

Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis

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Aims

The aim of this study was to determine the diagnostic performance of single-photon emission computed tomography (SPECT), stress echocardiography (SE), invasive coronary angiography (ICA), coronary computed tomography angiography (CCTA), fractional flow reserve (FFR) derived from CCTA (FFR_{CT}), and cardiac magnetic resonance (MRI) imaging when directly compared with an FFR reference standard.

Method and results

PubMed and Web of Knowledge were searched for investigations published between 1 January 2002 and 28 February 2015. Studies performing FFR in at least 75% of coronary vessels for the diagnosis of ischaemic coronary artery disease (CAD) were included. Twenty-three articles reporting on 3788 patients and 5323 vessels were identified. Meta-analysis was performed for pooled sensitivity, specificity, likelihood ratios (LR), diagnostic odds ratio, and summary receiver operating characteristic curves. In contrast to ICA, CCTA, and FFR_{CT} reports, studies evaluating SPECT, SE, and MRI were largely retrospective, single-centre and with generally smaller study samples. On a per-patient basis, the sensitivity of CCTA (90%, 95% CI: 86–93), FFR_{CT} (90%, 95% CI: 85–93), and MRI (90%, 95% CI: 75–97) were higher than for SPECT (70%, 95% CI: 59–80), SE (77%, 95% CI: 61–88), and ICA (69%, 95% CI: 65–75). The highest and lowest per-patient specificity was observed for MRI (94%, 95% CI: 79–99) and for CCTA (39%, 95% CI: 34–44), respectively. Similar specificities were noted for SPECT (78%, 95% CI: 68–87), SE (75%, 95% CI: 63–85), FFR_{CT} (71%, 95% CI: 65–75%), and ICA (67%, 95% CI: 63–71). On a per-vessel basis, the highest sensitivity was for CCTA (pooled sensitivity, 91%: 88–93), MRI (91%: 84–95), and FFR_{CT} (83%, 78–87), with lower sensitivities for ICA (71%, 69–74), and SPECT (57%: 49–64). Per-vessel specificity was highest for MRI (85%, 79–89), FFR_{CT} (78%: 78–81), and SPECT (75%: 69–80), whereas ICA (66%: 64–68) and CCTA (58%: 55–61) yielded a lower specificity.

Conclusions

In this meta-analysis comparing cardiac imaging methods directly to FFR, MRI had the highest performance for diagnosis of ischaemia-causing CAD, with lower performance for SPECT and SE. Anatomic methods of CCTA and ICA yielded lower specificity, with functional assessment of coronary atherosclerosis by SE, SPECT, and FFR_{CT} improving accuracy.

Keywords

Meta-analysis • Diagnostic accuracy • Cardiac imaging • Fractional flow reserve

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Introduction

Fractional flow reserve (FFR), a method to determine hyperemic pressure differences across coronary artery stenosis, is considered the 'gold standard' for diagnosis of ischaemia-causing coronary artery disease (CAD).^{1–3} The use of FFR to guide coronary revascularization, when compared with a coronary stenosis-guided strategy, improves event-free survival.^{4–6}

Numerous cardiac imaging methods exist to diagnosis ischaemia-causing CAD, including single-photon emission computed tomography (SPECT), stress echocardiography (SE), cardiac magnetic resonance imaging (MRI), coronary CT angiography (CCTA), fractional flow reserve derived from CCTA (FFR_{CT}), and invasive coronary angiography (ICA). To date, non-invasive cardiac imaging methods have been assessed for their diagnostic performance largely against an ICA reference standard. Numerous reports^{7–10} individually examining the performance of cardiac imaging methods against FFR have been hampered by incomplete performance of FFR and mixed FFR-ICA reference standards.¹¹ There is mounting evidence that the assessment of CAD severity by ICA is flawed, because the angiographic severity of a given epicardial stenosis does not necessarily commensurate with its functional significance.^{12,13} Therefore, assumptions regarding the hemodynamic relevance of stenosis based on their mere angiographic appearance results in erroneous interpretations with important clinical importance. The tailoring of revascularizations according to their angiographic severity of epicardial disease conveys no symptomatic or prognostic benefit to patients and is even detrimental.^{4–6}

We thus performed a meta-analysis comparing cardiac imaging methods for diagnosis haemodynamically significant CAD using FFR as a reference standard.

Methods

PubMed and the ISI Web of Knowledge were systematically searched for published investigations between January 2002 to February 2015 for articles in English using pre-defined search criteria (Table 1). A manual reference check of included articles was performed to identify potential studies missed by our search strategy. Reports that employed duplicative cohorts or overlapping data were excluded (I.D. and C.K.Z.), and the study with the largest population was included. Final screening of

reports for inclusion in the meta-analysis was performed by three independent reviewers (I.D., B.L.N., and C.K.Z.).

