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Prospective Comparison of FFR Derived From Coronary CT Angiography With SPECT Perfusion Imaging in Stable Coronary Artery Disease

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ABSTRACT

OBJECTIVES This study sought to compare the per-patient diagnostic performance of coronary computed tomography angiography (CTA)-derived fractional flow reserve (FFR_{CT}) with that of single-photon emission computed tomography (SPECT), using a fractional flow reserve (FFR) value of ≤0.80 as the reference for diagnosing at least 1 hemodynamically significant stenosis in a head-to-head comparison of patients with intermediate coronary stenosis as determined by coronary CTA.

BACKGROUND No previous study has prospectively compared the diagnostic performance of FFR_{CT} and myocardial perfusion imaging by SPECT in symptomatic patients with intermediate range coronary artery disease (CAD).

METHODS This study was conducted at a single-center as a prospective study in patients with stable angina pectoris (N = 143). FFR_{CT} and SPECT analyses were performed by core laboratories and were blinded for the personnel responsible for downstream patient management. FFR_{CT} ≤0.80 distally in at least 1 coronary artery with a diameter ≥2 mm classified patients as having ischemia. Ischemia by SPECT was encountered if a reversible perfusion defect (summed difference score ≥2) or transitory ischemic dilation of the left ventricle (ratio >1.19) were found.

RESULTS The per-patient diagnostic performance for identifying ischemia (95% confidence interval [CI]), FFR_{CT} versus SPECT, were sensitivity of 91% (95% CI: 81% to 97%) versus 41% (95% CI: 29% to 55%; $p < 0.001$); specificity of 55% (95% CI: 44% to 66%) versus 86% (95% CI: 77% to 93%; $p < 0.001$); negative predictive value of 90% (95% CI: 82% to 98%) versus 68% (95% CI: 59% to 77%; $p = 0.001$); positive predictive value of 58% (95% CI: 48% to 68%) versus 67% (95% CI: 51% to 82%; p = NS); and accuracy of 70% (95% CI: 62% to 77%) versus 68% (95% CI: 60% to 75%; p = NS) respectively.

CONCLUSIONS In patients with stable chest pain and CAD as determined by coronary CTA, the overall diagnostic accuracy levels of FFR_{CT} and SPECT were identical in assessing hemodynamically significant stenosis. However, FFR_{CT} demonstrated a significantly higher diagnostic sensitivity than SPECT. (J Am Coll Cardiol Img 2018;11:1640–50)

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In patients with suspected stable coronary artery disease (CAD), myocardial perfusion imaging (MPI) provides high diagnostic performance for identifying regional differences in myocardial blood flow supply when compared with coronary anatomy, and a normal MPI result has been associated with favorable clinical outcomes (1). Therefore, current guidelines recommend MPI as the frontline testing strategy in symptomatic patients with intermediate risk of CAD (2,3). Single-photon emission computed tomography (SPECT) is the diagnostic method most commonly used in patients with stable CAD (4), despite reports of a merely modest diagnostic sensitivity in high-risk subgroups (5) and inaccuracies in the selection of patients to undergo invasive coronary angiography (ICA) (6). Accordingly, coronary computed tomography angiography (CTA) has evolved as an alternative frontline testing strategy due to high diagnostic performance for detection and exclusion of CAD (7). However, the hemodynamic significance of lesions cannot be assessed by coronary CTA. Thus, guidelines recommend additional functional testing to be performed in patients with significant CAD determined by coronary CTA to increase appropriateness of referral to coronary angiography (3).

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Recently, improvements in computational fluid dynamics and individual image-based modeling have allowed estimation of coronary blood flow and pressure from standard acquired coronary CTA datasets (8). Coronary CTA-derived fractional flow reserve (FFR_{CT}) has shown high diagnostic performance, using measured fractional flow reserve (FFR) as the reference standard (9). Compared with coronary CTA assessment alone, FFR_{CT} demonstrates improved discrimination of ischemia (10), and FFR_{CT} utility in clinical practice has been demonstrated by safe reduction of downstream invasive angiography compared to that of usual care (11), as well as improvement of the diagnostic yield of coronary angiography (12). The value of FFR_{CT} versus that of SPECT as a gatekeeper to coronary angiography in patients with CAD determined by coronary CTA has not previously been prospectively assessed. Therefore, the aim of this study was to compare FFR_{CT} with MPI by SPECT in consecutive symptomatic patients suspected of having obstructive CAD as determined by coronary CTA.

METHODS

STUDY DESIGN AND PATIENT COHORT. This was a prospective study designed to compare the diagnostic performance of FFR_{CT} with that of SPECT for, first, the diagnosis of at least 1 hemodynamically significant stenosis, using measured FFR as the reference, and second, the prediction of standard-of-care-guided coronary revascularization.

