Original Article

Diagnostic performance of coronary computed tomography angiography versus exercise electrocardiography for coronary artery disease: a systematic review and meta-analysis

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Background: Both coronary computed tomography angiography (CCTA) and exercise electrocardiography (ExECG) are non-invasive testing methods for the evaluation of coronary artery disease (CAD). However, there was controversy on the diagnostic performance of these methods due to the limited data in each single study. Therefore, we performed a meta-analysis to address these issues.

Methods: We searched PubMed and Embase databases up to May 22, 2015. Two authors identified eligible studies, extracted data and accessed quality. Pooled estimation of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), summary receiver-operating characteristic curve (SROC) and the area under curve (AUC) of CCTA and ExECG for the diagnosis of CAD were calculated using Stata, Meta-Disc and Review Manager statistical software.

Results: Seven articles were included. Pooled sensitivity of CCTA and ExECG were 0.98 [95% confidence intervals (CIs): 0.95–0.99] and 0.66 (95% CIs: 0.59–0.72); pooled specificity of CCTA and ExECG were 0.84 (95% CIs: 0.81–0.87) and 0.75 (95% CIs: 0.71–0.79); pooled DOR of CCTA and ExECG were 110.24 (95% CIs: 35.07–346.55) and 6.28 (95% CIs: 2.06–19.13); and AUC of CCTA and ExECG were 0.9950±0.0046 and 0.7727±0.0638, respectively. There is no heterogeneity caused by threshold effect in CCTA or ExECG analysis. The Deeks' test showed no potential publication bias (P=0.17).

Conclusions: CCTA has better diagnostic performance than ExECG in the evaluation of CAD, which can provide a better solution for the clinical problem of the diagnosis for CAD.

Keywords: Coronary computed tomography angiography (CCTA); exercise electrocardiography (ExECG); diagnostic performance; coronary artery disease (CAD); meta-analysis

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Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in both developed and developing countries (1). Coronary atherosclerosis involves a prolonged asymptomatic developmental phase, with its clinical manifestations often resulting in angina pectoris, acute myocardial infarction or cardiac death. In addition to invasive coronary angiography (ICA), which is the reference

standard for assessing anatomical stenosis severity, a variety of non-invasive testing methods have been advocated recently to provide an anatomic and/or functional evaluation of coronary artery. Available methods include exercise/stress electrocardiography (ExECG), single proton emission computed tomography (SPECT), myocardial perfusion imaging (MPI), coronary computed tomography angiography (CCTA) and coronary computed tomography with fractional flow reserve (FFRCT). Despite these facts, assessment of the presence of CAD remains challenging.

Among these diagnostic methods, ExECG is a well-established and inexpensive procedure to evaluate intermediate risk patients with angina pectoris (2). However, ExECG has relatively limited diagnostic performance in patients with silent CAD (3). As a new non-invasive alternative test, CCTA has high diagnostic performance to rule out CAD (4,5). Moreover, CCTA can be used in patients with equivocal stress test or unable to exercise stress test (6). But this method also suffers a number of limitations, such as a progressive loss of sensitivity and specificity as the pretest probability of disease decreases (7).

To date, several studies have compared the effectiveness of CCTA with that of ExECG for the diagnosis of CAD (8-14). But there was controversy about the specificity of two arms (12,13). Additionally, a major limitation of these investigations was their reliance, by necessity, on observational studies due to the limited data in each single study. Therefore, we performed a meta-analysis to compare the diagnostic performance of CCTA and ExECG for CAD based on a larger data, which indicates a more specific comparison about the value of anatomic and functional evaluation in clinical decisions.

Methods

Literature search

To identify relevant articles eligible for the meta-analysis, we searched PubMed and Embase databases up to May 22, 2015 using the following search terms: coronary computed tomography angiography, CCTA, stress ECG, exercise ECG, ExECG, non-invasive coronary angiography CT or exercise testing. To reduce the impact of individual differences in the maximum degree, we only selected the articles compared CCTA with ExECG and limited to articles published in English. We additionally searched the references of all articles retrieved. All relevant articles identified through the search were scanned on the basis of title and abstract. The articles which clearly didn't meet the inclusion criteria were rejected in the initial screening. The potentially associated articles were read in their entirety to assess their appropriateness for inclusion in the analysis.

