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Workstation-Based Calculation of CTA-Based FFR for Intermediate Stenosis

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ABSTRACT

OBJECTIVES This study sought to evaluate the proportion of patients with intermediate coronary stenosis diagnosed on computed tomography angiography (CTA), which may be saved from any further testing due to use of CTA-based fractional flow reserve (FFR).

BACKGROUND Coronary CTA often results in diagnosis of intermediate stenosis, triggering further physiological testing. CTA-based FFR (CTA-FFR) is a promising diagnostic tool, which may obviate the need for further testing. However, the specific thresholds for CTA-FFR values predicting ischemic versus nonischemic FFR with acceptable confidence are unknown, obscuring clinical utility of the diagnostic strategy using CTA-FFR.

METHODS We analyzed 96 lesions (mean CTA stenosis: 69.7 ± 11.7%) in 90 patients (63.4 ± 8.2 years, 32% were men) who underwent CTA for suspected CAD and were diagnosed with at least 1 intermediate coronary stenosis (50% to 90%) scheduled for further physiological testing. All patients underwent routine invasive FFR and CTA-FFR evaluation. The objective was to determine the proportion of patients falling between the lower and upper CTA-FFR thresholds that predict ischemic and nonischemic stenosis, respectively (on the basis of an invasive FFR cutpoint of ≤0.80), with ≥90% accuracy.

RESULTS The invasive FFR ≤0.8 was observed in 41 of 96 lesions (42.7%). According to Bland-Altman analysis, the CTA-FFR underestimated FFR by 0.01 and the 95% limits of agreement were ±0.19. Receiver-operating characteristic area under the curve was significantly higher for CTA-FFR than that for CTA (per lesion 0.835 vs. 0.660, respectively; $p = 0.007$). The CTA-FFR thresholds for which the positive and negative predictive values were each ≥90% (corresponding to an FFR of ≤0.80) were >0.87 or <0.74, respectively, encompassing 49 lesions (51%) and 45 of 90 patients.

CONCLUSIONS In around one-half of the patients diagnosed with intermediate stenosis, coronary CTA-based FFR may confidently discriminate between ischemic versus nonischemic stenoses. Our findings require validation in an independent cohort. (J Am Coll Cardiol Img 2016;9:690–9) © 2016 by the American College of Cardiology Foundation.

Coronary computed tomography angiography (CTA) is a common diagnostic test indicated in patients with intermediate probability of coronary artery disease (CAD). However, it often ends up in a diagnosis of intermediate coronary stenosis, triggering further functional testing (1,2). Coronary computed tomography angiography-based fractional flow reserve (CTA-FFR) is an emerging method for noninvasive functional diagnosis of CAD (3–6). In this scenario, a complete diagnosis is provided due to fusion of both the anatomical test and computationally simulated surrogate of FFR, providing a "one-stop-shop" diagnostic tool. The success of the novel modality would deeply affect diagnostics of CAD, by significant reduction of any additional functional testing following coronary CTA.

Despite CTA-FFR feasibility and crude diagnostic superiority over angiography alone, reported in the previous trials, its direct clinical utility remains obscured due to the following: 1) relatively wide limits

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of agreement (~0.20); 2) significantly different accuracies reported; and 3) the weaknesses of the reference test itself, with FFR reproducibility lower than 80% within 0.77 to 0.83 range (3–7). These methodological issues pose a challenge for both the method developers and clinicians in understanding and comparing the clinical value across different CTA-FFR studies and methods. Despite the previous reports, it remains unknown in what proportion of subjects undergoing coronary CTA in clinical practice CTA-FFR can provide a reliable alternative to further functional testing.

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In this study, we sought to evaluate the proportion of patients with intermediate stenosis diagnosed on CTA, which could be saved from any further testing due to use of CTA-FFR (Siemens cFFR, version 1.4, Siemens AG Healthcare, Forchheim, Germany), while maintaining high agreement with the invasive FFR. It involved determination of the lower and upper CTA-FFR thresholds that predicted ischemic and non-ischemic stenosis, respectively (on the basis of an invasive FFR cutpoint of ≤0.80) with ≥90% accuracy and subsequently finding out the proportion of patients falling between these thresholds.

Our results are also reviewed in the context of previous CTA-FFR data to analyze and discuss optimal conditions for future testing and reporting of the studies.

METHODS

This was a prospective cohort, single-center study. From January 1, 2013 to December 31, 2014, we included 98 patients (63.4 ± 8.2 years, 32% were men), who underwent routine coronary CTA due to intermediate probability of having a significant coronary artery stenosis, and due to CTA diagnosis of at least 1 intermediate coronary stenosis (50% to 90% by visual estimation) in artery with ≥2 mm diameter were scheduled to undergo invasive FFR within 6 months of CTA, and gave consent to be included in the study (2). The exclusion criteria included previous myocardial infarction, atrial fibrillation, previous bypass surgery, unstable coronary disease, presence of total occlusion in any coronary artery on CTA, body mass index >40 kg/m^2, contraindications to adenosine, and significant motion artifacts during the index CTA. The CTA stenosis was diagnosed as intermediate by experienced (>5,000 coronary CTA examinations evaluated) invasive cardiologists (M.K., C.K., J.P.). The selection process is presented in **Figure 1**.

