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ORIGINAL RESEARCH

Second-Line Myocardial Perfusion Imaging to Detect Obstructive Stenosis

Head-to-Head Comparison of CMR and PET

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ABSTRACT

BACKGROUND Guidelines recommend verification of myocardial ischemia by selective second-line myocardial perfusion imaging (MPI) following a coronary computed tomography angiography (CTA) with suspected obstructive coronary artery disease (CAD). Head-to-head data on the diagnostic performance of different MPI modalities in this setting are sparse.

OBJECTIVES The authors sought to compare, head-to-head, the diagnostic performance of selective MPI by 3.0-T cardiac magnetic resonance (CMR) and ^{82}rubidium positron emission tomography (RbPET) in patients with suspected obstructive stenosis at coronary CTA using invasive coronary angiography (ICA) with fractional flow reserve (FFR) as reference.

METHODS Consecutive patients (n = 1,732, mean age: 59.1 ± 9.5 years, 57.2% men) referred for coronary CTA with symptoms suggestive of obstructive CAD were included. Patients with suspected stenosis were referred for both CMR and RbPET and subsequently ICA. Obstructive CAD was defined as FFR ≤0.80 or >90% diameter stenosis by visual assessment.

RESULTS In total, 445 patients had suspected stenosis on coronary CTA. Of these, 372 patients completed both CMR, RbPET and subsequent ICA with FFR. Hemodynamically obstructive CAD was identified in 164 of 372 (44.1%) patients. Sensitivities for CMR and RbPET were 59% (95% CI: 51%-67%) and 64% (95% CI: 56%-71%); $P = 0.21$, respectively, and specificities 84% (95% CI: 78%-89%) and 89% (95% CI: 84%-93%]); $P = 0.08$, respectively. Overall accuracy was higher for RbPET compared with CMR (73% vs 78%; $P = 0.03$).

CONCLUSIONS In patients with suspected obstructive stenosis at coronary CTA, CMR, and RbPET show similar and moderate sensitivities but high specificities compared with ICA with FFR. This patient group represents a diagnostic challenge with frequent mismatch between advanced MPI tests and invasive measurements. (Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease 2 [Dan-NICAD 2]; NCT03481712)
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Coronary computed tomographic angiography (CTA) is recommended as the initial diagnostic test in patients with de novo chest pain,[1] but stenosis severity is often overestimated.[2] Hence, guidelines recommend selective second-line myocardial perfusion tests (MPI) to verify the presence of inducible myocardial ischemia.[1,3] MPIs compromise conventional single photon emission computed tomography, positron emission tomography (PET) with different radiotracers including ^{82}rubidium positron emission tomography (RbPET), and cardiac magnetic resonance (CMR) imaging.

As first-line investigations in patients with established or a high risk of obstructive coronary artery disease (CAD), all MPIs have shown moderate to high diagnostic accuracy.[2] However, despite guideline recommendations,[1,3] the diagnostic performance of selective second-line MPIs in patients with de novo chest pain and suspected obstructive CAD at coronary CTA has only been sparsely evaluated. The Dan-NICAD 1 (Danish Study of Non-Invasive Testing in Coronary Artery Disease 1) evaluated the accuracy of single photon emission computed tomography and CMR using a 1.5-T MR system and found similar moderate sensitivities but high specificities of both modalities.[4] Data on the performance of more advanced MPI tests in a similar setting are missing: in particular, using a prospective head-to-head design, which is considered an evidence gap.[1,5]

The aim of this study was, therefore, to investigate and compare the diagnostic performance of 3.0-T CMR and RbPET in patients with symptoms suggestive of obstructive CAD and suspected obstructive CAD at coronary CTA using invasive coronary angiography (ICA) with fractional flow reserve (FFR) as reference.

METHODS

PATIENTS AND STUDY DESIGN. A detailed description of the study protocol including inclusion and exclusion criteria has been reported previously.[6] In brief, the Dan-NICAD 2 trial was a prospective, multicenter, open-labeled, randomized controlled trial including 1,732 patients referred for coronary CTA with low to intermediate pretest risk of obstructive CAD. Patients with suspected obstructive CAD at coronary CTA underwent—in randomized order—both 3.0-T CMR and RbPET, and regardless of the findings, the examinations were followed by subsequent ICA with FFR. Patients were randomized using a web-based system and stratified according to enrollment site and sex. Physicians performing ICA were blinded to the results of CMR and RbPET, and the primary core lab analyses of the MPIs were blinded to the coronary CTA and ICA results. The prespecified criterium for sufficient sample size was 368 patients, with completed CMR, RbPET, and invasive assessment.[6]

The study was conducted according to the declaration of Helsinki. The Danish Data Protection Agency and the Central Denmark Regional Committee on Health Research Ethics (case number: 1-10-72-64-17) approved the study. All patients signed written informed consent forms. The study was registered at ClinicalTrials.gov (NCT03481712).

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY. Coronary CTA scans were performed using a 320 multislice volume computed tomography (CT) scanner (Aquilion One, Toshiba Medical Systems) or a Siemens Flash scanner (Siemens Healthcare) with electrocardiographic gating. Coronary CTAs were performed at 4 hospitals, which enrolled patients and had high experience in performing coronary CTA (>800 coronary CTA scans annually). Images were analyzed onsite, using a dedicated workstation (Vitrea Advanced Workstation, Vital Images or Syngo.Via, Siemens Healthcare). Using the 18-segment model, the luminal diameter stenosis was evaluated

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTA = computed tomography angiography

DS = diameter stenosis

FFR = fractional flow reserve

ICA = invasive coronary angiography

MPI = myocardial perfusion imaging

RbPET = ^{82}rubidium positron emission tomography

3D-QCA = 3-dimensional quantitative coronary angiography

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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in each segment of the coronary tree. Suspected obstructive CAD was defined as segments with a diameter exceeding 2 mm and 50% to 100% reduction of diameter.

CARDIAC MAGNETIC RESONANCE. CMR scans were conducted using a 3.0-T CMR system (Siemens Skyra, Software release E11A, Siemens Healthcare), using the Body18 and Spine32 receiver coils. Hyperemia was induced using a continuous infusion of adenosine (140 mg/kg/min, increasing to 210 mg/kg/min if the response was assessed as insufficient) over 7 minutes. Criteria for sufficient adenosine response are outlined in the Supplemental Methods. A gadolinium contrast agent (Gadovist, Bayer Schering Pharma AG) was injected during stress and rest, using a dual-bolus method.

The CMR analyses were carried out by an independent core lab (William Harvey Research Institute, Queen Mary University of London, London, UK). Abnormality was prespecified as ≥2 contiguous segments with either: 1) significant perfusion defect, either subendocardial or transmural by stress imaging; 2) presence of late gadolinium enhancement (LGE); 3) wall-motion abnormalities (WMA); or 4) nonevaluable examination because of low examination quality.

RbPET. The RbPET scans were obtained in list mode using a Siemens Biograph mCT/64 PET-scanner (Siemens Healthcare). Hyperemia and criteria for sufficient adenosine response was similar to that of CMR, as outlined in the Supplemental Methods.

Imaging analyses were performed by an independent core lab blinded for additional patient information and results (Department of Nuclear Medicine, Aarhus University Hospital, Denmark). Abnormality was prespecified as either: 1) summed stress score (SSS) ≥4 in ≥2 contiguous segments; 2) regionally reduced myocardial blood flow (MBF) <2 mL/g/min during adenosine stress; 3) myocardial blood flow reserve (MBFR) ≤1.8 corrected for the rate pressure product; 4) transient ischemic dilation (TID) ratio >1.13; or 5) nonevaluable examination because of low examination quality.

