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Stress Computed Tomography Perfusion Versus Fractional Flow Reserve CT Derived in Suspected Coronary Artery Disease

The PERFECTION Study

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ABSTRACT

OBJECTIVES This study sought to compare the diagnostic accuracy of coronary computed tomography angiography (cCTA) with that of cCTA+fractional flow reserve derived from cCTA datasets (FFR_{CT}) and that of cCTA+static stress-computed tomography perfusion (stress-CTP) in detecting functionally significant coronary artery lesions using invasive coronary angiography (ICA) plus invasive FFR as the reference standard.

BACKGROUND FFR_{CT} and static stress-CTP are new techniques that combine anatomy and functional evaluation to improve assessment of coronary artery disease (CAD) using cCTA.

METHODS A total of 147 consecutive symptomatic patients scheduled for clinically indicated ICA+invasive FFR were evaluated with cCTA, FFR_{CT}, and stress-CTP.

RESULTS Vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values, and accuracy rates of cCTA were 99%, 76%, 100%, 61%, 82%, and 95%, 54%, 94%, 63%, 73%, respectively. cCTA+FFR_{CT} showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 88%, 94%, 95%, 84%, 92%, and 90%, 85%, 92%, 83%, 87%, respectively. Finally, cCTA+stress-CTP showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 92%, 95%, 97%, 87%, 94% and 98%, 87%, 99%, 86%, 92%, respectively. Both FFR_{CT} and stress-CTP significantly improved specificity and positive predictive values compared to those of cCTA alone. The area under the curve to detect flow-limiting stenoses of cCTA, cCTA+FFR_{CT}, and cCTA+CTP were 0.89, 0.93, 0.92, and 0.90, 0.94, and 0.93 in a vessel-based and patient-based model, respectively, with significant additional values for both cCTA+FFR_{CT} and cCTA+CTP versus cCTA alone ($p < 0.001$) but no differences between cCTA+FFR_{CT} versus cCTA+CTP.

CONCLUSIONS FFR_{CT} and stress-CTP in addition to cCTA are valid and comparable tools to evaluate the functional relevance of CAD. (J Am Coll Cardiol Img 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

ASIR-V = adaptive statistical iterative reconstruction algorithm

AUC = area under the curve

CAD = coronary artery disease

cCTA = coronary computed tomography angiography

FFR_{CT} = fractional flow reserve derived from cCTA datasets

HR = heart rate

ICA = invasive coronary angiography

SCCT = Society of Cardiovascular Computed Tomography

stress-CTP = stress-computed tomography perfusion

Coronary computed tomography angiography (cCTA) has been introduced as an alternative imaging modality to diagnose coronary artery disease (CAD) with low radiation exposure (1,2) and excellent prognostic assessment (3-6). However, there is concern regarding use of cCTA in the subset of patients who are at intermediate-to-high risk due to the limited positive predictive value of cCTA (7,8). In this regard, new techniques such as fractional flow reserve derived from cCTA datasets (FFR_{CT}) (9-11) and stress computed tomography perfusion (stress-CTP) (12-15) recently emerged as potential strategies to combine anatomy and functional evaluations of CAD.

However, there are few data (16) for direct comparison among these techniques. Therefore, this study sought to compare the diagnostic accuracy of cCTA versus cCTA+FFR_{CT} versus cCTA+stress-CTP to detect functionally significant coronary artery lesions by using invasive coronary angiography (ICA) plus invasive FFR as the reference standard.

METHODS

SCREENING PROCEDURE AND ENROLMENT. The PERFECTION (PERfusion Versus Fractional Flow Reserve CT Derived In Suspected CoroNary) study was a longitudinal, prospective, consecutive cohort study designed to compare the feasibility and accuracy of integrated cCTA+FFR_{CT} versus that of cCTA+stress-CTP for the diagnosis of functionally significant CAD (17). We screened consecutive symptomatic patients with suspected CAD referred for nonemergent, clinically indicated ICA between October 2015 and May 2017. From an original cohort of 928 patients, 781 were excluded according to the criteria shown in Figure 1, which included low to intermediate pre-test likelihood of CAD according to the updated Diamond-Forrester risk model score (18) (n = 82); prior clinically documented myocardial infarction (n = 40); history of surgical or percutaneous coronary artery revascularization (n = 415); suspicion of acute coronary syndrome (n = 21); need for an emergent procedure within 48 h of presentation (n = 13); evidence of clinical instability (n = 9); contraindications to contrast agents or impaired renal function (n = 47); inability to sustain a breathhold (n = 9); pregnancy (n = 0); atrial fibrillation or flutter (n = 40); body mass index (BMI) >35 kg/m² (n = 26); presence of a pacemaker or implantable cardioverter-defibrillator (n = 34); contraindications to sublingual nitrates, beta-blockade, and adenosine (n = 42).

The institutional ethical committee study approved the protocol, and all patients meeting the selection criteria were asked to sign an informed consent. A structured interview was performed to collect a clinical history and cardiac risk factors.

PATIENT PREPARATION. Figure 2 shows the study protocol. Patients were asked to refrain from smoking and caffeine for 24 h and to maintain fasting for 6 h before the scan. In patients with a resting heart rate (HR) >65 beats/min, metoprolol was intravenously administered, with a titration dose up to 15 mg to achieve a target HR of ≤65 beats/min. Before the rest scan, all patients received sublingual nitrates to ensure coronary vasodilation.

