ORIGINAL PAPER

Influence of Cardiac CT based disease severity and clinical symptoms on the diagnostic performance of myocardial perfusion

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Abstract

We aimed to identify factors influencing the sensitivity of perfusion imaging after an initial positive coronary computed tomography angiography (CCTA) using invasive coronary angiography (ICA) with conditional fractional flow reserve (FFR) as reference. Secondly we aimed to identify factors associated with revascularisation and to evaluate treatment outcome after ICA. We analysed 292 consecutive patients with suspected significant coronary artery disease (CAD) at CCTA, who underwent perfusion imaging with either cardiac magnetic resonance (CMR) or myocardial perfusion scintigraphy (MPS) followed by ICA with conditional FFR. Stratified analysis and uni- and multiple logistic regression analyses were performed to identify predictors of diagnostic agreement between perfusion scans and ICA and predictors of revascularisation. Myocardial ischemia evaluated with perfusion scans was present in 65/292 (22%) while 117/292 (40%) had obstructive CAD evaluated by ICA. Revascularisation rate was 90/292 (31%). The overall sensitivity for perfusion scans was 39% (30–48), specificity 89% (83–93), PPV 69% (57–80) and NPV 68% (62–74). Stratified analysis showed higher sensitivities in patients with multi-vessel disease at CCTA 49% (37–60) and typical chest pain 50% (37–60). Predictors of revascularisation were multi-vessel disease by CCTA (OR 3.51 [1.91–6.48]) and a positive perfusion scan (OR 4.69 [2.49–8.83]). The sensitivity for perfusion scans after CCTA was highest in patients with typical angina and multiple lesions at CCTA and predicted diagnostic agreement between perfusion scans and ICA. Abnormal perfusion and multi vessel disease at CCTA predicted revascularisation.

Abbreviations

CCTA	Coronary Computed tomographic angiography
CACS	Coronary artery calcium score.
CAD	Coronary artery disease
ICA	Invasive Coronary Angiography
CMR	Cardiac Magnetic Resonance
LGE	Late gadolinium enhancement
MPS	Myocardial Perfusion Scintigraphy
FFR	Fractional Flow Reserve
PPV	Positive Predictive Value
QCA	Quantitative Coronary Analysis
ECG	Electrocardiography
SCCT	Society of cardiovascular computed tomography
CACS	Coronary artery calcium score
NPV	Negative predictive value

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bpm	Beats pr. minute
SSS	Summed stress score
SRS	Summed rest score
SDS	Summed difference score
CI	Confidence interval
SPECT	Single-photon emission computed tomography
HR	Heart rate
OR	Odds ratio
PET	Positron emission tomography
JOPCAB	J-incision off pump coronary artery bypass
PCI	Percutaneous coronary intervention
CTO	Coronary total occlusion
CABG	Coronary artery bypass grafting
OMT	Optimal medical therapy

Introduction

Despite guideline recommendations of non-invasive imaging testing for diagnosing stable coronary artery disease CAD) in patients with low/intermediate pre-test probability of CAD [1, 2], invasive coronary angiography ICA) continues to be used early on in the diagnostic pathway in patients with suspected CAD. Evidence from large populations presenting with chest pain has confirmed that the majority will not have obstructive CAD [3, 4]. Moreover, a large US study reported that approximately 60% of elective ICAs found no obstructive CAD [5]. Avoiding unnecessary ICA would reduce patient risk and provide significant financial savings.

Non-invasive testing depicts anatomy, detects coronary atherosclerosis or identifies myocardial ischemia. Coronary computed tomography angiography CCTA) assesses coronary anatomy [6] and is particularly useful for exclusion of CAD in low/intermediate-risk patients due to the high negative predictive value NPV). Perfusion imaging e.g. cardiac magnetic resonance CMR) or myocardial perfusion scintigraphy MPS) assesses myocardial ischemia and the modalities provides strong prognostic information on mortality and morbidity [7, 8].

Several head-to-head studies have evaluated a combined diagnostic set-up with CCTA and perfusion imaging in high risk patients [9, 10].

In the Danish study of Non-Invasive testing in Coronary Artery Disease Dan-NICAD) 1 trial [11, 12], the diagnostic accuracy of perfusion imaging with either CMR or MPS was tested in patients with significant CAD on CCTA, using ICA+conditional FFR measurements as the reference standard. In contrast to studies conducted in patients with high pre-test risk evaluated clinically, we found low sensitivity for both perfusion techniques [12].

The primary aim of this Dan-NICAD 1 sub-study was to evaluate if clinical parameters and CAD severity added independent predictive value to the diagnostic performance of perfusion imaging in patients with a low/intermediate risk of CAD and a CCTA suggestive of CAD. Secondarily, we evaluated the treatment outcome after ICA to further analyse the clinical consequence of potentially using perfusion imaging as a second line test instead of ICA.

Methods

Patients and study design

This was a sub-study comprising all randomized patients from the Dan-NICAD 1 trial with a CCTA result suggesting obstructive CAD [12]. A detailed description of the Dan-NICAD 1 trial has been published [11]. In short, the trial was a two-centre, randomised, open label, head-to-head clinical trial including consecutive patients referred for CCTA with low/intermediate risk of CAD (n = 1675). Patients suspected of obstructive CAD at CCTA (n = 392) were randomized 1:1 to CMR or MPS and scheduled for subsequent ICA with conditional FFR. The core labs analysing the CMR and MPS scans were blinded to clinical information and the results of the ICA. Physicians performing ICA-FFR decided patient treatment blinded to the results of the perfusion scans.

The study followed the Declaration of Helsinki. The Danish Data Protection Agency and the Central Denmark Regional Committee on Health Research Ethics approved the study. All patients provided informed written consent.

The study was registered at ClinicalTrials.gov (identifier: NCT02264717).

