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Metaanalysis of Diagnostic Performance of Computed Coronary Tomography Angiography, Computed Tomography Perfusion and Computed Tomography-Fractional Flow Reserve in Functional Myocardial Ischemia Assessment versus Invasive Fractional Flow Reserve

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Abstract

We sought to compare the diagnostic performance of computed coronary tomography angiography (CCTA), computed tomography perfusion (CTP) and computed tomography fractional flow reserve (CT-FFR) for assessing the functional significance of coronary stenosis as defined by invasive fractional flow reserve (FFR), in patients with known or suspected coronary artery disease. CCTA has proven clinically useful for excluding obstructive CAD due to its high sensitivity and negative predictive value (NPV), however the ability of CTA to identify functionally significant CAD has remained challenging. We searched PubMed/Medline for studies evaluating CCTA, CTP or CT-FFR for the non-invasive detection of obstructive CAD as compared to catheter-derived FFR as the reference standard. Pooled sensitivity, specificity, PPV, NPV, likelihood ratios (LR), odds ratio (OR) of all diagnostic tests were assessed. Eighteen studies involving a total of 1535 patients were included. CTA demonstrated a pooled sensitivity of 0.92, specificity 0.43, PPV of 0.56 and NPV of 0.87 on a per-patient level. CT-FFR and CTP increased the specificity to 0.72 and 0.77 respectively (P=0.004 and P=0.0009)) resulting in higher point estimates for PPV 0.70 and 0.83 respectively. There was no improvement in the sensitivity. The

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CTP protocol involved more radiation (3.5 mSv CCTA VS 9.6 mSv CTP) and a higher volume of iodinated contrast (145 mL). In conclusion, CTP and CT-FFR improve the specificity of CCTA for detecting functionally significant stenosis as defined by invasive FFR on a per-patient level; both techniques could advance the ability to non-invasively detect the functional significance of coronary lesions.

Keywords

Computed coronary tomography angiography; coronary tomography perfusion; CT-FFR; coronary artery disease

Coronary artery disease (CAD) is responsible for 17% of all death worldwide.[1] Given that nearly 40% of patients without known CAD who undergo coronary angiography have non-obstructive disease, improved techniques for non-invasive assessment of CAD are of considerable clinical importance.[2] Coronary computed tomographic angiography (CCTA) has demonstrated high sensitivity and negative predictive value (NPV) for excluding significant CAD. However, given the known discordance between anatomic severity and functional significance of a lesion, CCTA is only modestly predictive of an abnormal invasive fractional flow reserve (FFR) which has become the clinical reference standard for defining significant lesions as the DEFER and FAME studies demonstrated that the strategy of revascularization based on FFR is associated with a low risk of adverse cardiovascular outcomes. [3-7] CT perfusion (CTP) and CT-FFR are novel CT imaging techniques which can help determine the physiological significance of a coronary lesion detected by CCTA, and could thus avoid unnecessary referrals to the catheterization laboratory for non-significant stenoses. To date, most of the studies examining stress CTP imaging have been small and single-center. CT-FFR has been evaluated in a limited number of multi-center trials but has not been widely available clinically. [8, 9] Prior CCTA and CT-FFR metanalyses have been published [10, 11] however, a systematic comparison between CTA, CTP and CT-FFR to assess the diagnostic performance of a functional assessment versus an anatomic assessment by CT has not. We thus performed a meta-analysis of the diagnostic performance of CCTA, CTP and CT-FFR to assess for functional ischemia of coronary lesions as compared with catheter based-FFR as the gold standard.

Methods

The meta-analysis was performed using standard guidelines from the MOOSE (Meta-analysis of Observational Studies in Epidemiology) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) documents.[12, 13] We conducted a systematic search using MEDLINE (search last updated April 2015) for studies published in English using CCTA, CTP and CT-FFR as diagnostic techniques. Key words used were “computed tomography” AND “fractional flow reserve” OR “FFR” OR “Perfusion”. The search was limited to studies published in peer-reviewed journals. Abstracts from meetings were excluded due to limited information regarding data. The retrieved studies were examined for potentially overlapping data. The references of these articles were evaluated, as well as key publications, related articles and citations. Three investigators (J.A.G., M.J.L.

and MS) independently scanned all abstracts and performed data extraction. General consensus was achieved after reviewing full text articles. We included a study if: 1) it used CTA, CTP or CT-FFR for non-invasive evaluation of CAD; and 2) it compared the non-invasive results with catheter-derived FFR. Data regarding the independent performance of CTA, CTP and CT-FFR were used for the analysis.