REST-cCTA PERFORMANCE AND INTERPRETATION. Rest-cCTA was performed using a Revolution CT scanner (GE Healthcare, Milwaukee, Wisconsin) according to the recommendations of the Society of Cardiovascular Computed Tomography (SCCT) (19), using the following parameters: slice configuration of 256 × 0.625 mm with scintillator detector (Gemstone detector, GE Healthcare); gantry rotation time of 280 ms; tube voltage of 120 KVp and 100 KVp in patients with BMI >30 kg/m² and ≤30 kg/m², respectively; and effective tube current of 500 mA. One-beat axial scan was used in all patients, with variable padding ranging between 70% to 80% and 40% to 80% of cardiac cycle in patients with HR <65 beats/min and those with ≥65 beats/min, respectively. All patients received a 70-ml bolus of iodixanol 320 (320 mg/ml, Visipaque, GE Healthcare) at an infusion rate of 6.2 ml/s, followed by 50 ml of saline solution. All scans were performed using the bolus tracking technique by using visual assessments to determine timing of image acquisition. A new generation post-processing adaptive statistical iterative reconstruction algorithm (ASIR-V, GE Healthcare) was used instead of the standard filtered back-projection algorithm. Datasets of cCTA were transferred to an image-processing workstation (Advantage Workstation version 4.7, GE Healthcare) to perform quantitative coronary analysis

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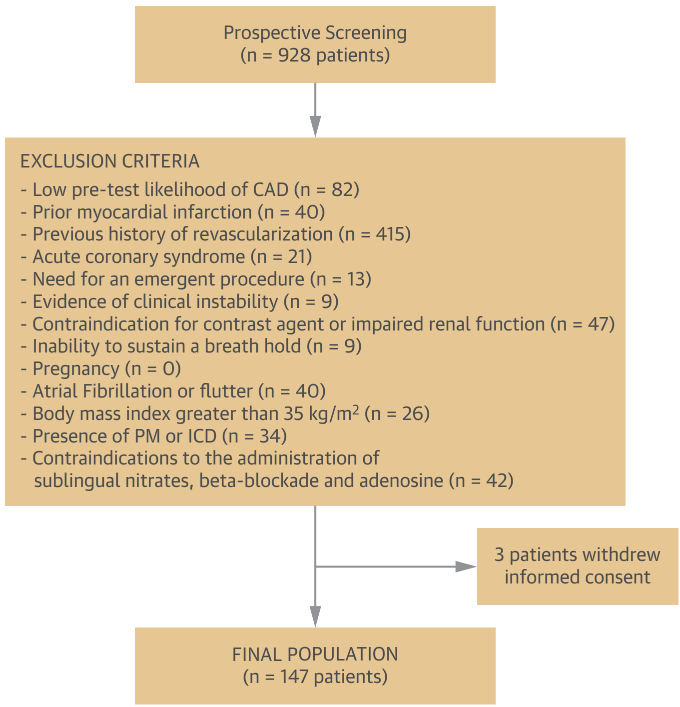
according to SCCT guidelines for reporting (19). Two cardiac imagers who were blinded to clinical history, stress-CTP, and invasive evaluation findings independently evaluated the reconstructed images. For analysis of cCTA, coronary arteries were segmented as suggested by the American Heart Association (AHA) (20). Causes of artifacts and image quality evaluation with a Likert score were established as previously described (8). In each coronary artery, coronary atherosclerosis was defined as the presence of any tissue structures larger than 1 mm^2, either within the coronary artery lumen or adjacent to it that could be discriminated from the surrounding pericardial tissue, epicardial fat, or vessel lumen itself. The severity of coronary lesions was quantified in multiplanar curved reformatted images by identifying the minimum diameter and reference diameter of all stenoses and quantified according to SCCT guidelines (19). Stenosis >50% was considered significant from an anatomical point of view. A third cardiac imager adjudicated the scores in cases of disagreement.

FFR_{CT} PERFORMANCE AND INTERPRETATION. All cCTA datasets were sent to HeartFlow (Redwood City, California) for FFR_{CT} analysis as previously described (11,21). An FFR_{CT} <0.80 was considered significant.

STATIC STRESS-CTP PERFORMANCE AND INTERPRETATION. Vasodilation was induced by IV administration of adenosine (0.14 mg/kg/min over 4 min). At the end of the third minute of adenosine infusion, a single data sample was acquired during first-pass enhancement of cCTA by using the same protocol described for rest-cCTA (Figure 2). All datasets of static stress-CTP were transferred to an image-processing workstation (Advantage Workstation Version 4.7, GE Healthcare), and 2 cardiac imagers blinded to clinical history, rest cCTA, and invasive evaluation findings independently evaluated the reconstructed images. The myocardial wall was evaluated on short-axis (apical, mid, and basal slices) and long-axis views (2-, 3- and 4-chamber projections) with 4-mm-thick average multiplanar reformatted images in diastolic phases (70% and 80% of cardiac cycle). A narrow window width and level (350 W and 150 L) was used for perfusion defect evaluation. Each myocardial segment was correlated to the specific coronary territory according to a modified AHA classification as described by Cerci et al.(22). In detail, the entry criterion for the algorithm was the presence of both at least 1 coronary arterial lesion >50% diameter stenosis and at least 1 myocardial perfusion defect. For each vessel, the following territories were identified: 1) primary territory consisting of myocardial territories in which blood flow is supplied by the coronary vessel in the most common right dominant anatomic coronary pattern; 2) secondary territories consisting of myocardial territories for which blood flow may be supplied by the coronary vessel under some normal anatomic variations that need confirmation; and 3) tertiary territories consisting of myocardial territories where blood flow is usually not supplied by the coronary vessel. The adjudication process was applied each time there was a coronary arterial lesion with >50% diameter stenosis and at least 1 myocardial perfusion defect in the secondary territories. After myocardial segmentation, a 4-point image quality score was assigned to each myocardial segment regarding the diagnostic confidence of perfusion defect evaluation 1 = very uncertain (i.e., poor confidence; could be an artifact or poor image quality); 2 = uncertain (i.e., moderate confidence, probably an artifact and less likely a perfusion defect); 3 = rather certain (i.e., good confidence, probably a defect, good image quality/no or minor artifacts); and 4 = very certain (i.e., excellent image quality/no artifacts).