Procedures

Coronary computed tomography angiography

CCTA scans were performed using a 320 slice volume CT scanner Aquillion One, Toshiba Medical Systems, Japan) with prospective electrocardiographic ECG) gating. The images were analysed on a dedicated workstation Vitrea Advanced Workstation, Vital Images, USA) by an experienced cardiologist. Luminal diameter stenosis was evaluated in each segment using the 18-segment Society of Cardiovascular Computed Tomography SCCT) model [13]. Coronary lesions were quantified for stenosis by visual assessment; and severity was classified as no stenosis: 0% diameter reduction; mild stenosis: 1% to 29% diameter reduction; moderate stenosis: 30% to 49% diameter reduction; and severe stenosis: 50% to 100% diameter reduction. Severe stenosis and non-evaluable segments with a diameter exceeding 2 mm were defined as obstructive CAD.

Myocardial perfusion scintigraphy

MPS was obtained using a dedicated gamma camera (Cardio MD, Phillips Healthcare, Best, Holland). Patients conducted a standard symptom-limited bicycle exercise test preceded by 48 h beta-blocker withdrawal. If patients were unable to reach target heart rate ($\geq 85\%$ of 220-age), adenosine stress was performed. If stress images revealed any abnormalities, a resting study was obtained.

Images were analysed using Cedar Sinai AutoQuant software by an independent core lab (Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark) using a 17-segment model. For each segment, the perfusion defect was scored in a 5-point scoring system (0: normal and up to 4: absence of tracer uptake) and summed into a summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS). Images were also evaluated qualitatively with a binary outcome (normal/abnormal). An abnormal MPS scan was defined as 1) an SDS ≥ 4 involving ≥ 2 contiguous segments (reversible defect), 2) an SRS ≥ 4 involving ≥ 2 contiguous segments (irreversible defect) 3) a combination of 1) and 2) (mixed defect).

Cardiac magnetic resonance imaging

The CMR scans were conducted using a 1.5 Tesla system (Siemens MAGNETOM Avanto, Siemens Healthcare GmbH, Erlangen, Germany). Stress perfusion imaging was conducted after intravenous injection of either 0.4 mg (5 ml) of Regadenosone® (Lexiscan, Astellas Pharma, USA) or intravenous adenosine-induced hyperaemia 140 µg/kg/min over 4 min. A stepwise increase in adenosine dose was administered in case of inadequate response. For adenosine stress an increase of > 10 bpm or a blood pressure reduction > 10 mm Hg from baseline was considered sufficient [14]. For Regadenosone® an increase in heart rate of > 10 bpm was considered a sufficient clinical response. Splenic switch-off was registered in all patients stressed with adenosine. As contrast agent, either Gadovist® (Bayer Schering Pharma AG, Germany) or Dotarem® (GD-DOTA, Guerbet LCC, USA), was used.

CMR analysis was performed in an independent core lab (William Harvey Research Institute, Queen Mary University of London, London, United Kingdom) blinded from additional patient information and results. Diagnostic confidence was evaluated using a scale from 1–3, indicating high, medium or low image quality. Images were evaluated qualitatively with a binary outcome (normal/abnormal) based on the perfusion analysis. Significant perfusion defects were defined as subendocardial or transmural signal changes by stress imaging or irreversible defects in ≥ 2 contiguous segments by late gadolinium enhancement (LGE) imaging.

Invasive coronary angiography with fractional flow reserve

ICA was performed approximately 4 weeks after CCTA using a routine procedure. FFR measurements (St. Jude Medical, MN, USA and Volcano, San Diego, USA) were performed if technically possible in all coronary segments with a diameter > 2 mm where ICA showed a stenosis with a diameter ≥ 30 and $< 90\%$ by visual assessment. All pressure waveforms were analysed by a core lab (Interventional Coronary Imaging Core Laboratory, Aarhus University Hospital, Denmark).

Two-dimensional (2D) quantitative coronary analysis (QCA) was performed in an independent core lab (ClinFact, Leiden, The Netherlands) using QAngioXA 7.3 QCA software. Haemodynamically obstructive CAD was defined as FFR ≤ 0.80, or as a visual high-grade stenosis ($> 90\%$ diameter stenosis) in a vessel with a reference diameter above ≥ 2.0 mm. If FFR was not technically possible, a QCA-measured stenosis exceeding $\geq 50\%$ diameter stenosis defined a significant lesion.

Statistical analysis

Continuous variables were expressed using mean ($\pm$ SD) and categorical variables as frequency n, %). Frequencies were compared by Fischer's exact test or Chi-square test as appropriate. The perfusion scans were analysed as one group due to the similar diagnostic performance of the CMR and MPS [12]. Only patients with complete data were included in the analyses. Data were binary grouped by sex, age (above/below 60 years), clinical presentation ($\pm$ typical angina), CACS (above/below of 400) and single vs. multi-vessel disease by CCTA and the associated sensitivities, specificities and predictive values were calculated. These strata and the perfusion data were added to logistic regression models as independent variables to identify possible predictors of revascularisation after ICA (dependent variable). Model overfitting was balanced by limiting 1 variable in the multi-variable model for every 10 outcome. All results were presented with 95% CI and two-sided p-value < 0.05 were considered statistically significant.