READING STRATEGIES OF CMR AND RbPET. Both CMR and RbPET scans were assessed in 3 consecutive settings. First, scans were evaluated according to the prespecified cutoffs by the expert reader blinded to coronary CTA results and additional baseline characteristic (prespecified read). Second, the expert reader made an overall interpretation of the scans and classified the results according to a binary outcome (normal or abnormal) (blinded read). Finally, the expert reader was presented with knowledge on patient demographics, risk factors, and results of the coronary CTA, and another binary outcome read was performed (prior knowledge read).

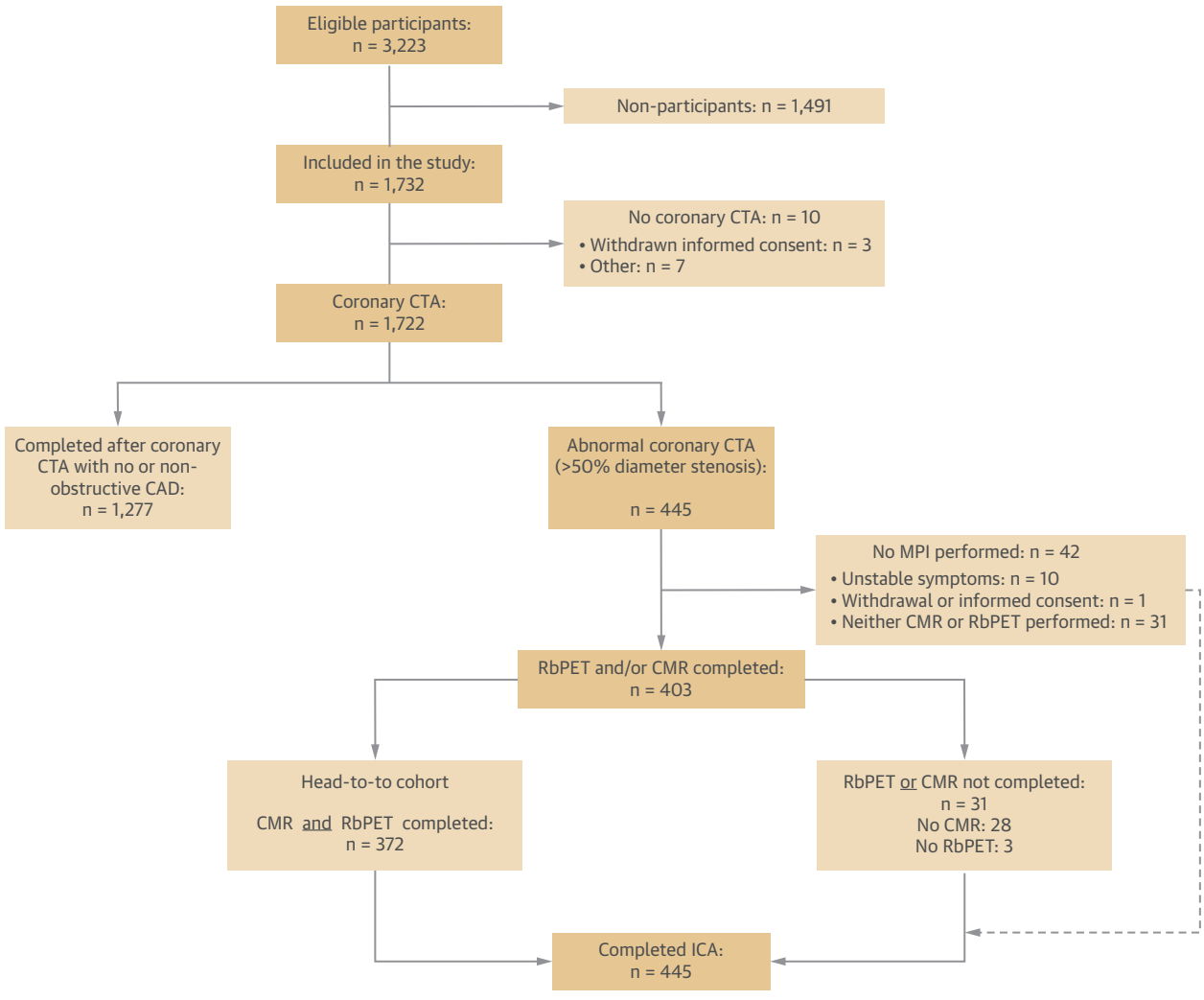
INVASIVE FRACTIONAL FLOW RESERVE. All ICAs were performed approximately 4 weeks following coronary CTA. FFR measurements were obtained if technically possible (eg, no vessel tortuosity) in all coronary segments with a diameter >2 mm, in which ICA showed a stenosis with a diameter ≥30 and <90% by visual assessment. Similar to CMR and RbPET, hyperemia was induced using a 1 mg/mL concentration of intravenous adenosine at 140 mg/min/kg increasing to 200 μg/min/kg if a stable FFR value was not achieved. Routine checks were made to ensure that "drift" did not occur before the recordings, and drift of ≤±0.02 was accepted. All pressure waveforms were analyzed by a core lab (Interventional Coronary Imaging Core Laboratory, Aarhus University Hospital, Denmark), using dedicated software (Coroventis CoroFlow Cardiovascular System).

Three-dimensional (3D) quantitative coronary angiography (QCA) and quantitative flow ratio (QFR) core lab analyses were performed in a core lab setting (Aarhus University Hospital, Skejby, Denmark), using the latest version of the software QAngio XA 3D version X (Medis Medical Imaging System).

Hemodynamically obstructive CAD was defined as high-grade stenosis (>90% diameter stenosis) by visual assessment, ICA FFR ≤0.80 in a vessel with a diameter stenosis of 30% to 90%, or 3D-QCA-based diameter stenosis (≥50% diameter) if FFR were not possible to perform.

STATISTICAL ANALYSES. Variables are expressed as mean ± SD (total range) or median (range), categorical variables reported as frequencies (percentages). Pretest probability was estimated based on European Society of Cardiology (ESC) 2019 guideline recommendations.[1] The diagnostic performance of both MPIs was evaluated by sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy. Comparison of sensitivities and specificities was tested using McNemar test and a weighted generalized score statistics for comparison of predictive values of diagnostic tests. The reference standard used for the primary analysis was invasive hemodynamically obstructive CAD by FFR. The primary analysis was performed on a per-patient level. Per-vessel level analyses were performed so that each segment was assigned to a vessel according to standard recommendations.[6]

FIGURE 1 **Study Design and Patient Flow**



CONSORT diagram of the Dan-NICAD 2 (Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease 2) study. CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; RbPET = ^{82}rubidium positron emission tomography.

An intention-to-diagnose analysis was performed when patients with either missing CMR or RbPET were classified as positives in the prior-knowledge CMR and RbPET reads, respectively.

Several sensitivity analyses were conducted with altered thresholds for abnormality of the MPIs and ICA. First, the threshold for abnormality of CMR and RbPET were lowered to ≥1 segment with significant perfusion defect. Second, analyses were conducted by different reference standards of obstructive CAD: 1) 3D-QCA by different thresholds of diameter stenosis; 2) a combined endpoint of FFR with additional invasive QFR in patients without invasively measured FFR by a cutoff ≤0.80 by both; and 3) FFR in patients without concurrent high-grade stenosis by visual assessment by a cutoff ≤0.80 and ≤0.75, respectively.