FIGURE 1 **PERFECTION Study Workflow**



CAD = coronary artery disease; ICD = implantable cardiac device; PM = pacemaker; PERFECTION = stress computed tomography PERfusion versus Fractional flow rEserve CT derived In suspected corONary artery disease study.

JACC: CARDIOVASCULAR IMAGING, VOL. ■, NO. ■, 2018
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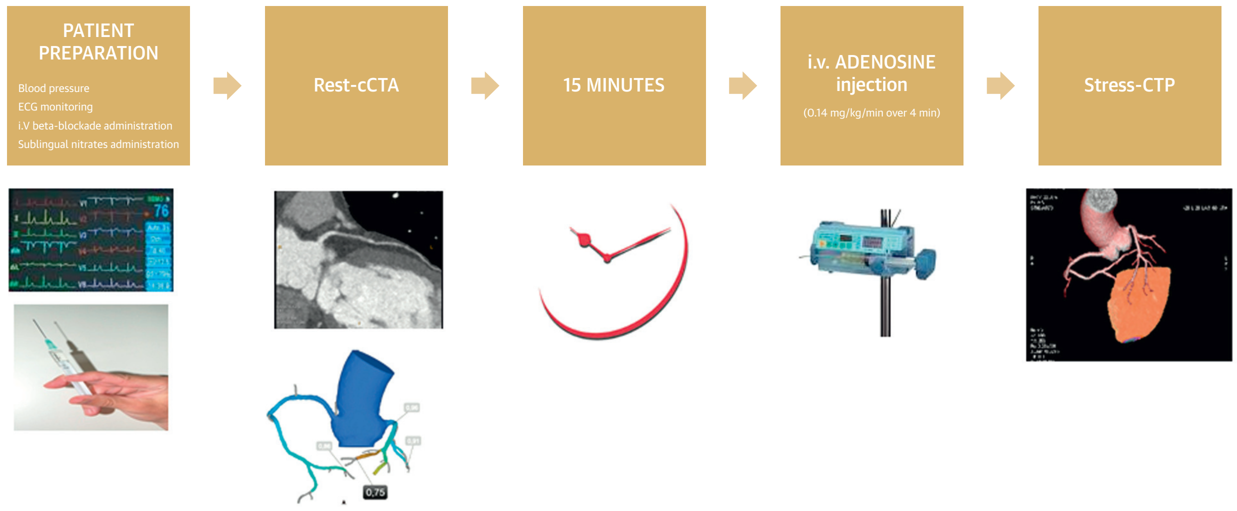
FIGURE 2 Study Protocol



cCTA = cardiac computed tomography angiography; CTP = computed tomography perfusion; ECG = electrocardiography; stress-CTP = stress computed tomography perfusion. See Methods for further details.

Perfusion defects were defined as subendocardial hypoenhancements encompassing ≥25% of transmural myocardial thickness within a specific coronary territory.

ICA AND INVASIVE FFR PERFORMANCE AND INTERPRETATION. In all patients, certified interventional cardiologists performed ICA within 60 days after the cCTA examination according to the American College of Cardiology/AHA Task Force on Practice Guidelines and the Society for Cardiac Angiography and Interventions (23). Coronary angiograms were analyzed at the clinical site by an interventional cardiologist blinded to cCTA, stress-CTP, and FFR_{CT} findings. Severity of luminal narrowing was assessed using the same semiquantitative score previously described for cCTA. Coronary artery stenoses ≥80% or totally occluded vessels were considered functionally significant without performing invasive FFR measurements, although all stenoses ranging between 30% and 80% were evaluated by clinically indicated invasive FFR (24,25). For FFR, the pressure wire (Certus pressure wire; St. Jude Medical Systems, St. Paul, Minnesota) was calibrated and electronically equalized using the aortic pressure before being placed distal to the stenosis in the distal third of the coronary artery being interrogated. Glyceryl trinitrate (100 mg) was injected intracoronary to prevent vasospasm. Adenosine was administered (140 μg/kg/min) intravenously. At steady-state hyperemia, FFR was assessed using the RadiAnalyzer Xpress (Radi Medical Systems, Uppsala, Sweden), calculated by dividing the mean coronary pressure, measured with the pressure sensor placed distal to the stenosis, by the mean aortic pressure measured through the guide catheter. Intermediate stenoses ≤0.8 found by invasive FFR or stenoses with >80% diameter reduction or total occlusions were considered functionally significant.

RADIATION EXPOSURE. For cCTA, the dose-length product, defined as total radiation energy absorbed by the patient body, was measured in mSv/mGy·cm. The effective radiation dose was calculated as the product of dose-length product times a conversion coefficient for the chest (K = 0.014 mSv/mGy·cm). For ICA, the effective radiation dose was calculated by multiplying the dose-area product by a conversion factor (K = 0.21 mSv/mGy·cm^2) for lateral and posteroanterior radiation exposure in the chest area.

