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ORIGINAL RESEARCH

Prediction of Coronary Revascularization in Stable Angina

Comparison of FFR_{CT} With CMR Stress Perfusion Imaging

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ABSTRACT

OBJECTIVES This study was designed to compare head-to-head fractional flow reserve (FFR) derived from coronary computed tomography angiography (CTA) (FFR_{CT}) and cardiac magnetic resonance (CMR) stress perfusion imaging for prediction of standard-of-care–guided coronary revascularization in patients with stable chest pain and obstructive coronary artery disease by coronary CTA.

BACKGROUND FFR_{CT} is a novel modality for noninvasive functional testing. The clinical utility of FFR_{CT} compared to CMR stress perfusion imaging in symptomatic patients with coronary artery disease is unknown.

METHODS Prospective study of patients (n=110) with stable angina pectoris and 1 or more coronary stenosis ≥50% by coronary CTA. All patients underwent invasive coronary angiography. Revascularization was FFR-guided in stenoses ranging from 30% to 90%. FFR_{CT} ≤0.80 in 1 or more coronary artery or a reversible perfusion defect (≥2 segments) by CMR categorized patients with ischemia. FFR_{CT} and CMR were analyzed by core laboratories blinded for patient management.

RESULTS A total of 38 patients (35%) underwent revascularization. Per-patient diagnostic performance for identifying standard-of-care–guided revascularization, (95% confidence interval) yielded a sensitivity of 97% (86 to 100) for FFR_{CT} versus 47% (31 to 64) for CMR, $p < 0.001$; corresponding specificity was 42% (30 to 54) versus 88% (78 to 94), $p < 0.001$; negative predictive value of 97% (91 to 100) versus 76% (67 to 85), $p < 0.05$; positive predictive value of 47% (36 to 58) versus 67% (49 to 84), $p < 0.05$; and accuracy of 61% (51 to 70) versus 74% (64 to 82), $p > 0.05$, respectively.

CONCLUSIONS In patients with stable chest pain referred to invasive coronary angiography based on coronary CTA, FFR_{CT} and CMR yielded similar overall diagnostic accuracy. Sensitivity for prediction of revascularization was highest for FFR_{CT}, whereas specificity was highest for CMR. (J Am Coll Cardiol Img 2019;■:■–■) © 2019 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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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTA = computed tomography angiography

CX = circumflex coronary artery

FFR = fractional flow reserve

FFR_{CT} = coronary computed tomography angiography–derived fractional flow reserve

LAD = left anterior descending coronary artery

LM = left main coronary artery

RCA = right coronary artery

Current guidelines recommend myocardial perfusion imaging as the frontline testing strategy in symptomatic patients with intermediate risk of coronary artery disease (CAD) (1,2) before referral to invasive coronary angiography (ICA) and decision making on coronary revascularization. Meta-analyses (3,4) have indicated that stress perfusion imaging by cardiac magnetic resonance (CMR) is more accurate than commonly applied perfusion techniques by single-photon emission computed tomography (SPECT) for the diagnosis of CAD. Still, CMR has not yet been generally implemented as a first-line testing strategy in patients with symptoms of stable CAD. Coronary computed tomography angiography (CTA) has evolved as an alternative due to a high diagnostic performance for exclusion of CAD (5). However, the hemodynamic significance of lesions cannot be assessed by coronary CTA. Computational fluid dynamics and individual image-based modelling now allow estimation of coronary blood flow and blood pressure from standard acquired coronary CTA datasets (6). Subsequent processing of the data derived from computed tomography (CT) permits calculation of noninvasive fractional flow reserve (FFR_{CT}). The new metric, FFR_{CT}, has good diagnostic performance using invasive FFR as the reference standard (7,8) and its utility in clinical practice has been shown by improvements in diagnostic sensitivity compared to SPECT (9), diagnostic yield of coronary angiography (10), and prognosis (11).

A direct comparison of the clinical utility of FFR_{CT} and CMR as second-line sequential testing strategies has not previously been assessed. Consequently, the aim of this study was to compare, head-to-head, FFR_{CT} and CMR for predicting standard-of-care-guided coronary revascularization in patients with new onset stable chest pain and obstructive CAD as determined by coronary CTA.

METHODS

STUDY DESIGN AND PATIENT COHORT. This study is a pre-specified substudy of the Dan-NICAD (Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease) trial (12), which was designed to compare the diagnostic performance of SPECT and CMR in diagnosing invasively determined obstructive CAD in consecutive symptomatic patients having obstructive CAD as determined by coronary CTA. This substudy represents a head-to-head comparison of the clinical utility of FFR_{CT} and CMR-testing for the prediction of standard-of-care-guided coronary revascularization.