RESULTS

In total, 3,223 patients with low to intermediate probability of obstructive CAD referred for a primary examination by coronary CTA because of symptoms suggestive of obstructive CAD were eligible for study enrollment before the coronary CTA (Figure 1). A total of 1,491 (45.6%) patients declined participation; mean age of 58.1 ± 7.3 years, of whom 876 patients (58.8%)

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TABLE 1 Patient Characteristics

	Included Patients at Coronary CTA, Total Cohort (n = 1,732)	Head-to-Head Perfusion, Subcohort (n = 372)
Women	742 (42.8)	109 (29.3)
Age, y	59.1 ± 9.5	63.6 ± 7.6
Risk factors		
Family history of early CAD	576 (33.3)	142 (38.2)
Current smoking	241 (13.9)	58 (15.6)
Antihypertensive treatment	717 (41.4)	188 (50.5)
Lipid-lowering treatment	440 (25.4)	144 (38.7)
Diabetes	106 (6.1)	34 (9.1)
BMI	27.6 ± 4.3	27.3 ± 3.9
Symptoms		
Typical angina	348 (20.1)	110 (29.6)
Atypical angina	673 (38.9)	131 (35.2)
Nonanginal chest pain	405 (23.4)	85 (22.8)
Other, dyspnea or arrythmia	306 (17.7)	46 (12.4)
Pretest probability		
<5%	220 (12.7)	10 (2.7)
5%-15%	680 (39.3)	101 (27.2)
>15%	832 (48.0)	261 (70.1)
Coronary CTA		
Calcium score, Agatson	193.2 (0-119)	607.4 (92-840)
0	740 (42.7)	27 (7.3)
1-399	773 (44.6)	194 (52.1)
≥400	219 (12.6)	151 (40.6)
Nonobstructive disease	1,277 (74.2)	0
1-vessel disease	243 (14.1)	210 (56.5)
2-vessel disease	115 (6.7)	98 (26.3)
3-vessel or LM disease	87 (5.0)	64 (18.0)
ICA		
Nonobstructive disease	1,520 (88.3)	208 (56.1)
1-vessel disease[a]	131 (7.6)	105 (28.2)
2-vessel disease[a]	38 (2.2)	28 (7.5)
3-vessel or LM disease[a]	33 (1.9)	31 (8.3)

Values are n (%), mean ± SD, or median (IQR). [a]Denotes the prespecified cutoff with visual high-grade stenosis (>90% diameter stenosis) or FFR ≤0.80 in lesions with 30% to 90% diameter stenosis.

BMI = body-mass index; CAD = coronary artery disease; CTA = computed tomography angiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; LM = left main.

were female; 1,732 patients (54.4%) accepted study enrollment; mean age of 59.1 ± 9.5, of whom 742 (42.8%) were female. Of the enrolled patients, 445 (25.7%) had suspected obstructive CAD on coronary CTA; 372 (83.4%) completed CMR, RbPET, and the following ICA with FFR (head-to-head cohort). Baseline demographics for the overall study and the head-to-head cohorts are presented in **Table 1**.

At ICA on a per-patient level, 100 of 372 (26.9%) patients had ≥1 lesion with high-grade stenosis by visual assessment not available for FFR assessment, and 208 of 372 (55.9%) patients had ≥1 lesion with 30% to 90% diameter stenosis (DS) available for FFR assessment. Median per-patient lowest FFR was 0.81 ± 0.11, and 78 of 208 (37.5%) patients had FFR values ranging from 0.75 to 0.85. Finally, 89 of 372 (23.9%) patients had ≥1 lesion with <30% DS without indication for FFR-assessment.

Hemodynamically obstructive CAD at ICA in the head-to-head cohort was identified in 164 of 372 (44.1%) patients: 100 of 164 (61.0%) were visually defined by high-grade stenosis, 57 of 164 (34.8%) by FFR ≤0.80, and 7 of 164 (42.7%) by 3D QCA DS >50%.

DIAGNOSTIC PERFORMANCE OF CMR. Findings in the blinded expert analysis, with some overlap between the listed findings on a per-patient level, are shown in Supplemental Table 1. In the blinded expert interpretation of the CMR examinations, 130 of 372 (34.9%) were classified as abnormal. The subsequent prior-knowledge analysis by the expert reader classified 130 of 372 (34.9%) patients as abnormal, of which 4 of 372 (1.1%) patients changed disease status from the blinded to the prior-knowledge analyses.

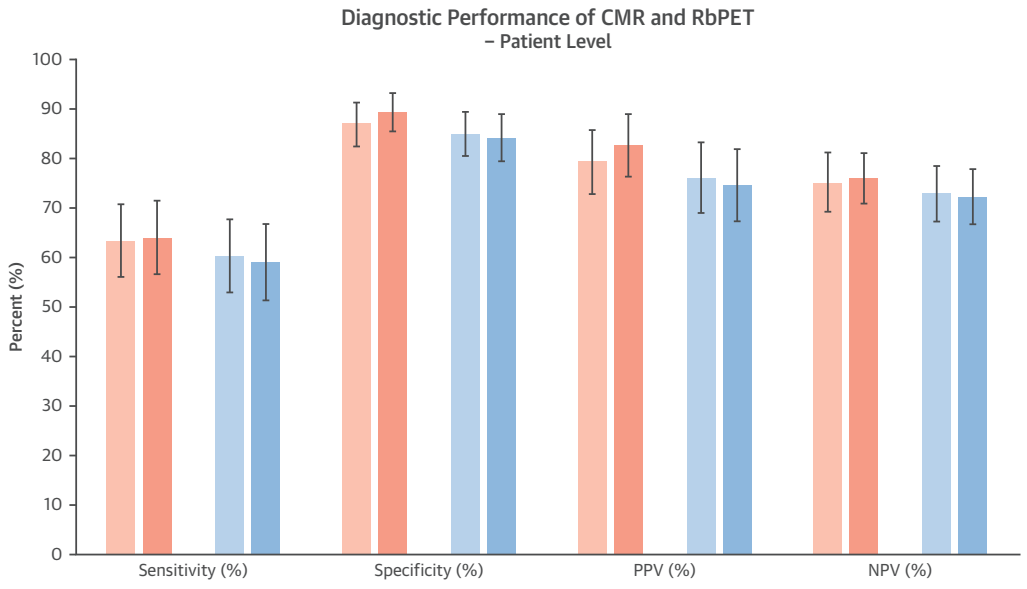
The diagnostic performance of the blinded and prior-knowledge analyses of CMR to discriminate obstructive CAD is outlined in **Figure 2**. For the blinded and prior-knowledge reads, sensitives and specificities were similar: sensitivities 60.4% (95% CI: 52.4-67.9) vs 59.1% (95% CI: 51.2-66.7); $P = 0.16$, and specificities 85.1% (95% CI: 79.5-89.6) vs 84.1% (95% CI: 78.4-88.8); $P = 0.15$, respectively. Overall, the diagnostic accuracy of the blinded and prior-knowledge analyses of CMR was similar (74% vs 73%; $P = 0.27$). In the prior-knowledge analysis, CMR misclassified 7 of 31 (22.6%) patients with prognostic high-risk disease (left main [LM] 3-vessel CAD) (**Table 2**).

Diagnostic performance of a subanalysis with rigorous adherence to the prespecified cutoffs (prespecified read) is shown Supplemental Table 2.