In Denmark, coronary CTA has emerged as the preferred nonemergent testing strategy in patients with new onset stable chest pain in many centers. Generally, patients with a low-to-intermediate pre-test risk of having significant CAD, with no prior revascularization, with a body mass index ≤40 kg/m^2, with a glomerular filtration rate ≥45 ml/min, and no persistent atrial fibrillation are eligible for coronary CTA. Consequently, clinical criteria for inclusion in this study were stable chest pain in patients without known CAD and a Diamond-Forrester risk score between 15% and 85%. Moreover, study inclusion required the presence of at least 1 coronary stenosis of 40% to 90%, as determined by coronary CTA, or 1 or more focal lesions with severe calcification compromising stenosis assessment. Exclusion criteria were known CAD or a summed Agatston score ≥1,000 U. Patients with inability to undergo adenosine testing, allergy to iodinated contrast media, noncardiac illness with life expectancy <2 years, or pregnancy were excluded. Patients were included prior to functional testing. All CT data underwent FFR_{CT} analysis, and all patients underwent SPECT perfusion imaging and invasive procedures performed as illustrated in **Figure 1**. All patients were referred to ICA per-protocol, and the physicians responsible for downstream patient management were blinded to results of FFR_{CT} and SPECT analyses, including those who were performing the ICA and FFR investigations. FFR_{CT} and SPECT assessments were performed at core laboratories by personnel who had information about the lesion(s) of interest by coronary CTA; otherwise, the laboratory staff was blinded to clinical data. Patients were thoroughly instructed to stop

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CTA = computed tomography angiography

CX = circumflex coronary artery

FFR = fractional flow reserve

FFR_{CT} = coronary CTA-derived fractional flow reserve

LAD = left anterior descending coronary artery

MPI = myocardial perfusion imaging

RCA = right coronary artery

RPD = reversible perfusion defect

SPECT = single-photon emission computed tomography

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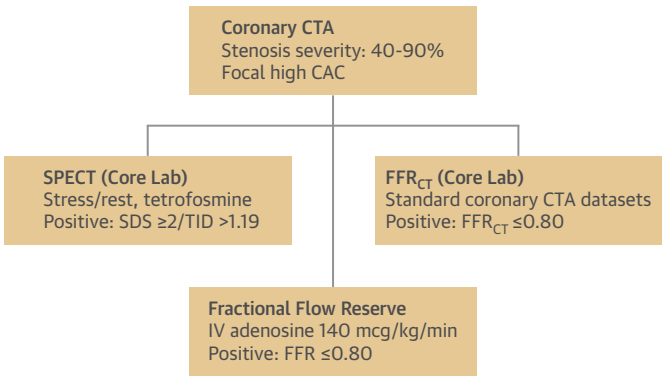
FIGURE 1 Schematic Illustration of the Study Protocol



SPECT perfusion imaging and FFR_{CT} analysis were performed at core laboratories between the time of the coronary CTA examination and the invasive procedure. The results of core laboratory FFR_{CT} analysis and SPECT test assessments had no impact on referral to invasive angiography and were blinded to the interventionalists. CAC = coronary artery calcification; CTA = computed tomography angiography; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; SDS = summed difference score; SPECT = single-photon computed tomography angiography; TID = transient ischemic dilation.

ingestion of caffeine for 24 h prior to undergoing SPECT and invasive procedures. Coronary angiography was performed in all patients, with measurement of FFR in lesions of interest as outlined by a CT cardiologist. Inconclusive noninvasive test results were registered as positive for ischemia. Informed consent was obtained from all participants. The study was approved by the regional ethical committee of Southern Denmark (S-20150085) and the data protection registry of Southern Denmark (2008-58-0035; 1563).

CORONARY CTA. Coronary CTA was performed using either a SOMATOM Definition Flash or a FORCE CT scanner (both from Siemens, Forchheim, Germany). Oral beta-blockers or ivabradine was administered, if necessary, targeting a heart rate ≤60 beats/min. All patients received sublingual nitroglycerin. An initial nonenhanced scan for calcium scoring was performed. Coronary CTA was assessed by skilled CT cardiologists (all having more than 10 years of experience in coronary CTA interpretation). Vessels ≥2 mm in diameter were evaluated and graded visually by the interpreters. Location of lesions was reported using a 17-segment model (13). Lesion locations were classified as proximal if located in segments 1, 2, 5, 6, 7, 11, or 13; all other lesion locations were classified as distal.

FFR_{CT} AND ANALYSIS. Standard acquired coronary CTA data sets were transmitted for central analysis (HeartFlow Inc., Redwood City, California) as previously described (12). The principles behind FFR_{CT} computation have been described in detail previously (8). FFR_{CT} was displayed for each point in the coronary tree. Any FFR_{CT} value in the major coronary arteries ≥2 mm in diameter, including side branches, were registered. Patients were classified as having significant ischemia if at least 1 vessel had an FFR_{CT} ≤0.80.

SPECT. MPI was performed in accordance with society guidelines (14) as gated SPECT by using a 2-day stress-rest protocol. A dose of 740 MBq of technitium-99m- labeled tetrofosmin (Myoview, GE Healthcare, Milwaukee, Wisconsin) was timed to the pharmacologic stress agent or injected at peak exercise.

Adenosine-based stress studies were recommended in order to simulate the scenario of vasodilation in the catheterization laboratory and assumptions of vascular reactions to adenosine.