The CTA scan preceded invasive coronary angiography (ICA) and FFR by a median of 1.0 (interquartile range [IQR]: 0.0 to 2.3) month. Baseline clinical data were obtained from medical records, and standard definitions of risk factors for CAD were used (8). The study protocol was approved by the ethics committee of the Institute of Cardiology. All participating patients gave their informed consent for the study.

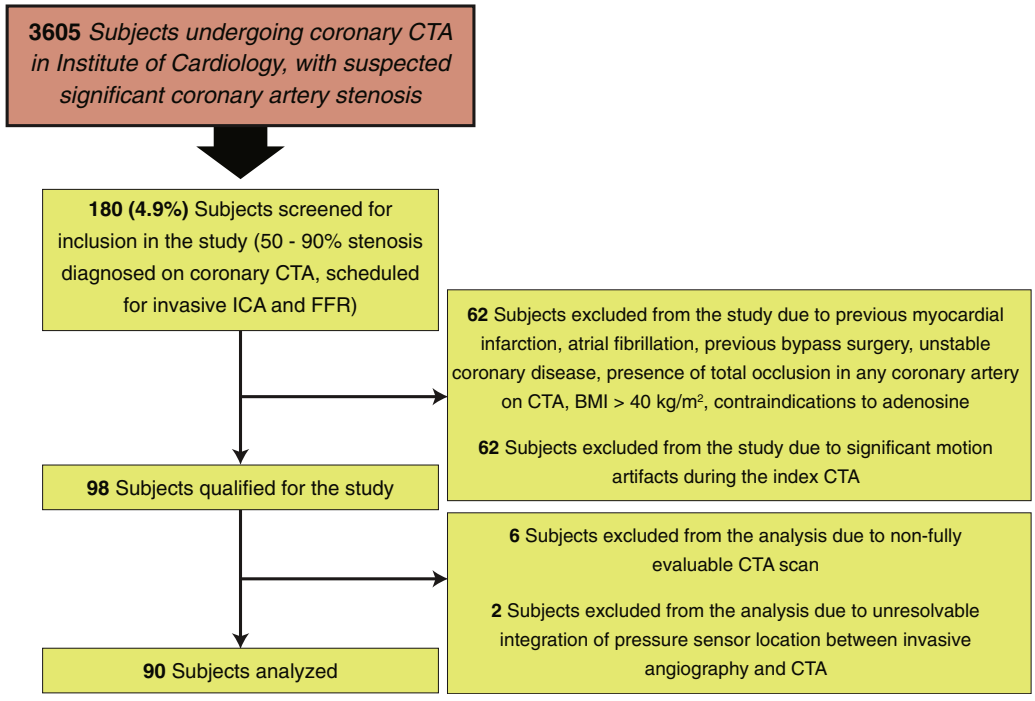
CORONARY CTA AND FFR. Coronary CTA was performed with a dual source 2 × 128-slice CT scanner (Somatom Definition FLASH, Siemens Medical Solutions, Forchheim, Germany) with 280 ms gantry rotation time. In all patients, sublingual nitrates (0.8 mg) were administered prior to the scan. In case of heart rate ≥70 beats/min, an intravenous metoprolol (sequence of 5 mg, up to 20 mg) was given. A 60- to 80-ml bolus of iomeprol (Iomeron 400, Bracco, Italy) was injected intravenously at 6.0 ml/s. A retrospective, electrocardiogram-gated acquisition protocol was used, with 128 × 0.6-mm collimation, and 80 to 120 kV tube voltage adjusted manually depending on body mass. Coronary datasets were reconstructed in mid-diastole (60% to 70% of R-R interval) and systole (40% to 50% of R-R interval) with 0.6-mm slice thickness and 0.4-mm increment. Image reconstruction was performed using routinely filtered sinogram-affirmed iterative reconstruction I36f, strength 3. The luminal diameter stenosis of the index lesion was determined visually by 1 of the experienced readers, using longitudinal and transverse sections and curved multiplanar reformats. The quantitative CTA analysis was performed by an experienced observer on a dedicated analysis platform (SyngoVia, Siemens).

ICA and FFR were performed using standard techniques by experienced invasive cardiologists (M.K., C.K., J.P.). FFR was measured with a ComboWire XT guidewire (Volcano Therapeutics, Rancho Cordova, California). The pressure sensor was advanced past the most distal stenosis and FFR was recorded during administration of intravenous adenosine 140 μg/kg/min for 3 min. FFR was automatically calculated as the ratio of mean coronary blood pressure distal to the stenosis and mean aortic pressure at the time of the induced hyperemia. Values of ≤0.80 were considered as indicating significant stenoses. The exact probe position at the measurement site was recorded on angiography. Based on the ICA examination, the luminal stenosis was visually graded by an experienced interventional cardiologist blinded to the CTA (M.K., C.K., J.P.).