The quality of included studies was assessed by three investigators (J.A.G., M.S. and P.S.) using the QUADAS instrument (Quality Assessment of Diagnostic Accuracy Studies). [14] It consists of a list of 14 questions with closed-ended questions (yes, no or unclear). The items included in this instrument covered patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawal and indeterminate results. Publication bias was assessed using the Peter's and Egger's methods.[15, 16]

Categorical data are presented as percentages and continuous variables as mean values. The analysis of diagnostic performance was carried out both at the per-patient and per-vessel levels. Sensitivity, specificity, PPV and NPV and their 95% confidence intervals were calculated using an exact method for binomial proportions using the F-distribution method. [17] Pooled estimates were determined by weighting the studies by the inverse of their sample size. [18] Likelihood ratios and diagnostic odds ratios were pooled using a random effects model using the DerSimonanian Laird method. Symmetric receiver operating curves (sROC) were created. Statistical analysis was performed using MetaDiSc, version 1.4 freeware package (Meta-analysis of diagnostic and screening tests, Universidad Complutense. Madrid, Spain) with statistical significance for hypothesis testing for a two-tailed test set at the 0.05 two-tailed level. We assessed heterogeneity between studies visually from Forest plots of the individual parameters, and using the Cochran-Q index and the inconsistency index (I^2). Bivariate comparison of sensitivity and specificity between the diagnostic modalities (CCTA, CTP and CT-FFR) was performed as described by Reitsmaa JB et al [19] and Van Houwelingen HC [20] using SAS/STAT software, version 9.4 of the SAS system for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Our literature search identified 1,292 relevant abstracts of full-text articles; of these, 43 unique articles were extracted for review. Twenty four studies were excluded for various reasons, including overlapping data with other articles, lack of FFR catheter-derived data and insufficient data to calculate sensitivity and specificity. Figure A shows the details of our literature search. A total of 18 studies were included in the study for analysis (Table 1). The 18 included studies had a total of 1535 patients. The mean age was 62 years, 68% of subjects were male, 68% had hypertension, 21% had diabetes, 25% were smokers, 33% had a family history of CAD, and the mean BMI was 27 kg/m^2 (Table 2). All studies used scanners with a minimum of 64 detectors, tube voltage between 100 and 120 kVp depending on the patient's BMI, and tube current between 200 and 500 mA. Protocols used a variety of techniques including single acquisition, retrospective or prospective triggering. Perfusion studies typically used a 3-5 minute infusion of adenosine at a dose of 140 mcg/kg/min for the vasodilator protocol. Protocols typically included stress and rest CCTA images using

retrospective triggering. In one study, delayed imaging for scar was performed [21], but the information from the delayed imaging was not used in our meta-analysis or for estimation of radiation dose.

The per-patient and per-vessel analysis results are included in Figure B and C and tables 3 and 4. The bivariate analysis for comparing the sensitivity and specificity across the included studies did not show a significant difference in a per-vessel analysis for either sensitivity or specificity between CCTA, CTP or CT-FFR. However, in analysis by patient, there was a significantly higher specificity of both CTP (p=0.004) and CT-FFR (p = 0.0009) as compared to CCTA. The specificity of CTP and CT-FFR was not different. There was no difference in sensitivity among the three different techniques.

To assess the impact of which invasive FFR cut-point was utilized to define a physiologically significant obstructive coronary lesion on per vessel diagnostic CCTA test performance, we abstracted data from studies using both FFR cut-point of 0.75 and 0.80. [4, 26, 27, 32, 34, 35] Per vessel CCTA test sensitivity was similar when using the 0.75 or 0.80 FFR cut-point (0.850 [0.802-0.890] vs 0.845 [0.800-0.884] respectively). Furthermore, per vessel CCTA specificity was also similar when using the 0.75 or the 0.80 FFR cut-point (0.591 [0.557-0.624] vs 0.602 [0.568-0.636] respectively).