Imaging was performed using a Discovery NM/CT 670 imaging system (GE Healthcare) 30 to 60 min after injection during stress and 60 min after injection at rest. Images were acquired by gated SPECT in a 64 × 64 matrix, using a low-energy high resolution collimator. Gating was performed in 8 time bins. Images were corrected for attenuation. All SPECT studies were performed at the Hospital of Southwest Denmark. Anonymized datasets were sent to the SPECT core laboratory (Department of Nuclear Medicine, Odense University Hospital, Denmark). SPECT studies were analyzed by 2 expert nuclear readers (S.S.N., A.J.), using gated and ungated short axes, horizontal and vertical long-axis myocardial tomograms, and a bull's eye-pattern plot (15). Perfusion was graded using a 5-point scale (0 to 4) in each of 20 segments. Summed rest scores, summed stress scores, and summed difference scores (SDS) were recorded for each patient. Reversible defects were graded as small if SDS was 2 to 4; moderate if SDS was 5 to 8; or large if SDS was >8. Study subjects were categorized as having ischemia if more than 1 of the following criteria was present: SDS was ≥2 and/or there was an ungated stress-and-rest volume (transitory ischemic dilation) ratio of >1.19 (16). Final classification of studies was obtained by consensus.

CORONARY ANGIOGRAPHY AND FFR. Coronary angiography was performed by standard techniques. Coronary lesion severity was evaluated on-site at the discretion of the respective interventionalist and was categorized according to either a 50% or a 70% threshold. Patients were categorized as having single-vessel to 3-vessel disease by using a 17-segment

model (13). Intracoronary nitroglycerin was administrated before pressure wire measurements were made. A 0.014-inch pressure wire (Verrata pressure wire, Volcano Phillips, San Diego, California) was placed distal to the coronary artery lesion. Maximal hyperemia was induced by intravenous adenosine (140 μg/kg per min). Recordings of aortic and distal coronary pressures were obtained by manual pull-back during sustained hyperemia (after 2 min of adenosine infusion). Patients were classified as having significant ischemia if the measured FFR value was ≤0.80 in at least 1 vessel.

STATISTICAL ANALYSES. Sample size calculations were based on paired comparison of sensitivities of FFR_{CT} and SPECT relative to FFR reference ≤0.80. The expected sensitivity of FFR_{CT} was 0.86 (10) and that of SPECT was 0.60 (17). The prevalence of patients with FFR ≤0.80 was expected to be 30%, as an equal distribution between grades of stenosis was anticipated. Given significance level of 0.05 and a power of 0.8, 150 patients were needed for the study. The McNemar test was used to compare sensitivity, specificity, and accuracy of FFR_{CT} and SPECT. Logistic regression using robust cluster estimation was used to compare positive predictive value (PPV) and negative predictive value (NPV). The Fisher exact test and chi-square test were used for comparison of proportions as appropriate. Associations between proportions of patients with an FFR value ≤0.80 and decreasing patient level minimum FFR_{CT} value and size of perfusion defects, respectively, were tested using weighted linear regression with robust estimation. Kendall's tau was used to evaluate correlations between different RPD categories and FFR and FFR_{CT} values.

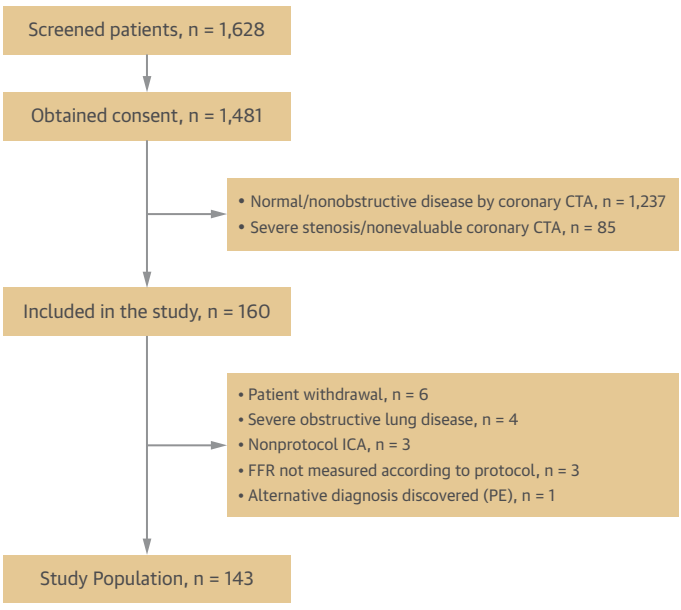
A p value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 14.0 software (Stata Corp, College Station, Texas).

RESULTS

Between September 2015 and July 2017, 1,628 consecutive symptomatic patients were referred to undergo coronary CTA and screened for enrollment in this study. In 160 patients, stenosis ranged between 40% and 90%, of whom 143 patients underwent all tests (Figure 2). Basic characteristics of the study cohort are shown in Table 1. Median (interquartile range [IQR]) time delay between coronary CTA and coronary catheterization was 24 (IQR: 18 to 31) days.

CORONARY CTA. Selected preparation parameters and coronary characteristics by CTA are presented in Table 2.