Inclusion and exclusion criteria

All studies had to meet the following inclusion criteria: (I) studies that determined the comparison of CCTA and ExECG; (II) patients with the symptoms of stable angina, atypical chest pain or silent ischaemia; (III) sensitivity and specificity results in the diagnosis of CAD were reported; (IV) significant coronary stenosis was defined as at least ≥50% luminal obstruction on ICA; (V) prospective or retrospective studies. The exclusion criteria were study type being a review, case report, commentary or outcome without raw data.

Data extraction

Two authors extracted the data from each article independently to increase objectivity using a standardized data extraction form including study characteristics (study design, total patient number, mean age ± SD, male/female ratio, pretest probability, CT-imaging technique, lumen diameter reduction, treatment) and true positive (TP), false positive (FP), true negative (TN) and false negative (FN) results. During data extraction, we performed the quality assessment of included studies using an updated quality assessment tool "Quality Assessment of Diagnostic Accuracy Studies-2" (QUADAS-2) guidelines. The QUADAS-2 tool consists of four key domains that discuss patient selection, index test, reference standard and flow of patients. We selected seven items to assess risk of bias and applicability which was shown in *Table S1*. The answer to each item was "yes", "no" or "unclear" ("yes" indicates low risk of bias, "no" indicates high risk of bias, "unclear" indicates unclear risk of bias). If a study was judged as "low" on all domains relating to bias or applicability, then it was appropriate to have an overall judgment of "low risk of bias" or "low concern regarding applicability" for that study. If a study was judged "high" or "unclear" in one or more domains, then it might be judged as "at risk of bias" or "concerns regarding applicability" (15).

Data analysis

We first did the spearman correlation analysis and the ROC

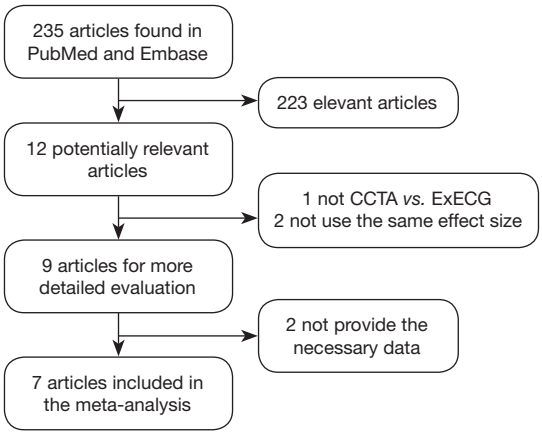

Figure 1 Process of studies inclusion/exclusion in the meta-analysis.

plane plot to confirm whether there was heterogeneity. If ROC plane appeared "shoulder-arm shape" or spearman correlation analysis showed P<0.05, there was heterogeneity caused by threshold effect in the statistics. In addition, the likelihood ratio (I^2) index and Cochran Q test were used to quantify heterogeneity of the included studies (I^2 >25% or P_Q<0.05 indicated heterogeneity among studies). If there was heterogeneity among studies, the random-effect model was used for the meta-analysis; otherwise, the fixed-effect model was chosen.

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and 95% confidence interval (CI), summary receiver-operating characteristic curve (SROC), area under curve (AUC) were calculated in this meta-analysis. If the sensitivity and specificity were more close to 100%, the results would have more diagnostic value. Furthermore, positive predictive value (PPV) and negative predictive value (NPV) were calculated, which could provide additional evidence. These effort sizes were used to compare the diagnostic accuracy of CCTA and ExECG for CAD.

In addition to main (overall) analysis, which evaluated all available data, subgroup analyses were also performed by risk of bias of included studies and characteristic of disease (stable or unstable angina). We also performed the meta-regression for age, gender and diabetes mellitus. The potential presence of publication bias was evaluated using Deeks' funnel plots (16).

Statistical analysis was performed with Stata statistical software (Version 12.0, Stata Corp LP, College Station, TX, USA), Meta-Disc software (Version 1.4, Madrid, Spain) and Review Manager (RevMan) (Version 5.0, Copenhagen, Nordic Cochrane Centre, The Cochrane Collaboration, 2010). When the P value was less than 0.05, the difference was considered statistically significant.