DIAGNOSTIC PERFORMANCE OF RbPET. Findings in the blinded expert analysis, with some overlap between the listed findings on a per-patient level, are shown in Supplemental Table 1. In the blinded expert interpretation of the RbPET examinations, 131 of 372 (35.2%) patients were classified as abnormal. The subsequent prior-knowledge analysis by the expert reader classified 127 of 372 (34.1%) patients as abnormal; 13 of 372 (3.5%) patients changed status form the blinded to the prior-knowledge analysis.

The diagnostic performance of the blinded and prior-knowledge analyses of RbPET to discriminate obstructive CAD is outlined in **Figure 2**. For the blinded and prior-knowledge reads, sensitives and specificities were similar: sensitivities 63.4% (95% CI: 55.5-70.8) vs 64.0% (95% CI: 56.2-71.4); $P = 0.78$, and specificities 87.0% (95% CI: 81.7-91.3) vs 89.4%

FIGURE 2 **Diagnostic Performance of RbPET and CMR**



Abnormal Test Results Defined by Blinded Corelab Read (Blinded Read)				
RbPET	63.4 (55.5-70.8)	87.0 (81.7-91.3)	79.4 (71.4-86.0)	75.1 (69.1-80.4)
CMR	60.4 (52.4-67.9)	85.1 (79.5-89.6)	76.2 (67.9-83.2)	73.1 (67.1-78.6)
Abnormal Test Results Defined by Corelab Read With Clinical and Coronary CTA Information (Prior Knowledge)				
RbPET	64.0 (56.2-71.4)	89.4 (84.4-93.3)	82.7 (75.0-88.8)	75.9 (70.1-81.1)
CMR	59.1 (51.2-66.7)	84.1 (78.4-88.8)	74.6 (66.2-81.8)	72.3 (66.2-77.9)

RbPET Blinded				
		Abnormal	**Normal**	**Total**
ICA-FFR	Abnormal	104	60	164
	Normal	27	181	208
	Total	131	241	372

CMR Blinded				
		Abnormal	**Normal**	**Total**
ICA-FFR	Abnormal	99	65	164
	Normal	31	177	208
	Total	130	242	372

RbPET Prior Knowledge				
		Abnormal	**Normal**	**Total**
ICA-FFR	Abnormal	105	59	164
	Normal	22	186	208
	Total	127	245	372

CMR Prior Knowledge				
		Abnormal	**Normal**	**Total**
ICA-FFR	Abnormal	97	67	164
	Normal	33	175	208
	Total	130	242	372

Diagnostic performance of the blinded and prior-knowledge RbPET and CMR readings by a reference standard defined as >90% diameter stenosis or invasive FFR-patient level. FFR = fractional flow reserve; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Figure 1.

(95% CI: 84.4-93.3); $P = 0.23$, respectively. Overall, the diagnostic accuracy of the blinded and prior-knowledge analyses of RbPET was similar (76% vs 78%; $P = 0.21$). In the prior-knowledge analysis, RbPET misclassified 1 of 31 (3.2%) patients with prognostic high-risk disease (LM 3-vessel CAD) (Table 2).

Diagnostic performance of a subanalysis with rigorous adherence to the prespecified cutoffs (pre-specified read) is shown Supplemental Table 2.

TABLE 2 True and False Classification of Patients According to the Prior-Knowledge RbPET and CMR Readings Alone and Combined Stratified by CAD Severity

Identification of Patients With Disease	RbPET[a]	CMR[a]	RbPET-CMR Both MPIs Normal/ 1 Abnormal MPI/ Both MPIs Abnormal	Total Number
Patients with hemodynamically obstructive CAD				
1-vessel disease	54/51	51/54	38/32/35	105[b]
2-vessel disease	21/7	19/9	18/4/6	28[b]
3-vessel and LM disease	30/1[c]	24/7	24/6/1	31[b]
Patients without hemodynamically obstructive CAD				
Nonobstructive CAD	186/22	175/33	161/39/8	208

Values presented are absolute numbers (n). [a]True positives/false negatives. [b]Total number stratified by CAD severity. [c]$P < 0.05$ for difference between RbPET and CMR.

CMR = cardiac magnetic resonance; MPI = myocardial perfusion imaging; RbPET = ^{82}rubidium positron emission tomography; other abbreviations as in Table 1.

COMPARISON OF DIAGNOSTIC PERFORMANCE OF CMR AND RbPET. In the blinded analyses, CMR and RbPET showed similar sensitivities and specificities: sensitivities 60.4% (95% CI: 52.4-67.9) vs 63.4% (95% CI: 55.5-70.8); $P = 0.41$, and specificities 85.1% (95% CI: 79.5-89.6) vs 87.0% (95% CI: 81.7-91.3); $P = 0.53$, respectively. Similarly, in the prior-knowledge analyses, there were no difference in sensitivities and specificities between CMR and RbPET: sensitivities 59.1% (95% CI: 51.2-66.7) vs 64.0% (95% CI: 56.2-71.4); $P = 0.21$, and specificities 84.1% (95% CI: 78.4-88.8) vs 89.4% (95% CI: 84.4-93.3); $P = 0.08$, respectively. Overall, the diagnostic accuracy of the blinded analyses of CMR and RbPET were similar (74% vs 76%; $P = 0.30$), whereas the prior-knowledge analyses showed increased accuracy of RbPET compared with CMR (78% vs 73%; $P = 0.03$). In addition, CMR misclassified more patients with prognostic high-risk disease (LM 3-vessel CAD) compared with RbPET: 7 of 31 (22.6%) vs 1 of 31 (3.2%); $P = 0.03$ (Central Illustration).

Tabulation of patients classified as normal and abnormal by the prior-knowledge reads of CMR and RbPET are outlined in Table 3, and characteristics of MPI concordance-discordance are similarly presented. In addition, Supplemental Table 3 shows QCA, RbPET, and CMR findings stratified by lowest per-patient invasive FFR. To mimic clinical routine, Supplemental Table 4 outlines an intention-to-diagnose analysis in which patients with missing MPIs (CMR: n = 28, RbPET: n = 3) were classified as abnormal.

DIAGNOSTIC PERFORMANCE VESSEL LEVEL. Abnormal perfusion was detected in 337 of 1,116 (32.7%) and 166 of 1,116 (14.9%) vessels by the prespecified RbPET and CMR reads, respectively. Results are presented in Supplemental Figure 1. Compared with CMR, using the prespecified criteria for abnormality, RbPET showed higher sensitivity (65.1% [95% CI: 58.6-71.2] vs 38.5% [95% CI: 32.2-45.0]; $P < 0.001$) but reduced specificity (79.0% [95% CI: 76.1-81.6] vs 91.4 [95% CI: 89.3-93.2]; $P < 0.001$).

SENSITIVITY ANALYSIS: THRESHOLDS FOR ABNORMALITY AND DIFFERENT REFERENCE STANDARDS. Supplemental Tables 5 and 6 outline the impact of lowering the thresholds for abnormality for both CMR and RbPET. For CMR and RbPET, lowered thresholds for abnormality increased sensitivity and reduced specificity.

The ability of CMR and RbPET to detect obstructive CAD by different reference standards is shown in Table 4. CMR and RbPET showed only moderate prediction of obstructive CAD by FFR with imputed QFR and FFR alone, respectively. However, both modalities accurately identified the most severe coronary stenoses by QCA with sensitivities >90%. Other sensitivity analyses are shown in Supplemental Tables 7 and 8 and Supplemental Figure 2.