STATISTICAL ANALYSIS. Statistical analysis was performed using a dedicated SPSS version 21.0 software (SPSS, Chicago, Illinois) and R version 2.15.2 ((R Foundation for Statistical Computing, Vienna, Austria). The sample size was estimated assuming a 30% prevalence of functionally significant CAD and diagnostic accuracy for FFR_{CT} in a vessel-based model of 86%. A sample size of 150 patients, corresponding to 450 vessels, was considered powered to detect a difference of 4% between FFR_{CT} and stress myocardial CTP at a significance level of 5% and at least 90% power, using a 2-sided test. Continuous variables were expressed as mean ± SD and discrete variables as absolute numbers and percentages. The Spearman correlation and Bland-Altman analyses were used for comparing FFR_{CT} to invasive FFR values. The chi-squared test or Fisher exact test was used to study differences in categorical data. For cCTA and integrated cCTA+FFR_{CT} or cCTA+CTP protocols, the overall evaluability (i.e., number of evaluable coronary artery segments-to-all coronary artery segments ratio), sensitivity, specificity, negative and positive predictive values, and accuracy were calculated compared to those of ICA+ invasive FFR as reference standards. Specifically, the integrated evaluation was performed according to the following interpretation: A) non-obstructive CAD with negative matched functional evaluation was considered negative; B) nonobstructive CAD with positive matched functional evaluation was considered still negative; C) obstructive CAD with negative matched functional evaluation was considered negative; and D) obstructive CAD with positive matched functional evaluation was deemed positive. The McNemar test was used to calculate differences in terms of sensitivity, specificity, negative predictive value, positive predictive value, and accuracy; and area under the receiver operating characteristics (AUC) curves for each model was measured and compared using the DeLong method.

RESULTS

STUDY POPULATION. Table 1 lists patients' clinical characteristics. All patients underwent ICA, and invasive FFR was measured in 98 of 147 patients (67%). Obstructive CAD was observed in 94 of 147 patients (64%), whereas the prevalence of functionally significant CAD was detected in 66 of 147 patients (45%). Among 122 vessels with functionally significant CAD, 53 (43%) were left anterior descending arteries, 32 (26%) were left circumflex coronary arteries, and 37 (30%) were right coronary arteries.

IMAGE QUALITY AND OVERALL EVALUABILITY OF REST-cCTA. Rest-cCTA was successfully performed in all patients. The mean Likert score was 3.6 ± 0.8, and the overall evaluability of native coronary arteries was 98% (Online Table 1).

IMAGE QUALITY AND OVERALL EVALUABILITY OF FFR_{CT}. FFR_{CT} was successfully performed in 143 of 147 patients (98%). The analysis was rejected in the remaining 4 patients for motion artifacts.

TABLE 1 Characteristics of the Study Population

Baseline Characteristics	
n	147
age, yrs	65.8 ± 9.2
Men	105 (71)
BMI, kg/m^2	27.1 ± 3.9
Risk factors	
Hypertension	114 (77)
Smoker	39 (26)
Hyperlipidemia	43 (29)
Diabetes	29 (20)
Family history	91 (62)
Symptoms	
Typical angina	82 (56)
Atypical angina	65 (44)
Pre-test likelihood of CAD (%)	67 ± 12
Pre-invasive coronary angiography testing	
None	40 (27)
Positive exercise-ECG	59 (40)
Positive stress echocardiography	9 (6)
Positive single photon emission computed tomography	36 (25)
Positive stress cardiac magnetic resonance	3 (2)
cCTA scan protocol, REST	
HR before scanning, beats/min	68.8 ± 12.4
Beta-blocker	74 (50)
Beta-blocker dosage (mg)	5.1 ± 6.2
HR during scanning, beats/min	63.6 ± 9.4
Dose length product, mGy × cm	196.7 ± 95.9
Effective dose, mSv	2.7 ± 1.3
cCTA scan protocol, STRESS	
HR during scanning, beats/min	77.5 ± 14.1
Dose length product, mGy-cm	217.3 ± 65.4
Effective dose, mSv	2.5 ± 1.1
Prevalence of obstructive CAD (≥50%) at ICA	
Absence of obstructive CAD	53 (36)
1-vessel disease	45 (31)
2-vessel disease	21 (14)
3-vessel disease	28 (19)
Prevalence of functionally significant CAD*	
Absence of functionally significant CAD	81 (55)
1-vessel disease	31 (21)
Left anterior descending coronary artery	20
Left circumflex coronary artery	4
Right coronary artery	7
2-vessel disease	14 (10)
Left anterior descending + left circumflex coronary artery	5
Left anterior descending + right coronary artery	7
Left circumflex coronary artery + right coronary artery	2
3-vessel disease	21 (14)

Values are n, mean ± SD, or n (%). *>80% diameter or FFR <0.8 in intermediate stenosis (30% to −80% diameter reduction).

BMI = body mass index; CAD = coronary artery disease; cCTA = cornary computed tomography angiography; ECG = electrocardiography; FFR = fractional flow reserve; HR = heart rate; ICA = invasive coronary angiography.