Results

Literature evaluation and study characteristics

The article search results were shown in *Figure 1*. The number of search records was 235. After initial evaluation, 226 search records were removed and the remaining nine articles were further evaluated by reading the full text. Two studies did not provide the raw data. Thus, only seven articles were appropriate for the meta-analysis (All articles could be found in PubMed or Embase) (8-14). One study was retrospective (10) and six studies were prospective (8,9,11-14). *Table 1* showed the general characteristics of the seven studies. In total, 1,242 patients undergoing CCTA and 1,122 patients undergoing ExECG were included. Among them, data from 804 patients undergoing CCTA and 672 patients undergoing ExECG were eligible for the analysis after excluding the equivocal results, which could affect the system evaluation. The pretest probability was varied from low to high and we evaluated the risk factors of all studies. But the significant stenosis standard of all studies was different (50% or 70%), indicating that there was partially potential verification bias. All patients received a sublingual dose of nitroglycerin and patients in six studies were administered with beta blockers (atenolol, metoprolol) before the CCTA scan. All studies processed the related data of age, gender and diabetes mellitus.

Five articles were evaluated as low risk of bias, and two articles were deemed unclear risk of bias. *Table S1* showed the quality assessment of all included studies based on the QUADAS-2. Absolute incidences of clinical outcomes for each of the studies were reported in *Table S2*.

Heterogeneity

The spearman correlation coefficients for CCTA and ExECG were −0.60 (P=0.285) and −0.50 (P=0.391), respectively, which indicated there was no heterogeneity caused by threshold effect in each arm. The results were confirmed by the performance of ROC plane plots, in which no pattern of "shoulder-arm" was observed.

The heterogeneity caused by other factors was assessed by I^2 index to choose the appropriate calculation model.

Table 1 Characteristics of eligible studies included in the meta-analysis

First author (publish year)	Country	Total population	Study design	Mean age ± SD	M:F	β-blocker before CCTA scan	Pre-test probability	CT-imaging technique	Reference standard (significant stenosis)
Cademartiri F *et al.* [2009] (8)	Italy	43	Prospective	58.8±7.70	1:0.4	Metoprolol	Intermediate-high	64-slice	>50%
Hamilton-Craig *et al.* [2014] (9)	Australia	562	Prospective	52.3±10.40	1:0.7	Metoprolol	Low-intermediate	64-slice	>70%
Maffei E *et al.* [2010] (10)	Italy	236	Retrospective	62.7±10.10	1:0.5	Atenolol	Intermediate	64-slice	>50%
Mollet NR *et al.* [2007] (11)	Netherlands	62	Prospective	60.4±9.30	1:0.4	Metoprolol	Intermediate-high	16-slice	>50%
Nagori M *et al.* [2014] (12)	India	81	Prospective	52.1±0.35	1:1	Metoprolol	Low-intermediate	64-slice	>50%
Nieman K *et al.* [2009] (13)	Netherlands	471	Prospective	56.0±10.00	1:0.9	No	Low-intermediate	64-slice	>70%
Ovrehus KA *et al.* [2010] (14)	Denmark	100	Prospective	61.0±9.00	1:1	Metoprolol	Low-intermediate-high	64-slice	>50%

M, male; F, female. Total population, population analyzed in each study.

In CCTA arm, the I^2 of sensitivity, specificity, PLR, NLR and DOR were 9.9% (P=0.353), 93.8% (P=0.000), 94.2% (P=0.000), 0.0% (P=0.803), and 45.4% (P=0.089), respectively. Therefore, the random-effect model was used for calculating pooled specificity, PLR and DOR, and the fixed-effect model was used for calculating pooled sensitivity and NLR. In ExECG arm, the I^2 of sensitivity, specificity, PLR, NLR and DOR were 68.7% (P=0.004), 94.4% (P=0.000), 90.4% (P=0.000), 75.3% (P=0.001), and 80.4% (P=0.000), respectively. So, the random-effect model was used for calculating all the effect sizes.

Diagnostic accuracy of CCTA and ExECG for CAD

Figure 2 showed the results of the sensitivity and specificity of CCTA in the diagnosis of CAD using the combined data from the included studies. The pooled sensitivity and specificity of CCTA were 98% (95% CIs: 95–99%) and 84% (95% CIs: 81–87%), respectively. The overall PLR and NLR were 5.62 (95% CIs: 2.49–12.68) and 0.05 (95% CIs: 0.03–0.10), respectively. The pooled DOR of CCTA was 110.24 (95% CIs: 35.07–346.55) (*Figure 3*). The data showed that the SROC curve of CCTA was positioned near the desirable upper left corner and the Q-value was 0.972; while the AUC area was 0.100±0.005 (*Figure 4*). We counted the PPV and NPV of CCTA of each study, which was shown in *Table S2*. Six studies showed higher PPV and NPV in CCTA arm, which was consistent with effect sizes.