Statistical analysis was performed using STATA-15 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 292 patients with suspected obstructive CAD on CCTA completed perfusion imaging with either CMR or MPS followed by ICA. Among these, 148 patients completed CMR and ICA and 144 completed MPS and ICA.
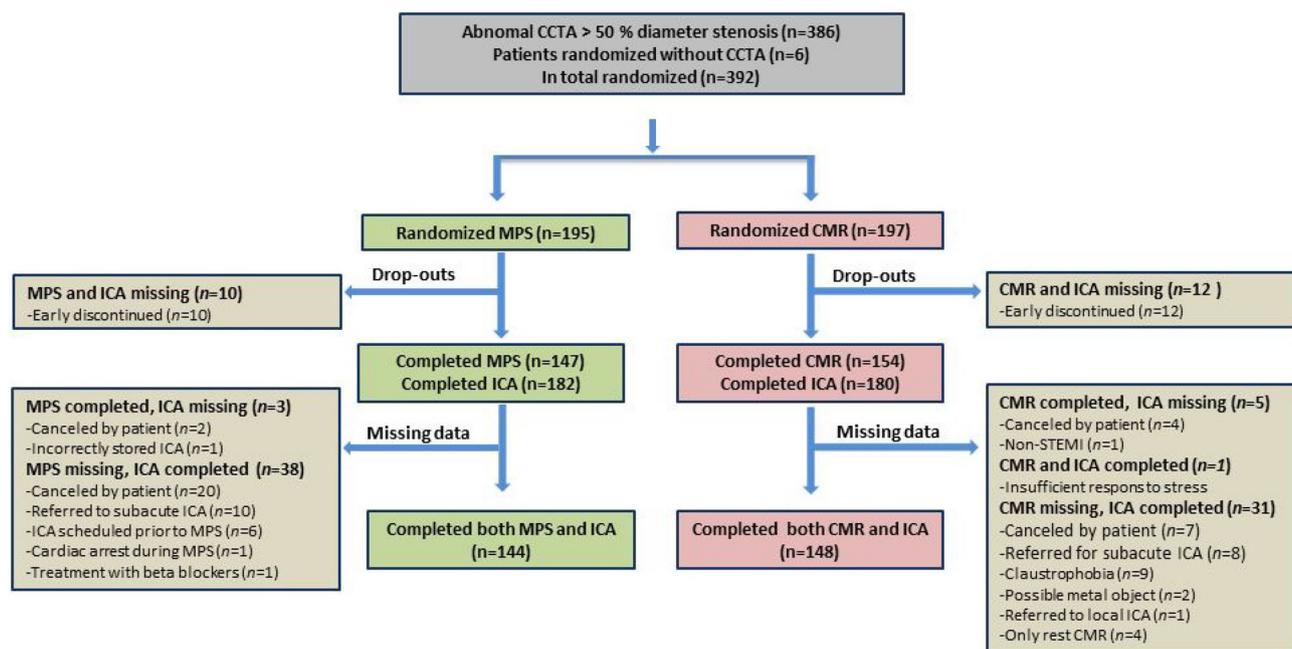
Fig. 1 Patient flowchart. *CCTA* coronary computed tomography angiography, *CMR* cardiac magnetic resonance, *MPS* myocardial perfusion scintigraphy, *ICA* invasive coronary angiography, *CACS* coronary artery calcium score

Study flowchart and baseline characteristics are presented in Fig. 1 and Table 1.

Imaging characteristics including CACS, CCTA, perfusion imaging and ICA are also presented in Table 1. Significant perfusion defects were identified in 65/292 (22%) patients. In the 27 patients with a positive MPS, SSS, SRS and SDS were 11.2 ± 6.2, 4.2 ± 3.4 and 7.6 ± 5.3, respectively (mean ± 2SD). In the 38 patients with a positive CMR, the number of segments with a perfusion defect was 5.1 ± 2.3 (mean ± 2SD). The reference test (ICA with conditional FFR) classified 117/292 (40%) patients with obstructive CAD, 75 due to a FFR ≤ 0.80, the rest a high-grade stenosis. FFR was measured in 167 patients and mean FFR was 0.83 ± 0.09. Accuracy measures for the whole population are presented in Fig. 2. Forty-five patients had coinciding abnormal perfusion imaging and obstructive CAD at ICA and 155 coinciding normal perfusion and non-obstructive CAD, Table 3 and Fig. 2, yielding an accuracy of 68%. Case examples of false negative and true positive CMR and MPS images are presented in Fig. 3 and Fig. 4.

Stratified analysis on patient related factors, coronary artery calcium score, and disease severity on the performance of perfusion imaging

Stratification was performed according to sex, age above or below 60 years, clinical presentation, CACS above or below 400 and single/multi vessel disease at CCTA as shown

in Table 2. Except sensitivity and positive predictive value PPV) for multi- vs. single vessel disease, the 95% CI intervals overlapped Marked with fat typing in table 2.

The proportion and absolute numbers of correctly classified patients with no CAD, one, two or three vessel disease is presented in Table 3. The proportion of correctly classified patients improved significantly for one vs. two vessel CAD (p = 0.025) and for one vs. three vessel CAD (p = 0.01).

Logistic regression models estimating predictors for diagnostic agreement between perfusion imaging and invasive coronary angiography and regression models predicting revascularisation

The same variables used for stratification were also used in the regression models and the result of the perfusion imaging was included as a variable.

OR for diagnostic agreement between perfusion imaging and ICA, was significantly higher at multi-variable regression analysis for typical angina (p = 0.03) and multi-vessel disease by CCTA (p < 0.01). All results from uni- and multi-variable regression analysis are presented in Table 4. In the multi-variable regression analysis, significant predictors of revascularisation after ICA were multi-vessel disease by CCTA (p < 0.01) and positive perfusion imaging (p < 0.01). All results are presented in Table 5.