IMAGE QUALITY AND OVERALL EVALUABILITY OF STRESS-CTP. Stress-CTP was successfully performed in 144 of 147 patients with a mean HR during the scan of 77.5 ± 14.1 beats/min (Table 1). The stress

TABLE 2 Comparison of Diagnostic Performance of cCTA, FFR_{CT}, Stress-CTP, cCTA+FFR_{CT}, and cCTA+stress-CTP in Detecting Functionally Significant CAD*

	cCTA (n = 147)	cCTA+FFR_{CT} (n = 143)	cCTA+CTP (n = 144)	p Value		
				cCTA+FFR_{CT} vs. cCTA	cCTA+CTP vs. cCTA	cCTA+FFR_{CT} vs. cCTA+CTP
Vessel-based analysis						
True positive	121	102	109	-	-	-
True negative	241	293	296	-	-	-
False positive	78	20	17	-	-	-
False negative	1	14	10	-	-	-
Sensitivity	99 (98-100)	88 (82-94)	92 (87-97)	<0.001	0.005	0.353
Specificity %	76 (71-80)	94 (91-96)	95 (92-97)	<0.001	<0.001	0.611
Negative predictive value	100 (99-100)	95 (93-98)	97 (95-99)	0.849	0.002	0.409
Positive predictive value	61 (54-68)	84 (77-90)	87 (81-92)	<0.001	<0.001	0.521
Accuracy	82 (79-86)	92 (90-95)	94 (91-96)	<0.001	<0.001	0.338
Patient-based analysis						
True positive	63	57	64	-	-	-
True negative	44	68	69	-	-	-
False positive	37	12	10	-	-	-
False negative	3	6	1	-	-	-
Sensitivity %	95 (90-100)	90 (83-98)	98 (95-100)	0.267	0.31	0.055
Specificity %	54 (43-65)	85 (77-93)	87 (80-95)	<0.001	<0.001	0.668
Negative predictive value	94 (87-100)	92 (86-98)	99 (96-100)	0.724	0.15	0.062
Positive predictive value	63 (54-72)	83 (74-92)	86 (79-94)	0.005	<0.001	0.520
Accuracy	73 (66-80)	87 (82-93)	92 (88-97)	0.001	<0.001	0.164

Values are n or % (95% confidence interval). *Stenosis >80% diameter reduction or FFR <0.80 in intermediate stenosis (30% to 80% diameter reduction).
cCTA = coronary computed tomography angiography; CI = confidence interval; CTP = computed tomography perfusion; FFR = fractional flow reserve.

phase was interrupted because of dyspnea in 2 patients and chest pain in 1 patient. In most myocardial segments, myocardial perfusion interpretation was classified as very certain or rather certain (61% and 22%, respectively), whereas it was classified as very uncertain in only 1%. The mean image quality score for myocardial perfusion was 3.4 ± 0.3 (Online Table 2).

DIAGNOSTIC ACCURACY OF REST-cCTA. The diagnostic performance of rest-cCTA, compared to ICA+invasive FFR, is listed in Table 2. Rest-cCTA demonstrated a vessel-based and patient-based sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy of 99%, 76%, 100%, 61%, 82% and 95%, 54%, 94%, 63%, 73%, respectively (Table 2).

DIAGNOSTIC ACCURACY OF cCTA+FFR_{CT}. There was good direct correlation of per-vessel FFR_{CT} to invasive FFR (Pearson's correlation coefficient 0.69; $p < 0.001$), with a slight underestimation of FFR_{CT} compared with FFR (mean difference: 0.02 ± 0.13). The vessel-based and patient-based sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy of integrated cCTA+FFR_{CT} were 88%, 94%, 95%, 84%, 92% and 90%, 85%, 92%, 83%, 87%, respectively (Table 2).

DIAGNOSTIC ACCURACY OF REST-cCTA+STRESS-CTP. The diagnostic performance of the integrated cCTA+stress-CTP protocol is listed in Table 2. The vessel-based and patient-based sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy were 92%, 95%, 97%, 87%, 94% and 98%, 87%, 99%, 86%, 92%, respectively (Table 2).

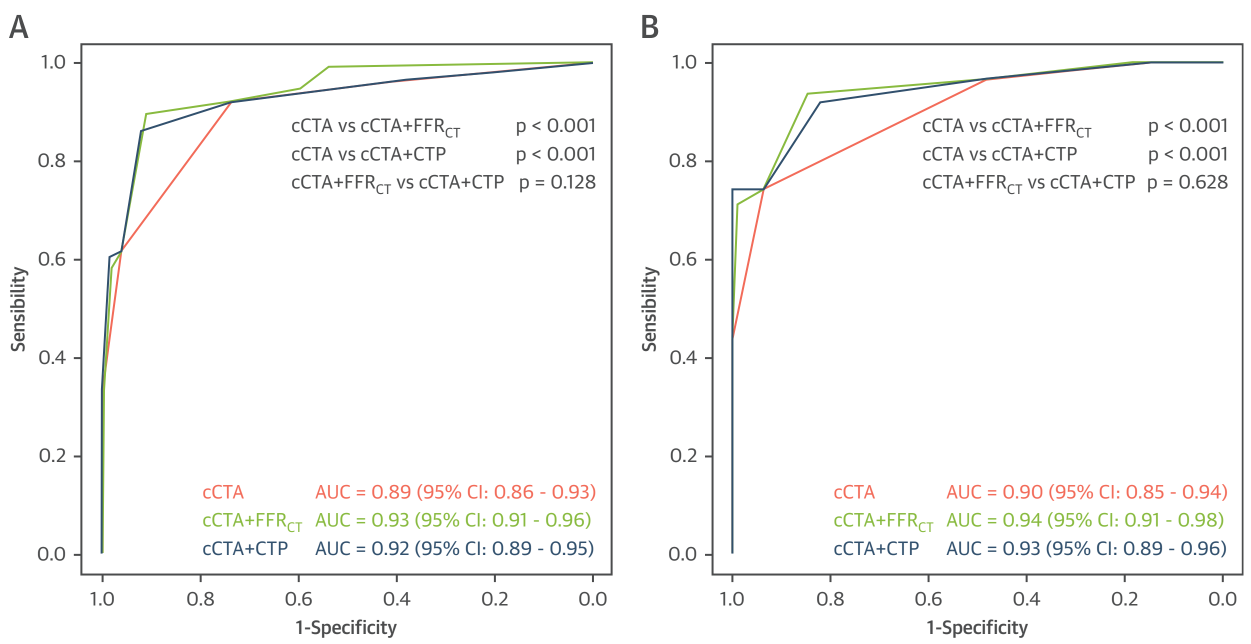
COMPARISON BETWEEN INTEGRATED PROTOCOLS OF cCTA ALONE, cCTA+FFR_{CT}, AND cCTA+STRESS CTP. The AUCs to detect flow-limiting stenosis of cCTA, cCTA+FFR_{CT} and cCTA+CTP were 0.89, 0.93, 0.92 and 0.90, 0.94, 0.93 in vessel- and patient-based models, respectively (Figure 3), with significant additional values of both cCTA+FFR_{CT} and cCTA+CTP versus cCTA alone ($p<0.001$) but no differences between cCTA+FFR_{CT} versus cCTA+CTP. Figures 4 and 5 show representative cases of comparison between cCTA+stress-CTP and cCTA+FFR_{CT}.