FIGURE 2 Flowchart



Patients with a normal scan or minimal disease did not undergo any further testing. Patients with high-risk anatomy (severe left main or 3-vessel disease) by coronary CTA were referred to ICA. ICA = invasive coronary angiography; PE = pulmonary embolism; other abbreviations as in Figure 1.

SPECT. Stress studies were performed using adenosine (n = 139), regadenoson (n = 2), or symptom-limited treadmill exercise testing (n = 2). Overall, 32 patients (23%) had ischemia, including 26 patients (18%) with reversible perfusion defects (RPD): 7 of 26 (27%) with small RPDs; 11 of 26 (42%) with moderate RPDs; and 8 of 26 (31%) with large RPDs, and 10 patients (7%) who had transitory ischemic dilation. A combination of the 2 measurements of ischemia was found in 4 patients (3%). In 7 patients, no side effects to adenosine (dyspnea, chest pain, dizziness, or headache) were registered, of whom 3 patients had signs of reversible ischemia.

FFR_{CT}. FFR_{CT} analysis was performed successfully in 139 patients (97%). Overall, 87 patients (63%) had a minimum of 1 vessel with an FFR_{CT} value ≤0.80. The overall distribution of patient-level FFR_{CT} values is shown in Table 3.

INVASIVE PROCEDURES. Using a threshold of 50%, there were 55 patients (38%) with single-vessel disease, 23 patients (16%) with 2-vessel disease, and 1 patient (1%) with 3-vessel disease; using a 70% threshold, there were 39 patients (27%) with single-vessel disease, 8 patients (6%) 2-vessel disease, and 1 patient (1%) with 3-vessel disease.

TABLE 1 Patient Characteristics (N = 143)

Demographics	
Age, yrs	64 ± 11
Males	84 (59)
Body mass index, kg/m^2	27 ± 4
Caucasian	143 (100)
Symptoms	
Typical angina	47 (33)
Atypical angina	30 (21)
Nonanginal chest pain	54 (38)
Dyspnea	12 (8)
Diamond-Forrester Score, %	49 (25-69) [12-89]
Risk factors	
Ever smoker	94 (66)
Hypertension	89 (62)
Hypercholesterolemia	75 (52)
Diabetes	17 (12)
Family history of CVD*	33 (23)
Medical therapy	
Statins	67 (47)
Platelet inhibitors	66 (46)
Beta-blockers	37 (26)
Anticoagulants	4 (3)
Angiotensin inhibitors	53 (37)
Calcium antagonists	33 (23)
Diuretics	26 (18)
Peroral antidiabetics	14 (10)
Insulin	4 (3)

Values are mean ± SD, n (%), or median (interquartile range) [range]. *Defined as a family history of cardiovascular disease in a male first-degree relative before 55 years of age or in a female first-degree relative before 65 years of age.

CVD = cardiovascular disease.

Data for FFR measurements and patient treatment are presented in Table 4. In 10 patients with an FFR ≤0.80 (median 0.78; IQR: 0.77 to 0.79) revascularization was not performed due to small vessel dimension, vessel tortuosity, or paucity of symptoms at the time of coronary angiography. In 39 patients (81%), the treated lesions were located proximally.

TABLE 2 Coronary CTA (N = 143)

Preparation and basic information	
Nitroglycerine	143 (100)
Medication for reduction of heart rate	123 (86)
Heart rate, beats/min	55 ± 7
Radiation dose, mSv	3.3 (2.2-5.6) [0.6-14.5]
Analysis	
Agatston score, U	176 (72-438) [0-989]
0-99	49 (34)
100-399	56 (39)
400-999	38 (27)
Lesion severity	
≤70	63 (44)
≥70	50 (35)
Nonassessable due to focal high CAC	30 (21)

Values are n (%), mean ± SD, or median (interquartile range) [range].

CAC = coronary artery calcification; CTA = computed tomography angiography.

TABLE 3 Association Between Patient-Level Minimum FFR_{CT} Value and FFR (n = 139)

FFR_{CT} Range	Patients	FFR ≤0.80
≥0.85	22	0 (0)
0.81–0.85	30	5 (17)
0.76–0.80	25	8 (32)
0.71–0.75	25	16 (64)
0.61–0.70	18	11 (61)
≤0.60	19	16 (84)

Values are n or n (%). Test for trend $p < 0.001$.

FFR = fractional flow reserve; FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve.

FFR_{CT} VERSUS SPECT. The occurrence of ischemia was significantly different between modalities for all grades of lesion severity, as determined by coronary CTA (Figure 3). These differences were mainly due to underestimation of ischemia by SPECT. In patients with FFR_{CT} ≤0.80 and no signs of ischemia by SPECT (n = 61), the percentage of patients having an FFR ≤0.80 was 49%, whereas the corresponding percentage of patients having an FFR ≤0.80 in patients with an FFR_{CT} ≥0.80 and ischemia by SPECT (n = 6) was 17% ($p < 0.001$).