Table 1 Baseline characteristics and patient characteristics according to CACS, CCTA, perfusion imaging, and ICA

	Patients per protocol		
	Totals (N = 292)	CMR (N = 148)	MPS (N = 144)
Gender, women, n	118 (40%)	60 (41%)	58 (40%)
Age, years	61.3 ± 8.1	61.9 ± 7.9	60.8 ± 8.1
BMI, mean	26.9 ± 3.9	26.8 ± 3.9	27.1 ± 4.0
Risk factors			
Current smoking	52 (18%)	23 (16%)	29 (20%)
Antihypertensive treatment	135 (46%)	75 (51%)	60 (42%)
Lipid-lowering treatment	91 (32%)	48 (33%)	43 (30%)
Diabetes	22 (8%)	14 (10%)	8 (6%)
Family history of early CAD[a]	123 (42%)	60 (41%)	63 (44%)
Symptoms			
Typical angina	94 (32%)	47 (32%)	47 (33%)
Atypical angina	94 (32%)	52 (35%)	42 (29%)
Non-angina chest pain	43 (15%)	20 (14%)	23 (16%)
Dyspnea or arrhythmia	61 (21%)	29 (20%)	32 (22%)
Pretest probability[b]			
Low (< 0.15)	14 (5%)	8 (5%)	6 (4%)
Moderate (≥ 0.15 and < 0.85)	261 (89%)	132 (89%)	129 (90%)
High (≤ 0.85)	17 (6%)	8 (5%)	9 (6%)
CACS			
CACS < 400	183 (63%)	88 (60%)	95 (66%)
CACS ≥ 400	109 (37%)	60 (40%)	49 (34%)
CCTA[c]			
One-vessel CAD	157 (54%)	77 (52%)	80 (56%)
Two-vessel CAD	75 (26%)	42 (28%)	33 (23%)
Three-vessel or LM CAD	59 (20%)	29 (20%)	30 (21%)
Perfusion imaging			
Abnormal perfusion	65 (22%)	37 (25%)	27 (19%)
Poor Image quality	1 (0.3%)	1 (0.7%)	0 (0%)
One-vessel territory	14 (5%)	8 (5%)	6 (4%)
Two-vessel territory	37 (13%)	25 (17%)	12 (8%)
Three-vessel territory	13 (4%)	4 (3%)	9 (7%)
ICA			
CAD	117 (40%)	59 (40%)	58 (41%)
One-vessel CAD	69 (24%)	33 (22%)	36 (25%)
Two-vessel CAD	32 (11%)	19 (13%)	13 (9%)
Three-vessel or LM CAD	16 (5%)	7 (5%)	9 (6%)

Values are n (%) or mean ± SD

CMR cardiac magnetic resonance imaging, *MPS* myocardial perfusion scintigraphy, *BMI* body mass index, *CCTA* coronary computed tomography angiography, *ICA* invasive coronary angiography, *CACS* coronary artery calcium score

[a]Family history of coronary artery disease among 1'st degree relatives before the age of 60

[b]Pre-test probability assessed using the updated Diamond-Forrester score

[c]One patient was randomized without a CCTA due to a high calcium-score

Treatment consequence after invasive coronary angiography

The clinical treatment consequences are presented in Fig. 5. Of the 292 patients, 91 (31%) were revascularized with percutaneous coronary intervention (PCI) (47, 52%), J-incision off pump coronary artery bypass (JOPCAB) (7, 8%), coronary total occlusion (CTO) (4, 4%) or coronary artery bypass grafting (CABG) (33, 36%). Another 27 patients (9%) with abnormal ICA were treated medically based on a clinical decision, 5 of these had an abnormal perfusion scan.

Among the 91 revascularized patients, 40 (44%) had a positive perfusion test and 51 (56%) had a normal perfusion test. Revascularization was performed in 62% (40/65) patients with abnormal perfusion and in 22% (50/227) with a normal perfusion. Of the patients with normal perfusion, 32 underwent PCI, 4 JOPCAB (25 with one-vessel disease, 10 with two-vessel disease and 1 with three-vessel disease) and 14 CABG (7 with one-vessel disease, 5 with two-vessel disease and 2 with three-vessel disease). The revascularisation strategy was different as patients with abnormal perfusion underwent more extensive procedures (CTO and CABG) compared to patients with normal perfusion (PCI and JOPCAB), p = 0.004.

One patient undergoing PCI had a normal ICA according to our diagnostic criteria, but during the ICA a clinical decision of revascularisation was made.

Discussion

In the Dan-NICAD 1 trial, we found a sensitivity of 39% and a specificity of 89% for perfusion imaging (CMR and MPS) using ICA with conditional FFR as reference standard, in symptomatic patients with a CCTA suspected of obstructive CAD. Subgroup analyses in the present paper revealed that the sensitivity of perfusion imaging was slightly higher (around 50%) in patients with typical angina and multi-vessel disease at CCTA. In accordance with this, we showed that typical angina and multi-vessel disease had an independent predictive value regarding abnormal ICA. Additionally, we noticed that multi-vessel disease at CCTA and a positive perfusion scan, but not typical angina, were independent predictors of revascularisation. Suggestively, only half of the revascularized patients, including patients undergoing CABG, had abnormal perfusion.

Many former studies testing perfusion imaging with CMR or MPS against ICA with either QCA or FFR showed high sensitivities (70–90%) and specificities (75–94%) [7, 9, 15-17]. The inclusion criteria and pre-test likelihood of CAD in these studies were diverse. In the present study, patients were included according to the CCTA findings, i.e. beforehand selected as suitable for this modality implying

Fig. 2 Results of perfusion imaging compared with invasive angiography with conditional FFR. **a** Sensitivity, specificity, PPV and NPV measured at the patient level for the perfusion imaging. Results are presented with 95% CI. **b** Results in absolute numbers at patient level. *PPV* positive predictive value, *NPV* negative predictive value, *ICA* invasive coronary angiography