Coronary CTA is used as the recommended first-line testing strategy in patients with new-onset stable chest pain in Denmark. In general, patients with a low-to-intermediate pretest risk of having obstructive CAD and no prior revascularization, a body mass index <40 kg/m^2, a glomerular filtration rate >45 ml/min, and no persistent atrial fibrillation are eligible for coronary CTA. Consequently, the Dan-NICAD criteria for inclusion were new-onset stable chest pain in low-to-intermediate-risk patients referred for a first-line coronary CTA to rule out CAD. This substudy included patients randomized to the CMR arm of the Dan-NICAD trial due to the presence of at least 1 coronary stenosis >50% as determined by coronary CTA. Exclusion criteria were known CAD, inability to undergo adenosine testing or CMR, allergy to iodinated contrast media, noncardiac illness with life expectancy less than 2 years, or pregnancy. All patients underwent subsequent coronary angiography. The decision on revascularization was guided by invasive FFR in stenosis ranging from 30% to 90% and was made at the discretion of the operator or the Heart Team. The study flow chart is shown in **Figure 1**.

FFR_{CT} and CMR assessments were performed at core laboratories and test results were unknown to interventionalists and surgeons of the Heart Team. To mimic clinical practice, the CMR core laboratory had information regarding symptoms, medicine, risk factors, and the result of the coronary CTA; whereas the FFR_{CT} core laboratory only had access to the coronary CTA dataset.

Informed consent was obtained from all participants. The study was approved by The Central Denmark Region Committees on Health Research Ethics (S-20150085) and registered by the Data Protection Registry (2008-58-0035; 1563) of The Central Region of Denmark.

CORONARY CTA. Coronary CTA was performed at 2 centers in Denmark. Both centers used a 320-slice volume CT scanner (Aquillion One, Toshiba Medical Systems, Japan) with prospective electrocardiographic gating. Oral beta blockers or ivabradine were administered if necessary, targeting a heart rate <60 beats/min. Administration of sublingual nitroglycerine was given to all patients without known side effects of this drug. An initial non-enhanced scan for calcium scoring was performed. Coronary CTA was assessed and graded visually by skilled CT cardiologists. Lesions were reported using an 18-segment model (13) and classified as proximal if located in

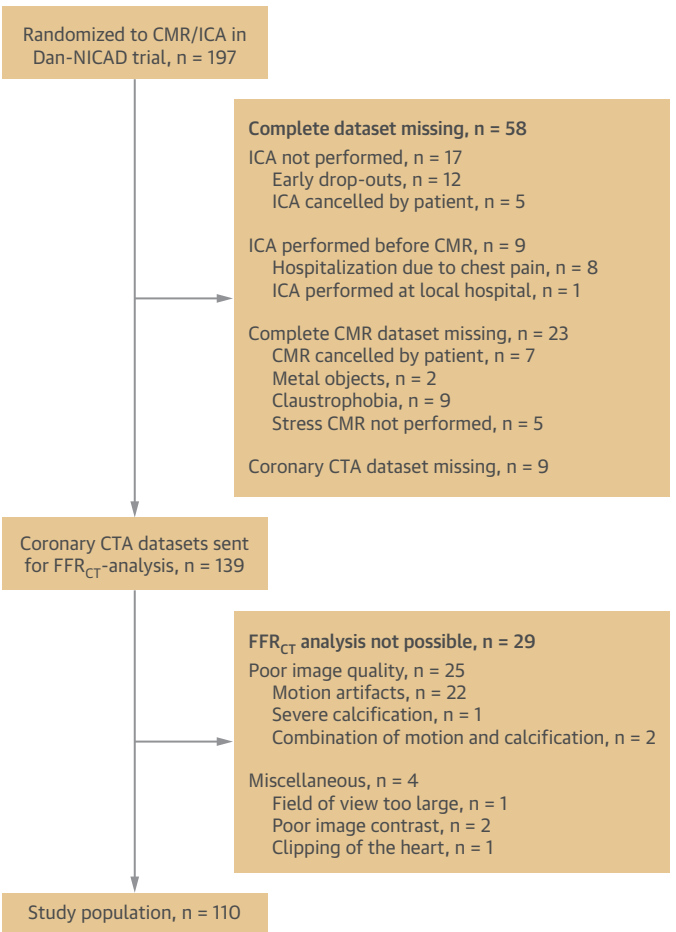
segments 1, 2, 5, 6, 7, 11, or 13; all other lesion locations were classified as distal.

INVASIVE PROCEDURES AND REVASCULARIZATION. Ingestion of caffeine was not allowed for 24 hours before invasive procedures. Coronary angiography was performed by standard techniques. FFR measurements (St. Jude Medical, St. Paul, Minnesota and Volcano, San Diego, California) were performed in coronary stenosis ranging from 30% to 90% (visual assessment by the treating physician) and a reference diameter ≥2 mm. Maximal hyperemia was induced by intravenous adenosine (140 μg/kg/min). Recordings of aortic and distal coronary pressures were obtained during sustained hyperemia (after 2 min of adenosine infusion). Patients were classified as having obstructive CAD, if there was 1 or more high-grade stenosis >90% (visual assessment) by invasive coronary angiography or if there was 1 or more coronary artery with an FFR value ≤ 0.80 distal to stenosis ranging from 30% to 90%. Physicians responsible for downstream patient management were blinded to the results of FFR_{CT} and CMR analyses, including those performing the ICA and FFR investigations. All patients revascularized by coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) or a combination of the 2 were registered.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY–DERIVED FRACTIONAL FLOW RESERVE. Standard acquired coronary CTA data sets were transmitted for core laboratory analysis (HeartFlow Inc., Redwood City, California). The principles behind FFR_{CT} computation have been described in detail previously (6). Any FFR_{CT} values in the major coronary arteries ≥1.8 mm in diameter, including side branches, were registered. Patients were classified as having obstructive CAD if the per-patient lowest FFR_{CT} value was ≤0.80 (distal tip FFR_{CT} value). In addition, patients were classified according to the per-patient lowest FFR_{CT} value registered 2 cm distal to lesion (lesion-specific FFR_{CT} value) using an identical threshold-value for ischemia (14). Occluded vessels were assigned an FFR_{CT} value of 0.50. The distal tip FFR_{CT} value was used for the main comparisons with CMR.