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CI = confidence interval
CTA = computed tomography angiography
FFR = fractional flow reserve
ICA = invasive coronary angiography
IQR = interquartile range
NPV = negative predictive value
PPV = positive predictive value

FIGURE 1 Study Enrollment



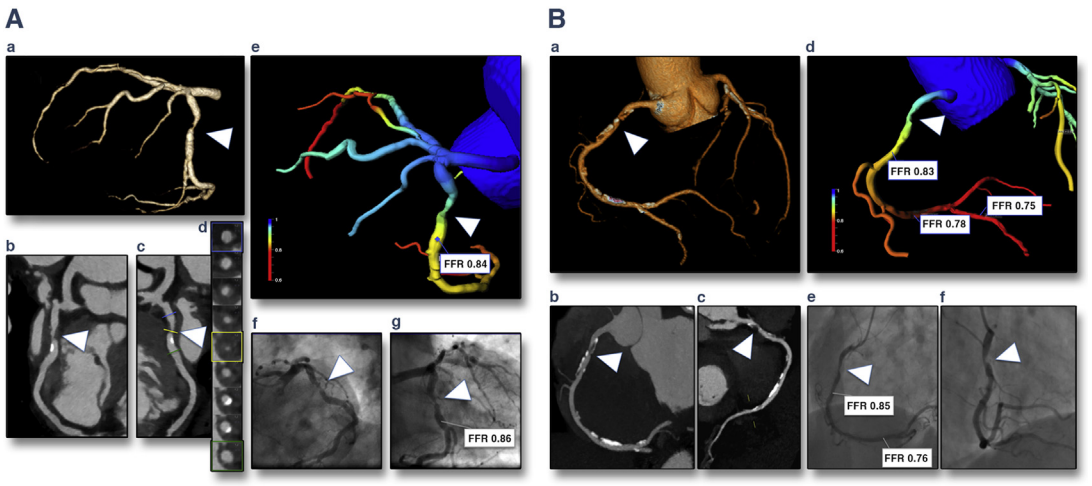
CTA = computed tomography angiography; FFR = fractional flow reserve; ICA = invasive coronary angiography.

CTA-FFR. CTA-FFR calculations were performed on routine coronary CTA datasets using a software research prototype (cFFR version 1.4, Siemens AG Healthcare, Forchheim, Germany). It allows the computation of CTA-FFR values in selected locations of the coronary tree that then can be compared with corresponding invasive FFR measurements. The algorithm uses both anatomical data and physiological models to compute FFR values. The anatomy of the coronary tree and left ventricular myocardium are deduced from routine coronary CTA images. Having the coronary tree data in 3-dimensions, a model of the lumen is semiautomatically segmented and the myocardial mass is calculated. The resting total coronary flow is estimated by applying allometric scaling laws that describe the relationship between form and function (9). In the next step, vascular resistance is calculated using a parameter estimation process (10). Using the principles of fluid dynamics, the algorithm simulates coronary blood flow. Different methods are applied for nonstenotic arteries and in stenosis regions. By changing the computation parameters (reducing coronary resistance index), hyperemia state can be simulated (10,11). Thus, virtual FFR values can be calculated throughout the whole coronary tree. The software was available on-site on a dedicated workstation (commercially available hardware).

The simulated CTA-FFR value was established by an experienced observer (Ł.W.), blinded to the results of both the invasive FFR and ICA. Data preparation required acceptance or correction of the luminal contours and centerlines generated automatically by the software, to produce a patient-specific 3-dimensional mesh of the coronary artery tree. The mesh was checked by a second experienced observer (M.K.), and discrepancies were solved by consensus. The standard deviation and coefficient of variation from duplicate measurements of CTA-FFR made on 16 subjects, used to determine the reproducibility of the measurements, were low at 0.04 and 5.3%, respectively (12). The point of CTA-FFR measurement was carefully matched based on the respective ICA evidence registered during the invasive FFR, by independent observer not involved in the CTA-FFR analysis (**Figure 2**). The results are presented "per lesion" and "per patient."