Perfusion examination	Sensitivity	Specificity	PPV	NPV
	39% (30-48)	87% (83-93)	69% (57-80)	68% (62-74)
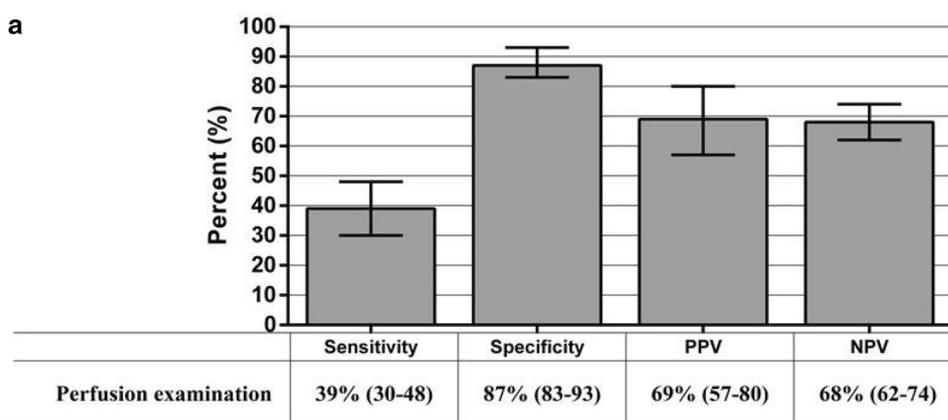
Perfusion examinations	ICA		
	Disease	Normal	total
Abnormal	45	20	65
Normal	72	155	227
Total	117	175	292

low/intermediate risk with a frequent prevalence of atypical symptoms and one-vessel disease 54%) [12]. A recent Danish study including 143 patients from CCTA calculated similar diagnostic values of MPS including a sensitivity of 41%, indicating that patients selected by CCTA have a lower ischemic burden than patients traditionally referred for MPS [18]. This is well understood considering that many high-risk patients are excluded from CCTA due to e.g. high BMI, high age, suspicion of high CACS (e.g. diabetics of whom we only have 22 (8%) in the trial), irregular hear rhythm or kidney disease. Among the positive perfusion scans in the present study, 50/65 (77%) covered 2–3 vessel territories, indicating that a larger ischemic burden is needed to cause substantial myocardial ischemia detected by perfusion imaging.

Obstructive multi-vessel disease by CCTA was an independent predictor of both diagnostic agreement between perfusion imaging and ICA and revascularisation. This is in concordance with the CONFIRM study showing multi-vessel disease to be the strongest predictor of ICA utilization after CCTA [19]. The results from the regression analysis indicate that disease severity and extent is part of the explanation for the low overall sensitivity in the Dan-NICAD

trial, as most patients have one-vessel CAD and atypical symptoms.

The Dan-NICAD 1 trial raises the question whether to manage patients according to the results of perfusion scan or ICA. Patient management can be driven by prognosis or symptoms. A strong argument for prognosis guided management is the widely accepted fact that a normal perfusion carries a favourable patient outcome [20-22]. A recent study evaluating a diagnostic strategy using positron emission tomography PET) perfusion in patients with suspected CAD at CCTA [22] showed event rates 5 times higher for patients with an abnormal PET compared to a normal PET. In addition, event rates were similar for patients with a normal PET and an abnormal CCTA compared to patients with a normal CCTA. This study population resembles the Dan-NICAD patients and we expect a similar favourable outcome for patients with normal perfusion in our trial. Whether revascularisation with PCI improves patient prognosis in terms of mortality is debated. The COURAGE trial [23] evaluated the effect of revascularisation with PCI and optimal medical therapy OMT) in patients with stable CAD or OMT alone and found no difference in terms of prognosis. Oppositely FAME 2 found reduced event rates in patients
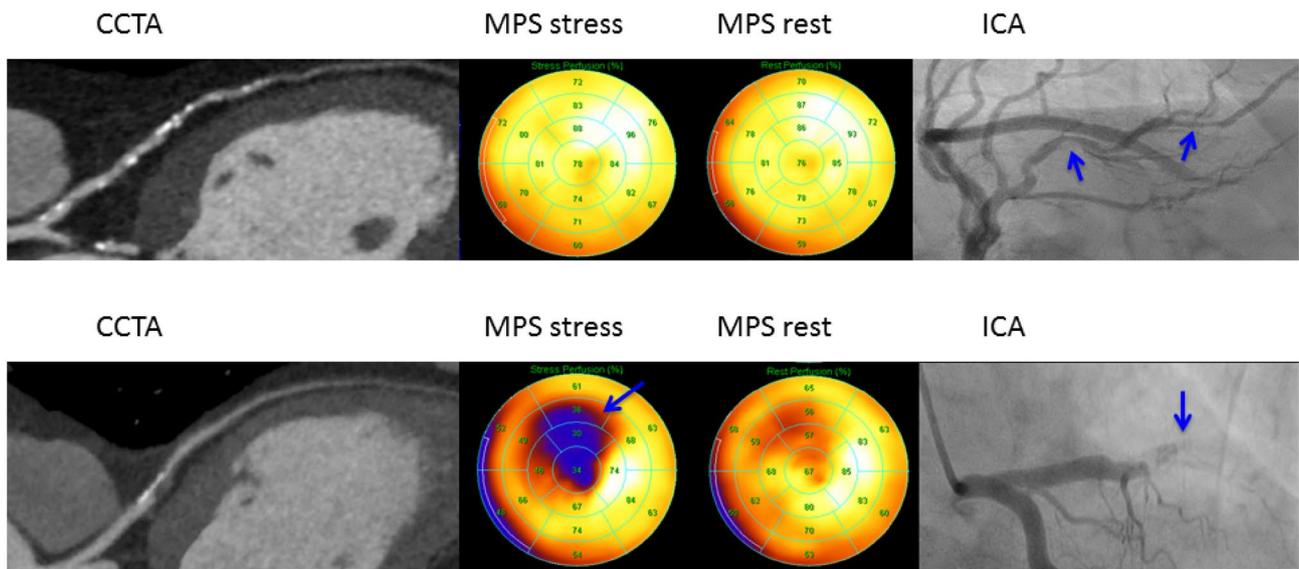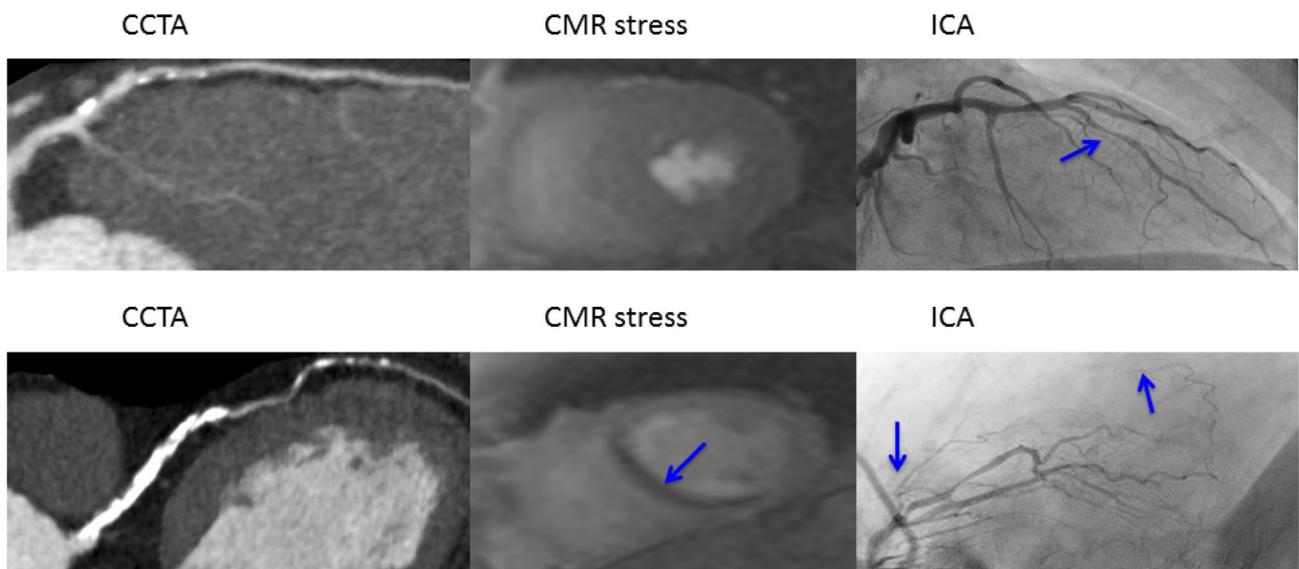
Fig. 3 Two case examples of CCTA, MPS and ICA findings. Upper example; a false negative MPS: CCTA showed diffuse mixed calcified and soft plaques throughout LAD. Both rest and stress MPS were normal without perfusion defects. ICA showed an elongated severe stenosis in LAD visually assessed as > 90% stenosis. Patient was treated with a graft, LIMA to LAD. Lower example; a true positive MPS: CCTA showed a severe proximal stenosis in LAD, the plaque was mixed soft and calcified. Stress and rest MPS showed both fixed and reversible perfusion defects in the anterior wall. ICA showed an occluded LAD with only retrograde contrast filling. The patient was treated with PCI in the proximal LAD. *CCTA* coronary computed tomography angiography. *MPS*: myocardial perfusion scintigraphy. *ICA* invasive coronary angiography, *LAD* left anterior descending artery, *LIMA* left internal mammary artery, *PCI* percutaneous coronary intervention