Six studies using CTP included radiation dosages in millisieverts (mSv) for both the CTA and CTP components of the examination (Table 5). Data was available for a total of 407 patients. The effective radiation dose was calculated by multiplying the dose-length product by the same constant (k=0.014 mSv/mGy/cm) in all studies. The CCTA and CTP protocols delivered a pooled average effective radiation dose of 3.5 mSv and 6.1 mSv respectively and 9.6 mSv for the total study protocol. The amount in milliliters (mL) of iodinated contrast material is shown in table 5. The average use of contrast volume among the six studies that used a combined protocol of CCTA and CTP was 145 mL.

The selected studies showed overall high-quality scores in all the 14 items of the QUADAS questionnaire as shown in Table 6. There is no indication of publication bias when using the Egger's test for any of the diagnostic modalities (p>0.05 for all analyses). Likewise, the Peter's test did not suggest presence of publication bias (p>0.05 for all analyses).

Discussion

This study compared the pooled diagnostic performance of CTP and CT-FFR with conventional coronary CTA using FFR as the gold standard technique. The ability to rule out significant CAD or acute coronary syndrome (ACS) due to its high NPV is the reason CCTA has become a useful tool among clinicians. [3] In our analysis, CCTA demonstrated a high sensitivity and NPV (92% and 87% respectively) for ruling out functionally significant stenosis as defined by FFR on a per-patient basis, comparable to previous published data.[36] CTP and CT-FFR had similar sensitivity (94% and 90% respectively) and NPV (92% and 90% respectively) on a per-patient basis. Given the high sensitivity and NPV of CCTA in ruling out CAD in a per-patient or per-vessel analysis, the sensitivity and NPV are not improved by using CTP or CT-FFR. While the point estimates for the sensitivities of CT-

FFR and CTP on a per-vessel analysis are lower than those of CTA, they were not different using bivariate analysis. This suggests that if CCTA does not show evidence of significant obstruction, the performance of CTP or CT-FFR is unlikely to improve the ability to exclude a functionally significant stenosis. As shown in prior studies, CCTA demonstrated only moderate specificity and PPV (43% and 57% respectively on a per-patient basis). CTP and CT-FFR had higher estimates for specificity (77% and 72%) and PPV (83% and 70% respectively) on a per-patient analysis. In cases where CCTA demonstrates obstructive CAD, CTP or CT-FFR may help differentiate a true-positive from a false-positive study. The specificity of CTP and CT-FFR were higher than CTA on a per-patient basis using bivariate statistical analysis. While prior meta-analyses have evaluated the performance of CTP or CT-FFR to invasive FFR, [37, 38] our study is the first to directly compare the diagnostic performance of CTA, CTP, and CT-FFR to invasive FFR in a comparative meta-analysis using a bivariate model to account for correlations between sensitivity and specificity.

A number of points regarding limitations of this analysis are worth mentioning. In the majority of the studies in this analysis, CTP and CT-FFR data were analyzed independently of the CTA data to determine the specific performance of the CTP or CT-FFR components of the study. In clinical practice, the practitioner would have access to the CTA data, and whether or not CTP or CT-FFR will have a large incremental benefit over CTA alone remains unclear. Notably, all published studies used in this analysis define a 50% stenosis as the cut-off for defining a positive CTA study. Utilization of a >70% stenosis as the cut-off would have likely increased the specificity and PPV of CTA reducing the gain that may be afforded by the addition of CTP or CT-FFR. In the PROMISE [39] and Scot Heart trials [40], performance of CTA resulted in an increase in referrals for coronary angiography, however the majority of these patients were found to have obstructive CAD, and in PROMISE the rate of non-obstructive coronary angiograms in patients undergoing CTA was substantially lower than that of the functional arm (27.2% versus 52.5% respectively). Whether the addition of functional data by CTP or CT-FFR can further reduce the number of false-positive coronary angiograms, or reduce referral to coronary angiography has not been prospectively evaluated to date. Further studies will be needed to explore whether the added time and cost of CT-FFR, or additional radiation and contrast of CTP will be worth the incremental gain in test performance. While it would have been useful to analyze CTP diagnostic performance with and without the incorporation of CCTA data, the majority of studies included in the analysis did not report the results from an integrated approach using both CTA and CTP or CT-FFR.