The pooled sensitivity and specificity of ExECG were 66% (95% CIs: 59–72%) and 75% (95% CIs: 71–79%), respectively (*Figure 2*). The overall PLR and NLR were 2.74 (95% CIs: 1.35–5.55) and 0.45 (95% CIs: 0.27–0.76), respectively. The pooled DOR was 6.28 (95% CIs: 2.06–19.13) (*Figure 3*). Compared with CCTA arm, the SROC curve for ExECG was not positioned near the desirable upper left corner, the Q-value was 0.712 and the AUC area was 0.773±0.064, indicating that the diagnostic accuracy of ExECG was lower than that of CCTA arm (*Figure 4*). We also calculated the PPV and NPV of ExECG of each study, and the results were no difference to CCTA arm's (*Table S2*).

Subgroup analysis

Two studies included patients with stable angina and five studies included patients with unstable angina. Thus we analyzed the diagnostic accuracy of CCTA and ExECG for CAD in these two subgroups. In the stable angina group, the pooled sensitivity and specificity of CCTA were 100%

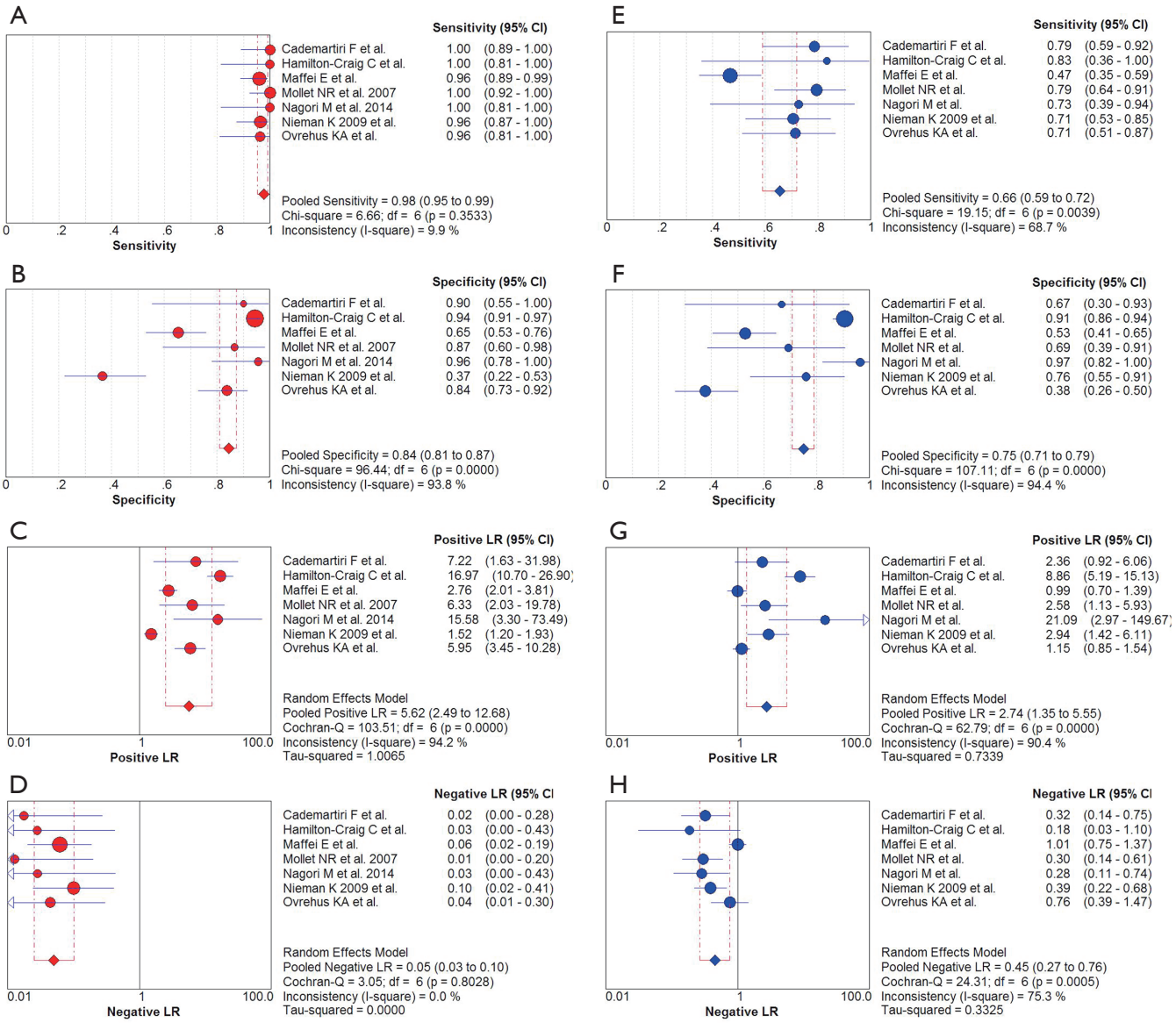

Figure 2 Pooled diagnostic indexes of CCTA and ExECG. (A–D) Pooled sensitivity, specificity, PLR and NLR of CCTA for diagnosis of CAD, respectively; (E–H) pooled sensitivity, specificity, PLR and NLR of ExECG in diagnosis of CAD respectively. CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CAD, coronary artery disease.