TABLE 4 Fractional Flow Reserve and Treatment (N = 143)

FFR assessment of number of vessels per patient	
1	93 (65)
2	38 (27)
3	12 (8)
Lowest FFR location	
LAD	112 (78)
CX	8 (6)
RCA	23 (16)
FFR ≤0.80	58 (41)
FFR ≤0.75	40 (28)
Treatment	
Optimized medical treatment, FFR ≥ 0.80	85 (59)
Optimized medical treatment, FFR ≤ 0.80	10 (7)
1-vessel PCI	36 (25)
2-vessel PCI	5 (4)
3-vessel PCI	1 (1)
CABG	6 (4)

Values are n (%). In 4 patients, in whom 2-vessel disease was suspected, FFR was performed only in 1 vessel due to subocclusion of LAD (FFR value in the RCA: 0.76) in 1 patient who subsequently underwent CABG; subocclusion of CX (FFR-value in the LAD: 0.66) in 1 patient who subsequently underwent CABG; severe dyspnea during measurement of FFR in the LAD (FFR value in the LAD: 0.65) with subsequent 2-vessel PCI (LAD/RCA) in 1 patient; and in 1 patient who had a severe proximal RCA lesion treated directly by PCI (FFR value in the LAD: 0.81). In 1 patient who was suspected of having 1-vessel disease, FFR was not performed due to severe spasm during FFR measurement in the RCA (the underlying coronary stenosis was deemed nonsignificant, and the patient was treated medically).

CABG = coronary artery bypass grafting; CX = circumflex coronary artery; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; other abbreviations as in Table 3.

FIGURE 3 Head-to-Head Comparison of SPECT and FFR_{CT}

	Total N = 143	
MPI/FFR_{CT}	FFR_{CT} ≤0.8	FFR_{CT} >0.8
Ischemia	30 (23 [77])	6 (1 [17])
No ischemia	61 (30 [49])	46 (4 [8])

	Focal high CAC n = 30		Degree of stenosis <70% n = 63		Degree of stenosis ≥70% n = 50	
MPI/FFR_{CT}	FFR_{CT} ≤0.8	FFR_{CT} >0.8	FFR_{CT} ≤0.8	FFR_{CT} >0.8	FFR_{CT} ≤0.8	FFR_{CT} >0.8
Ischemia	4 (3 [75])	1 (0 [0])	6 (3 [50])	2 (0 [0])	20 (17 [85])	3 (1 [33])
No ischemia	15 (7 [47])	10 (1 [10])	27 (12 [44])	28 (0 [0])	19 (11 [58])	8 (3 [38])

Direct comparisons between SPECT and FFR_{CT} are shown for both the entire population and for subgroups of patients with different stenosis severity. For each **cell**, the **number in first row** represents the actual number of patients with the specific combination of SPECT and FFR_{CT} test results; **numbers in second row** indicates the number of patients (n [%]) with an FFR value ≤0.80. MPI = myocardial perfusion imaging; other abbreviations as in Figure 1.

Overall, there was a significant association between the per-patient minimum FFR_{CT} value and the patient-level FFR value (Table 3). Five patients (9%) had false-negative FFR_{CT} results. The median of the lowest FFR_{CT} and FFR values in these patients were 0.82 (range 0.82 to 0.84) and 0.75 (range 0.45 to 0.78), respectively. A significant association between magnitude of ischemia by SPECT and patient-level FFR ≤0.8 was registered (Table 5). Both the per-patient minimum FFR ($\tau = -0.34$; $p < 0.0001$) and the FFR_{CT} values ($\tau = -0.29$; $p < 0.0001$) were negatively associated with the size of RPD.

Six patients with no RPDs had transient ischemic dilation, of whom 3 patients had an FFR ≤0.80. Overall, 34 patients (59%) were misclassified as normal by SPECT. The median FFR value in these patients was 0.75 (range 0.43 to 0.80).

DIAGNOSTIC PERFORMANCE OF FFR_{CT} VERSUS SPECT. Patient diagnostic performances for SPECT and FFR_{CT} are shown in Figure 4. The per-patient diagnostic performance of FFR_{CT} compared with SPECT for identifying ischemia (95% confidence interval [CI]) for sensitivity was 91% (95% CI: 81% to 97%) versus 41% (95% CI: 29% to 55%; $p < 0.001$); for specificity was 55% (95% CI: 44% to 66%) versus 86% (95% CI: 77% to 93%; $p < 0.001$); for NPV was 90% (95% CI: 82% to 98%) versus 68% (95% CI: 59% to 77%; $p = 0.001$); for PPV was 58% (95% CI: 48% to 68%) versus 67% (95% CI: 51% to 82%; p = NS); and for accuracy was 70% (95% CI: 62% to 77%) versus 68% (95% CI: 60% to 75%; p = NS), respectively. The sensitivity of FFR_{CT} for predicting ischemia by FFR remained constantly high over a broad range of parameters, whereas the sensitivity for SPECT was consistently low (Table 6).

Patients with an FFR ≤0.75 (n = 40) were significantly more often falsely diagnosed as having a normal test result by SPECT (n = 19) than by FFR_{CT} (n = 3; $p < 0.001$).