Fig. 4 Two case examples of CCTA, CMR and ICA findings. Upper example; a false negative CMR: CCTA showed diffuse mixed calcified and soft plaques throughout LAD. Stress CMR was normal without hypo perfused areas. ICA showed an elongated stenosis in LAD, FFR was 0.72. The patient was treated with a graft, LIMA to LAD. Lower example; a true positive CMR; CCTA showed severe calcified plaques throughout LAD. Stress CMR showed a large transmural perfusion defect in the antero-septal wall. ICA showed an occluded LAD with only retrograde contrast filling. The patient was treated with CABG, grafts for LAD and RCA. *CCTA* coronary computed tomography angiography, *CMR* cardiac magnetic resonance, *ICA* invasive coronary angiography, *LAD* left anterior descending artery, *FFR* fractional flow reserve, *LIMA* left internal mammary artery, *CABG* coronary artery bypass grafting, *RCA* right coronary artery

Table 2 Stratified analysis on diagnostic accuracy for perfusion imaging vs. ICA

	Prevalence of CAD	Sensitivity	Specificity	PPV	NPV
Female	36/118 (31%)	33% (19–51)	88% (79–94)	55% (32–76)	75% (65–83)
Male	81/174 (47%)	41% (30–52)	89% (81–95)	77% (61–88)	63% (55–72)
AGE < 60	45/110 (41%)	31% (18–47)	85% (74–92)	58% (37–78)	64% (53–74)
AGE ≥ 60	72/182 (40%)	43% (31–55)	91% (84–96)	76% (60–88)	71% (63–78)
Typical angina	42/94 (45%)	50% (34–66)	85% (72–93)	72% (53–87)	68% (55–79)
Other*	75/198 (38%)	32% (22–44)	90% (84–95)	67% (49–81)	69% (61–76)
CACS < 400	63/183 (34%)	32% (21–45)	87% (79–92)	56% (38–72)	71% (63–78)
CACS ≥ 400	54/109 (50%)	46% (33–60)	93% (82–98)	86% (68–96)	64% (52–74)
Single-vessel (CCTA)	41/157 (26%)	**20% (9–35)**	86% (79–92)	**33% (16–55)**	75% (67–82)
Multi-vessel (CCTA)	76/134 (57%)	**49% (37–60)**	93% (83–98)	**90% (77–97)**	58% (47–68)

Stratified analyses on sex, age ± 60, typical angina symptoms or *other covering atypical, non-specific, dyspnoea or arrhythmia, CACS ± 400 and single versus multi-vessel disease classified by CCTA

Values are proportions and 95% CI are shown in the parentheses. All analyses are per-patient

CAD coronary artery disease, *PPV* positive predictive value, *NPV* negative predictive value, *CACS* coronary artery calcium score, *CCTA* coronary computed tomography tomography