Statistics. All data were expressed as mean ± SD or median (IQR), as appropriate. Binary variables were compared using chi-square testing. The relationship between FFR and CTA-FFR was quantified with a

FIGURE 2 Examples of the Study Subject



(A) Eighty percent stenosis **(white arrow)** of the left circumflex artery without functional ischemia; 3-dimensional (volume rendering) **(a),** multiplanar reformat **(b,c),** and transverse cross sections **(d)** on coronary computed tomography angiography (CTA), CTA-based fractional flow reserve (CTA-FFR) **(e),** and invasive angiography **(f,g)**. **(B)** Eighty percent stenosis **(white arrow)** of the right coronary artery with functional ischemia: 3-dimensional (volume rendering) **(a),** multiplanar reformat **(b,c),** on coronary CTA, CTA-FFR **(d),** and invasive angiography **(e,f)**.

coefficient of correlation. Agreement between the methods was assessed by Bland-Altman plots and corresponding 95% limits of agreement. The performance of CTA-FFR was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (the percentage of patients correctly diagnosed by CTA-FFR). CTA-FFR was compared with several coronary CTA stenosis characteristics (either visual or quantitative) by using receiver-operating characteristic area under the curve analysis according to DeLong et al. (13), using invasive FFR ≤0.80 as the reference standard. The optimal criterion for CTA-FFR was established taking into account disease prevalence and estimated costs. As part of the primary analysis, CTA-FFR thresholds were determined for which the PPV and NPV were both >90%, corresponding to an FFR of ≤0.80 and >0.80, respectively, and the proportion of lesions (and patients) meeting these criteria was determined (14). For the per-patient analyses, a patient was considered positive for ischemia, if the FFR value of any evaluated vessel was ≤0.80. Values of $p < 0.05$ were considered statistically significant. Calculations were performed with MedCalc version 13.1.2.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

BASELINE CHARACTERISTICS. In 90 patients, 96 lesions were analyzed. The mean age of the population was 63.4 ± 8.2 years, and 29 (32%) were men. Median heart rate during the CTA scan was 61 beats/min (IQR: 56 to 65 beats/min). The median radiation dose during the coronary CTA examination was 7.3 (IQR: 5.6 to 12) mSv.

Detailed patient characteristics are summarized in Table 1. Forty-one stenoses (42.7%) were significant based on FFR, and median invasive FFR was 0.83 (IQR: 0.74 to 0.90); the median values and the 25th and 75th percentiles reflecting overall the borderline character of the stenoses. Median CTA-FFR was 0.81 (IQR: 0.75 to 0.89). Mean coronary stenosis degree based on ICA and CTA was 67.4 ± 11.9% and 69.7 ± 11.7%, respectively ($p = 0.0626$, paired Student *t* test for comparison with ICA); median minimal lumen area based on CTA was 1.9 mm^2 (IQR: 1.3 to 2.9 mm^2); median CTA quantitative angiography diameter stenosis was 52% (IQR: 43% to 61%); and median CTA quantitative angiography area stenosis was 77% (IQR: 68% to 85%). Forty-one patients (45.6%) had at least 1 significant stenosis according to invasive FFR.

DIAGNOSTIC ACCURACY AND CLINICAL UTILITY OF CTA-FFR. Spearman coefficient of correlation (rho) was 0.67 (95% confidence interval [CI]: 0.54 to 0.77; $p < 0.001$), demonstrating moderate rank correlation between the virtual and the true FFR measures. Bland-Altman plots for CTA-FFR versus FFR are shown in Figure 3. On average, FFR exceeded CTA-FFR by 0.01, indicating low systematic error. The

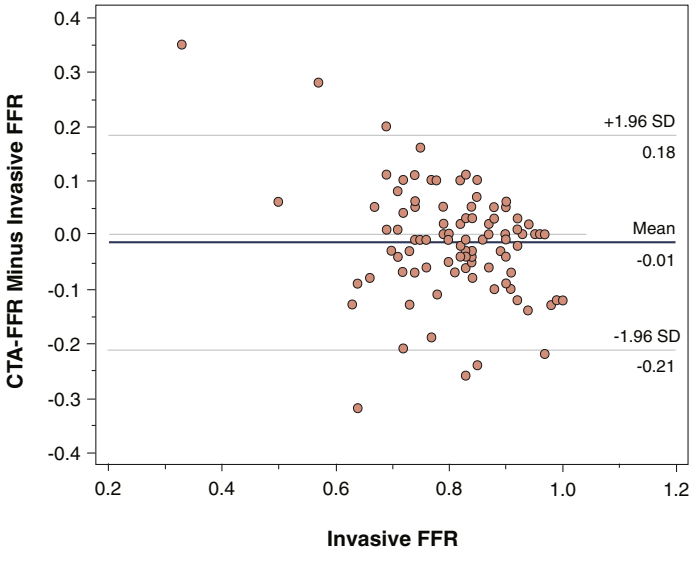
TABLE 1 Baseline Patient and Lesion Characteristics

Interrogated Vessel per Lesion (n = 96)	
LAD	58 (60.4)
LCX	12 (12.5)
LM	2 (2.1)
RCA	24 (25.0)
Patient Characteristics (n = 90)	
1-Vessel disease*	46 (51.1)
2-Vessel disease*	30 (33.3)
3-Vessel disease*	14 (15.6)
Calcium score (n = 76)	154 (33–557)
Risk Factors of CAD (n = 90)	
Family history of CAD	20 (22.5)
Past smokers	20 (22.5)
Current smokers	18 (20.2)
Diabetes	13 (14.4)
IGT	5 (5.6)
Hypertension	79 (87.8)
Hyperlipidemia	81 (90)
BMI, kg/m^2	28.5 (26.5–30.1)
Body mass, kg	82.9 ± 11.9

Values are n (%), median (interquartile range), or mean ± SD. *Number of major vessels with coronary stenosis ≥50% on invasive angiography.