PREDICTION OF REVASCULARIZATION BY FFR_{CT} AND SPECT. The diagnostic performances for predicting revascularization for SPECT and FFR_{CT} are shown in Table 7. The sensitivity of FFR_{CT} remained constantly high and the sensitivity of SPECT consistently low over a broad range of parameters including the degree of coronary calcification, stenosis severity, and lesion location (Online Table 1).

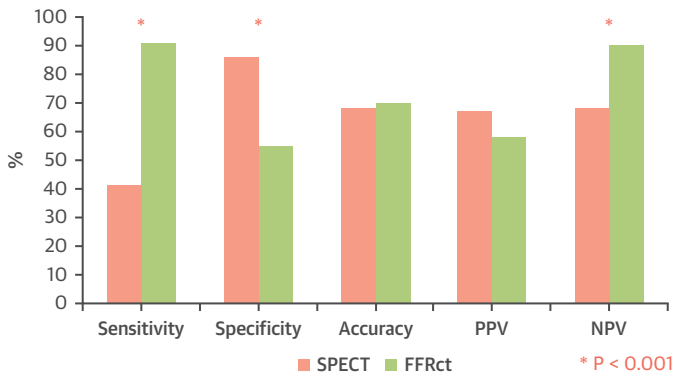
TABLE 5 Association Between Size of Reversible Perfusion Defects by SPECT and FFR (n = 139)

Size of Reversible Perfusion Defect	Patients	FFR ≤0.80
No reversible perfusion defect	113	34 (30)
Small reversible perfusion defect	7	3 (43)
Moderate reversible perfusion defect	11	8 (73)
Large reversible perfusion defect	8	8 (100)

Values are n or n (%). Test for trend p ≤ 0.001.

SPECT = single-photon emission computed tomography; other abbreviations as in Table 3.

FIGURE 4 Patient Diagnostic Performances of FFR_{CT} and SPECT Using FFR as the Reference Standard



The results of core laboratory FFR_{CT} analysis and SPECT test assessments had no impact on referral to invasive angiography and were blinded to the interventionalists. NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Figure 1.

TABLE 6 Patient Diagnostic Sensitivity of FFR_{CT} and SPECT in Subgroups of Patients With Stable Chest Pain Using FFR as the Reference Standard

	FFR_{CT}		SPECT	
	Sensitivity	p Value	Sensitivity	p Value
Male	93	0.609	43	0.773
Female	88		38	
Age				
≤64 yrs	91	1.000	49	0.283
≥64 yrs	92		32	
Agatston score				
≤100	94	1.000	55	0.377
100-399	91		33	
≥400	89		37	
Stenosis severity, coronary CTA				
40%-69%	100	0.376	27	0.040
70%-90%	88		56	
Nonassessable, focal high CAC	91		20	
Diseased vessels by ICA				
50%, threshold				
0	100	0.113	0	0.118
1	84		52	
≥2	100		35	
70%, threshold				
0	92	0.817	17	0.170
1	89		49	
≥2	100		44	
Revascularization				
1 vessel	86	0.312	47	1.000
≥2 vessels	100		50	
LAD	89		43	
Non-LAD	91	1.000	64	0.311
Proximal	87	0.568	51	0.466
Distal	100		33	

Values are %.
Abbreviations as in Tables 1 and 3.

False-negative test results were significantly more frequent by SPECT than by FFR_{CT} assessment, both in patients undergoing multivessel revascularization: SPECT (n = 6 [50%]) versus FFR_{CT} (n = 0; $p < 0.05$), and in patients treated by single-vessel revascularization: SPECT (n = 19 [53%]) versus FFR_{CT} (n = 5 [14%]; $p < 0.001$). In those 6 patients with multivessel disease and a false negative SPECT result, coronary artery bypass graft was performed in 4 patients, triple-vessel percutaneous coronary intervention in 1 patient, and double-vessel PCI in 1 patient. Patient examples are shown in Figure 5.

DISCUSSION

In this prospective clinical study of symptomatic stable patients with intermediate range lesions determined by coronary CTA, no significant differences in diagnostic accuracy between FFR_{CT} and SPECT were shown using invasive FFR as the reference standard. However, significant differences in test sensitivity in favor of FFR_{CT} for identifying hemodynamically significant stenosis and for predicting subsequent revascularization were demonstrated.

Recent landmark trials have demonstrated that an FFR threshold of 0.80 distinguishes patients and coronary lesions who will benefit from coronary revascularization (18,19) from those who will not (20). Based on these data, FFR has become the gold standard for making decisions about revascularization in patients with stable CAD (2,3) and the contemporary reference standard when evaluating the diagnostic performance of noninvasive testing strategies in stable CAD (21,22). Coronary CTA is increasingly used in the diagnostic work-up of patients suspected of stable CAD. However, coronary CTA cannot assess the hemodynamic effect of lesions, especially in intermediate range stenosis, where the disconnection between anatomy and physiology is most profound (23). Thus, in patients with moderate CAD determined by coronary CTA, functional testing is now recommended before referral to ICA (2,24). Therefore, the current study was designed to compare, for the first time in a prospective fashion, the diagnostic performance of FFR_{CT} with that of SPECT for identification of ischemia, using FFR as the reference standard. The strategy of frontline coronary CTA testing followed by functional testing in patients with CAD had 2 main purposes. The first purpose was to exclude a significant number of patients with no or minimal CAD, in whom prognosis was excellent and thus did not need further testing (25). The second purpose was to assess the ICA gate-keeping potentials of the 2 test strategies in a head-to-head fashion. Thus, this study provides