(95% CIs: 90–100%) and 95% (95 CIs: 91–96%); the pooled sensitivity and specificity of ExECG were 77% (95% CIs: 50–93%) and 91% (95 CIs: 87–94%), respectively. In the unstable angina group, the pooled sensitivity and specificity of CCTA were 97% (95% CIs: 95–99%) and 68% (95 CIs: 61–75%); the pooled sensitivity and specificity of ExECG were 64% (95% CIs: 58–71%) and 52% (95 CIs: 45–60%), respectively. These results indicated that CCTA was better than ExECG in both stable and unstable angina subgroups.

We also found the diagnostic performance of CCTA was better than that of ExECG regardless of the different significant stenosis standard (50% or 70%) (*Table S3*). We did not find the sources of heterogeneity by getting rid of the two studies which deemed unclear risk of bias.

Additionally, we performed the subgroup analysis of low risk of bias and unclear risk of bias articles, but we did not find any statistically significant results.

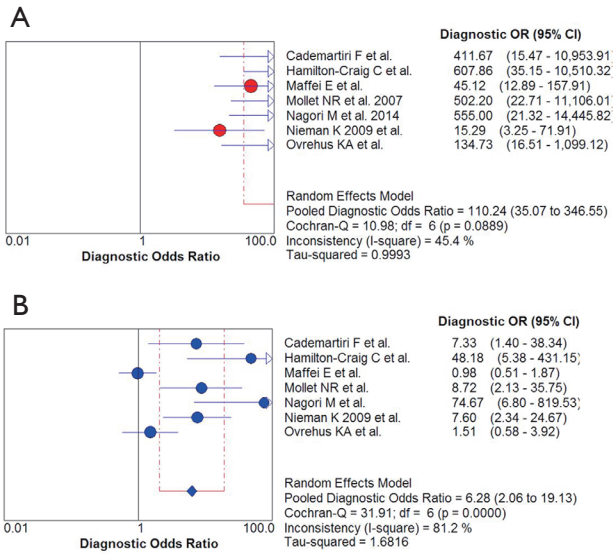

Figure 3 Forest plots of DOR of CCTA and ExECG for diagnosis of CAD. DOR, diagnostic odds ratio; CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; CAD, coronary artery disease.

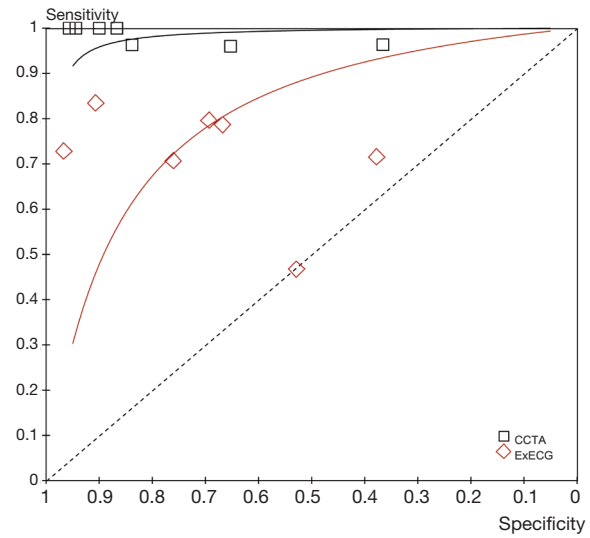

Figure 4 SROC curves of CCTA and ExECG for diagnosis of CAD. SROC, summary receiver-operating characteristic curve; CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; CAD, coronary artery disease.