CARDIAC MAGNETIC RESONANCE. Patients were instructed to stop ingestion of caffeine for 24 hours before stress studies. CMR scans were conducted using a 1.5-Tesla system (Siemens MAGNETOM Avanto, Siemens Healthcare GmbH, Erlangen, Germany) as previously described (15). In brief, stress perfusion imaging was conducted either after intravenous injection of 0.4 mg (5 ml) of Regadenoson (Lexiscan, Astellas Pharma, Chuo, Tokyo, Japan) or infusion of adenosine 140 μg/kg/min over 4 min. Gadovist (Bayer Schering Pharma AG, Berlin, Germany) or Dotarem (GD-DOTA, Guerbet LCC, Princeton, New Jersey), were used as contrast agents. CMR data were analyzed by a core laboratory (William Harvey Research Institute, Queen Mary University of London, London, United Kingdom). CMR image quality was graded as high, medium, or poor. Stress perfusion CMR images were evaluated according to a standard 16-segment model by visual analysis (16). Perfusion defects were defined as subendocardial or transmural signal changes by stress imaging or irreversible defects by late gadolinium enhancement imaging. Abnormality of CMR studies were graded based on the number of segments involved:

FIGURE 1 Flowchart



This study represents a substudy of the Dan-NICAD (Danish Study of Non-Invasive testing in Coronary Artery Disease) trial (12). CMR = cardiac magnetic resonance; CTA = computed tomography angiography; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; ICA = invasive coronary angiography.

TABLE 1 Patient Characteristics

Demographics	
Age, yrs	61 ± 8
Male	66 (60)
Body mass index, kg/m^2	27 ± 4
Caucasian	110 (100)
Symptoms	
Typical angina	37 (34)
Atypical angina	37 (34)
Nonanginal chest pain	15 (13)
Dyspnea	21 (19)
Diamond-Forrester score, %	46 (30-63) [10-90]
Risk factors	
Smoking	66 (60)
Hypertension	55 (50)
Hypercholesterolemia	33 (31)
Diabetes	10 (9)
Family history of CVD*	46 (42)
Medical therapy	
Platelet inhibitors	30 (27)
Beta blockers	8 (7)
Angiotensin inhibitors	38 (35)
Calcium-antagonists	17 (15)
Diuretics	22 (20)
Peroral antidiabetics	7 (6)
Insulin	4 (4)
Anticoagulants	1 (1)

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 aged 55 years or in a female first-degree relative before aged 65 years.
CVD = cardiovascular disease.

TABLE 2 Coronary Computed Tomography Angiography

Preparation and basic information	
Nitroglycerine	107 (97)
Heart rate, beats/min	56 ± 9
Radiation dose, mSv	2.7 (1.7-3.4) [0.5-9.0]
Analysis	
Agatston score, U	261 (63-687) [0-2998]
0-99	35 (32)
100-399	32 (29)
400-999	27 (25)
≥1,000	16 (15)

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

0-1 = normal; 2-4 = small; 5-7= moderate; ≥8 = large. Patients were classified as having obstructive CAD if reversible changes from rest to stress were registered in ≥2 contiguous segments.

STATISTICAL ANALYSES. This substudy of the Dan-NICAD trial was planned and designed before the start of any data analysis in the main study (12). McNemar's test was used to compare the sensitivity, specificity, and accuracy of FFR$_{CT}$ and CMR as well was comparison of minimum distal tip- and minimal lesion-specific FFR$_{CT}$ values in relation to classification of patient-level ischemia. Logistic regression using cluster robust standard errors was used to compare positive predictive value (PPV) and negative predictive value (NPV). The Fisher exact test was used for comparison of proportions between subgroups. Associations between proportions of revascularized patients/proportions of patients with significant CAD and patient level minimum FFR$_{CT}$ values and size of CMR perfusion defects, respectively, were tested using weighted linear regression with robust standard errors. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata software, version 15.1 (Stata Corp, College Station, Texas).

ROLE OF THE FUNDING SOURCE AND THE CORE LABORATORY AT HEARTFLOW. The funders had no role in study design, data collection, analysis, interpretation, or writing of the report. HeartFlow only had access to the coronary CTA datasets and did not perform any data handling or data analysis, did not influence interpretation of data, and did not participate in writing of the manuscript. The contract with HeartFlow on FFR$_{CT}$-analysis was made using the price at cost.