TABLE 7 Diagnostic Performance of FFR_{CT} and SPECT for Prediction of FFR-Guided Revascularization in Stable Chest Pain

	FFR_{CT}	SPECT	p Value
Sensitivity	90 (77–97)	48 (33–63)	≤ 0.001
Specificity	50 (39–60)	86 (78–93)	≤ 0.001
PPV	47 (37–58)	64 (48–80)	0.028
NPV	90 (82–98)	77 (69–85)	0.031
Accuracy	63 (55–71)	73 (65–81)	0.067

Values are % (95% confidence interval).

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 1, 3, and 4.

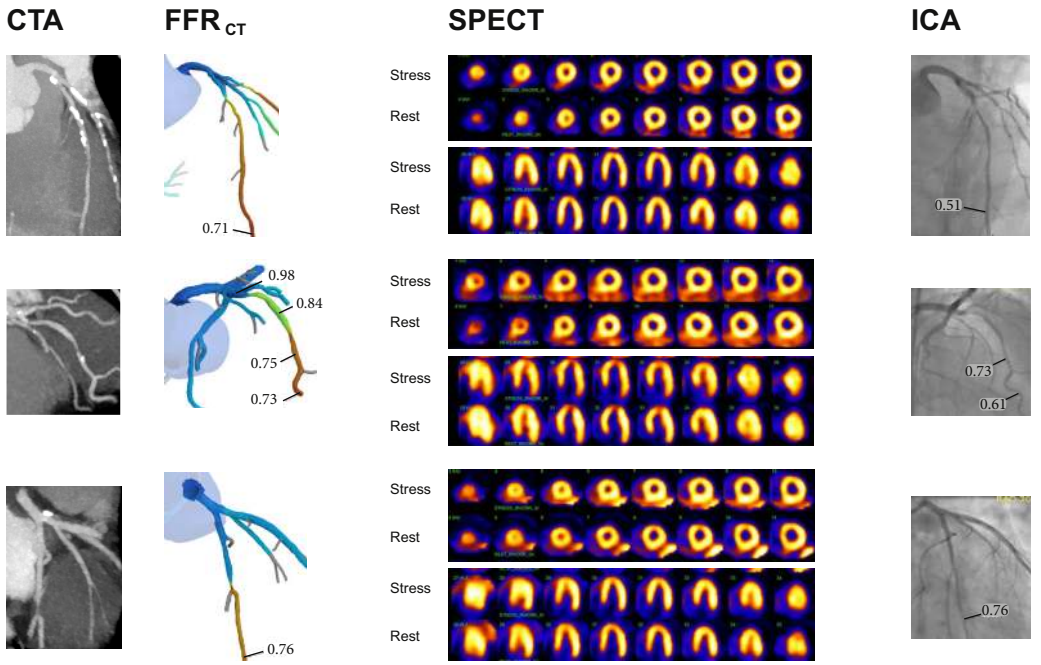
important evidence for an improved diagnostic sensitivity of FFR_{CT} relative to established noninvasive assessment in patients with stable chest pain and CAD determined by coronary CTA. The improved sensitivity of FFR_{CT} was further emphasized by the subanalysis demonstrating a maintained high sensitivity of FFR_{CT} over a broad range of subgroups.

Differences between FFR_{CT} and SPECT were in the same range, when considering FFR-guided revascularization.

SPECT performance in the current study is in line with that in previous studies (17,26,27), in which FFR was used as the reference standard. The Dan-NICAD trial (27) and the present study provided an almost identical sensitivity of SPECT (36% and 41%, respectively) for diagnosing physiologically significant lesions. These studies applied a different testing strategy compared with previous studies, as functional testing was performed exclusively in patients with moderate CAD, as determined by coronary CTA.

In the prospective PACIFIC trial (26) pre-selection of patients by coronary CTA was not performed, but the sensitivity of 56% by SPECT was in the same range as those in former studies. Moreover, both the PACIFIC trial and the meta-analyses (21,22) indicated a significantly lower accuracy by SPECT than other perfusion modalities for diagnosing FFR-defined ischemia. The low diagnostic sensitivity of SPECT perfusion imaging may be related to the nonlinear retention of SPECT tracers, tracer roll-off, at high coronary flow rates (28). Indeed, the saturation kinetics of SPECT tracers may hamper depiction of the entire range of increase in myocardial perfusion

FIGURE 5 Case Examples



Ischemia test results are shown for 3 patients. Test results for each patient are shown in the upper, mid, or lower panel. Exact values of measured FFR and FFR_{CT} are given as appropriate. All patients had an abnormal per-patient FFR_{CT} value and normal SPECT scan results; all patients were treated with PCI. From left to right results of coronary CTA, FFR_{CT}, SPECT and ICA/FFR are shown. PCI = percutaneous coronary intervention; other abbreviations as in Figures 1 and 2.

induced by adenosine, especially in myocardium supplied by normal coronary arteries. This disadvantage of most nuclear tracers reduces the ability to diagnose impairment in the vascular response to adenosine particularly in intermediate range coronary lesions, which not only seem most challenging but also, numerically, are more frequent than high-grade lesions in patients with stable chest pain (29).