BMI = body mass index; CAD = coronary artery disease; IGT = impaired glucose tolerance; LAD = left anterior descending; LCX = left circumflex; LM = left main; RCA = right coronary artery.

FIGURE 3 Bland-Altman Analysis Plot Comparing Per-Lesion CTA-Based FFR (CTA-FFR) Versus Invasive FFR



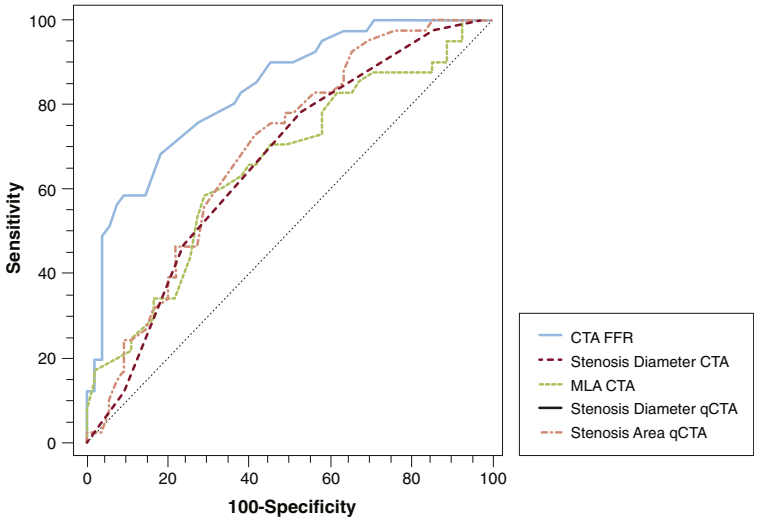
The mean difference between the 2 methods is 0.01, showing small systematic underestimation of FFR by CTA-FFR. The 95% limits of agreement for CTA-FFR are ±0.19 (of the mean difference). Abbreviations as in Figures 1 and 2.

area under the receiver-operating characteristic curve (C statistic) to predict an FFR ≤0.80 was highest for CTA-FFR, indicating good discrimination, significantly better than any of the other CTA-based parameters ($p \leq 0.01$ for any) (Figure 4). To predict FFR ≤0.80, the most optimal cutoff value of CTA-FFR was ≤0.75 (95% CI: 0.7 to 0.8), minimum lumen area on CTA was ≤1.6 mm^2 (95% CI: 0.7 to 2.6), stenosis diameter on quantitative CTA was ≥54% (95% CI: 47% to 67%), and for stenosis area quantitative CTA, it was ≥80% (95% CI: 73% to 93%). The overall sensitivity, specificity, PPV, NPV, and accuracy for these parameters are presented in Table 2. CTA-FFR reclassified 33.3% of all stenoses more accurately than the criterion of CTA stenosis of ≥50%, and ~11% more than the other CTA stenosis criteria (Table 2). Per-patient analysis indicated the optimal cutoff value of CTA-FFR at the same ≤0.75 level. The accuracy characteristics are presented in Table 2.

To achieve at least 90% diagnostic accuracy at each extreme, the overall CTA-FFR range had to be restricted to <0.74 (to predict an FFR ≤0.80; PPV = 90.9) and >0.87 (to predict an FFR >0.80; NPV = 92.0), comprising 49 study lesions (51.0%) and 45 patients (50.0%). The hybrid diagnostic approach, with "no-further-testing" value of >0.87, and treatment CTA-FFR value of <0.74 and further invasive FFR testing within stenoses with CTA-FFR values between 0.74 and 0.87, would result in an overall 95% agreement with the FFR-only strategy (Figure 5). For minimal lumen area, values <0.6 mm^2 (100% PPV) and >4.3 mm^2 (100% NPV), constituting 7 patients (8%), provided similar confidence. Of coronary CTA stenosis visual classification, none of the thresholds provided 95% agreement with FFR. According to quantitative CTA stenosis classification diameter stenosis of either >76% or <41% provided 95% agreement with FFR, represented by 16 patients (18%), and for quantitative area stenosis, respective values were either <65% or >94% (n = 14 [15%]).