Study eligibility

The inclusion criteria for studies in the analysis were as follows: (i) FFR served as the reference test and was measured in a minimum of 75% of patients, arteries and/or coronary segments included in the analyses of the respective studies. The threshold of 75% was chosen to provide for maximum inclusion of studies in which FFR was directly measured in the patients, vessels, or segments considered in the primary endpoint analysis. This same level has been previously used by Norgaard et al.¹¹

Data collection

Data extraction was initially performed by one reviewer (C.K.Z.) and subsequently verified by the two reviewers (I.D. and B.L.N.). For each eligible study, the following data were collected: year of publication; patient demographics; type of cardiac imaging evaluated; criteria for an abnormal scan defining ischaemia; FFR threshold used to describe ischaemia; and number of patients, vessels and/or segments compared with FFR. For the meta-analysis, absolute numbers of true and false positive, and true and false negative results were extracted from the articles or otherwise derived from the data provided in the articles. The findings were summarized in a 2 × 2 table. Subsequently, studies were grouped according to the cardiac imaging method, which included SPECT, SE, CCTA, FFR_{CT}, MRI, and ICA. If a study compared more than one modality to FFR, each test was evaluated separately. The quality of the included studies was evaluated by two independent reviewers (I.D. and C.Z.) and conformed to the revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS).¹⁴ Discrepancies in quality assessment were resolved by consensus discussion.

Statistical analysis

Intra-observer agreement between reviewers with regard to the quality assessment of the studies was assessed by the Cohen kappa test. On the basis of the results from the 2 × 2 tables, pooled measures for sensitivity, specificity, diagnostic odds ratio (DOR), and area under the curves (AUC) along with their 95% confidence intervals (CIs) were calculated using DerSimonian Lair methodology.¹⁵ Based on the pooled DOR of each index, test summary receiver-operator curves (sROC) were reconstructed using Moses–Shapiro–Littenberg methodology.¹⁶ The DOR reflects the ability of a test to distinguish, in this case, haemodynamic and non-haemodynamic significant CAD. A DOR of 1 indicates that the test has no discriminative power. The higher the DOR, the

Table 1 Search syntax

Source	Search terms	Filters
PubMed	(noninvasive fractional flow reserve OR noninvasive FFR OR coronary CT angiography OR coronary computed tomography angiography OR coronary angiography OR nuclear myocardial perfusion OR magnetic resonance perfusion OR myocardial perfusion scintigraphy OR SPECT OR stress echocardiography OR stress perfusion OR stress myocardial perfusion OR dobutamine stress) AND (fractional flow reserve OR FFR)	Humans and clinical trial
Web of Science	('noninvasive fractional flow reserve' OR 'noninvasive FFR' OR 'coronary CT angiography' OR 'coronary computed tomography angiography' OR 'coronary angiography' OR 'nuclear myocardial perfusion' OR 'magnetic resonance perfusion' OR 'myocardial perfusion scintigraphy' OR 'SPECT' OR 'stress echocardiography' OR 'stress perfusion' OR 'stress myocardial perfusion' OR 'dobutamine stress') AND ('fractional flow reserve' OR 'FFR')	Cardiovascular systems and 'article'

FFR, fractional flow reserve; SPECT, single-photon emission computed tomography.

better the diagnostic ability of the imaging modality. To evaluate heterogeneity between studies, a Cochran Q statistic and the I^2 index was used. A substantial I^2 index indicates heterogeneity beyond sampling variation. A meta-regression analysis was performed to identify predefined sources of heterogeneity (age, gender, prevalence of diabetes, prevalence of hypertension, prior myocardial infarctions, prior revascularizations, and multivessel disease). Analyses were performed using Meta-DiSc 1.4.¹⁷

Results

Systemic search resulted in 467 potentially relevant articles. After removal of duplicates and screening by title and abstract, 63 full

articles were retrieved and were read full-text. The flowchart of the article search and selection process is demonstrated in Figure 1. A total of 23 eligible studies met the study criteria and were included: 10 CCTA ($n = 1167$ patients), 3 SE ($n = 141$ patients), 3 FFR_{CT} ($n = 609$ patients), 6 ICA ($n = 2610$ patients), 4 MRI ($n = 132$ patients), and 6 SPECT studies ($n = 282$ patients). Inclusion of cardiac imaging methods in each study, along with the demographics of the study populations, is listed in Supplementary material online, Table S1. Finally, 1696 individuals were analysed, with 4740 vessels included for the per-vessel analysis. Haemodynamic significant CAD defined by FFR was identified in 720 (42%) patients and 1613 (34%) arteries. In 18 (78%) studies, FFR values were obtained in all coronary vessels that were included for analysis, with 5 studies

