td>
<td>73 (55-87)</td>
<td>33</td>
</tr>
<tr>
<td>PPV</td>
<td>61 (39-80)</td>
<td>23</td>
</tr>
<tr>
<td>NPV</td>
<td>86 (67-96)</td>
<td>28</td>
</tr>
<tr>
<td>AUC</td>
<td>0.75 (0.63-0.88)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>CT stenosis</strong></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>59 (44-72)</td>
<td>51</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>44 (22-69)</td>
<td>18</td>
</tr>
<tr>
<td>Specificity</td>
<td>67 (48-82)</td>
<td>33</td>
</tr>
<tr>
<td>PPV</td>
<td>42 (20-67)</td>
<td>19</td>
</tr>
<tr>
<td>NPV</td>
<td>69 (50-84)</td>
<td>32</td>
</tr>
<tr>
<td>AUC</td>
<td>0.56 (0.41-0.70)</td>
<td>-</td>
</tr>
</tbody>
</table>
Supplemental Figure 1.

Distributions of FFR by CT stenosis category. FFR = fractional flow reserve