There are several limitations of the current available data. The patients in each study may have had different pre-test likelihood of significant CAD which would impact PPV and NPV measurements. We looked at the pooled prevalence of significant CAD by modalities which were 45%, 54% and 42% for CTA, CTP and CT-FFR groups respectively. These small differences in prevalence do not significantly impact the trends between the techniques with respect to PPV, and NPV even after recalculating these proportions assuming a 50% prevalence of disease for each modality.

Another potential limitation is that FFR was not performed in all vessels and the range of stenosis for which FFR was performed varied between the studies (Table 1). Most studies

did not perform FFR in lesions of <30-50%, however these lesions are unlikely to be hemodynamically significant. Similarly, lesions with a stenosis > 75-90% which were not interrogated in all cases are highly likely to be functionally significant by FFR. Thus, this is unlikely to have a major impact on this analysis. Slightly different procedural cutoffs for significant FFR were used (0.75 or 0.8), but our analysis of studies reporting data at both cut-offs again suggests that this is not likely a major confounder. Furthermore, when invasive FFR is used as the reference standard for ischemia, careful interpretation is important. Whereas perfusion techniques such as CTP are sensitive to epicardial vessel obstruction and microvascular disease, CT-FFR and invasive FFR only are able to assess epicardial lesion specific ischemia.

Another limitation of the CTP studies has been that most are single center and they utilize different criteria to define a positive CTP study. In some cases fully quantitative analysis of flow is being performed similar to that used for PET or CMR, whereas in other cases a single CTP image is being acquired during adenosine infusion providing data about blood volume, but not directly measuring flow. A number of recent multi-center studies of CTP have recently been performed but were not included in this analysis as they did not use invasive FFR as the reference standard. [41] The inclusion of these studies would have contributed additional heterogeneity to this analysis. Furthermore, CT perfusion techniques have sensitivity to beam-hardening artifacts from the left ventricular blood pool which complicates the visualization of subendocardial ischemia. This attenuation occurs when the x-ray beams passes through soft tissue and organs, resulting in hypoenhanced regions that could mimic areas of true perfusion defects and create false positive results. This issue has become less problematic since the introduction of modern scanners and the use of dual energy sources and iterative reconstruction. Nonetheless, scanning at lower kVp, which is typically done to reduce radiation dose, results in lower energy x-rays and thus greater sensitivity to beam hardening artifacts, especially in small sized patients.

An additional limitation for CTP is that both the radiation dose (9.6 mSv) and contrast dose (145 mL) appear to be about twice the dose of a typical CCTA study. Radiation exposure is of particular importance in younger patients due to the association of ionizing radiation and cancer. This is potentially a problem in those with high BMI and fast heart rates (such as during vasodilator stress), when more radiation is needed to obtain a satisfactory study. In addition, the use of more iodinated contrast exposes the patient to an increased risk of contrast induced-nephropathy, particularly in those with borderline renal function. Additionally, CTP exposes the patient to the risks of vasodilator stress agents which include hypotension, bronchoconstriction, arrhythmias and heart block and increases procedural complexity.

In the case of CT-FFR, most of the studies have been performed in a multi-center approach using the same software which results in greater uniformity in the criteria that is used to perform the data analysis. However, the technique has primarily been performed using proprietary software, and analysis cannot be performed in real-time for clinical decision making. Also, CT-FFR depends on a good quality CTA acquisition, which could potentially limit the utility of the technique. The studies included in this paper report that a significant number of patients and vessels were not included for CT-FFR analysis due to technical

difficulties and poor image quality. The NXT [29] study reports that up to 13% of vessel segments (47 out of 357) were not included due to poor image acquisition. The DeFacto [28] study reports 11% vessels (31 out of 285) and Renker et al [31] reports 15% of patients (8 out of 53), suggesting that 10-15% of CTA studies will have inadequate image quality to perform CT-FFR. Secondly as CT-FFR utilizes the CCTA images as boundary conditions for the computational fluid dynamic analysis of the coronary tree, the technique is sensitive to factors which result in artifacts of the underlying CCTA images such as motion artifact or significant coronary calcification. Currently CTP and CT-FFR yield similar diagnostic performance. However, there are limited studies directly comparing CTP and CT-FFR [35], and such studies would be necessary to determine if one of these techniques yields better clinical utility (Table 7).