DISCUSSION

The main findings of this study are that both FFR_{CT} and stress-CTP provide additional value in terms of specificity, positive predictive value, and diagnostic accuracy compared to rest-cCTA, without significant difference between these 2 approaches.

Several studies demonstrated that optimal medical therapy alone has efficacy similar to revascularization when obstructive CAD is not associated with ischemia. Therefore, accurate identification of

FIGURE 3 **AUC Comparisons**



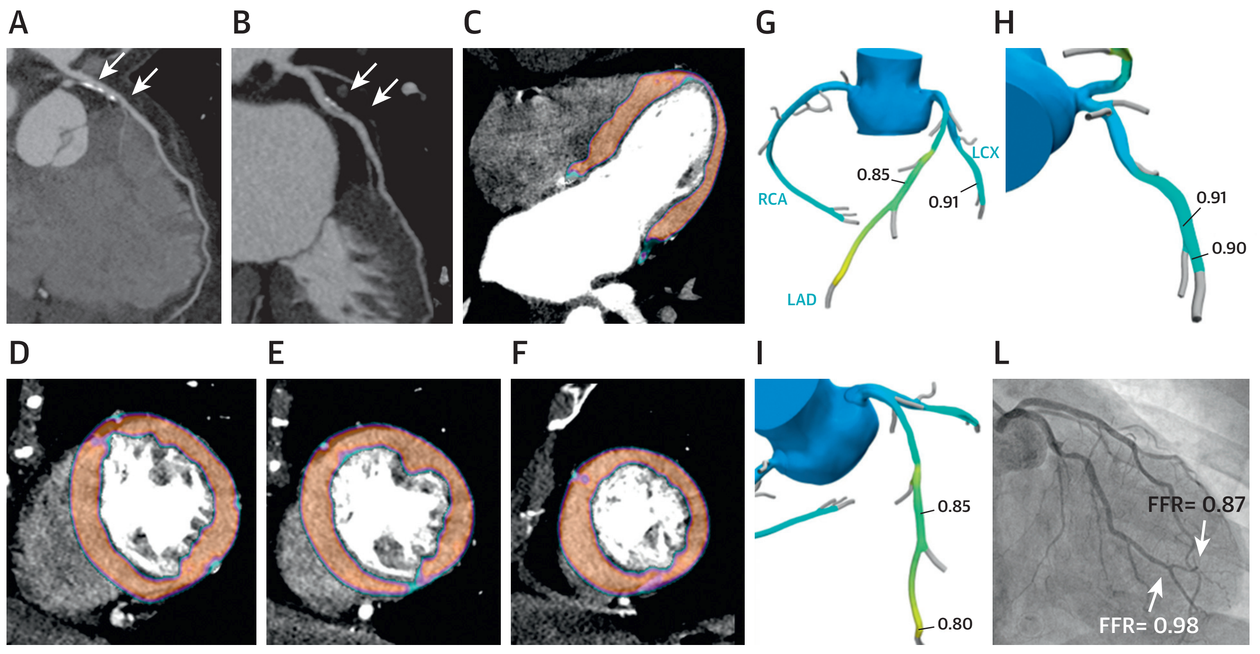
AUC comparisons of the diagnostic performance to detect flow-limiting stenosis of cCTA alone or combination of cCTA+FFR$_{CT}$ and cCTA+CTP at a vessel **(A)** and patient level **(B)**. AUC = area under the curve; FFRct = fractional flow reserve computed tomography; other abbreviations as in Figure 2.

patients with ischemic CAD is of major clinical importance. FFR$_{CT}$ demonstrated a 68% reduction of false positive cCTA cases in the NxT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial (11), and regarding stress-CTP, several prospective studies assessed the diagnostic performance of a rest+stress-CTP protocol versus ICA plus invasive FFR using both static (12-15,26,27) and dynamic techniques (28-30).

Despite the fact that FFR$_{CT}$ and stress-CTP share good overall diagnostic performance, both have strengths and weaknesses. FFR$_{CT}$ does not require additional scan time and use of stressors and, therefore, is associated with low radiation exposure. However, it is based on several geometric pathophysiological assumptions. On the other hand, stress-CTP is potentially more representative of the ischemic cascade but requires additional scan time and use of a stressor agent and is associated with higher radiation exposure. In addition, FFR$_{CT}$ cannot be used to evaluate vessel stenosis in case a stent is present, whereas stress-CTP has no restriction in this regard. There are only 2 previous studies comparing the 2 techniques (16,31). Yang et al. (16) compared FFR$_{CT}$ to stress-CTP in 72 consecutive patients and found no significant differences between the AUC values of the 2 techniques ($p = 0.84$) that, however, were higher than those of cCTA alone (AUC: 0.919; $p = 0.004$; and AUC: 0.913; $p = 0.004$; respectively). However, this study is limited by retrospective design and the use of a dual-source 128-slice scanner that, despite its excellent temporal resolution, does not allow for single-beat acquisition. Similarly, Coenen et al. (31) showed that both FFR$_{CT}$ and stress-CTP have increased AUC compared to cCTA alone (0.78 for both techniques) and found that stress-CTP performed better than FFR$_{CT}$ (AUC 0.85). However, their sample size was small (72 patients) and underpowered to evaluate differences between the 2 techniques, and they used a stress-CTP protocol based on dynamic acquisition with a 128-slice scanner that is associated with high radiation exposure.