RELATIONSHIP OF DIAGNOSTIC PERFORMANCE OF CTA-FFR AND DISTRIBUTION OF FFR VALUES. The subgroup of 37 stenoses (38.5%) fell into the "gray zone" invasive FFR between 0.75 and 0.85. The patients within the gray zone versus those beyond did not differ with regard to CTA percentage of stenosis, 68.4 ± 10.7% versus 70.5 ± 12.2% ($p = 0.3860$), respectively. The CTA-FFR diagnostic performance parameters for either lesions within or beyond the gray zone FFR are presented in Figure 6, indicating that the more lesions within the gray zone, the worse the overall accuracy of the novel method.

FIGURE 4 **Area Under the ROC Curve Comparison Between Several Coronary CTA Stenosis Characteristics and CTA-FFR on a Per-Lesion Level, Using Invasive FFR as the Reference Standard**



	CTA-FFR	Stenosis Diameter CTA	MLA CTA	Stenosis Diameter qCTA	Stenosis Area qCTA
Area Under the ROC Curve	0.835	0.660	0.655	0.690	0.690
Standard Error	0.041	0.054	0.0572	0.0537	0.0537
95% CI	0.745-0.903	0.557-0.754	0.551-0.749	0.588-0.781	0.588-0.781

The area under the curve (AUC) reached statistical significance for all comparisons between CTA stenosis characteristics and CTA-FFR. None of the CTA stenosis characteristics significantly differed from each other. "Stenosis diameter CTA" classification is categorical (rounded to the nearest 10). CI = confidence interval; MLA = minimal lumen area; qCTA = quantitative computed tomography angiography; ROC = receiver-operating characteristic; other abbreviations as in Figures 1 and 2.

DISCUSSION

According to our data, the prototype CTA-FFR based on coronary CTA may discriminate between ischemic versus nonischemic stenoses in around 50% of patients with intermediate coronary stenosis, potentially saving them from further functional testing. This study is the first evaluating the proportion of patients potentially benefitting from the hybrid diagnostic approach with use of CTA-FFR, maintaining high agreement with the invasive FFR strategy. If our findings are confirmed in larger, multicenter studies, the novel method application may have significant impact on diagnostic flow of CAD patients and related health care costs (15). In our report, we also uniquely evaluate the impact of baseline patient characteristics on the method accuracy and discuss its implications for testing and reporting of future CTA-FFR studies.

Our series of patients add 14% to the total of 659 cases of CTA-based FFR studied previously, including 3 previous multicenter trials (4–6). Currently applied prototype CTA-FFR was based on the desktop computer and it took on average 20 min (range 10 to 50 min) to analyze a single CTA study on-site, as compared to "1 to 4 h per examination" based on an off-site computational center for the other previously reported CTA-FFR system (HeartFlow Inc., Redwood City, California). In general, 95% limits of agreement (Bland-Altman analysis) reported for the CTA-FFR versus the reference FFR, at ~0.20, are similar to previous analyses of Renker et al. (3), narrower than reported in DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve), and wider than reported in NXT (Analysis of Coronary Blood Flow Using CT Angiography). The crude (per vessel) accuracy of CTA-FFR in our dataset (76%) is lower than that for DISCOVER-FLOW (84%) or NXT (86%), but higher than in DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) (69%) (4–7).

TABLE 2 Per-Vessel and Per-Patient Diagnostic Characteristics for Coronary CTA-Based Stenosis Diagnostics

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Per-vessel					
Stenosis diameter CTA ≥50%	100.0	1.8	43.2	100.0	43.8
CTA-FFR ≤0.80	75.6	72.3	67.4	80.0	74.0
CTA-FFR ≤0.75	56.1	92.7	85.2	73.9	77.1
Minimum lumen area CTA ≤1.6 mm^2	58.5	70.9	60.0	69.6	65.6
Stenosis diameter qCTA ≥54%	61.0	69.1	59.5	70.4	65.6
Stenosis area qCTA ≥80%	56.1	70.9	59.0	68.4	64.6
Per-patient					
Stenosis diameter CTA ≥50%	100.0	2.0	46.1	100.0	46.7
CTA-FFR ≤0.80	75.6	71.4	68.9	77.8	73.3
CTA-FFR ≤0.75	56.1	93.9	88.5	71.9	76.7
Minimal lumen area CTA ≤1.6 mm^2	58.5	69.4	61.5	66.7	64.4
Stenosis diameter qCTA ≥54%	61.0	67.4	61.0	67.3	64.4
Stenosis area qCTA ≥80%	46.3	71.4	57.6	61.4	63.3

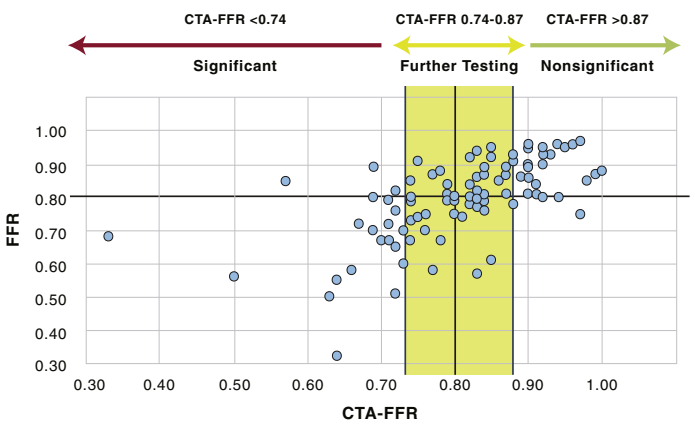
Presented values are optimal cutoff points for CTA-FFR, minimal lumen area CTA, stenosis diameter quantitative CTA (qCTA), stenosis area quantitative CTA (qCTA).
CTA = computed tomography angiography; NPV = negative predictive value; PPV = positive predictive value; qCTA = quantitative computed tomography angiography.

