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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) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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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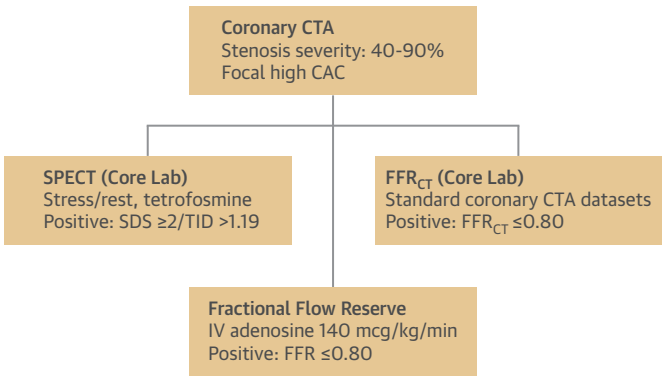
**FIGURE 1 Schematic Illustration of the Study Protocol**




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.

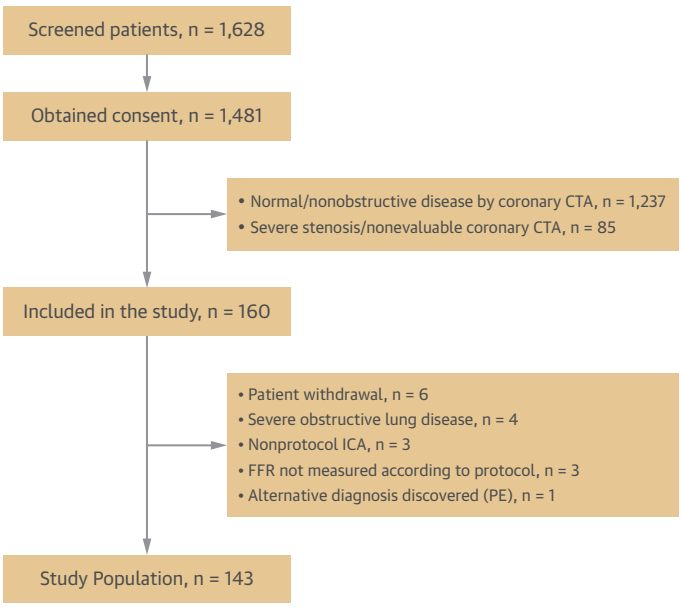
A p value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 14.0 software (Stata Corp, College Station, Texas).

## 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).

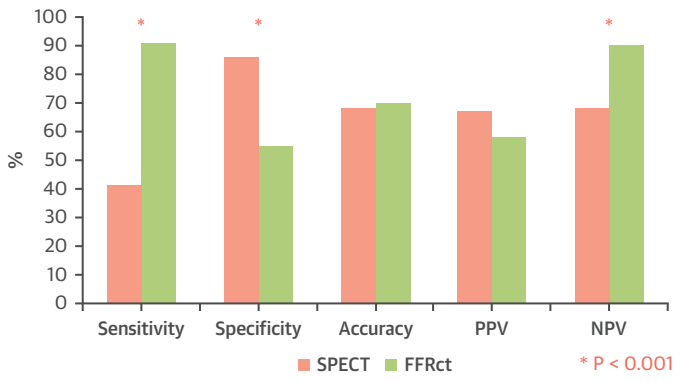
**TABLE 5 Association Between Size of Reversible Perfusion Defects by SPECT and FFR (n = 139)**

| 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.

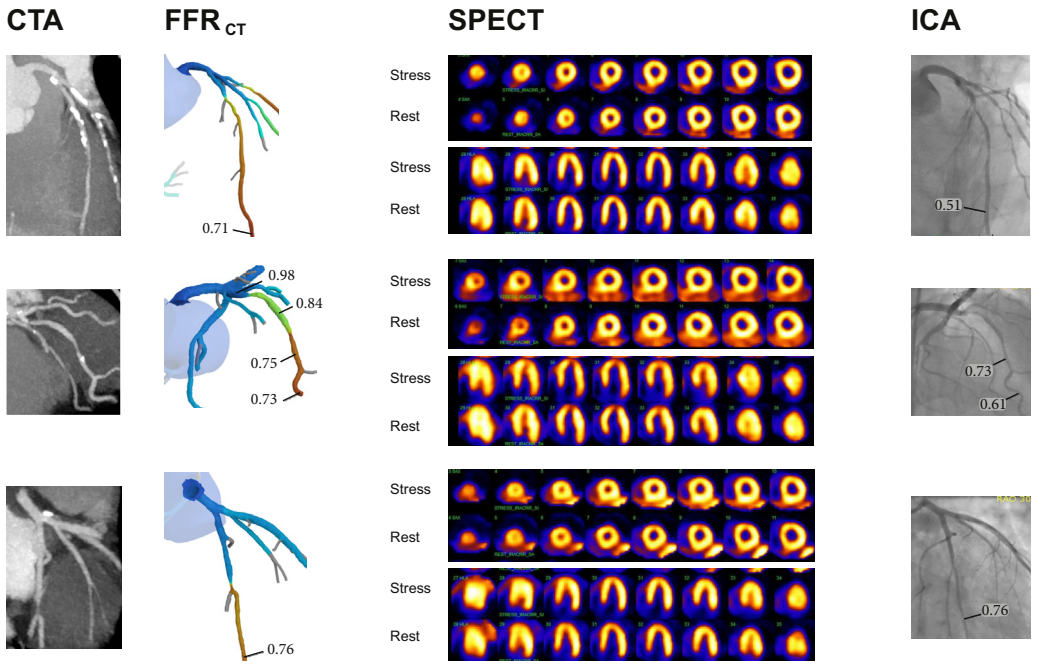
important evidence for an improved diagnostic sensitivity of $FFR_{CT}$ relative to established noninvasive assessment in patients with stable chest pain and CAD determined by coronary CTA. The improved sensitivity of $FFR_{CT}$ was further emphasized by the subanalysis demonstrating a maintained high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