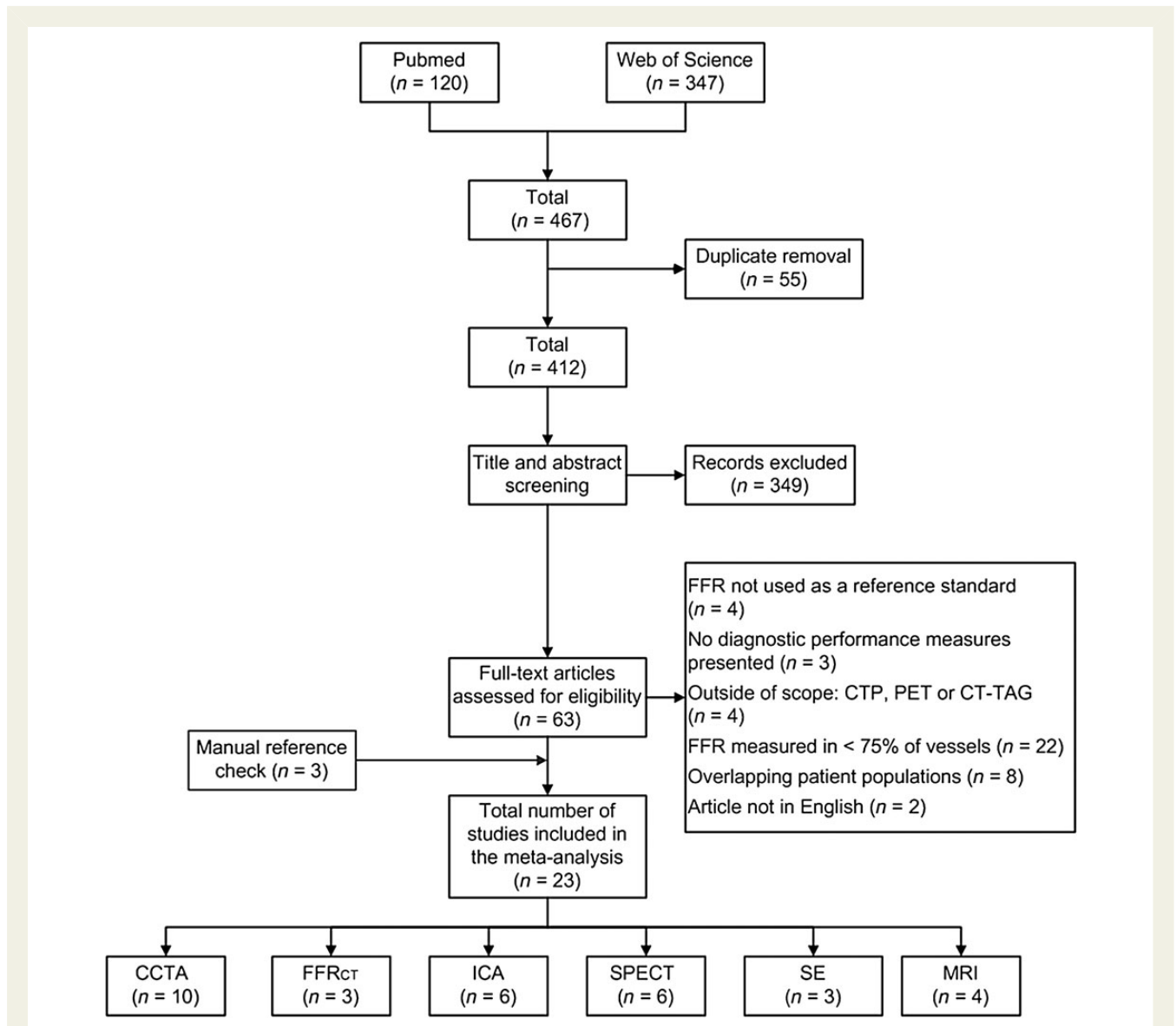


Figure 1 Flow chart showing the process of literature search and selection algorithm. A total of 23 studies were selected. Of note, there are studies that investigated multiple imaging modalities. FFR, fractional flow reserve; CTP, computed tomography perfusion; PET, positron emission tomography; CT-TAG, CT-derived transmural attenuation gradient; CCTA, coronary computed tomography angiography; FFR_{CT}, computed fractional flow reserve derived from CCTA; ICA, invasive coronary angiography; SPECT, single-photon emission computed tomography; SE, stress echocardiography; MRI, magnetic resonance imaging.

obtaining FFR vessels in >75% of coronary vessels (see Supplementary material online, Table S2).

The methodological quality of the included studies was assessed by two independent reviewers using the QUADAS-2 score with a good inter-rater reliability ($\kappa = 0.86$). Supplementary material online, Table S3 summarizes the QUADAS-2 quality score for each included study. Supplementary material online, Figure S1 displays the specific quality study items evaluated by the QUADAS-2 tool. The included studies rated generally poor for patient selection, suggesting a high risk of bias and concerns of applicability (Figure 2 and Supplementary material online, Table S3).