RESULTS

Between September 2014 and March 2016, 1,675 consecutive symptomatic patients were enrolled in the Dan-NICAD trial. A stenosis >50% was diagnosed by coronary CTA in 386 patients, of whom 197 patients were randomized to undergo CMR and ICA/FFR. Of these, 58 patients did not have a complete data set, and 29 (21%) coronary CTA datasets were rejected for FFR$_{CT}$ analysis (**Figure 1**). Basic characteristics of the 110 patients who constituted the study cohort are shown in **Table 1**. Median (interquartile range [IQR]) time delay between coronary CTA and coronary catheterization was 32 (25 to 39) days.

CORONARY CTA. Relevant preparation variables and Agatston scores are presented in **Table 2**.

INVASIVE PROCEDURES AND REVASCULARIZATION. Overall, 44 patients were diagnosed with obstructive CAD. Because of small vessel dimension, vessel tortuosity, or paucity of symptoms at the time of angiography, 6 of these patients were not revascularized; 3 patients with obstructive stenosis (FFR ≤ 0.80 [range, 0.76 to 0.80]) and 3 patients with an occluded coronary artery. The number of revascularized patients was not significantly different in this substudy (n = 38; 35%) compared to the number of

TABLE 3 Invasive Procedures and Treatment

Angiography (n = 110)	
Most severe stenosis <30%	27 (24)
Most severe stenosis 30% to 90%	57 (52)
Most severe stenosis >90%	26 (24)
FFR measurement (n = 69)	
FFR ≤ 0.80, no. of patients	23 (33)
FFR ≤ 0.75, no. of patients	15 (22)
Treatment	
Medical treatment only	72 (65)
PCI	25 (23)
1 vessel	20 (18)
2 vessel	5 (5)
3 vessel	0 (0)
CABG	13 (12)
1 vessel	4 (4)
2 vessel	7 (6)
3 vessel	2 (2)

Values are n (%).

CABG = coronary artery by-pass grafting; FFR = invasively measured fractional flow reserve; PCI = percutaneous coronary intervention.

revascularizations performed in patients in the CMR-arm of the Dan-NICAD cohort (n = 25; 36%) who were excluded due to missing data.

A total of 55 vessels were revascularized and distributed as follows: left main coronary artery (LM), 1 (2%); left anterior descending artery (LAD), 27 (49%); circumflex coronary artery (CX), 9 (16%); right coronary artery (RCA) 11 (20%); and side branches 7 (13%). Revascularized lesions were located in proximal coronary segments in 34 (89%) patients. In 26 patients with a maximal stenosis >90%, 23 (88%) patients were revascularized, whereas 12 of 26 patients had an FFR performed in another stenosis ranging from 30% to 90%. In 57 patients with a maximal stenosis ranging from 30% to 90%, 15 (26%) patients underwent revascularization. No patient with stenosis <30% was revascularized. Three of 25 PCI procedures were performed in chronic total occlusions, and 3 of 13 surgical procedures were performed as off-pump coronary artery bypass operations. An overview of invasive procedures and given treatments is presented in Table 3.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY-DERIVED FRACTIONAL FLOW RESERVE. The number of patients classified with obstructive CAD, FFR_{CT} value ≤0.80, was higher when classification was based on the per-patient minimum distal-tip compared to per-patient minimum lesion-specific FFR_{CT} value (n = 79 [72%] versus n = 55 [50%], respectively; p < 0.001). The overall distributions of patient-level FFR_{CT} values and the associations to the occurrence of significant CAD and revascularization are shown in Tables 4 and 5. Of 55 revascularized vessels, 50 (91%) vessels had an FFR_{CT} value ≤0.80. All occluded vessels were correctly identified by FFR_{CT}.

TABLE 4 Association Between Patient-Level Minimum Distal-Tip FFR_{CT},* Obstructive CAD,† and Standard of Care Guided Coronary Revascularization in Stable Chest Pain

FFR_{CT} Range	Patients	Obstructive CAD	Revascularization
>0.90	2 (2)	0 (0)	0 (0)
0.81-0.90	29 (26)	1 (3)	1 (3)
0.71-0.80	37 (34)	15 (41)	14 (37)
0.61-0.70	21 (19)	9 (43)	8 (38)
0.51-0.60	7 (6)	5 (71)	5 (71)
≤0.50	14 (13)	14 (100)‡	10 (71)‡

Values are n (%). *Distal-tip FFR_{CT} defined as the per-patient lowest FFR_{CT}-value in coronary arteries ≥1.8 mm in diameter. †Defined as high-grade stenosis >90% (visual assessment) by invasive coronary angiography or a measured FFR value ≤0.80 in at least 1 vessel. ‡Tests for trend p < 0.001.

CAD = coronary artery disease; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography.