## REFERENCES

**1.** Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535–43.

**2.** Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.

**3.** Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929–49.

**4.** Shaw LJ, Marwick TH, Zoghbi WA, et al. Why all the focus on cardiac imaging? J Am Coll Cardiol Img 2010;3:789–94.

**5.** Berman DS, Kang X, Slomka PJ, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. J Nucl Cardiol 2007;14:521–8.

**6.** Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–96.

**7.** Menke J, Kowalski J. Diagnostic accuracy and utility of coronary CT angiography with consideration of unevaluable results: a systematic review and multivariate Bayesian random-effects meta-analysis with intention to diagnose. Eur Radiol 2016;26:451–8.

**8.** Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol 2013;61:2233–41.

**9.** Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.

**10.** Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of non-invasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145–55.

**11.** Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies versus usual care in patients with suspected coronary artery disease: the Prospective Longitudinal Trial of $FFR_{CT}$: outcome and resource impacts (PLATFORM) study. Eur Heart J 2015;36:3359–67.

**12.** Nørgaard BL, Gormsen L, Bøtker HE, et al. Myocardial perfusion imaging versus computed tomography angiography-derived fractional flow reserve testing in stable patients with intermediate-range coronary lesions: influence on downstream diagnostic workflows and invasive angiography findings. J Am Heart Assoc 2017;6:e005587.

**13.** Adjedj J, De Bruyne B, Floré V, et al. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. Circulation 2016;133:502–8.

**14.** Verberne HJ, Acampa W, Anagnostopoulos C, et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT. Eur J Nucl Med Mol Imaging 2015;42:1929–40.

**15.** Berman DS, Kang X, Van Train KF, et al. Comparative prognostic value of automatic quantitative analysis versus semiquantitative visual analysis of exercise myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 1998;32:1987–95.

**16.** Kakhki VRD, Sadeghi R, Zakavi SR. Assessment of transient left ventricular dilation ratio via 2-day dipyridamole Tc-99m sestamibi nongated myocardial perfusion imaging. J Nucl Cardiol 2007;14:529–36.

**17.** Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. J Am Coll Cardiol Intv 2010;3:307–14.

**18.** Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

**19.** De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208–17.

**20.** Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 2015;36:3182–8.

**21.** Takx RAP, Blomberg BA, Aidi HE, et al. Diagnostic accuracy of stress myocardial perfusion

imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging 2015;8:e002666.

**22.** Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J 2017;38:991–8.

**23.** Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.

**24.** Timmis A, Roobottom CA. National Institute for health and care excellence updates the stable chest pain guideline with radical changes to the diagnostic paradigm. Heart 2017;103:982–6.

**25.** Adamson PD, Hunter A, Williams MC, et al. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institutes for Health and Care Excellence guidance within a randomised trial. Heart 2017;104:207–14.

**26.** Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. JAMA Cardiol 2017;2:1100–7.

**27.** Nissen L, Winther S, Westra J, et al. Diagnosing coronary artery disease after a positive coronary computed tomography angiography—the DanNICAD open label, parallel, head to head, randomized controlled diagnostic accuracy trial of cardiovascular magnetic resonance and myocardial perfusion scintigraphy. Eur Heart J Cardiovasc Imaging 2018;19:369–77.

**28.** deKemp RA, Renaud JM, Klein R, Beanlands RSB. Radionuclide tracers for myocardial perfusion imaging and blood flow quantification. Cardiol Clin 2016;34:37–46.

**29.** Nielsen LH, Bøtker HE, Sørensen HT, et al. Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study. Eur Heart J 2017;38:413–21.

**30.** Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015;8:e002179.

**31.** Rabbat MG, Berman DS, Kern M, et al. Interpreting results of coronary computed tomography angiography-derived fractional flow reserve in clinical practice. J Cardiovasc Comput Tomogr 2017;11:383–8.

**32.** Pfister M, Seiler C, Fleisch M, Göbel H, Lüscher T, Meier B. Nitrate induced coronary vasodilation: differential effects of sublingual application by capsule or spray. Heart 1998;80:365–9.

**33.** Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates. The CE-MARC 2 randomized clinical trial. JAMA 2016;316:1051–60.

**34.** Foy AJ, Dhruva SS, Peterson B, Mandrola JM, Morgan DJ, Redberg RF. Coronary computed tomography angiography versus functional stress testing for patients with suspected coronary artery disease: a systematic review and meta-analysis. JAMA Intern Med 2017;177:1623–31.

**35.** Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;135:2320–32.

**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.