Per-patient diagnostic performance of cardiac imaging methods compared with FFR

Pooled estimates of sensitivity, specificity, on both a per-patient and per-vessel level are summarized in Table 2. Forest plots for sensitivity and specificity are shown in Supplementary material online, Figure S2. At the patient-level CCTA (90%, 95% CI: 86–93), FFR_{CT} (90%, 95% CI: 85–93), and MRI (90%, 95% CI: 75–97) had the highest sensitivity, with lower sensitivity for SPECT (70%, 95% CI: 59–80), SE (77%, 95% CI: 61–88), and ICA (69%, 95%

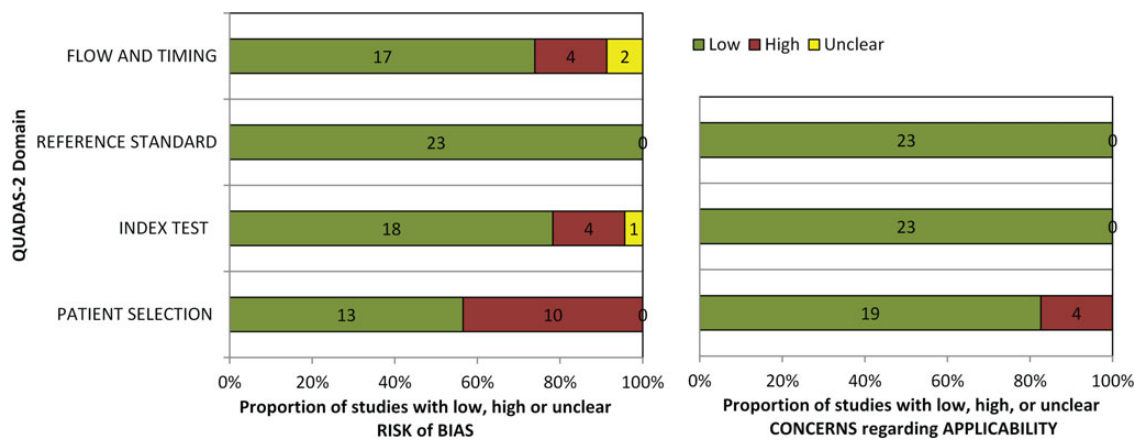


Figure 2 Assessment of methodological quality of included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) revised criteria. Stacked bars represent the number of studies with a low risk of bias (green), unclear risk of bias (yellow), or high risk of bias (red) with regard to patient selection, utilized reference standard, and imaging modality (index test).

Table 2 Diagnostic performance of CCTA, SE, FFR_{CT}, ICA, MRI, and SPECT for the detection of haemodynamic significant coronary artery disease

Index test	N ^a	Sensitivity	Specificity	PLR	NLR	DOR
Patient-based analysis						
CCTA	694	0.90 (0.86–0.93)	0.39 (0.34–0.44)	1.54 (1.25–1.90)	0.22 (0.10–0.50)	6.91 (2.80–17.03)
SE	115	0.77 (0.61–0.88)	0.75 (0.63–0.85)	3.00 (1.94–4.65)	0.34 (0.17–0.66)	9.51 (3.87–23.38)
FFR _{CT}	609	0.90 (0.85–0.93)	0.71 (0.65–0.75)	3.34 (1.78–6.25)	0.16 (0.11–0.23)	21.94 (9.07–53.07)
ICA	954	0.69 (0.65–0.75)	0.67 (0.63–0.71)	2.54 (1.25–5.13)	0.46 (0.39–0.55)	5.46 (2.54–11.76)
MRI	70	0.90 (0.75–0.97)	0.94 (0.79–0.99)	10.31 (3.14–33.88)	0.12 (0.05–0.30)	92.15 (16.35–519.42)
SPECT	110	0.70 (0.59–0.80)	0.78 (0.68–0.87)	3.40 (1.04–11.08)	0.40 (0.19–0.83)	9.06 (1.48–55.54)
Vessel-based analysis						
CCTA	2085	0.91 (0.88–0.93)	0.58 (0.55–0.61)	2.09 (1.74–2.49)	0.17 (0.12–0.24)	13.15 (8.47–20.41)
SE	NA	–	–	–	–	–
FFR _{CT}	1050	0.83 (0.78–0.87)	0.78 (0.78–0.81)	4.02 (1.84–8.80)	0.22 (0.13–0.35)	19.15 (5.73–63.95)
ICA	3196	0.71 (0.69–0.74)	0.66 (0.64–0.68)	2.26 (1.71–2.99)	0.45 (0.36–0.56)	5.34 (3.38–8.45)
MRI	371	0.91 (0.84–0.95)	0.85 (0.79–0.89)	6.16 (2.10–18.02)	0.11 (0.06–0.20)	73.53 (22.17–243.82)
SPECT	470	0.57 (0.49–0.64)	0.75 (0.69–0.80)	2.34 (1.61–3.42)	0.55 (0.44–0.69)	4.72 (2.99–7.45)

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; NA, not available. Other abbreviations are as in Figure 1.

^aNumber of patients might differ from the total patients included in this meta-analysis, due to the difference in studies included in either the patient or vessel-based analysis (Supplementary material online, Tables S4 and S5 provide detailed information on the studies included in the patient- and vessel-based analysis).