Table 3 Patients with single or multi-vessel CAD by ICA

Disease by ICA	Perfusion imaging		
	Normal	Abnormal	Total
No CAD	155 (89%)	20	175
One-vessel CAD	50	19 (28%)	69
Two-vessel CAD	16	16 (50%)	32
Three-vessel CAD or LM CAD	6	10 (63%)	16
Total	227	65	292

Numbers in parentheses are proportions of correctly classified patients. The total proportion of correctly classified patients are (155 + 19 + 16 + 10)/292 68%

CAD coronary artery disease, *ICA* invasive coronary angiography, *LM* left main

with stable CAD treated with FFR guided PCI and OMT compared to OMT alone [24]. The COURAGE trial nuclear sub-study showed that treatment with PCI + OMT in patients with myocardial ischemia at MPS reduced risk of death and cardiac events, especially in patients with moderate to severe ischemia [25]. Interestingly, if our patients had been treated according to the result of the perfusion scan, only 20% ((292–65)/292) would have been referred for ICA, presumably without impact of prognosis. Furthermore around half of the revascularisation procedures (50/90) would have been saved. These high percentages seem provocative and challenge current patient management strategies.

Performing symptom driven treatment, the anti-anginal effect of revascularisation is the primary goal. Little substantial knowledge exists regarding this management

Table 4 Simple and multiple logistic regressions to identify predictors of diagnostic agreement between perfusion imaging and ICA

Variable (reference group)	Simple logistic regression model, OR	Multiple logistic regression model, OR
Female		
Male	1.40 (0.60–3.13; p = 0.45)	1.61 (0.65–3.95; p = 0.30)
Age < 60		
Age ≥ 60	1.67 (0.76–3.67; p = 0.19)	1.34 (0.55–3.25; p = 0.52)
Chest pain other[a]		
Typical	2.13 (0.98–4.61; p = 0.06)	2.57 (1.11–5.98; p = 0.03)
CACS < 400		
CACS ≥ 400	1.85 (0.87–3.94; p = 0.12)	0.95 (0.38–2.36; p = 0.91)
Single-vessel by CCTA		
Multi-vessel by CCTA	3.91 (1.60–9.57; p < 0.001)	4.53 (1.61–12.71; p < 0.001)

Simple and multiple logistic regression models to identify predictors of diagnostic agreement between perfusion imaging and ICA. Values are (95% CI; p-value)

ICA invasive coronary angiography, *OR* odds ratio, *CACS* coronary artery calcium score, *CCTA* coronary computed tomography angiography

[a]Other covering atypical, non-specific, dyspnoea or arrhythmia

Table 5 Simple and multiple logistic regression predictors of revascularisation

Variable (reference group)	Simple logistic regression model OR	Multiple logistic regression model OR
Female		
Male	1.70 (1.01–2.86; p = 0.05)	1.47 (0.82–2.64; p = 0.19)
Age < 60		
Age ≥ 60	0.89 (0.54- 1.48; p = 0.65)	0.67 (0.37–1.21; p = 0.19)
Chest pain other[a]		
Typical	1.31 (0.77–2.20; p = 0.32)	1.06 (0.58–1.94; p = 0.84)
CACS < 400		
CACS ≥ 400	2.24 (1.35–3.72; p = 0.002)	1.47 (0.80–2.72; p = 0.21)
CCTA CAD extent (single-vessel)		
Multi-vessel	3.51 (1.91–6.48; p < 0.001)	4.40 (2.58–7.52; p < 0.001)
No perfusion defect		
Perfusion defect	5.52 (3.06–9.95; p < 0.001)	4.69 (2.49–8.83; p < 0.001)

Simple and multiple logistic regression models to identify predictors of revascularisation. Values are (95% CI; p-value)

ICA invasive coronary angiography, *OR* odds ratio, *CACS* coronary artery calcium score, *CCTA* coronary computed tomography angiography

[a]Other covering atypical, non-specific, dyspnoea or arrhythmia

strategy, and the pathophysiology of angina is complex. It can be speculated that revascularisation of larger ischemic areas detected by MPS / CMR provides more pronounced symptom relief compared to treatment of smaller areas of ischemia although the supplying vessel to this area has a FFR below 0.8. However, we do not know whether the clinical benefit of revascularisation differed between patients with or without perfusion defects in our study population.

In our study 51 patients without a perfusion defect were revascularized; some will argued that these patients were missed calls by perfusion imaging and others will state that these patients were over treated. As FFR is measured in epicardial arteries > 2 mm and CMR/MPS detects ischemia at tissue level, it is possible that the discrepancy between the two examinations merely reflects the different nature of the modalities rather than the inferiority of the one over the over.

Many years ago Diamond and Forrester published a highly cited paper on how to use probability as an aid in the clinical diagnosis of CAD[26]. Their data revealed that CAD was far more common among patients with typical angina compared to atypical angina and non-cardiac chest pain. Although questioning a patient about symptoms remains a corner stone in modern cardiology, we nowadays do not base diagnosis on clinical information alone. In this perspective, we find it interesting that out of other known high-risk markers of CAD (age, gender, CACS), typical angina turns out to be the one correlating with ischemia, emphasising that clinical history should not be forgotten in a world of advanced technology.

Given the discrepancy between the invasive and non-invasive techniques it seems that the population of patients with initially low to intermediate risk of CAD and a CCTA suggestive of obstructive CAD constitute a particular challenge for perfusion scans.

This study adds an important contribution to the on-going discussion on which diagnostic strategy to use in patients suspected of CAD and specifically address the problems evolving from comparing results of diagnostic methods evaluating CAD on a vessel level and myocardial level.

However, results from studies quantifying flow from perfusion imaging and estimating absolute flow during FFR will likely help to further clarify the discrepancy observed between the invasive and non-invasive techniques.