Meta-regression

We performed the meta-regression for age, gender and diabetes mellitus (*Figure S1*). We found that sensitivity of CCTA was inversely related to the age and diabetes, while directly related to the male/female ratio. Similarly, ExECG arm also got the same result. The adjusted R^2 of ExECG was 0.94 and the P>F was 0.01. The adjusted R^2 of CCTA was 0.64, but the P>F was 0.12. So we further performed CCTA's meta-regression for age, gender and diabetes mellitus, respectively. The results showed that only the P value of diabetes group was less than 0.05 (*Figure S2*).

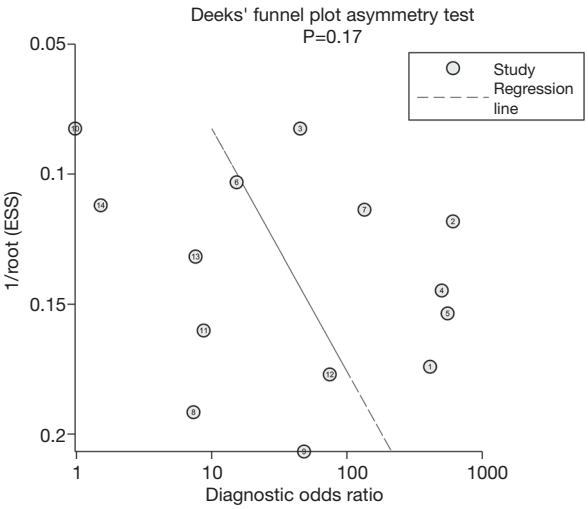

Figure 5 Deeks' funnel plot for the meta-analysis.

Publication bias

The potential presence of publication bias was explored by Deeks' funnel plot. The shape of the funnel plot for CCTA and ExECG did not reveal any evidence of obvious asymmetry. The Deeks' test did not show potential publication bias (P=0.17) (*Figure 5*).

Discussion

Exercise testing is widely used as the convenient detecting tool in the diagnosis of CAD for patients with angina pectoris. The test is non-invasive, not involving radiation exposure, and is simple to perform. Patients with stable or unstable angina, especially those with major cardiovascular risk factors, prefer to undergo stress testing (17,18). Objectively, it can reveal the functional performance of the coronary artery. CCTA can be used to rule out CAD in anatomic performance, particularly in patients with low to intermediate risk of CAD. In an outpatient population, CCTA has emerged as an accurate and rapid tool for the exclusion of CAD (19,20). Several studies compared the

diagnostic performance of ExECG versus CCTA to evaluate the clinical value of functional and anatomic methods (21).

In our study, the sensitivity and specificity of CCTA were significantly higher than those of ExECG, indicating that it was the first choice to use the CCTA to detect CAD. The PLR and NLR of CCTA were also significantly higher than ExECG arm, which was similar to the DOR estimation. AUC area was considered the critical standard in judging diagnostic performance, and there was a difference between the CCTA and ExECG. According to the results of subgroup analysis, the diagnostic accuracy of CCTA was superior to ExECG both in stable and unstable angina subgroups. According to the results of meta-regression, we considered that ExECG has higher sensitivity in low-age groups and in patients without diabetes. Moreover, the sensitivity of ExECG will be increased, along with the increase of male/female ratio. We also found CCTA had higher sensitvity in patients without diabetes.

We also confirmed that the diagnostic performance of CCTA, which was better than ExECG regardless of the different significant stenosis standard (50% or 70%). The results indicated the results of the analysis were not influenced by factors such as the selection of significant stenosis standard. But we did not find any statistically significant results between low risk of bias and unclear risk of bias articles.

To provide additional comprehensive evidence of the conclusion, we also calculated the PPV and NPV (*Table S2*). It changed with the prevalence of CAD and it was helpful to clinical physicians. But in this meta-analysis, we did not put emphasis on these effect sizes due to it can't be used as a diagnostic test evaluation index.

A comparative effectiveness report conducted a systematic review of the accuracy of different non-invasive technologies including CCTA and ExECG, for diagnosing CAD in women with symptoms suspicious of CAD. But for CCTA, the number of male patients was substantially higher than that of female patients. Thus our results increased the proportion of women. In some extent, we improved the total female ratio to make up the shortage of the meta-analysis. Another previous meta-analysis found CCTA reduced costs of care and the time to diagnosis in the emergency department, while rates of direct discharge were lower than standard care. However, the meta-analysis had some limitations, such as the absence of long-term follow-up and economic analysis of all studies. Thus, we must view the results objectively (22).