CI: 65–75). The highest and lowest specificity was seen for MRI (94%, 95% CI: 79–99) and CCTA (39%, 95% CI: 34–44), respectively. Intermediate specificity was observed for SPECT, SE, FFR_{CT}, and ICA (Table 2 and Supplementary material online, Figure S2). The NLR of MRI (12, 95% CI: 5–30), FFR_{CT} (16, 95% CI: 11–23), and CCTA (22, 95% CI: 10–50) were better than SPECT (40, 95% CI: 19–83) and SE (34, 95% CI: 17–66), as described in Table 2. The diagnostic odds ratio (DOR) on a per-patient basis was the highest for MRI and FFR_{CT} (Table 2 and Supplementary material online, Figure S3). Figure 3A depicts the sensitivity and specificity of the individual studies in an ROC space and the summary ROC curves for CCTA, SE, FFR_{CT}, ICA, MRI, and SPECT imaging.

On a per-patient level, significant heterogeneity for sensitivity was observed for CCTA ($I^2 = 80\%$, $P < 0.01$). Significant heterogeneity for specificity was found for CCTA, FFR_{CT}, ICA, and SPECT. With regard to specificity, SE showed no heterogeneity ($I^2 = 0\%$; $P = 0.68$), whereas slight heterogeneity was seen for MRI ($I^2 = 54\%$, $P = 0.14$) (see Supplementary material online, Figure S2).

Per-vessel diagnostic performance of cardiac imaging methods compared with FFR

At the vessel level, CCTA (91%, 95% CI: 88–93) and MRI (91%, 95% CI: 84–95) exhibited the highest sensitivity, with the lowest sensitivity observed for SPECT (57%, 95% CI: 49–64) (Table 2 and Supplementary material online, Figure S4). The NLR for MRI (11, 95% CI: 6–20), CCTA (17, 95% CI: 12–24), and FFR_{CT} (0.22, 95% CI: 13–35) was better than for SPECT (55, 95% CI: 44–69) and ICA (45, 95% CI: 36–56) (see Supplementary material online, Table S5). With regard to specificity, functional techniques were superior to anatomic methods for diagnosis of ischaemia: MRI (85%, 95% CI: 79–89), FFR_{CT} (78%, 95% CI: 78–81), and SPECT (75%, 95% CI: 69–80) vs. CCTA (58%, 95% CI: 55–61) and ICA (66%, 95% CI: 64–68) (see Supplementary material online, Figure S4). The highest PLR was observed for MRI (6.16, 95% CI: 2.10–18.02) and FFR_{CT} (4.02, 95% CI: 1.84–8.80), with lower values for SPECT (2.34, 95% CI: 1.61–3.42), CCTA (2.09, 95% CI: 1.74–2.49), and ICA (2.26, 95% CI: 1.71–2.99). The per-vessel DOR is shown in Supplementary material online, Figure S5, whereas the summarized ROC curves on a per-vessel basis are shown in Figure 3B.

At the artery level, significant heterogeneity for sensitivity was seen only for ICA studies ($I^2 = 90\%$, $P < 0.001$), whereas the heterogeneity was significant for specificity for all imaging modalities (see Supplementary material online, Figure S4).

Predictors of study heterogeneity

Meta-regression analysis to identify factors impacting heterogeneity was only performed for CCTA, ICA, MRI, and SPECT studies on a per-vessel level, since these were the only imaging modalities that had included more than three studies. Age ($P = 0.01$) and prevalence of diabetes ($P = 0.02$) were identified as predictors of heterogeneity for CCTA studies. For the ICA studies, meta-regression analysis revealed that the year of publication ($P < 0.01$), age ($P < 0.01$), percentage males ($P < 0.01$), prevalence of diabetes ($P < 0.01$), and hypertension ($P < 0.01$) were independent

predictors of heterogeneity. Only prevalence of hypertension was a significant predictor ($P = 0.02$) of heterogeneity in SPECT.

Discussion

The results of this present meta-analysis show a high performance for MRI for the diagnosis of hemodynamically significant CAD on both a per-patient as well as per-vessel basis, when compared directly with an FFR reference standard. Both CCTA and FFR_{CT} yielded high diagnosis sensitivity, with low specificity for CCTA. Diagnostic performance for SPECT, SE, and ICA was generally poorer.