CARDIAC MAGNETIC RESONANCE. Stress studies were performed using regadenoson (n = 48) or adenosine (n = 62). Image quality was high in 90 (82%) patients and medium in 20 (18%). In 4 (4%) patients, no side effects to adenosine (dyspnea, chest, pain, dizziness, or headache) were registered, of whom 1 patient had a reversible perfusion defect (RPD). Mean left ventricular ejection fraction by CMR was 66% (SD was 10%). Irreversible perfusion defects were identified in 4 (4%) patients, all of whom had an RPD as well. Of 83 (75%) patients who were classified as having normal CMR test results, 82 (99%) had completely normal stress perfusion. An RPD was observed in 27 (25%) patients (small RPD in 8 of 27 [30%]; moderate RPD in 13 of 27 [48%]; large RPD in 6 of 27 [22%]). The associations between the size of perfusion defects by CMR and the occurrence of significant CAD and revascularization are shown in

TABLE 5 Association Between Patient-Level Minimum Lesion-Specific FFR_{CT},* Obstructive CAD,† and Standard-of-Care-Guided Coronary Revascularization in Stable Chest Pain

FFR_{CT} Range	Patients	Obstructive CAD	Revascularization
>0.90	13 (12)	0 (0)	0 (0)
0.81-0.90	42 (38)	7 (17)	6 (14)
0.71-0.80	27 (25)	16 (63)	16 (59)
0.61-0.70	13 (12)	6 (46)	5 (38)
0.51-0.60	6 (5)	5 (83)	5 (83)
≤0.50	9 (8)	10 (100)‡	6 (67)‡

Values are n (%). *Lesion-specific FFR_{CT} defined as the per-patient lowest FFR_{CT} value 2 cm distal to lesions in coronary arteries ≥1.8 mm in diameter. †Defined as ≥1 high-grade stenosis >90% (visual assessment) by invasive coronary angiography or a measured FFR-value ≤0.80 in ≥1 coronary artery. ‡Tests for trend p < 0.001.

Abbreviations as in Table 4.

TABLE 6 Association Between the Size of RPD by CMR Stress Perfusion Imaging, Obstructive CAD and Standard-of-Care-Guided Coronary Revascularization in Stable Chest Pain

Size of RPD	Patients	Obstructive CAD*	Revascularization
No RPD	83 (75)	23 (27)	20 (24)
Small RPD	6 (5)	4 (67)	3 (50)
Moderate RPD	10 (9)	7 (70)	7 (70)
Large RPD	11 (10)	10 (90)†	8 (73)†

Values are n (%). *Defined as ≥1 high-grade stenosis >90% (visual assessment) by invasive coronary angiography or a measured FFR-value ≤0.80 in ≥1 coronary artery. †Tests for trend p<0.001.

CMR = cardiac magnetic resonance; RPD = reversible perfusion defect; other abbreviation as in Table 4.

Table 6. Of 8 patients diagnosed with an occluded coronary artery, 7 (88%) patients had an RPD by CMR.

HEAD-TO-HEAD COMPARISON: FFR$_{CT}$ VERSUS CMR. The number of patients classified as having obstructive CAD differed between the noninvasive modalities (FFR$_{CT}$ n = 79 [72%] versus CMR n = 27 [25%], p < 0.001). Concordant FFR$_{CT}$ and CMR test results were found in 58 (53%) patients, of whom 27 (47%) patients had obstructive CAD by both tests and 31 (53%) patients normal test results by both FFR$_{CT}$ and CMR. In the former group, revascularization was performed in 18 (67%) patients, in the latter 1 (3%) (p < 0.001). Discordant test results were seen in 52 (47%) patients, all having a normal test result by CMR and signs of obstructive CAD by FFR$_{CT}$, of whom 19 (37%) patients were revascularized. No patients were classified as abnormal by CMR and as normal by FFR$_{CT}$.

PREDICTION OF REVASCULARIZATION: FFR$_{CT}$ VERSUS CMR. The per-patient diagnostic performance for identifying standard-of-care-guided revascularization yielded a sensitivity of 97% (95% confidence interval [CI]: 86% to 100%) for FFR$_{CT}$ versus 47% (95% CI: 31% to 64%) by CMR (p < 0.001); corresponding specificity was 42% (95% CI: 30% to 54%) versus 88% (95% CI: 78% to 94%) (p < 0.001); NPV was 97% (95% CI: 91% to 100%) versus 76% (95% CI: 67% to 85%) (p < 0.05); PPV was 47% (95% CI: 36% to 58%) versus 67% (95% CI: 49% to 84%) (p < 0.05); and accuracy was 61% (95% CI: 51% to 70%) versus 74% (95% CI: 64% to 82%), respectively (p > 0.05) (Central Illustration). The sensitivity of FFR$_{CT}$ for predicting revascularization remained constantly high in all tested strata, whereas the sensitivity of CMR was consistently low (Table 7). False-negative test results were more frequent by CMR (n = 20) than classification of obstructive CAD by distal-tip FFR$_{CT}$ values (n = 1; p < 0.001) among patients undergoing multivessel revascularization (CMR n = 7 [50%] versus FFR$_{CT}$ n = 0 [0%]; p < 0.05), patients treated by single-vessel revascularization (CMR n = 13 [54%] versus FFR$_{CT}$ n = 1 [4%]; p < 0.001), and patients undergoing CABG (CMR n = 8 [62%] versus FFR$_{CT}$ n = 0 [0%]; p < 0.01). Significantly more patients with a false-negative CMR test result compared to patients with a false-negative FFR$_{CT}$ test result underwent revascularization for proximal LAD stenosis (CMR n = 17 [61%] versus FFR$_{CT}$ n = 0 [0%]; p < 0.001) and had a stenosis severity >90% by ICA (CMR n = 14 [61%] versus FFR$_{CT}$ n = 1 [4%]; p < 0.01). The only patient who was falsely classified as normal by FFR$_{CT}$ had a >90% stenosis of the RCA-1 and was treated directly with PCI.