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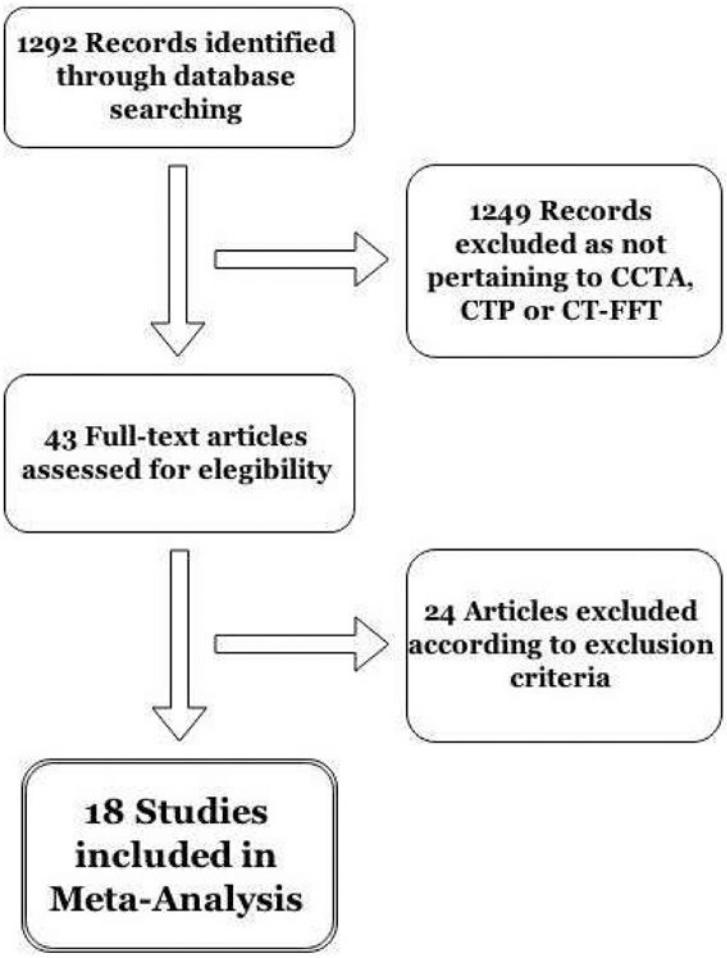

Figure A. Flow diagram of the review process

CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve.