The diagnostic specificity of SPECT in the PACIFIC trial (94%) and in the present study (86%) were higher than both previous studies of SPECT performance (30) and significantly higher than for FFR_{CT} in the present study. The only modest per-patient specificity of FFR_{CT} in this study may in part be explained by using the nadir per-vessel FFR_{CT} value rather than the translesional value (31). Moreover, the use of pre-coronary CTA nitroglycerine tablets rather than spray may be associated with a more heterogenous vasodilatory response (32); hence, more falsely positive FFR_{CT} results compared to invasive FFR.

It should be acknowledged, that the selection of the patient population by coronary CTA as applied in the present study is critical for interpretation of results. Although studies have shown that stable patients with a normal test result by first-line perfusion imaging have favorable clinical outcomes (1,33), it should be acknowledged that visualization of coronary anatomy was not undertaken in these patients. In both the present study and the DanNICAD trial, a substantial number of patients would actually have been undiagnosed by SPECT if invasive measurements had not been undertaken. Accordingly, 2 recently published studies, a meta-analysis (34) and a substudy of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial (35) comparing outcomes in patients tested with coronary CTA versus functional testing strategies demonstrated a significantly lower incidence of major adverse cardiac events following anatomic assessment by coronary CTA. These data indicate that a normal perfusion scan cannot automatically be taken as a marker for normal coronary arteries, and importantly, the overall cohort prognosis cannot inevitably be translated into those patients who are misclassified as normal by perfusion imaging. However, more studies are needed to confirm the present results and ultimately to assess the influence of a first-line testing strategy using FFR_{CT} instead of SPECT on clinical outcomes.

STUDY LIMITATIONS. Patients in this study were included at 1 center. Although the cohort reflects consecutive patients in whom frontline coronary CTA testing was relevant in contemporary practice, it may be speculated that core laboratory adjudication of coronary CTA and FFR tracings would have been valuable. However, off-line core laboratory test adjudication in this trial was restricted to the blinded analyses of the 2 modalities being evaluated in order to mirror as much as possible real-world clinical practice. The time span between coronary CTA and following per-protocol invasive study modalities was 24 days, but it seems unlikely that any significant changes in the atherosclerotic disease occurred between tests within this short time frame.

Referring patients who were eligible for coronary CTA testing directly to SPECT might have biased the results. However, this study was conducted in consecutive patients at 1 single center with strictly defined algorithms for ruling out coronary artery disease by first-line coronary CTA; thus, we do not believe that this factor influenced the results of this study. This study only applied to patients in whom coronary CTA testing was appropriate. In addition, FFR_{CT} cannot be calculated in all patients, especially in the event of deteriorated CT image quality (10). However, in this and in recent studies (12) from clinical practice, FFR_{CT} could be performed in most patients.

Finally, it should be noted that sensitivity analyses in subgroups should be interpreted with caution, as no sample size estimations for performing these analyses were done.

CONCLUSIONS

This prospective study of patients with intermediate coronary lesions determined by coronary CTA did not show any difference in the diagnostic accuracy of FFR_{CT} and SPECT when using invasive FFR as the reference standard. However, the diagnostic sensitivity for predicting FFR-guided revascularization by FFR_{CT} was superior to SPECT. Future studies are needed in order to clarify, whether the reported improvement in diagnostic sensitivity by FFR_{CT} over SPECT can be translated into improved clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary CTA is increasingly used as the first-line test in patients suspected of stable CAD. However, patients with intermediate range stenosis often require further testing, and the optimal downstream management strategy in such patients is unclear. We prospectively evaluated the diagnostic performance of FFR_{CT} and myocardial perfusion imaging by SPECT in symptomatic patients with intermediate range coronary stenosis by using measured FFR as the reference standard. Observers performing FFR were blinded to the results of FFR_{CT} and SPECT. We found a comparable diagnostic accuracy of the two non-invasive testing strategies. However, the diagnostic sensitivity for assessing hemodynamically significant coronary stenosis was significantly higher for FFR_{CT} compared to SPECT perfusion imaging.

TRANSLATIONAL OUTLOOK: The current study advocates, as a first-line strategy, coronary CTA for ruling out the existence of CAD and selective FFR_{CT}-testing in patients with intermediate range lesions as gatekeeping to invasive coronary angiography. Further large scale studies are needed to assess cost efficiency and safety of the reported first-line/2-step coronary CTA strategy versus conventional myocardial perfusion imaging strategies.

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KEY WORDS coronary CTA, FFR_{CT}, SPECT myocardial perfusion imaging, stable angina

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