Limitations

Not all patients in this cohort obtained a complete dataset. Patients with incomplete data, approximately 25% of the randomized patients, did not complete the entire study protocol for various reasons specified in Fig. 1. However this is not unexpected and similar findings were seen in e.g. the EVINCI study [1]. Patients did not drop out or were selected but the missing data mainly occurred due to logistic reasons as examinations were spread on multiple days and locations and this would not have influenced the prevalence of disease. Also FFR was not measured in all vessels but only in lesions with a diameter stenosis between (30–90%) evaluated by the clinician performing the procedure. Performing FFR measures in all lesions might have changed the number of patients classified with CAD. Patients with a recent myocardial infarct, previous revascularisation with PCI or CABG were not included in this study and the results can therefore not be generalized to patients with known CAD.

Fig. 5 Treatment consequence of ICA stratified by the results of perfusion imaging. *ICA* invasive coronary angiography, *JOPCAB* J-incision off pump coronary artery bypass, *PCI* percutaneous coronary intervention, *CTO* coronary total occlusion, *CABG* coronary artery bypass grafting
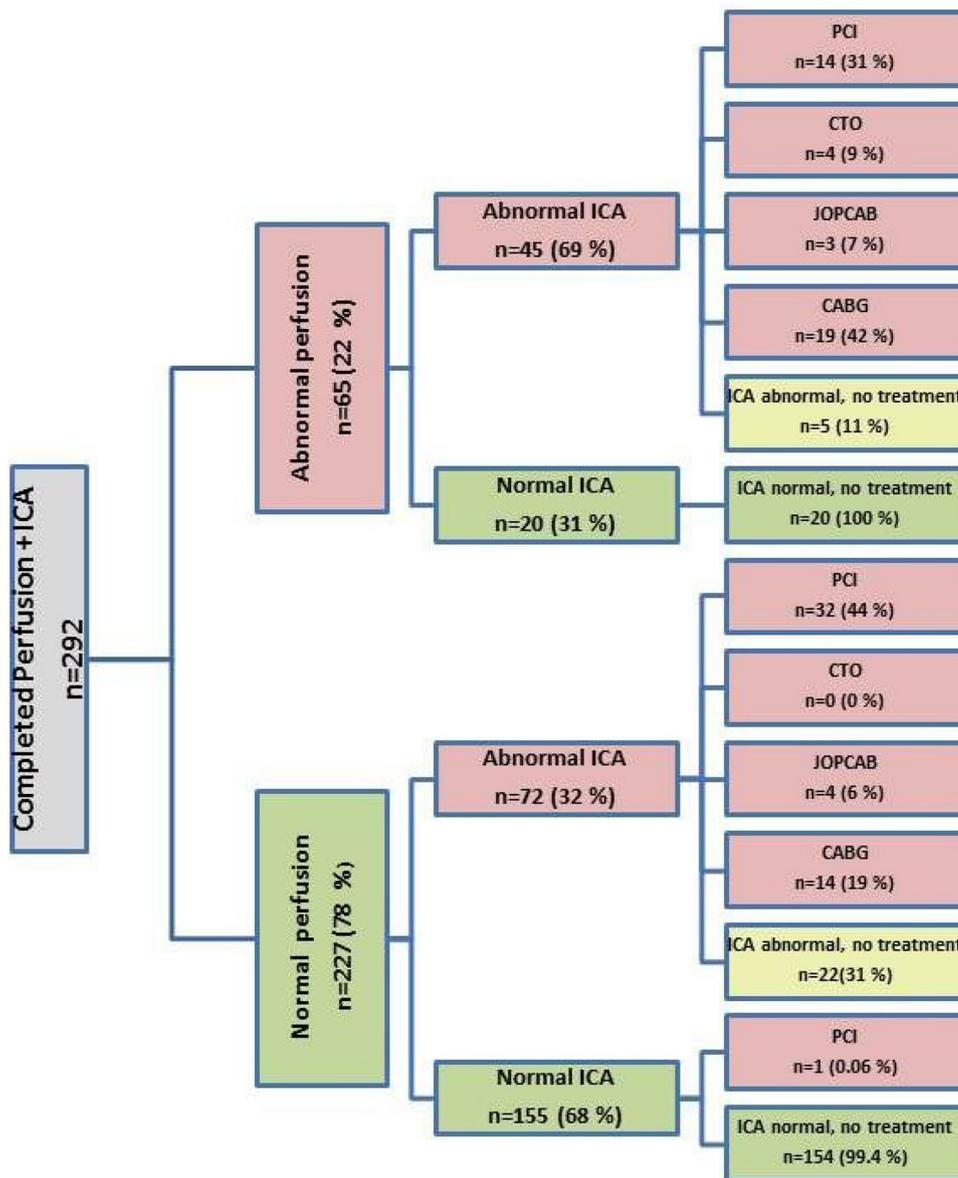
Conclusion

In patients suspected of CAD and a CCTA with obstructive CAD, the sensitivity for perfusion scans were in general low compared to a reference standard of ICA with conditional FFR, but improved significantly in patients with typical chest pain symptoms and multi-vessel disease by CCTA. Multi-vessel disease at CCTA and abnormal perfusion predicted revascularisation.

Author contributions LN, MB and SW participated in the conception and design of the study. CI obtained the CMR scans. LB provided assistance with the CMR scans and helped draft this manuscript. GU enrolled patients at Silkeborg Regional Hospital and analysed the CCTA scans. LF participated in the design and coordination of the study. JAE obtained the MPS scans. LHM and LLK enrolled patients and analysed CCTA scans at Hospital Unit West. NRH and JW coordinated the ICAs and collected data regarding this. EHC, MM and HEB conducted ICAs and FFR measurements at the Department of Cardiology, Aarhus University Hospital. SP and AR analysed the CMR scans as core lab. LCG analysed the MPS scans as core lab. All authors have critically reviewed, read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest All other authors state no conflict of interest.

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