DISCUSSION

This first prospective head-to-head comparison of diagnostic performance of CMR and RbPET in a large cohort of patients with suspected obstructive CAD at coronary CTA found similar moderate sensitivities but high specificities for diagnosing obstructive CAD using invasive FFR as reference-standard. Despite guideline recommendations,[1,3] our findings indicate that patients selected by coronary CTA represents a diagnostic challenge with frequent mismatch between advanced MPI tests and invasive measurements of physiology.

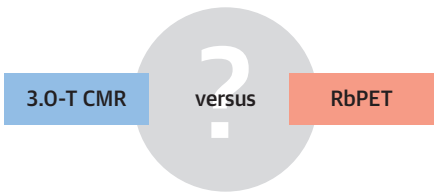
PREVIOUS STUDIES ON CMR. In general, the diagnostic performance of CMR has been investigated extensively.[2] Overall diagnostic performance is good, with sensitivities and specificities ranging from 78% to 95% and 57% to 100%, respectively. Large-scale studies of CMR to detect obstructive CAD, however, are not directly comparable with our findings as either the reference standard for obstructive CAD is QCA-based alone,[7,8] patients with known CAD are included,[7,8] the study design is referral biased,[9]or the thresholds for abnormality on CMR is lower (perfusion defect in ≥1 of 16 AHA segments).[8,9] Similar to previous hallmark trials with rather strict reference standard cutoffs,[7] a QCA-based reference standard of 70% diameter stenosis by QCA increased sensitivity to 83% without substantial decrease in specificity (Table 4).

CENTRAL ILLUSTRATION **Diagnostic Performance of CMR and PET Against Invasive FFR**

Performance of Second-Line Selective CMR and RbPET for Diagnosis of Obstructive CAD

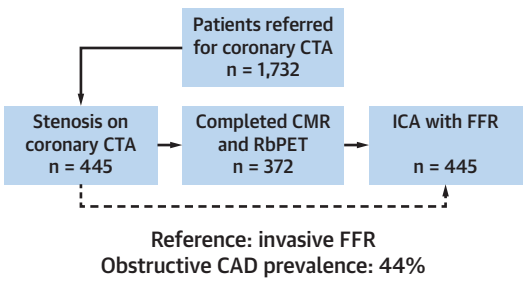
Aim

To investigate the diagnostic performance of second-line selective myocardial perfusion imaging with 3.0-T CMR and RbPET for diagnosis of obstructive CAD



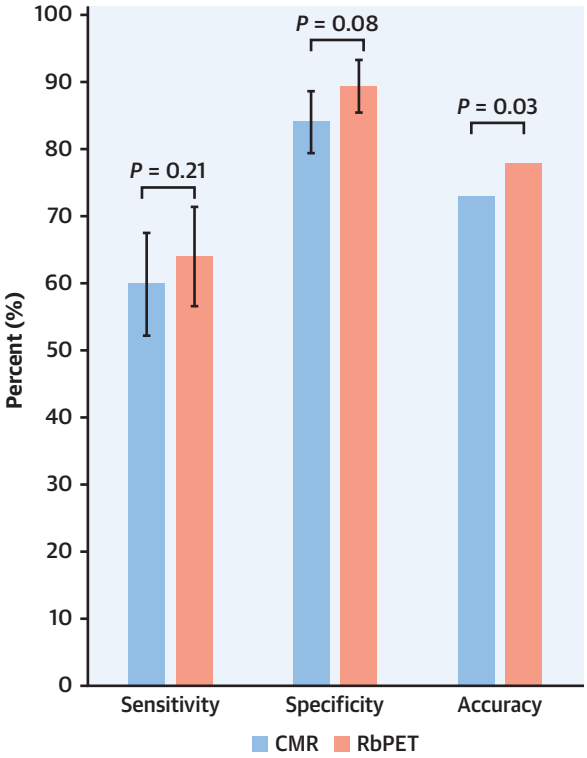
Design

Prospective head-to-head study of patients with stenosis on coronary CTA undergoing both 3.0-T CMR and RbPET



Main Results

Diagnostic Performance of Second-Line Selective CMR and RbPET for Identification of Hemodynamically Obstructive CAD
(Visual Diameter Stenosis >90% or FFR ≤0.80)



Second-line selective CMR and RbPET have similar moderate sensitivities but high specificities by a FFR-based reference standard.

Rasmussen LD, et al. J Am Coll Cardiol Img. 2023;16(5):642-655.

Aim: Guidelines endorse secondary ischemia verification before ICA in patients with suspected obstructive CAD on coronary CTA. However, data on MPI in such settings are sparse. Design: A cohort of prospectively included patients with de novo chest pain and coronary CTA-suspected obstructive CAD (n = 372) underwent both 3.0-T CMR and RbPET and subsequent ICA with measurement of FFR. Prevalence of obstructive CAD was 44%. In this cohort, the diagnostic accuracy of CMR and RbPET was investigated. Main results: Second-line selective MPI with CMR and RbPET have similar and moderate sensitivities but high specificities with higher accuracy of RbPET in patients with de novo chest pain and suspected stenosis on coronary CTA. CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; FFR = fraction flow reserve; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; PET = positron emission tomography; RbPET = ^{82}rubidium positron emission tomography.

Previously, Nissen et al[4] (Dan-NICAD 1) reported a large-scale randomized trial of diagnostic accuracy of SPECT vs 1.5-T CMR in patients with suspected obstructive CAD on coronary CTA. In 148 patients, sensitivity and specificity was 41% and 84%, respectively. Common for the Dan-NICAD 1 and the current Dan-NICAD 2 studies are both cohorts being referred for second-line selective diagnostic testing based on a coronary CTA with suspected stenosis. In addition, the 2 populations also have similar disease prevalence in the randomized patients (40%-44%), and the criterion for CMR abnormality and the reference standard for obstructive CAD are also alike. In Dan-NICAD 2, however, we used a 3.0-T CMR system,

TABLE 3 RbPET and CMR Concordance-Discordance by Hemodynamically Obstructive CAD

	Tabulation of Normal and Abnormal		
	CMR		
	Normal	Abnormal	Total
All patients			
RbPET			
Normal	203 (54.6)	42 (11.3)	245
Abnormal	39 (10.5)	88 (2.7)	127
Total	242	130	372
Patients with obstructive CAD[a] at ICA			
RbPET			
Normal	42 (25.6)	17 (10.4)	59
Abnormal	25 (15.2)	80 (48.8)	105
Total	67	97	164
Patients with nonobstructive CAD[a] at ICA			
RbPET			
Normal	161 (77.4)	25 (12.0)	186
Abnormal	14 (6.7)	8 (3.8)	22
Total	175	33	208