Our study confirms that both FFR$_{CT}$ and stress-CTP provide additional diagnostic value compared to rest-cCTA and that there are no significant differences in term of diagnostic performance alone. However, our results have some strengths. First, the study design is prospective. Second, the target study population was at intermediate-to-high risk for CAD. This is the ideal setting for the use of additional functional testing with CT. Indeed, a high pre-test

FIGURE 4 Example Demonstrating the Additional Value of FFR_{CT} and Stress-CTP Over Rest-cCTA To Rule Out Functionally Relevant Coronary Stenoses



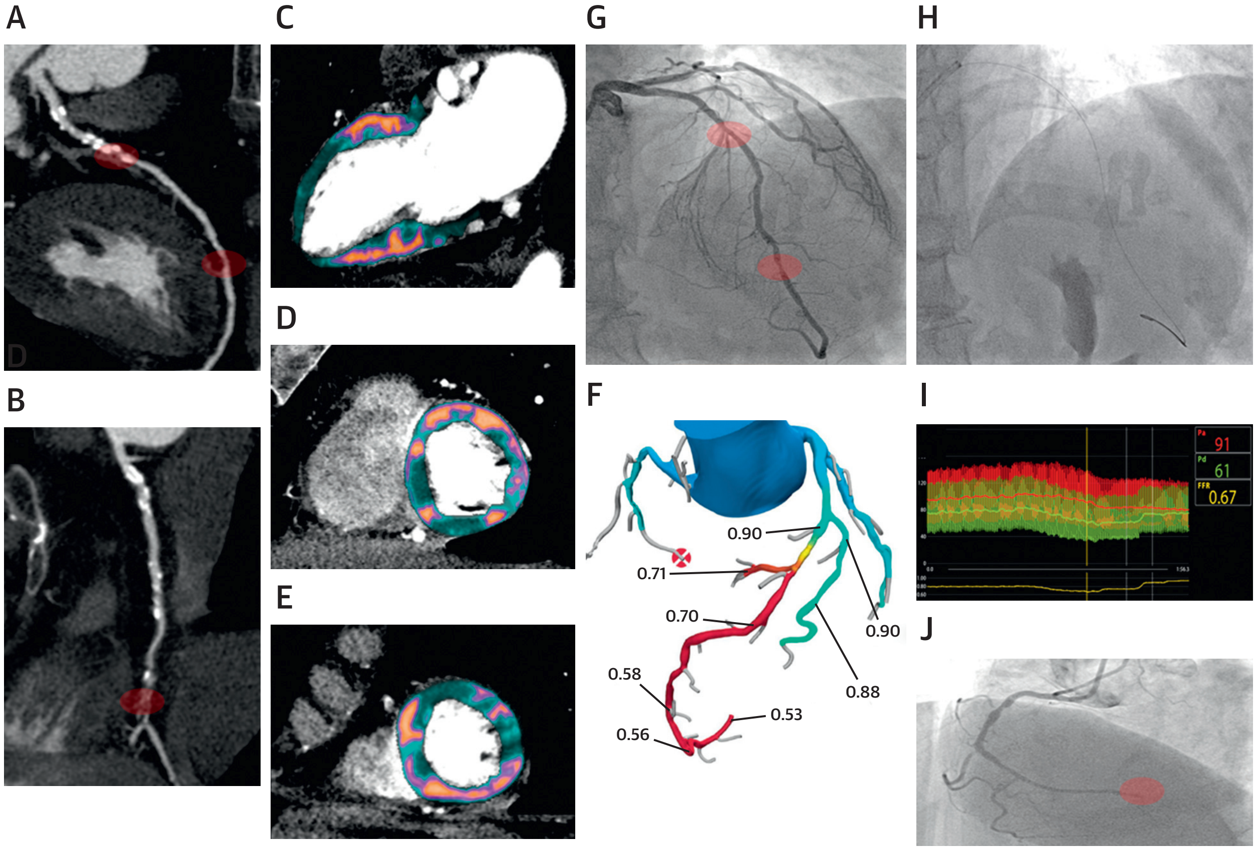
Studies from a 74-year-old woman who presented with atypical chest pain, hypertension, dyslipidemia, and positive exercise ECG. BMI was 22 kg/m^2. Tube voltage was 100 KVp; tube current was 500 mA. Total DLP (rest+stress) was 302 mGy-cm. **(A)** Rest-cCTA shows a calcified stenosis of the proximal LAD. **(B)** Rest-cCTA shows a calcified stenosis of the proximal OM. **(C), (D), (E), (F)** Stress-CTP during adenosine infusion showing normal myocardial perfusion. **(G), (H), (I)** FFRct demonstrates normal values in the LAD and OM. **(L)** ICA shows mild LAD and OM stenoses with normal FFR (0.87 and 0.98, respectively). BMI = body mass index; DLP = dose length product; ICA = invasive coronary angiography; LAD = left anterior descending artery; LCX = XXX; OM = obtuse marginal; RCA = XXX; other abbreviations as in **Figures 2 and 3**.

likelihood of CAD is associated with an increased burden of calcified atherosclerotic disease that impairs the value of cCTA to correctly rule out CAD (8,32). Third, the whole-heart CT scanner technology used in this study enables isophasic, single-beat imaging of the entire coronary tree, and it could be particularly suitable for static CTP (33). Finally, our choice of ICA plus invasive FFR as the reference standard was considered state of art for validation studies.