Importantly, NXT trial results represent the performance of the state-of-the-art CTA-FFR system, as opposed to older DISCOVER-FLOW and DeFACTO studies.

CLINICAL APPLICABILITY OF CTA-FFR. Our study is relatively small and single center; however, it provides some unique insights. First of all, our patients in several aspects may reflect the cohort, which would require further testing following coronary CTA in clinical practice. We did not exclude patients based on calcifications or other challenging vessel characteristics, which contribute to the diagnostic ambiguity of CTA in clinical practice (8). Our stenoses were not a priori significant, as opposed to NXT, where 18 of 484 total occlusions (3.3%) were arbitrarily assigned FFR = 0.5, or DeFACTO, where even 19% had >90% stenosis. Not only do the occluded or tight stenoses not represent a clinically relevant environment for application of CTA-FFR, but also they falsely improve the method accuracy characteristics. Our mean calcium score (unreported due to non-normal distribution) was 288 ± 310 (similar to that of NXT at 302 ± 468), which reflect a moderately diseased population, implying our results are less applicable to severely calcified coronary arteries.

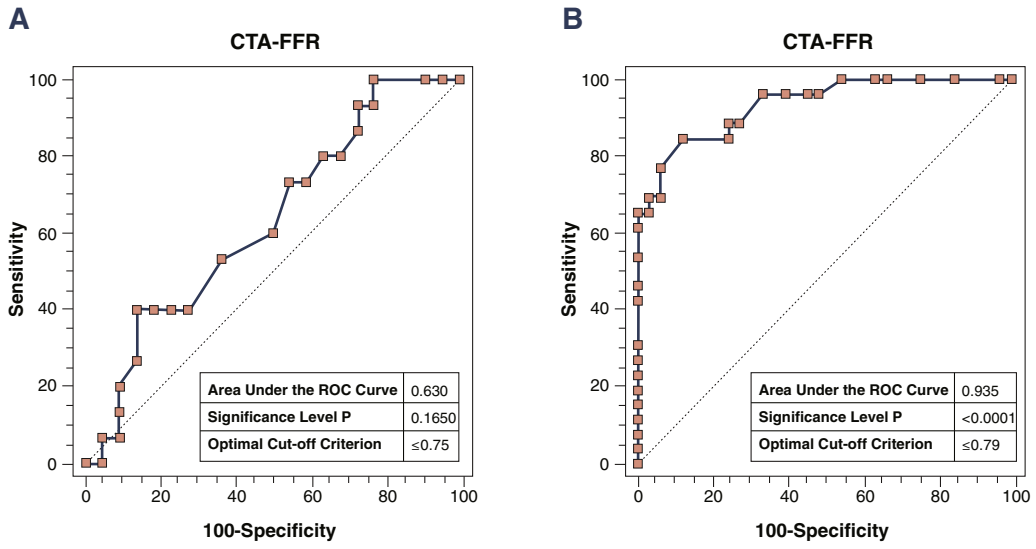
We also provide a unique analysis, indicating which patients or stenoses may be confidently diagnosed with the novel method. Based upon our analysis, use of the single cutoff point in the clinical application of CTA-FFR should be discouraged, unless the values of both NPV and PPV are sufficiently high for the single point. The previous reports provide crude diagnostics accuracy characteristics, the main shortcomings of which are strong dependence on the inclusion criteria and inability to provide information how and in whom the novel method can be applied with appropriate confidence. Another characteristic of CTA-FFR that is helpful in understanding its true clinical utility is improvement of accuracy over CTA stenosis classification, which was 33%, as compared to the previous studies: NXT—21%; DeFACTO (per patient)—9%;

FIGURE 5 Hybrid Diagnostic Strategy With Use of CTA-FFR



Coronary stenoses can be qualified as nonsignificant when CTA-FFR is >0.87 (negative predictive value >90%) **(green zone)** or as significant when CTA-FFR is <0.74 (positive predictive value >90%) **(red zone)**. In clinical practice, 50% of patients can be qualified for treatment based solely on CTA-FFR, leaving only 50% of patients with the need of further diagnostic testing **(yellow zone)**. The hybrid approach has a 95% classification agreement with an FFR-only strategy. Abbreviations as in Figures 1 and 2.