Our study findings are novel, and directly additive to prior reports.^{7–10} Specifically, our study differs from prior published investigations in that we constrained our analyses solely to studies that evaluated cardiac imaging methods to an invasive FFR standard. Prior reports—including meta-analyses—have included admixtures of study designs that included individuals undergoing imaging methods that were compared with ICA or to convenience samples that comprised FFR and, when absent, ICA standards.^{7–10} Indeed, in a recently published meta-analysis by Takx *et al.*, 19 out of the 37 (51%) included studies had measured FFR in <75% of coronary vessels, while the routine interrogation of all arteries by FFR was only performed in 16 (43%) studies.¹⁰ As such, the routine assessment of FFR has not been fully exploited yet, while studies have unveiled an important discordance between the angiographic severity of CAD and its haemodynamic significance. Data from the landmark FAME trial taught us that 20% of stenosis in the range of 70–90% were not severe enough to impede coronary flow.¹² Similarly, the recently published FAMOUS-NSTEMI trial that has been conducted among 350 patients with non-ST-elevation myocardial infarctions showed discordance between angiography and FFR in 32% of cases.¹⁸ Notably, they also found that the 70% threshold by ICA failed to delineate the haemodynamic significance in 47% of epicardial lesions.¹⁸ Interestingly, even at both ends of the angiographic spectrum, namely the 'low' (<30%) and 'high-grade' (>90%) stenosis, assumptions on the functional relevance based on their mere angiographic appearance may be misleading. In fact, abnormal FFR values in the absence of focal epicardial disease are not uncommon and were observed in 18% of coronary arteries by De Bruyne *et al.*¹³ On the other hand, 19% of high-grade lesions, which are generally considered flow-limiting, were shown to underestimate the pathophysiologic consequences as indicated by FFR.¹⁹ Therefore, the angiographic appearance of coronary atherosclerosis does not always commensurate with its functional significance and may lead to erroneous interpretations with important clinical implications. Indeed, tailoring of revascularizations according to their functional relevance, as indicated by FFR, rather than on their mere angiographic appearance improves event-free survival,^{4–6} whereas angiography-guided revascularizations convey neither symptomatic nor prognostic benefit to patients and may be even detrimental.⁴ As such, we restricted our analyses to studies that performed invasive FFR in at least 75% of study subjects to avoid confounding related to a mixed anatomic/physiologic endpoint.

The study results are of considerable importance, given the availability of multiple cardiac imaging methods to diagnosis haemodynamically significant CAD, which serve as guides to consider coronary revascularization. Importantly, our present study findings