	Characteristics of RbPET and CMR Concordance-Discordance[b]			
	RbPET+/CMR+[c] (n = 88)	RbPET+/CMR−[c] (n = 39)	RbPET−/CMR+[c] (n = 42)	RbPET−/CMR−[c] (n = 203)
Demographics				
Women	9 (10.2)	12 (30.8)	12 (28.6)	76 (37.3)
Age, y	64.0 ± 7.11	65.6 ± 6.46	61.5 ± 7.60	63.5 ± 8.01
Risk factors				
Family history of CAD	31 (35.2)	12 (30.8)	18 (42.9)	81 (39.9)
Current smoking	28 (31.8)	16 (41.0)	10 (23.8)	71 (35.0)
Antihypertensive treatment	48 (54.59	15 (38.5)	24 (57.1)	92 (45.3)
Lipid-lowering treatment	31 (35.2)	18 (46.2)	20 (47.6)	75 (36.9)
Diabetes	6 (6.8)	9 (23.1)	7 (16.7)	12 (5.9)
Symptoms				
Typical angina	50 (56.8)	13 (33.3)	9 (21.4)	38 (18.7)
Atypical angina	17 (19.3)	11 (28.2)	18 (42.9)	85 (41.9)
Nonanginal chest pain	9 (10.2)	8 (20.5)	11 (26.2)	57 (28.1)
Other, dyspnea/arrythmia	12 (13.6)	7 (17.9)	4 (9.5)	23 (11.3)
CTA				
Calcium score, Agatson	1,131 (141-1,753)	800 (290-1,106)	340 (81-425)	398.3 (56.0-512.0)
0	3 (3.4)	3 (7.7)	2 (4.8)	19 (9.4)
1-399	34 (38.6)	10 (25.6)	29 (69.0)	121 (59.6)
≥400	51 (58.0)	26 (66.6)	11 (26.2)	63 (31.0)
Nonobstructive disease	0 (0)	0 (0)	0 (0)	0 (0)
1-vessel disease	30 (34.1)	18 (46.2)	27 (64.3)	135 (66.5)
2-vessel disease	24 (27.3)	9 (23.1)	12 (28.6)	53 (26.1)
3-vessel or LM disease	51 (58.0)	12 (30.8)	3 (7.1)	15 (7.4)
CMR according to prespecified thresholds for abnormality[d]				
Positive stress perfusion[d]	72 (81.8)	0 (0)	29 (69.0)	0 (0)
Positive LGE[d]	17 (19.3)	0 (0)	3 (7.1)	0 (0)
Positive WMA[d]	23 (26.1)	0 (0)	10 (23.8)	1 (0.5)
Positive by nondiagnostic image quality	0 (0)	0 (0)	2 (4.7)	1 (0.5)
RbPET according to prespecified thresholds for abnormality[d]				
Positive SSS[d]	83 (94.3)	21 (53.8)	0 (0)	0 (0)
Positive MBF[d]	76 (86.3)	27 (69.2)	6 (14.3)	17 (8.4)
Positive MBFR[d]	33 (37.5)	8 (20.5)	3 (7.1)	4 (2.0)
Positive TID[d]	17 (19.3)	2 (5.1)	1 (2.4)	3 (1.6)
Positive by nondiagnostic image quality	1 (1.1)	4 (8.1)	1 (2.4)	4 (2.0)

Continued on the next page

TABLE 3 Continued

Characteristics of RbPET and CMR Concordance-Discordance[b]	RbPET+/CMR+[c] (n = 88)	RbPET+/CMR−[c] (n = 39)	RbPET−/CMR+[c] (n = 42)	RbPET−/CMR−[c] (n = 203)
ICA				
Nonobstructive disease[a]	8 (9.1)	14 (35.9)	25 (59.5)	161 (79.3)
1-vessel disease[a]	38 (43.2)	16 (41.0)	16 (38.1)	35 (17.2)
2-vessel disease[a]	18 (20.5)	3 (7.7)	1 (2.4)	6 (3.0)
3-vessel or LM disease[a]	24 (27.3)	6 (15.4)	0 (0)	1 (0.5)
Mean FFR	0.77 ± 0.11	0.77 ± 0.13	0.80 ± 0.09	0.84 ± 0.09
Severe lesions with >70% DS by 3D QCA	56 (63.3)	7 (17.9)	3 (7.1)	5 (2.5)

Values are n (%), mean ± SD, or median (IQR). Prior-knowledge RbPET and CMR concordance-discordance by tabulation according to hemodynamically obstructive CAD and characteristics within concordance-discordance groups. [a]The prespecified cutoff with visual high-grade stenosis (>90% diameter stenosis) or FFR ≤0.80 in lesions with 30% to 90% diameter stenosis. [b]Comparisons of concordance-discordance were performed by the prior-knowledge analyses of RbPET and CMR. [c]The plus symbol (+) denotes abnormal examination for RbPET and CMR, respectively, and the minus symbol (−) denotes normal examination for RbPET and CMR, respectively. [d]Denotes abnormalities by the prespecified thresholds for abnormality (abnormality in ≥2 adjacent segments by the respective modality. For RbPET, <2.0 mL/g/min, <1.8 and >1.13 were additionally used as thresholds for territorial MBF, MBFR, and TID, respectively). For the blinded and prior-knowledge analyses depicted in Figure 2, the expert reader could optionally adhere or abdicate the thresholds based on clinical judgment.

3D = 3-dimensional; DS = diameter stenosis; LGE = late gadolinium enhancement; MBF = myocardial blood flow; MBFR = myocardial blood flow reserve; SSS = summed stress score; TID = transient ischemic dilation; WMA = wall-motion abnormalities; other abbreviations as in Tables 1 and 2.

which previously has been found superior compared with 1.5-T for obstructive CAD discrimination.[10]

PREVIOUS STUDIES ON RbPET. Similar to CMR, the diagnostic performance of RbPET for discriminating obstructive CAD has been investigated extensively. However, previous studies are retrospective, are conducted in high-risk cohorts referred for ICA, or are subject to referral bias, as not all patients undergo ICA.[11,12] Other prospective studies have found high sensitivities and specificities of PET but use ^{15}O-water,[13] not Rb as radiotracer. Overall, Rb is recognized as the most used radiotracer at present.[14]

The diagnostic performance of RbPET for discriminating obstructive CAD has been sparsely investigated in larger prospective studies. In smaller studies with high disease prevalence (69%-74%), sensitivities and specificities range from 78% to 93% and 50% to 75%, respectively.[15,16] However, the studies are not directly comparable with our findings, as the reference standard for obstructive CAD is QCA-based alone, patients are high risk with clinical indication of ICA, and the readings of RbPET are qualitatively based on SSS without consideration of additional flow measurements. As reported by previous studies, a QCA-based reference standard of 70% diameter stenosis by QCA increased sensitivity to 89% without substantial decrease in specificity by RbPET (Table 4).

THRESHOLDS FOR ABNORMALITY. In contrast to previous studies,[8,9,15,16] our predefined cutoff to detect obstructive CAD by both CMR and RbPET compromised ≥2 of 16 or ≥2 of 17 American Heart Association (AHA) segments with perfusion abnormalities, respectively. Based on extent and severity of ischemia, 2 diseased segments on MPI identify patients at increased risk of future events[17] in which observational evidence with guideline-endorsement[1,3] suggests prognostic benefit of revascularization.

SELECTIVE MPI STRATEGY. The Dan-NICAD work-up algorithm is in accordance with current guidelines[1,3] in which second-line ischemia testing is endorsed before referral for ICA in patients with suspected stenosis on coronary CTA ("selective MPI strategy"). The evidence, however, is limited, and only few prospective studies, including the Dan-NICAD 1[4] trial, have reported low sensitivities and high specificities of selective MPI tests. As a selective MPI strategy excludes patients without suspected obstructive CAD, the specificity of the MPI examinations would be expected to decrease. In contrast, as few patients undergoing coronary CTA have high-risk prognostic CAD (8.3% in our study) or previously unrecognized myocardial infarction (20 of 372 [5.4%] by LGE at CMR), sensitivity of the MPIs examined may decrease. Overall, the selective MPI strategy might induce a smaller selection bias, as the reading physicians could be influenced by knowing that patients are selected by a coronary CTA with suspected stenosis.