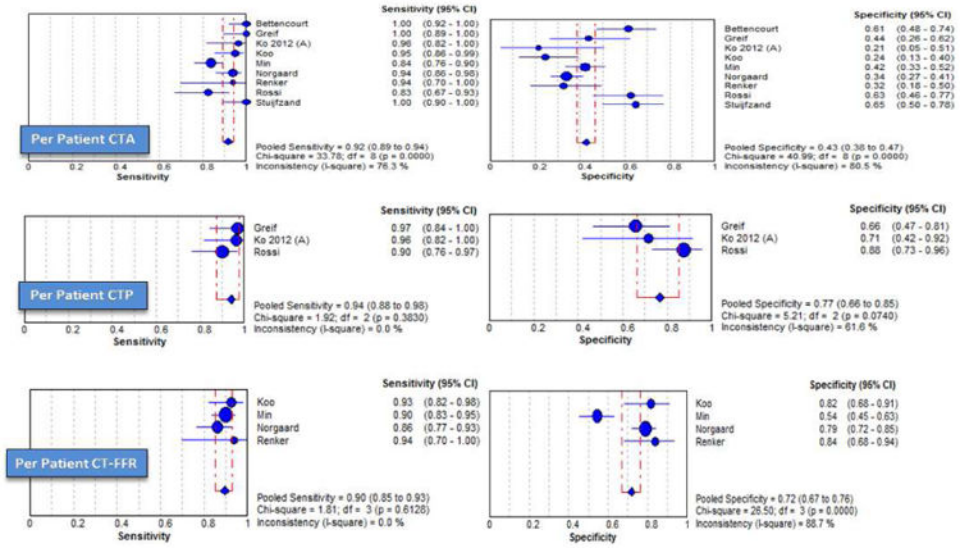

Figure B. Forrest Plots with pooled sensitivities and specificities across all the modalities (Per-Patient analysis)

CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve.

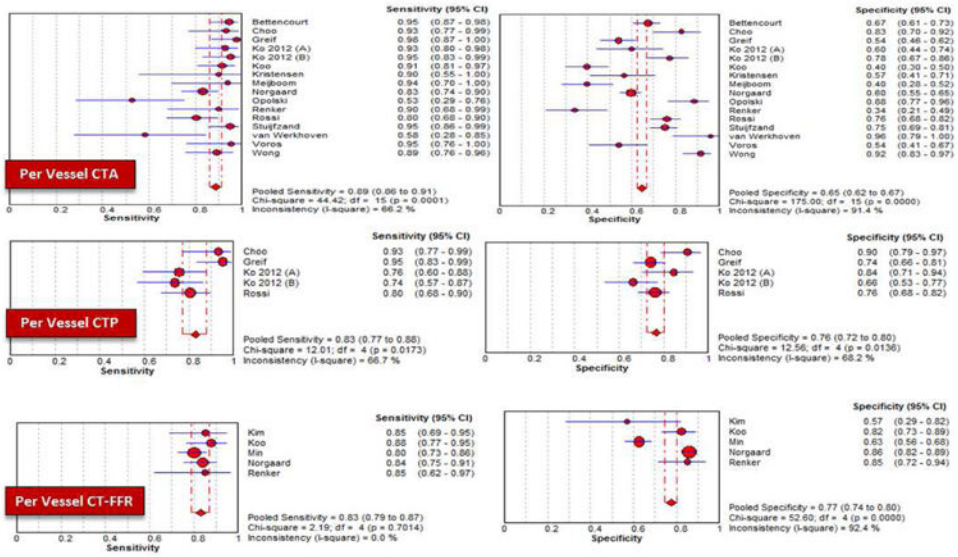

Figure C. Forrest Plots with pooled sensitivities and specificities across all the modalities (Per-Vessel analysis)

CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve.

Table 1

Characteristics of included studies

First Author	Year Published	Patients (n)	Study Design	Population	Modality	FFR Cut-off	FFR Procedural Criteria	Criteria for positive CTA
Bettencourt [21]	2013	105	Prospective	Suspected CAD	CCTA, CTP	0.80	50-90%	>50% stenosis
Choo [22]	2013	37	Prospective	Suspected CAD	CCTA, CTP	0.75	50-85%	>50% stenosis
Greif [9]	2013	65	Prospective	CP with known CAD or suspected CAD	CCTA,CTP	0.80	50-85%	>50% stenosis
Kim [23]	2013	44	Prospective	Suspected or known CAD with + CAD on CCTA	CCTA, CTFFR	0.80	>30%	>50% stenosis
Ko [24 (A)]	2012	42	Prospective	Known CAD by CA scheduled for revascularization	CCTA, CTP	0.80	> 50%	>50% stenosis
Ko [25 (B)]	2012	40	Prospective	Suspected CAD (High Risk Patients)	CCTA, CTP	0.80	>30%	>50% stenosis
Koo [26] (DISCOVER-FLOW Study)	2011	103	Prospective	Suspected or known CAD	CCTA, CTFFR	0.80	Not Specified	>50% stenosis
Kristensen [27]	2009	42	Prospective	Intermediate lesions on CCTA	CCTA	0.75	Not Specified	>50% stenosis
Meijboom [4]	2008	79	Retrospective	Suspected CAD	CCTA	0.75	Not Specified	>50% stenosis
Min [28] (DeFacto Study)	2012	252	Prospective	Suspected or known CAD	CCTA,CTFFR	0.80	30-90%	>50% stenosis
Norgaard [29] (NXT Trial)	2014	254	Prospective	Suspected CAD	CCTA, CTFFR	0.80	Not Specified	>50% stenosis
Opolski [30]	2013	61	Prospective	Intermediate lesions on CCTA	CCTA	0.80	Not Specified	>50% stenosis
Renker [31]	2014	53	Retrospective	Suspected or known CAD	CCTA, CTFFR	0.80	>30%	>50% stenosis
Rossi [8]	2014	80	Prospective	Suspected CAD	CCTA,CTP	0.75	30-90%	>50% stenosis
Stuijfzand [32]	2014	85	Prospective	Suspected CAD	CCTA	0.80	>30%	>50% stenosis
Van Werkhoven [33]	2009	33	Prospective	Suspected or known CAD	CCTA	0.75	> 50%	>50% stenosis
Voros [34] (ATLANTA Study)	2014	85	Prospective	Known CAD by CA or CCTA	CCTA	0.75	40-90%	>50% stenosis
Wong [35]	2014	75	Retrospective	Suspected or known CAD	CCTA, CTP	0.80	>30%	>50% stenosis