The diagnostic sensitivity of CMR was not different among patients with analyzable coronary CTA data sets compared to patients in whom CTA data sets were rejected for FFR$_{CT}$ analysis (18 of 38 (47%) versus 4 of 7 (57%), p > 0.05). No difference in the diagnostic performance of CMR, regadenoson versus adenosine, was shown (data not shown).

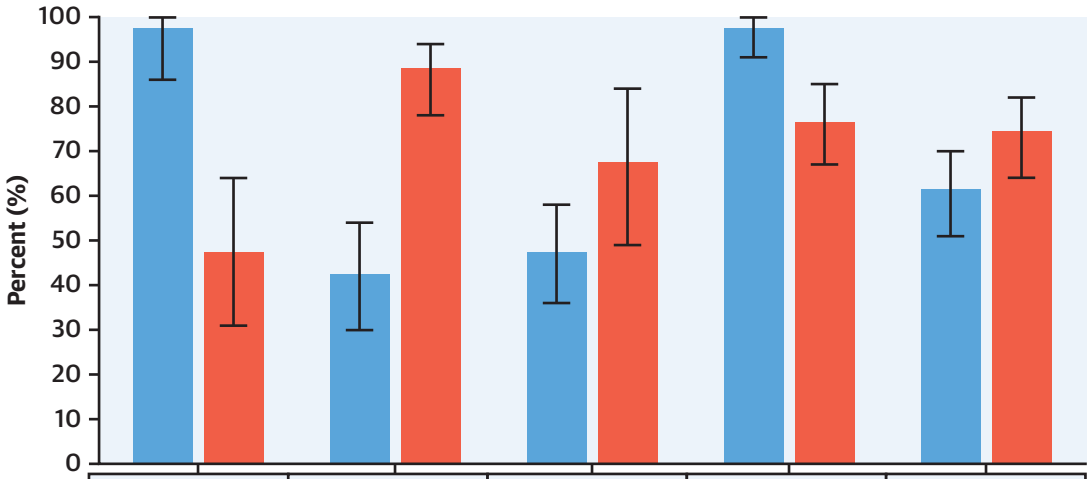
The specificity for predicting revascularization was significantly improved from 42% to 68% (p < 0.001) by using lesion-specific FFR$_{CT}$ values rather than distal-tip FFR$_{CT}$ values for classification of obstructive CAD, which caused a nonsignificant decrease in test sensitivity of FFR$_{CT}$ from 97% to 84% (p > 0.05) (Central Illustration and Table 8).

DISCUSSION

This prospective clinical study comparing FFR$_{CT}$ and CMR stress perfusion imaging in symptomatic stable patients with CAD as determined by coronary CTA did not show any difference in the diagnostic accuracy of FFR$_{CT}$ and CMR in predicting standard-of-care-guided coronary revascularization. However, a significant difference in sensitivity in favor of FFR$_{CT}$ was shown, while the specificity of CMR was highest. The current study included patients in whom guidelines recommend adjunctive noninvasive functional testing. To avoid deferral from invasive investigation of obstructive coronary disease a high diagnostic sensitivity and NPV of the second-line tests is essential. Accordingly, this first head-to-head comparison between second-line FFR$_{CT}$ and CMR testing strategies is relevant.

In this study, patients undergoing revascularization were more often classified as having functional impairment by FFR$_{CT}$ as compared to CMR. These results are in line with 2 recent studies in which FFR$_{CT}$ had a higher diagnostic sensitivity for prediction of revascularization compared to the severity of stenosis by coronary CTA (17) and compared to the occurrence of reversible perfusion defects by SPECT

CENTRAL ILLUSTRATION **FFR_{CT} Compared With CMR Stress Perfusion Imaging for Prediction of Standard-of-Care-Guided Coronary Revascularization in Patients With Stable Chest Pain**



	Sensitivity	Specificity	PPV	NPV	Accuracy
FFR_{CT}	97 (86-100)	42 (30-54)	47 (36-58)	97 (91-100)	61 (51-70)
CMR	47 (31-64)	88 (78-94)	67 (49-84)	76 (67-85)	74 (64-82)
p-value	< 0.001	< 0.001	0.017	0.023	0.070

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FFR_{CT} defined as the per-patient lowest FFR_{CT}-value in coronary vessels ≥1.8 mm in diameter. The results of core laboratory FFR_{CT} analysis and CMR test assessments had no impact on referral to invasive angiography and were blinded to decision makers. CMR = cardiac magnetic resonance; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; NPV = negative predictive value; PPV = positive predictive value.