Based on the study design using selection of patients by coronary CTA, the sensitivity, specificity, and negative predictive value (NPV) of coronary CTA were for comparisons of diagnostic performances not possible to calculate.

TABLE 4 Diagnostic Performance of the Prior-Knowledge Readings of RbPET and CMR by Different References for Obstructive CAD

		Sensitivity	Specificity	PPV	NPV	+LR	-LR
Applied prespecified reference standard: high-grade stenosis by visual assessment + FFR ≤0.80 + QCA DS >50% Obstructive CAD prevalence=164/372	RbPET	64.0 (56.2-71.4)	89.4 (84.4-93.3)	82.7 (75.0-88.8)	75.9 (70.1-81.1)	6.05 (4.01-9.13)	0.40 (0.33-0.50)
	CMR	59.1 (51.2-66.7)	84.1 (78.4-88.8)	74.6 (66.2-81.8)	72.3 (66.2-77.9)	3.73 (2.66-5.23)	0.49 (0.40-0.59)
Clinically relevant reference standard: high-grade stenosis by visual assessment + FFR ≤0.80 + QCA DS >70% Obstructive CAD prevalence = 158/372	RbPET	63.9 (55.9-71.4)	87.9 (82.7-91.9)	79.5 (71.5-86.2)	76.7 (70.9-81.9)	5.26 (3.60-7.68)	0.41 (0.33-91.9)
	CMR	60.1 (52.0-67.8)	83.6 (78.0-88.3)	73.1 (64.6-80.5)	74.0 (68.0-79.4)	3.68 (2.65-5.11)	0.48 (0.39-0.58)
High-grade stenosis by visual assessment + FFR ≤0.80 (no QCA DS imputation in 30%-90% stenoses without measured FFR) Obstructive CAD prevalence = 156/365	RbPET	63.5 (55.4-71.0)	88.0 (82.9-92.1)	79.8 (71.7-86.5)	76.3 (70.5-81.6)	5.31 (3.60-7.81)	0.42 (0.34-0.51)
	CMR	59.6 (51.5-67.4)	83.7 (78.0-88.5)	73.2 (64.6-80.7)	73.5 (67.4-79.0)	3.66 (2.63-5.12)	0.47 (0.40-0.57)
Anatomic disease by 3D QCA (n = 372)							
QCA >90% Obstructive CAD prevalence = 41/372	RbPET	95.1 (83.5-99.4)	73.4 (68.3-78.1)	30.7 (22.8-39.5)	99.2 (97.1-99.9)	3.58 (2.95-4.34)	0.07 (0.02-0.26)
	CMR	97.6 (87.1-99.9)	72.8 (67.7-77.5)	30.8 (23.0-39.5)	99.6 (97.7-100)	3.59 (2.99-4.31)	0.03 (0.00-0.23)
QCA >80% Obstructive CAD prevalence = 42/372	RbPET	95.2 (83.8-99.4)	73.6 (68.5-78.3)	31.5 (23.5-40.3)	99.2 (97.1-99.9)	3.61 (2.98-4.38)	0.06 (0.02-0.25)
	CMR	97.6 (87.1-99.9)	73.0 (67.9-77.7)	31.5 (23.7-40.3)	99.6 (97.7-100)	3.62 (3.01-4.35)	0.03 (0.00-0.23)
QCA >70% Obstructive CAD prevalence = 71/372	RbPET	88.7 (79.0-95.0)	78.7 (73.7-83.2)	49.6 (40.6-58.6)	96.7 (93.7-98.6)	4.17 (3.31-5.27)	0.14 (0.07-0.28)
	CMR	83.1 (72.3-91.0)	76.4 (71.2-81.1)	45.4 (36.6-54.3)	95.0 (91.5-97.4)	3.52 (2.80-4.43)	0.22 (0.13-0.37)
QCA >60% Obstructive CAD prevalence = 107/372	RbPET	76.6 (67.5-84.3)	83.0 (77.9-87.3)	64.6 (55.6-72.8)	89.8 (85.3-93.3)	4.51 (3.39-6.01)	0.28 (0.20-0.40)
	CMR	70.1 (60.6-78.6)	79.2 (73.9-84.0)	57.7 (48.7-66.3)	86.8 (81.8-90.8)	3.38 (2.59-4.41)	0.38 (0.28-0.51)
QCA >50% Obstructive CAD prevalence = 172/372	RbPET	59.3 (51.6-66.7)	87.5 (82.1-91.7)	80.3 (72.3-86.8)	71.4 (65.3-77.0)	4.74 (3.22-6.99)	0.47 (0.39-0.56)
	CMR	55.2 (47.5-62.8)	82.5 (76.5-87.5)	73.1 (64.6-80.5)	68.2 (61.9-74.0)	4.74 (3.22-6.99)	0.47 (0.39-0.56)
Invasive disease by physiology (FFR) and imputed measures of epicardial flow (QFR) (n = 370)[a]							
FFR + QFR ≤0.80 Obstructive CAD prevalence = 153/370	RbPET	64.1 (55.9-71.6)	87.1 (81.9-91.3)	77.8 (69.5-84.7)	77.5 (71-7-82.5)	4.96 (3.44-7.15)	0.41 (0.33-0.51)
	CMR	59.5 (51.3-67.3)	82.9 (77.3-87.7)	71.1 (62.4-78.8)	74.4 (68.4-79.8)	3.49 (2.53-4.81)	0.49 (0.40-0.60)
Invasive physiology alone in patients with 30-90 diameter stenosis visually (FFR) (n =160)[b]							
FFR ≤0.80 Obstructive CAD prevalence = 53/160	RbPET	39.6 (26.5-54.0)	92.5 (85.8-96.7)	72.4 (52.8-87.3)	75.6 (67.3-82.7)	5.30 (2.52-11.16)	0.65 (0.52-0.82)
	CMR	39.6 (26.5-54.0)	87.9 (80.1-93.4)	61.8 (43.6-77.8)	74.6 (66.1-81.9)	3.25 (1.77-5.99)	0.69 (0.55-0.86)
FFR ≤0.75 Obstructive CAD prevalence = 40/160	RbPET	35.0 (20.6-51.7)	87.5 (80.2-92.8)	48.3 (29.4-67.5)	80.2 (72.3-86.6)	2.80 (1.48-5.28)	0.74 (0.59-0.94)
	CMR	37.5 (22.7-54.2)	84.2 (76.4-90.2)	44.1 (27.2-62.1)	80.2 (72.1-86.7)	2.37 (1.33-4.21)	0.74 (0.58-0.96)

Values are percent (95% CI). [a]QFR analyses were not available in n = 2 of 372 patients with occluded vessels. [b]Analyses of patients with FFR invasively measured. Hence, patients with visually no stenosis (diameter stenosis <30%) and high-grade stenosis (diameter stenosis >90) were excluded according to guideline-endorsed praxis.

QCA = quantitative coronary angiography; QFR = quantitative flow ratio; LR = likelihood ratios; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 1 and 3.