Despite those strengths, in our study, we did not find differences between FFR_{CT} and CTP and their clinical applications could sometimes be different based on their strengths and weaknesses. For example, in case of standard 64-slice scanner technology, FFR_{CT} could be preferred to stress-CTP. Indeed, the acquisition of data from sequential heartbeats affects the attenuation gradient and may result in a heterogeneous iodine distribution, mimicking perfusion defects. Similarly, in case of perfusion defect that does not match with obstructive CAD, a beam-hardening artifact should be taken into account, and the addition of FFR_{CT} could be useful. Finally, in case of 3-vessel disease, CTP may not unmask balanced ischemia that could be better detected by FFR_{CT}. On the other hand, CT-FFR_{CT} uses the cCTA images as boundary conditions for the computational fluid dynamic analysis of the coronary tree, and therefore, the technique is sensitive to factors that result in artifacts of the underlying coronary artery images, such as motion artifact or significant coronary calcification that usually does not affect the performance of CTP.

STUDY LIMITATIONS. Our study has limitations. First, we used static stress-CTP rather than dynamic stress-CTP. Therefore, a quantitative analysis of myocardial perfusion was not feasible (34). Second, invasive FFR was not performed in all vessels but only in those with intermediate lesions. Considering that a significant percentage of coronary artery stenosis >80% is associated with a normal, invasive FFR, a potential overestimation of functionally significant CAD could be occurred. However, considering that the same reference standard was used for both FFR_{CT} and stress-CTP, this limitation

FIGURE 5 Case Illustrating How Stress-CTP and FFRct Can Identify Flow-Limiting Stenoses Confirmed by ICA and Invasive FFR



Studies from a 75-year-old woman who presented with a history of hypertension, symptomatic for suspected angina, and a recent inconclusive exercise-ECG test. **(A), (B)** Rest cCTA shows 2-vessel disease with moderate-to-severe stenoses of mid and distal LAD **(A)** and occlusion of distal RCA **(B). (C)** Static stress-CTP long-axis view shows severe inducible perfusion defect at the mid to distal anterior wall and basal inferior wall. **(D), (E)** Static stress-CTP basal and apical short axis views show inducible ischemia at the mid to distal septal wall, mid inferior wall, mid to distal inferolateral wall, and mid to distal anterior wall. **(F)** FFR_{CT} shows pathology of value from mid LAD stenosis. No FFR_{CT} value was measured after the occlusion of distal RCA. **(G), (H), (I)** ICA shows moderate mid and distal LAD stenoses with positive invasive FFR **(H)** by pressure wire placed at the distal LAD. **(I)** FFR measurement. **(J)** ICA shows occluded distal RCA. Abbreviations as in Figures 2 to 4.

should have minimal impact on the comparison of diagnostic accuracy of these two techniques. Third, we used narrow exclusion criteria, and our results are therefore limited to this populations, with the same prevalence of functionally significant disease. Further studies should test these techniques in the general population. Fifth, according to our standard clinical practice, we did not perform calcium score before cCTA. Therefore, no subanalysis can be performed in terms of impact of calcium score on FFR_{CT} compared to stress CTP performance. Finally, it is noteworthy that perfusion techniques are sensitive to both epicardial vessel obstruction and microvascular disease, whereas FFR_{CT} and invasive FFR are only able to assess epicardial lesions and vessel-specific ischemia.

CONCLUSIONS

The addition of both FFR_{CT} and stress-CTP to cCTA is a valid and feasible strategy to evaluate the functional relevance of CAD. Based on these results, in most patients with suspected CAD, cCTA alone and integrated with FFR_{CT} or CTP is a robust tool to diagnose functionally relevant stenoses.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary computed tomography angiography (cCTA) has been introduced as an alternative imaging modality to diagnose CAD with low radiation exposure and excellent prognostic assessment. However, there is concern regarding cCTA use in the subset of patients at intermediate-to-high risk due to the limited positive predictive value of cCTA, particularly in the presence of calcified coronary lesions. In this regard, new techniques such as fractional flow reserve derived from cCTA datasets (FFR_{CT}) and stress computed tomography perfusion (stress-CTP) recently emerged as potential strategies to combine anatomy and functional evaluation of CAD in a "one-stop-shop." The aim of this study was to compare the diagnostic accuracy of cCTA versus cCTA+FFR_{CT} versus cCTA+stress-CTP in detecting functionally significant coronary artery lesions in consecutive symptomatic patients at intermediate-to-high risk for CAD using ICA with invasive FFR as reference standard. We found that both FFR_{CT} and stress-CTP provides additional value in terms of specificity, positive predictive value and diagnostic accuracy when compared to rest-cCTA with no statistically significant difference between them.

TRANSLATIONAL OUTLOOK: Based on these results, in most patients with suspected CAD, cCTA alone is sufficient to exclude functionally relevant CAD when an obstructive CAD is absent. On the contrary, in the setting of obstructive CAD, both FFR_{CT} or CTP are equally accurate to detect functionally significant stenosis.

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KEY WORDS accuracy, computed tomography, coronary artery disease, fractional flow reserve, perfusion

APPENDIX For supplemental tables, please see the online version of this paper.