Except for CCTA and ExECG, there are several comparable diagnostic methods. A previous meta-analysis reported the diagnostic accuracy and posttest outcomes of ExECG and SPECT compared with CCTA in patients with suspected stable CAD (23). Patients with and without previously knowing CAD were considered eligible for inclusion in the meta-analysis, which were different from our analysis. Because ExECG was used more frequently than SPECT, we put the emphasis on the comparison between ExECG and CCTA using larger-size populations. Another diagnostic method is FFR_{CT}, which reduces the CCTA alone narrow degree classification of false positive rate and avoids the fractional flow reserve's invasive defect. FFRCT <0.80 was considered diagnostic of lesion specific ischaemia. A report said that low-density non-calcified plaque (LD-NCP) and FFRCT yielded diagnostic improvement over stenosis assessment with AUCs increasing from 0.71 by stenosis 50% to 0.79 and 0.90 when adding LD-NCP ≥30 mm^3 and LD-NCP ≥30 mm^3 + FFRCT ≤0.80, respectively (24). However, whether CCTA image can display the actual vascular elasticity still needs to be explored. Not only that, a complete FFRCT analysis usually takes 5 hours, the defect will limit its clinical application (25).

Nevertheless, we can't ignore the limitations of this meta-analysis: (I) we did not evaluate the cost and length of stay of the two arms due to limited available data. Among the studies included, two studies also included the analysis of cost and length of stay. One study showed the CCTA-based evaluation was less expensive than ExECG, while the other study pointed out the CCTA was more expensive than exercise test; (II) even though the total female radio was improved, but it still did not meet the best proportion (1:1), the low proportion of women in the present meta-analysis might have contributed to the higher specificity of ExECG, because exercise testing is known to have lower diagnostic performance on women than on men (7,26); (III) in ExECG arm, all of the effect sizes were highly heterogeneous, which might affect the pooled effect sizes.

Conclusions

CCTA in the diagnosis for CAD has higher sensitivity and specificity than ExECG evaluation, which may offer a better solution for the clinical problem of the diagnosis for CAD. It is worth mentioning that ExECG does not measure stenosis degree but functional CAD. The meta-analysis highlights the strength of CCTA, thus we should put more emphasis on the diagnostic performance of CCTA and do more comparison between anatomic and functional evaluation.

Acknowledgements

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Presentation for QUADAS-2 results

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Cademartiri F *et al*. (8)	☺	☺	☺	☹	☺	☺	☺
Hamilton-Craig *et al*. (9)	☺	☺	☺	☹	☺	☺	☺
Maffei E *et al*. (10)	☺	☺	☺	?	☺	☺	☺
Mollet NR *et al*. (11)	☺	☺	☺	☺	☺	☺	☺
Nagori M *et al*. (12)	☺	☺	☺	☺	☺	☺	☺
Nieman K *et al*. (13)	☺	☺	☺	?	☺	☺	☺
Ovrehus KA *et al*. (14)	☺	☺	☺	☺	☺	☺	☺

☺, low risk (yes); ☹, high risk (no); ?, unclear risk (unclear).

Table S2 Diagnostic accuracy of CCTA *vs.* ExECG in the included studies

Effort size	Cademartiri F *et al*. (8)		Hamilton-Craig *et al*. (9)		Maffei E *et al*. (10)		Mollet NR *et al*. (11)		Nagori M *et al*. (12)		Nieman K *et al*. (13)		Ovrehus KA *et al*. (14)	
	CCTA	ExECG	CCTA	ExECG	CCTA	ExECG	CCTA	ExECG	CCTA	ExECG	CCTA	ExECG	CCTA	ExECG
N	42	37	322	240	147	147	61	52	41	40	96	59	95	97
TP	32	22	18	5	72	35	46	31	18	8	53	24	26	20
FP	1	3	17	22	25	34	2	4	1	1	26	6	11	43
FN	0	6	0	1	3	40	0	8	0	3	2	10	1	8
TN	9	6	287	212	47	38	13	9	22	28	15	19	57	26
Sensitivity (%)	100	79	100	83	96	46.7	100	79.5	100	72.7	96	71	96	71
Specificity (%)	90	67	94	91	65.3	52.8	86.7	69.2	95.6	96.6	37	76	84	38
PPV (%)	97	88	51	19	74.2	50.7	95.8	88.6	94.7	88.9	67	80	70	32
NPV (%)	100	50	100	100	94	48.7	100	52.9	100	90.3	88	66	98	77
PLR	10.00	2.36	17.90	8.86	2.76	1.00	7.5	2.58	23.00	21.10	1.52	2.94	9.20	1.15
NLR	0.00	0.32	0.00	0.18	0.06	1.01	0	0.29	0	0.28	0.10	0.38	0.01	0.76

CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Table S3 Subgroup analysis of different significant stenosis standard (50% or 70%)

Effort size	CCTA		ExECG	
	50%	70%	50%	70%
Pooled sensitivity (%)	0.992	0.966	0.764	0.557
Pooled specificity (%)	0.871	0.837	0.575	0.813
Pooled PLR	6.626	4.085	2.610	2.926
Pooled NLR	0.026	0.067	0.398	0.519

CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

. reg sensitivity age gender Diabetes

CCTA

Source	SS	df	MS
Model	22.5048518	3	7.50161726
Residual	4.92371964	3	1.64123988
Total	27.4285714	6	4.57142857

Number of obs =7
F(3,3) =4.57
Prob > F =0.1219
R-squared =0.8205
Adj R-squared =0.6410
Root MSE =1.2811

Sensitivity	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	−0.4503155	0.1445056	−3.12	0.053	−0.9101969	0.0095659
gender	2.741008	0.8965136	3.06	0.055	−0.1120983	5.594115
Diabetes	−0.0304114	0.0446996	−0.68	0.545	−0.1726656	0.1118429
_cons	120.2068	7.643086	15.73	0.001	95.88313	144.5306

. reg sensitivity age gender Diabetes

ExECG

Source	SS	df	MS
Model	845.866804	3	281.955601
Residual	22.7902954	3	7.59676513
Total	868.657099	6	144.776183

Number of obs =7
F(3,3) =37.12
Prob > F =0.0072
R-squared =0.9738
Adj R-squared =0.9475
Root MSE =2.7562

Sensitivity	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	−1.656873	0.3108945	−5.33	0.013	−2.646278	−0.6674676
gender	8.936174	1.928791	4.63	0.019	2.797899	15.07445
Diabetes	−0.7736133	0.0961684	−8.04	0.004	−1.079664	−0.4675626
_cons	165.1693	16.44361	10.04	0.002	112.8384	217.5002

Figure S1 Meta-regression of CCTA and ExECG for age, gender and diabetes mellitus. CCTA, coronary computed tomography angiography; ExECG, exercise electrocardiography; SS, sum of squares of deviation from mean; df, degrees of freedom; MS, mean square; Coef., coefficient; Std. Err., standard error; Adj R-squared, adjusted R-squared.

. reg sensitivity age

Source	SS	df	MS	Number of obs =7
Model	6.98224135	1	6.98224135	F(1,5) =1.71
Residual	20.4463301	5	4.08926602	Prob > F =0.2482
Total	27.4285714	6	4.57142857	R-squared =0.2546
				Adj R-squared =0.1055
				Root MSE =2.0222

Sensitivity	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	–0.2545609	0.1948125	–1.31	0.248	–0.7553425	0.2462207
_cons	112.9521	11.24998	10.04	0.000	84.03307	141.8711

. reg sensitivity age gender

Source	SS	df	MS	Number of obs =7
Model	4.05985536	1	4.05985536	F(1,5) =0.87
Residual	23.3687161	5	4.67374321	Prob > F =0.3941
Total	27.4285714	6	4.57142857	R-squared =0.1480
				Adj R-squared =–0.0224
				Root MSE =2.1619

Sensitivity	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	1.214487	1.303076	0.93	0.394	–2.135178	4.564151
_cons	96.28355	2.29837	41.89	0.000	90.3754	102.1917

. reg sensitivity Diabetes

Source	SS	df	MS	Number of obs =7
Model	1.19010989	1	1.19010989	F(1,5) =0.23
Residual	26.2384615	5	5.24769231	Prob > F =0.6540
Total	27.4285714	6	4.57142857	R-squared =0.0434
				Adj R-squared =–0.1479
				Root MSE =2.2908

Sensitivity	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	–0.0365385	0.0767257	–0.48	0.654	–0.2337682	0.1606913
_cons	98.88077	1.520198	65.04	0.000	94.97298	102.7886

Figure S2 CCTA's meta-regression for age, gender and diabetes mellitus, respectively. CCTA, coronary computed tomography angiography; SS, sum of squares of deviation from mean; df, degrees of freedom; MS, mean square; Coef., coefficient; Std. Err., standard error; Adj R-squared, adjusted R-squared.