ADDITIONAL FLOW QUANTIFICATION BY PET. In contrast to our solely qualitatively assessed CMR readings, the predefined criteria including myocardial blood flow (MBF) for abnormality yielded improved sensitivity but impaired specificity of RbPET compared with expert reader opinion (**Figure 2**, Supplemental Table 2). By the prespecified reading, CMR classified 115 of 372 patients (30.9%) as abnormal, whereas RbPET qualitatively by SSS reported abnormal results for 104 of 372 (28.0%) patients (Supplemental Table 6). Thus, additional quantitative measurements change the diagnostic accuracy of RbPET, and, recently, MBF and myocardial blood flow reserve (MBFR) by both PET and CMR were guideline endorsed to increase discrimination of obstructive CAD.[3] Despite evidence level B, however, the PET studies are either based on prognosis, apply ^{15}O-water, not ^{82}Rb as radiotracer, or apply an

anatomic reference standard for obstructive CAD alone. The practical application of absolute flow on RbPET is sparsely elucidated, and for CMR, the incremental value of quantitative flow to a qualitative reading of CMR and RbPET has never been prospectively investigated.

MPI AND REFERENCE STANDARD FOR OBSTRUCTIVE CAD. In Dan-NICAD 2, mean FFR in the head-to-head cohort was 0.81. Consequently, the majority of patients had FFR values around the cutoff for obstructive CAD identification, and small inaccuracies in measurements would cause inappropriate reclassification. Moreover, as the applied selective MPI strategy restrain the spectrum of CAD severity (ie, no patients have no CAD, and few patients have very severe CAD), the agreement of MPIs and FFR is possibly different compared with correlations in high-risk high prevalence cohorts, and the FFR range of 0.75 to 0.80 outlines a gray zone in which data on the functional significance of a coronary lesion are ambiguous.[18] In our study, however, the majority of patients with obstructive CAD were identified by at least 1 high-grade stenosis by visual assessment (100 of 164, 61.0%), and, as visual assessment in general overestimates the functional severity of coronary lesions,[19] the relatively moderate sensitivities of RbPET and CMR are subject to potential bias. However, our primary invasive reference standard reflects guidelines on revascularization with FFR measurements in relevant segments with visually assessed diameter stenoses ranging from 40% to 90% and 40% to 69%, respectively.[20,21] Second, this endpoint is similar to that of other recent large-scale trials investigating diagnostic accuracy of noninvasive MPI.[9,13,22] In addition, having full physiology in all lesions by invasive FFR and imputed QFR, irrespective of initial visual diameter stenosis, diagnostic performances of CMR and RbPET were similar to a reading using our prespecified reference standard, including high-grade stenosis by visual assessment (**Table 4**).

Interestingly, the FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) investigators[23] reported only 35% of vessels with diameter stenosis of 50% to 70% to have hemodynamic significance by FFR, and in stenoses of 70% to 90%, 1 in 5 lesions did not have FFR values below the ≤0.80 threshold. Guidelines recommend FFR-guided revascularization based on studies of prognosis, not the presence perfusion defects,[20,21] and the original validation study of FFR found a FFR cutoff of 0.66 to detect myocardial ischemia.[24] Therefore, it could be questioned whether FFR is a suitable reference standard for MPIs in patients with suspected stenosis on coronary CTA.

Despite carrying prognostic information, FFR is a surrogate of coronary flow with documented limitations in detecting myocardial ischemia.[25] As FFR reflects a pressure drop dependent on the magnitude of baseline epicardial coronary flow, a well-perfused myocardium reflecting a normal MPI can possibly coexist with an abnormal FFR <0.80. The contrary is also possible if myocardial perfusion is impaired because of microvascular disease in the absence of epicardial CAD, which causes myocardial ischemia despite "normal" FFR above the 0.80 threshold.

CLINICAL IMPLICATIONS. In light of the ISCHEMIA trial,[26] one could argue that high-risk CAD should be ruled out by coronary CTA with revascularization only in patients with medically refractory symptoms, regardless of other coronary lesions and lesion severity. However, MPI-based referral for revascularization still identify patients for whom revascularization is beneficial for reduction of symptoms,[27] and progressive ischemia is associated with increased risk of cardiovascular events.[17] In addition, an ischemia-driven revascularization approach with FFR appears to improve hard outcomes,[28] and a CMR-based revascularization strategy is noninferior to a strategy of FFR on cardiovascular events.[29] Importantly, an inclusion criteria for ISCHEMIA enrolment was moderate to severe ischemia on MPI, and as advanced MPI testing with RbPET and CMR identifies the majority of cases with high-risk CAD (**Table 3**) and the most severe coronary stenoses (**Table 4**) with possibly greater potential of causing myocardial ischemia, and revascularization improves symptoms but not outcomes in MPI diseased patients,[26,27] MPI-based referral-deferral for invasive assessment seems appropriate and safe. An alternative to MPI testing with guideline endorsement is CT-derived FFR (FFR-CT)[3] but comparisons with MPI modalities as second-line tests are sparse.

STUDY STRENGTHS. First, the setup was a large-scale all-comer study in an unselected population using a head-to-head comparison method, which is ideal for comparison between 2 imaging modalities. Participants were sampled from a large geographical area, and, as 99% of hospital care in the uptake area is public, few alternative options were available beyond the 4 recruiting centers. Second, we used predefined criteria for abnormality and reference standard of FFR for obstructive CAD.

STUDY LIMITATIONS. First, a proportion of patients with female over-representation eligible for study enrollment declined participation, and our cohort consisted primarily of Caucasian patients. Second, a larger proportion of patients did not undergo CMR

(n = 28) than RbPET (n = 3), but the intention-to-diagnose analysis, however, revealed similar sensitivities and reduced specificity of CMR, not RbPET (Supplemental Table 4). In addition, a larger proportion of scans were nondiagnostic at RbPET compared with CMR. Third, a concern is insufficient adenosine stress during CMR and RbPET, but both MPIs and ICA used similar hyperemia protocols,[6] and we found no evidence that patients were insufficiently stressed (Supplemental Table 9, Supplemental Figures 3 and 4). Fourth, although the CMR readings were only qualitative based on visual expert reading, the RbPET assessment compromised both qualitative and quantitative measures, which could affect the comparison. Fifth, despite fulfilling the prespecified criteria for sufficient sample size,[6] it can always be argued that our minimal relevant difference is too high. Sixth, we did not obtain information on serial lesions and diffuse disease during ICA, which could have further elucidated the causes for concordance-discordance among CMR, RbPET, and FFR.

CONCLUSIONS

In patients with suspected obstructive CAD on coronary CTA, the guideline-endorsed use of a second-line selective perfusion scans with either CMR or RbPET appear to have similar and only moderate sensitivities but high specificities for hemodynamic obstructive CAD defined by invasive FFR. This patient group represents a diagnostic challenge with frequent mismatch between advanced MPI tests and invasive measurements.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Stress perfusion CMR and RbPET are established methods to diagnose obstructive CAD in high-risk, high-prevalence cohorts with clinical indication for invasive coronary angiography.

COMPETENCY IN MEDICAL KNOWLEDGE 2: To guide potential revascularization, guidelines recommend second-line ischemia verification by CMR or RbPET in patients with suspected obstructive CAD after a first-line coronary CTA.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: CMR and RbPET have similar moderate sensitivities and high specificities for obstructive CAD identification by a guideline-endorsed reference of invasive fractional flow reserve. However, both modalities show high sensitivities to identify severe stenoses and prognostic CAD cases.

TRANSLATIONAL OUTLOOK: Despite only moderate sensitivities for identification of obstructive CAD by a guideline-endorsed reference of invasive fractional flow reserve, the high sensitivities for identification of severe stenoses could potentially identify patients with symptomatic benefit of initial invasive assessment and hence revascularization.

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KEY WORDS **cardiac magnetic resonance, chronic coronary syndrome, coronary artery disease, fractional flow reserve, myocardial perfusion imaging, positron emission tomography**

APPENDIX **For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.**