CP = chest pain, CAD = coronary artery disease, FFR = fractional flow reserve, CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve

Table 2

Baseline patient characteristics

First Author	Age (yrs)	Age (SD)	Male (%)	HTN (%)	Smoking Hx (%)	HLD (%)	Diabetes (%)	Prior MI (%)	Fam Hx CAD (%)	BMI (kg/m2)	BMI SD	Known CAD (%)
Bettencourt	62	8	67	71	32	79	38	0	20	27.9	4.43	0
Choo	61.7	20.5	75.7	56.7	37.8	18.9	24.3	0	n/a	n/a	n/a	n/a
Greif	70.4	9	42	67.3	25.4	47.6	17.9	0	33.4	n/a	n/a	74.3
Kim	65	9.1	80	81	n/a	63	29	10	n/a	24.4	2.6	n/a
Ko 2012 (A)	65.1	8.3	64.3	88.1	16.7	69	21.4	11.9	40.5	27.9	6.5	n/a
Ko 2012 (B)	62.1	9.9	67.5	75	15	80	12.5	0	27.5	28.2	4.9	n/a
Koo	62.7	8.5	72	65	36	65	26	17	n/a	25.8	3.5	32
Kristensen	61	10	76	n/a	n/a	n/a	n/a	19	n/a	29	4	n/a
Meijboom	60	9	81	n/a	n/a	n/a	n/a	12.7	n/a	26.6	3.9	n/a
Min	62.9	8.7	70.6	71.2	17.5	79.8	21.2	6	19.9	n/a	n/a	12.3
Norgaard	64	10	64	69	18	79	23	2	n/a	26	3	n/a
Opolski	63	9	64	79	25	95	10	15	n/a	28	4	100
Renker	61.2	12	64	54	14	54	32	n/a	n/a	28.9	6.5	16
Rossi	60	10	79	60	33	66	20	0	44	27	4	n/a
Stuijfzand	57.3	9.7	60	37	45	38	16	0	46	27.1	4.1	n/a
Van Werkhoven	57	11	n/a	42	21	36	9	n/a	36	n/a	n/a	91
Voros	61.3	7.8	62	78	20	91	21	n/a	n/a	n/a	n/a	100
Wong	64	10.8	69.3	83	16	73	19	7	33	n/a	n/a	51

Yrs = years, SD = standard deviation, HTN = hypertension, Hx = history, HLD = hyperlipidemia, MI = myocardial infarction, Fam Hx = family history, CAD = coronary artery disease, BMI = body mass index