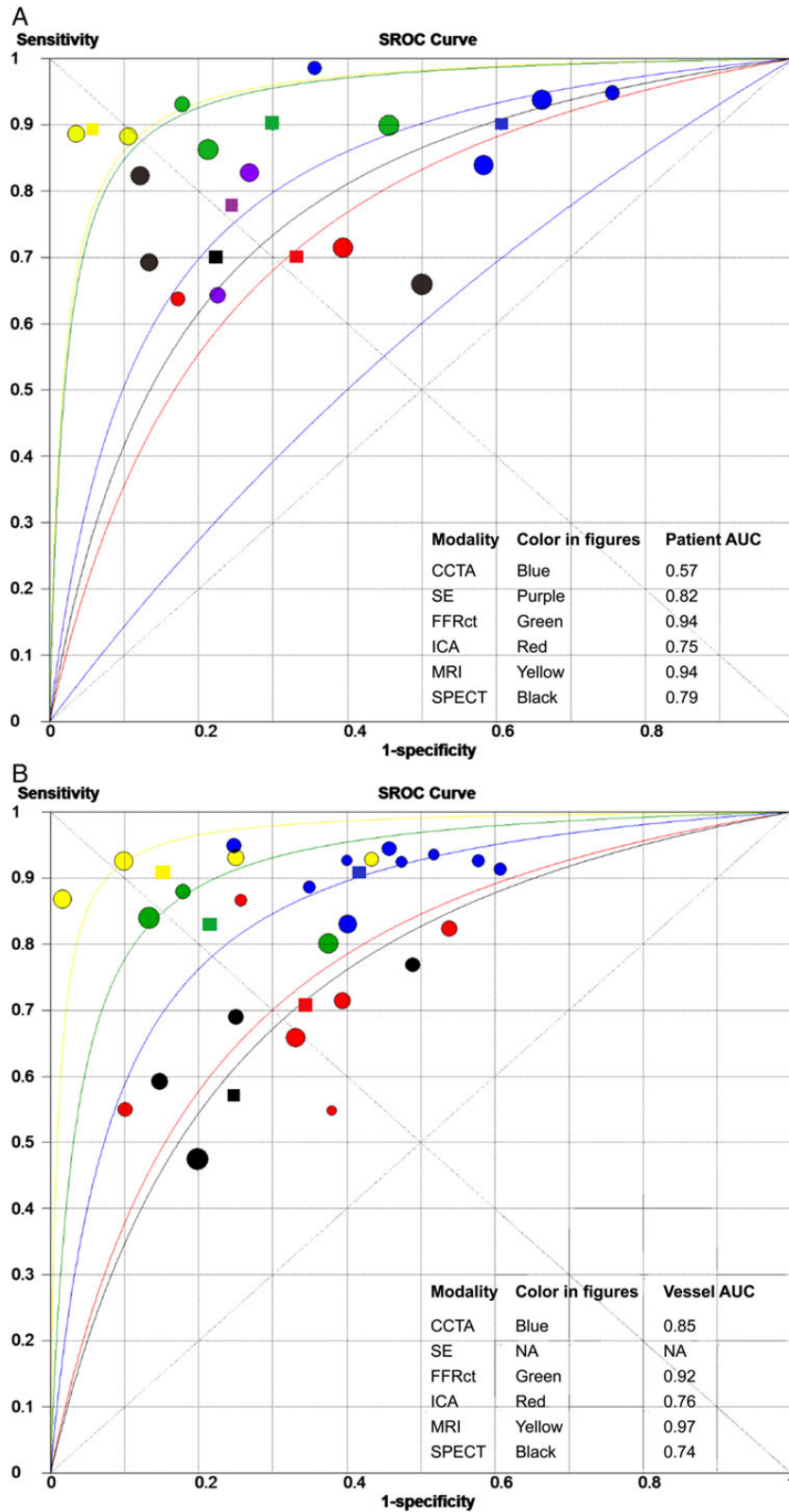


Figure 3 SROC curves of the diagnostic accuracy of cardiac imaging compared with fractional flow reserve. Summary receiver operating characteristic (SROC) curve of the diagnostic accuracy of (A) per-patient and (B) per-vessel data of studies comparing CCTA, FFR_{CT}, ICA, MRI, and SPECT to fractional flow reserve. Each study shows sensitivity and specificity of the different imaging modalities. Area under curve (AUC). The circles show the performance of the separate studies, while the diamond shapes reflect the pooled diagnostic performance of each imaging modality. Abbreviations as in Figure 1.

considerably add to the extant literature, which have largely compared individual modalities with FFR without adequate consideration of the totality of available cardiac imaging methods. These data may inform the use of testing, particularly in the non-invasive setting, to identify individuals who may be appropriately referred for further invasive testing. Traditionally, non-invasive stress tests evaluating myocardial ischaemia have served as the mainstay of diagnosis of CAD, and are a surrogate marker of coronary stenosis that cause ischaemia. More than 10 million stress tests are performed in the USA annually, with SPECT most commonly performed and comprising 90% of stress tests.^{20,21} Interestingly, both SE (DOR 9.51) and SPECT (DOR 9.06) appeared to be more accurate than ICA (DOR 5.46) for the depiction of lesion-specific ischaemia as reflected by a higher DOR, questioning the validity of prior studies that refereed SE and SPECT against ICA. Surprisingly, ICA exhibits both a low sensitivity (69%) and specificity (67%). This finding emphasizes the role of non-invasive imaging to guide clinical decision-making and questions the role of ICA for the initial diagnostic work-up of patients suspected of CAD. Consequently, the reliance on anatomical measures, even when supplied by ICA, is unreliable (see below), and hence referral to the 'cath lab' should be ischaemia-driven.

The present meta-analysis shows that the accuracy of SPECT myocardial perfusion imaging to detect haemodynamic significant CAD as indicated by FFR is moderate. Interestingly, SPECT is performing poorly on a per-vessel level (sensitivity 57 vs. 70% on a per-patient basis), which is arguably attributable to the lack of anatomical information. Indeed, Schindler *et al.*¹ showed a mismatch between SPECT defined myocardial territories and real coronary anatomy in more than half of the cases. Furthermore, in the presence of multivessel CAD, SPECT either misses ischaemia due to the presence of balanced ischaemia or recognizes only the most severe region. As such, in the latter scenario, the other vessel regions are neglected, which may have resulted in the lower sensitivity at the per-vessel region. Notably, the performance of SE in this study was comparable with SPECT, despite the operator-dependent bias of SE. In light of its high diagnostic accuracy, cardiac MRI might become a potential alternative for SPECT and SE. The reasons for MRI superiority are unknown, but may be related to its high spatial resolution, which may encourage the identification of subendocardial ischaemia that may be missed by SPECT. When considering SE, MRI may be superior owing to its diagnostic capabilities at an earlier point than may be present to induce stress-induced regional wall motion abnormalities, which occur conceptually at a later point in the ischaemic cascade.²² Yet, it is important to note that the number of studies directly comparing to FFR were the lowest for MRI, a finding that may underscore the limited availability of MRI to select and skilled centres. Paradoxically, a lower degree of accuracy is expected when cardiac MRI becomes more clinically available. Compared with study protocols, in routine clinical practice inclusion criteria are usually broad, which comes at a cost of lower accuracy. Therefore, large prospective multicentre studies are required to further elucidate the diagnostic value of MRI for the detection of myocardial ischaemia.

Importantly, we observed a high diagnostic sensitivity by CCTA, which is associated with a high NLR, rendering it an excellent technique for the exclusion of hemodynamically significant CAD. However, the specificity of CCTA as well as ICA is low, and emphasizes

the discordance between stenosis severity and ischaemia-causing coronary artery lesions. If identification of haemodynamically compromising CAD is the objective, the reliance upon visualized coronary luminal compromise thus appears to be inappropriate. Interestingly, FFR_{CT} emerged as a new tool for the non-invasive diagnosis of ischaemia-causing CAD by applying computational fluid dynamics on conventional CCTA images. In this study, we observed a high sensitivity of FFR_{CT} with moderate specificity, when compared with an invasive FFR reference standard. It is worthy to note that, in the included studies, FFR_{CT} was evaluated in isolation and did not assess the combination of FFR_{CT} to CCTA. This combination would be expected to significantly improve the diagnostic specificity of CCTA, given the coupling of anatomic and functional measures. In this regard, the recently published PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts) trial demonstrated that the addition of FFR_{CT} to CCTA increased the diagnostic certainty as reflected by a cancellation of 61% of ICAs in patients who were initially planned for an invasive procedure.²³ Notably, the incorporation of FFR_{CT} in the diagnostic strategy resulted in a substantially lower 'cath' normalcy rate in patients referred for ICA.²³ It should be noted, however, that in patients planned for non-invasive testing FFR_{CT} did not result in lower normalcy rates, while associated with higher radiation exposure compared with stress testing or conventional CCTA.² Therefore, whether FFR_{CT}-guided revascularization improves outcome analogue to invasive FFR remains to be elucidated in future studies.