FIGURE 6 AUC Comparison Between CTA-FFR in Lesions Within and Outside the Gray Zone of Invasive FFR



	Sensitivity	Specificity	+PV	–PV	Accuracy
A	40.00	86.36	66.7	67.9	67.6
B	76.92	93.94	90.9	83.8	86.4

Lesions within **(A)** and outside **(B)** the gray zone. The gray zone of invasive FFR represents values between 0.75 and 0.85. PV = predictive value; other abbreviations as in Figures 2 and 4.

DISCOVER FLOW—26%; however, our exact numerical result should be viewed cautiously, given the limitations of our study (4-7).

IMPACT OF BASELINE CHARACTERISTICS ON ACCURACY OF CTA-FFR. Crucially, the agreement between CTA-FFR and FFR depends on the sample characteristics. If extreme stenoses are included (either obviously significant or nonsignificant), the agreement will be higher (16). Moreover, the limits of agreement between CTA-FFR and invasive FFR narrow for higher FFR values as indicated by Martus et al. (16). Importantly, the more intermediate the values, the lower the agreement, even for repeatability of invasive FFR itself (7). Indeed, according to our analysis, the significantly lower accuracy of CTA-FFR within the gray zone of 0.75 to 0.85 was a major contributor to the overall method inaccuracy. Our study group comprised 39% of such patients as compared to only ~15% in NXT or ~19% in Renker et al. (3). In NXT the contribution of patients with low-grade stenoses is also reflected by a rightward shift of median FFR toward ~0.88 (not explicitly reported in the paper [6], data derived from the figure), the region with narrow limits of agreement, as compared to our median of 0.83 (4-7,16). It may be speculated that a part of the high accuracy reported in NXT (at 86%) may be attributed to the high proportion of patients with a priori either nonsignificant or significant stenoses.

It may be argued which stenoses are intermediate and thus most appropriate for analysis with CTA-FFR. The majority of published reports, including revascularization guidelines, refer to borderline/intermediate stenosis as either 40% to 50% to 70% or 50% to 90% by ICA (16-18). According to RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study, even 47% of angiographic stenoses >70% may be nonsignificant by FFR (19). On the other hand, even one-third of the milder stenoses (between 30% and 50%) may have FFR ≤0.8 (19). Therefore, in the context of CTA-FFR, the broader definition of 30% to 90% may be relevant, especially, that the evaluation itself is both harmless and costless.

STUDY LIMITATIONS. This is a relatively small, single-center study that is substantially methodologically

inferior to the previous multicenter, well-powered trials. For this reason, the numerical comparisons with the previous studies should be interpreted cautiously. Our patients did not comprise consecutive series of patients diagnosed with intermediate stenosis on coronary CTA, because the quality of the scan (26 patients excluded due to insufficient CTA quality) was an inclusion/exclusion criterion, as was done in the previous studies. Also, we neither collected data on the other patients' characteristics and diagnostic work-up, who underwent coronary CTA in our institution, nor the others undergoing ICA following CTA but not fulfilling inclusion/exclusion criteria (similarly to all the previous studies). Subsequently, impact of excessive calcium and suboptimal image quality on accuracy of the CTA-FFR remains unestablished. Neither costs nor cost-effectiveness of the CTA-FFR were analyzed. Another limitation is exclusion of patients with history of myocardial infarction or coronary artery bypass graft or having any total occlusions or in-stent restenosis. It may be discussed whether the applied threshold on either side at >90% diagnostic accuracy is sufficient. However, it was utilized in similar previous analyses, exceeded reported accuracy of most of the other noninvasive functional cardiac tests, and provided agreement with "FFR only strategy" in >95% of cases (2,14). Prior to any practical use, the clinical value of the established numerical CTA-based FFR thresholds require confirmation in an independent validation cohort. Our study was the first establishing the value of CTA-FFR in the context of the hypothetical hybrid strategy. Whether the examined diagnostic approach would result in noninferior clinical outcomes, as compared to the routine use of FFR, should be validated in a multicenter, prospective, randomized trial.

CONCLUSIONS

Our data suggest that in patients diagnosed with intermediate stenosis, CTA-FFR may be superior to anatomic stenosis evaluation methods and may confidently discriminate between ischemic versus nonischemic stenoses in around one-half of the patients. However, our findings require appropriately powered validation in an independent multicenter cohort.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with intermediate coronary stenosis, CTA-based FFR provides more accurate diagnosis of significant coronary stenosis than do classic parameters based on the anatomic stenosis metrics. The new method may confidently discriminate between ischemic or nonischemic stenosis (≥90% accuracy at either side) in around 50% of the cases.

TRANSLATIONAL OUTLOOK: Larger, multicenter studies are needed to validate current findings in a more diverse clinical population and test whether the routine performance of CTA-FFR in patients undergoing coronary CTA may help guide therapies to prevent subsequent adverse outcomes.

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