Table 3

Per-Patient analysis

Technique	# Studies	# Patients	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	Diagnostic OR
CTA	9	1039	0.92 [0.88-0.98]	0.43 [0.38-0.47]	0.57 [0.51-0.64]	0.87 [0.78-0.94]	1.64 [1.38-1.93]	0.19 [0.10-0.35]	9.17 [4.54-18.52]
CTP	3	187	0.94 [0.88-0.98]	0.77 [0.66-0.85]	0.83 [0.75-0.92]	0.92 [0.88-0.95]	3.85 [2.16-6.84]	0.09 [0.04-0.19]	63.42 [22.41-179.5]
CT-FFR	4	662	0.90 [0.85-0.93]	0.72 [0.67-0.76]	0.70 [0.58-0.82]	0.90 [0.84-0.95]	3.70 [2.11-6.49]	0.16 [0.11-0.23]	24.34 [1.84-54.65]

CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve, PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio, OR = odds ratio

Table 4

Per-Vessel analysis

Technique	# Studies	# Patients	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR	Diagnostic OR
CTA	16	1239	0.89 [0.86-0.91]	0.65 [0.62-0.67]	0.48 [0.38-0.58]	0.94 [0.82-0.94]	2.66 [2.13-3.31]	0.17 [0.11-0.26]	19.78 [11.98-32.66]
CTP	5	264	0.83 [0.77-0.88]	0.76 [0.72-0.80]	0.61 [0.46-0.75]	0.91 [0.84-0.99]	3.68 [2.60-5.21]	0.22 [0.12-0.39]	20.10 [7.89-51.2]
CT-FFR	5	714	0.83 [0.79-0.87]	0.77 [0.74-0.80]	0.63 [0.52-0.72]	0.91 [0.79-1.03]	3.76 [2.17-6.54]	0.23 [0.16-0.35]	18.21 [7.45-44.52]

CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, CT-FFR = computed tomography fractional flow reserve, PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio, OR = odds ratio

Table 5

Effective radiation dose and contrast volume used

Author	Patients (n)	CCTA Radiation Dose (mSv)	CTP Radiation Dose (mSv)	CCTA + CTP Combined Radiation Dose (mSv)	Contrast Used (mL)
Bettencourt	105	1.5	3.3	4.8	160
Greif	65	2.9	9.7	12.6	130
Ko	42	4.8	5.3	10.1	178
Ko	40	4.7	4.5	9.2	178
Rossi	80	4.2	9.4	13.6	115-135
Wong	75	4.6	4.8	9.4	122
Weighted Avg	407	3.5	6.1	9.6	145

AVG = average. CCTA = computed coronary tomography angiography, CTP = computed tomography perfusion, mL = milliliters

Table 6

Quadas questionnaire

Article	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bettencort 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	No	YES	YES
Choo 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Greif 2013	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	YES	YES
Kim 2013	YES	NO	YES	YES	YES	YES	YES	YES	NO	YES	Unclear	NO	NO	NO
Ko EHJ 2012 (A)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	Unclear	YES
Ko JACC 2012 (B)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	NO	YES
Koo 2011	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	NO	Unclear
Kristensen 2010	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	NO	NO
Meijboom 2008	YES	YES	YES	Unclear	YES	YES	YES	YES	YES	YES	YES	Unclear	NO	NO
Min 2012	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear	NO	NO
Norgaard 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Opolski 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear
Renker 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Rossi 2014	YES	YES	YES	Unclear	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Stuijfzand 2014	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Van Werkhoven 2009	YES	NO	YES	Unclear	YES	YES	YES	YES	YES	YES	YES	YES	YES	Unclear
Voros 2014	YES	NO	YES	Unclear	YES	YES	YES	YES	YES	Unclear	Unclear	Unclear	YES	NO
Wong 2014	YES	YES	YES	Unclear	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES

Table 7
Advantages and disadvantages of CTP and CT-FFR

CTP	CT-FFR
Predominantly single center	Multicenter
Faster analysis time	Longer analysis time
Not limited by CAC	Limited by CAC
Requires additional radiation	No additional radiation
Requires additional contrast use	No additional contrast use
Requires vasodilator use	No vasodilator required
Vasodilator associated risks	No added risks
Beam Hardening artifact	No Beam Hardening artifact
Independent of CCTA quality	Depends on CCTA quality

CTP= computed tomography perfusion, CT-FFR= computed tomography fractional flow reserve.