One particularly concerning finding of the present study is the high heterogeneity between different studies. Particularly, we identified generally biased patient selection, which by meta-analytic measures introduced a high risk of heterogeneity and concerns of applicability of our study findings. While we examined the extant literature and included the highest-quality studies available, this finding nevertheless underscores the need for high-quality, unbiased, prospective multicentre trials, which have the potential to mitigate bias related to patient referral, patient selection and centre expertise. Two such trials are ongoing. The PACIFIC (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion imaging and CT Coronary Angiography With Invasive Coronary Angiography) trial is examining the diagnostic performance CCTA, SPECT, and PET against invasive FFR, and is employing traditional metrics such as stenosis severity and myocardial ischaemia to diagnose hemodynamically significant CAD (NCT01521468). Importantly, this study performs these methods on all patients, thus minimizing the errors in diagnostic performance related to differential testing and referral of patients to invasive FFR. The CREDENCE (Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia) trial distinctly differs from the PACIFIC trial by examining metrics beyond stenosis severity and ischaemia (NCT02173275). Anatomic measures related to atherosclerotic plaque characteristics and aggregate plaque volume are being evaluated for their incremental diagnostic efficacy,²⁴ and the diagnostic value of FFR_{CT} as an adjunct to CCTA is subject of future studies. Similarly, stress testing is being evaluated not only for myocardial ischaemia but will include measures of left ventricular function, stress electrocardiographic findings, and other high-risk markers (such as transient ischaemic dilatation of the left ventricle). The outcomes of these trials will be directly additive to the present study findings.

This study is not without limitations. First, while we considered many of the most commonly employed cardiac imaging tests, we did not include all of them, including positron emission tomography and transmural attenuation gradients. This was due to the general paucity of data associated with these methods compared with those methods included in the present study. Whether these approaches are superior, or incremental, to the studies tested in this meta-analysis remains to be seen. Second, we did not include assessments by integration of anatomical and functional tests, including for a combination of SPECT, PET, or FFR_{CT} with either CCTA or ICA. However, it is anticipated, given the high negative predictive power of CCTA and high specificity of SPECT, SE, and FFR_{CT}, that by exploiting the synergistic capabilities of multimodality imaging, accuracy will be increased.²⁵ Interestingly, a recently published study by Beuchel *et al.* reported that, among patients scheduled for elective ICA ($n = 7530$), the use of SPECT prior to referral to ICA improved the diagnostic yield of ICA beyond clinical risk factors and symptoms.²⁶ Building on this, the mental integration of coronary anatomy as provided by ICA and myocardial perfusion imaging will not only improve ICA's ability to depict lesion-specific ischaemia, but will also shift its focus from a diagnostic tool to a gatekeeper for coronary revascularization. This is a particularly germane topic—particularly for FFR_{CT}—that allows the coupling of coronary stenosis with lesion-specific ischaemia without the need for additional imaging.²⁷ Future studies will be required to evaluate the performance of these hybrid strategies. Third, the studies included in this report were largely retrospective, single centre and small. Patients were often pre-selected for FFR measurements based on angiographic findings, which may improve sensitivity at the cost of specificity. These study characteristics may thus hamper the generalizability of their reported values. Fourth, the pooled studies in our study employed different FFR cut-off values to define ischaemia. Specifically, 8 (32%) studies used 0.75, whereas the majority used the ratio of 0.80 to define ischaemia, which is in line with current guidelines.^{2,3} Yet, this differential demarcation precludes definitive evaluation of functionally significant CAD in the 'gray zone' of FFR, namely that between 0.75 and 0.8. Finally, due to the small number of studies included for each imaging modality, we were unable to evaluate for publication bias.

Conclusion

In this comparative meta-analysis of available cardiac imaging methods directly referenced to FFR, MRI had the highest performance for diagnosis of ischaemia-causing CAD, with lower performance for SPECT and SE. Anatomic methods of CCTA and ICA yielded lower specificity, with functional assessment of coronary atherosclerosis by SE, SPECT, and FFR_{CT} improving accuracy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

J.S. and J.W.R.T. performed statistical analysis. I.D., C.K.Z., and B.L.N. acquired the data. J.K.M. handled funding and supervision. I.D., B.L.N., C.K.Z., P.K., and J.K.M. conceived and designed the research. I.D., J.S., B.L.N., C.Z., P.K., J.K.M. drafted the manuscript. I.D., J.S., C.K.Z.,

B.L.N., C.Z., P.K., and J.K.M. made critical revision of the manuscript for key intellectual content.

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