(9). Clinical decision-making on revascularization in these studies was made independently of FFR_{CT} analyses because test results were unknown to the caregivers.

Several factors might influence the only modest diagnostic sensitivity of CMR stress perfusion imaging shown in the present study. First, it should be recognized that studies included in recent meta-analyses (3,4) used CMR as a first-line rule-out in patients with chest pain, whereas the current applied CMR as a second-line testing strategy solely in those patients who had documented CAD by coronary CTA. Second, the disease prevalence in the current study was lower than in previous studies. In the CE-MARC (Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease) study, 11% of patients had a previous myocardial infarction or had undergone revascularization (18). In the MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease) study, 39% sustained a previous infarction and 31% had been treated by coronary angioplasty in the past (19), whereas patients with known CAD were excluded in our study. Third, an anatomic/physiologic mismatch is well-known (17,20), implying that a number of lesions in prior studies presumably would have been reclassified if physiologic measurements by FFR instead of morphologic degree of stenosis by ICA had been used as the reference. Fourth, it might be argued that 3T scanners yielding higher spatial resolution and giving the potential for quantification of perfusion might have increased the diagnostic sensitivity of CMR. However, 3T scanners have not been documented to yield superior results compared to 1.5 T systems, and the latter scanner type is by far the most prevalent system used for CMR stress perfusion studies. Furthermore, quantitative measures of

TABLE 7 Subgroup Sensitivity Analysis of FFR$_{CT}$ and CMR Stress Perfusion Imaging for Prediction of Standard-of-Care-Guided Coronary Revascularization in Stable Chest Pain

	Distal-Tip FFR$_{CT}$*		Lesion-Specific FFR$_{CT}$†		CMR	
	Sensitivity	p Value	Sensitivity	p Value	Sensitivity	p Value
Sex						
Male	100	0.316	85	1.000	46	1.000
Female	92		83		50	
Age, yrs						
<64	96	1.000	87	0.663	48	1.000
≥64	100		80		47	
Agatston score						
<100	88	0.421	75	0.061	50	0.765
100-399	100		63		36	
400-999	100		100		45	
≥1,000	100		100		63	
Grade of stenosis by ICA						
30%-90%	100	1.000	73	0.188	27	0.052
>90%	96		91		62	
Revascularization						
1 vessel	96	1.000	79	0.383	46	1.000
≥2 vessels	100		93		50	
LAD	100	0.263	86	0.644	39	0.144
Non-LAD	90		80		70	
Proximal	97	1.000	85	0.513	47	1.000
Distal	100		75		50	

Values are %. *Distal-tip FFR$_{CT}$ defined as the per-patient lowest FFR$_{CT}$-value in coronary vessels ≥1.8 mm in diameter. †Lesion-specific FFR$_{CT}$ defined as the per-patient lowest FFR$_{CT}$ value 2 cm distal to lesions in coronary vessels ≥1.8 mm in diameter. The results of core laboratory FFR$_{CT}$ analysis and CMR test assessments had no impact on referral to invasive angiography and were blinded to decision makers.

ICA = invasive coronary angiography; LAD = left anterior descending coronary artery; other abbreviations as in Tables 4 and 6.

perfusion by CMR have not yet been fully established. Fifth, the threshold for a reversible perfusion defect by CMR stress perfusion imaging in this study was defined as ≥2 segments in accordance with international guidelines. Applying a lower threshold for test positivity would not have changed test sensitivity for CMR, as 82 of 83 patients (99%) had completely normal CMR stress perfusion scans. Although a small myocardium-at-risk may be a reason for a false-negative CMR scan (21), it is unlikely to explain the demonstrated low sensitivity of CMR, as 89% of treated lesions were located proximal in the coronary arteries. Moreover, the modest diagnostic sensitivity of CMR was shown across subpopulations. Finally, the low diagnostic sensitivity of CMR in this study is unlikely to be caused by inappropriate CMR stress testing or data analysis, as 96% of patients had adverse effects during pharmacologic stress testing and as 82% of CMR data sets had good image quality.

TABLE 8 Lesion-Specific FFR$_{CT}$* Versus CMR Stress Perfusion Imaging for Prediction of Standard-of-Care-Guided Coronary Revascularization in Stable Chest Pain

	FFR$_{CT}$	CMR	p Value
Sensitivity	84 (69-94)	47 (31-64)	0.001
Specificity	68 (56-79)	88 (78-94)	0.003
PPV	58 (45-71)	67 (49-84)	0.314
NPV	89 (81-97)	76 (67-85)	0.017
Accuracy	74 (64-82)	74 (64-82)	1.000

Values are % (95% confidence interval). *Lesion-specific FFR$_{CT}$ defined as the per-patient lowest FFR$_{CT}$-value 2 cm distal to lesion in coronary vessels ≥1.8 mm in diameter. The results of core laboratory FFR$_{CT}$ analysis and CMR test assessments had no impact on referral to invasive angiography and were blinded to decision makers.

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 4 and 6.

The low rate of patients classified with obstructive CAD by CMR may seem in contrast to the medium-to-high burden of coronary atherosclerosis observed in patients in this study as shown by 40% of patients having an Agatston score greater than 400, 24% having a stenosis severity >90%, and 35% undergoing revascularization (of whom 37% were treated due to multivessel disease), and 34% were treated by CABG.

The modest per-patient FFR$_{CT}$ specificity detected in this study may in part be explained by the use of distal-tip FFR$_{CT}$ value rather than lesion-specific FFR$_{CT}$ value (22). The increase in test specificity by applying lesion-specific FFR$_{CT}$ for categorizing

patients was achieved with a nonsignificant decrease in test sensitivity, which is in accordance with a recent study (14). Still, the specificity of CMR remained significantly higher than that of FFR_{CT}.

Similarities between the vessel-specific approach elaborated by FFR and FFR_{CT} as opposed to evaluation by myocardial perfusion by CMR would be in favor of FFR_{CT} and an explanation for the difference in the diagnostic performance. However, FFR_{CT} modelling and principles underlying computational fluid dynamics are fundamentally different from FFR. In addition, revascularization was guided not only by FFR assessments but also by angiography in 48% of patients in our study.

How the differences of second-line FFR_{CT} and CMR test performance influence outcomes in terms of prognosis/costs for societies is at the moment unsettled. However, testing strategies using either first-line CMR (23-25) or selective FFR_{CT} (11) have both indicated a favorable prognosis considering death and myocardial infarction in stable patients with a normal test result and also a more favorable resource use compared to usage of first-line coronary angiography (26,27). The importance of choosing a first-line testing strategy with the ability to provide direct visualization of atherosclerotic coronary lesions has recently been shown in the SCOT-HEART (Scottish Computed Tomography of the Heart) randomized trial (28), in a substudy of the PROMISE (Prospective Multicentre Imaging Study for Evaluation of Chest Pain) trial (29), and by a meta-analysis (30), as the incidence of major adverse cardiovascular events was significantly lower following anatomic assessment by coronary CTA than following first-line functional testing strategies.

In this context, it is worth noticing that a number of obstructive lesions in the current study would have remained undiagnosed by CMR perfusion imaging if invasive angiography had not been performed, which is of special importance because first-line CMR have indicated more favorable resource use than first-line coronary angiography. We did not include any follow-up data on either symptomatic relief or incidence of coronary events in our study, so it remains unknown how the reported discrepancy in diagnostic performance of second-line FFR_{CT} and CMR following a first-line coronary CTA impact resource use and patient outcomes.

STUDY LIMITATIONS. The number of patients included in this prospective study is relatively small, which may give rise to spurious nonsignificant results. However, as our sample size was sufficient to detect significant differences between the main effect parameters, the diagnostic sensitivity and specificity of the 2 tests being compared, the risk of spurious nonsignificant results is not an issue for our primary outcomes.

A number of patients were unable to complete all planned series of tests. Our rejection rate for FFR_{CT} analysis was 21%, and was higher than reported in previous studies where CTA scan protocols were optimized for FFR_{CT} analysis (9,10), but at the same level as in a study without pre-scheduled FFR_{CT}-analysis (17). As the proportion of patients undergoing revascularization and the diagnostic sensitivity of CMR were similar in drop-outs and in the study population, we do not believe this had any impact on the result of this study.

The results of this study only apply to patients in whom coronary CTA testing is appropriate.

CONCLUSION

In patients with stable chest pain and documented CAD by coronary CTA adjunctive noninvasive functional testing by FFR_{CT} and CMR yielded similar overall accuracy for prediction of coronary revascularization. However, a significant difference in diagnostic sensitivity in favor of FFR_{CT} was shown, whereas the specificity of CMR was highest.

To the best of our knowledge, this prospective study is the first of its kind to compare the novel physiologic metric, FFR_{CT}, with CMR stress perfusion imaging for prediction of standard-of-care-guided coronary revascularization in real-world practice. The current study in stable symptomatic patients with coronary lesions as determined by coronary CTA did not show any difference in the overall accuracy of FFR_{CT} and CMR in predicting revascularization. However, FFR_{CT} had a significantly higher diagnostic sensitivity than CMR in identifying patients undergoing revascularization, whereas the specificity was highest for CMR. Randomized prospective trials are warranted to clarify whether the reported discrepancy between the applied adjunctive functional testing strategies in selecting patients for invasive procedures will have significant impact on patient outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Functional testing is recommended before referral to invasive angiography in patients with stable chest pain and obstructive CAD as determined by coronary CTA. A direct comparison of the clinical utility of FFR_{CT} and CMR as second-line sequential testing strategies has not previously been assessed. In this study we found a similar diagnostic accuracy of the two noninvasive testing strategies for prediction of standard-of-care-guided coronary revascularization. However, the diagnostic sensitivity was significantly higher for FFR_{CT} compared to CMR, whereas the specificity was highest for CMR.

TRANSLATIONAL OUTLOOK: The reported diagnostic performance of second-line FFR_{CT} and CMR following a first-line coronary CTA in patients with stable chest pain relates to prediction of standard-of-care–guided revascularization. Large prospective studies are warranted to evaluate if the reported discrepancy impact resource use and patient outcomes.

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