

Overview with Meta-analysis of Systematic Reviews of the Diagnostic and Prognostic Value of Coronary Computed Tomography Angiography in the Emergency Department

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Abstract

Background: The high prevalence of CAD, as well as your impact on health expenditure and the various treatment options to reduce morbidity and mortality related to CAD, comes to develop a diagnostic tool precis and with important findings in the Emergency Department.

Objective: To conduct an overview with meta-analysis to compile evidence from multiple systematic reviews (SR) on the diagnostic and prognostic value of coronary computed tomography angiography (CCTA) to assess acute chest pain in the emergency department (ED).

Methods: We included SR of primary studies that evaluated the diagnostic and prognostic value of CCTA ≥ 64 channels in the ED. The studies were conducted in patients at low and intermediate risk for coronary artery disease (CAD). Quality assessment was performed using PRISMA and approved reviews that scored $\geq 80\%$. Two authors independently extracted data using a standardized form. Spearman correlation test, Chi-square test, Cochran's Q test or Higgins and Thompson statistical I^2 were used. For meta-analysis, "mada" package statistical software R Core Team, 2015, was used. The significance level adopted was 95%.

Results: Four reviews were eligible for inclusion in this overview, resulting in 13 articles after applying the exclusion criteria, and only 10 of these were used for meta-analysis, adding up to a total of 4831 patients (mean age, 54 ± 6 years; 51% male), of whom 46% were hypertensive, 32% had dyslipidemia, 13% had diabetes and 26% had a family history of premature CAD. In the meta-analysis, 9 studies defined CCTA positive in the presence of luminal lesions $\geq 50\%$, while 1 study defined it as luminal lesions $\geq 70\%$. Sensitivity ranged from 77% to 98%, and specificity, from 73% to 100%. The univariate analysis showed homogeneity of diagnostic odds ratio (DOR) [$Q = 8.5$ (df = 9), $p = 0.48$ and $I^2 = 0\%$]. The pooled mean DOR for CCTA in primary analyses was 4.33 (95% CI: 3.47 - 5.18). The area under the curve (AUC) was 0.982 (95% CI: 0.967 - 0.999). There was no death, 29 (0.6%) infarcts, 92 (1.9%) revascularizations and 312 (6.4%) invasive coronary angiographies. The diagnosis of acute coronary syndrome occurred in 7.3% of the 1655 patients included in the meta-analysis.

Conclusions: The use of CCTA as a tool for stratification of patients at low or intermediate cardiovascular risk, who are in the ED with chest pain, has high accuracy, safety, reduces length of hospital stay and probably the costs, producing an early diagnosis and more effective decision making. (Int J Cardiovasc Sci. 2018;31(1)33-46)

Keywords: Coronary Artery Disease; Tomography, X-Ray Computed; Chest Pain; Emergency Medicine; Meta-Analysis as Topic.

Introduction

In 2010, in the United States of America, nearly 6 million patients with chest pain visited the emergency departments (ED); this is the second most frequent

reason for visits to this unit, although only a minority receives the diagnosis of acute coronary syndrome (ACS).¹ North American statistics show that in 2011 coronary artery disease (CAD) was responsible for about 1 of every 7 deaths, totaling 375,295 deaths.²

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Coronary artery disease is responsible for a substantial impact on the use of health care, with an estimated cost of US\$ 21.9 billion in 2011. Between 2013 and 2030 the costs are estimated to increase $\approx 100\%$.³ Due to the high prevalence of CAD, as well as its impact on health expenditure and the various treatment options to reduce morbidity and mortality related to CAD, accurate diagnosis is essential.

A high precision effective diagnostic test to exclude acute CAD could reduce the cost of the USA health care system by billions of dollars. The advent of coronary computed tomography angiography (CCTA), a noninvasive method to study the coronary anatomy, with tomography scanner ≥ 64 channels, reducing artifacts as well as increasing spatial and temporal resolution, has given rise to a quick test, effective to reliably exclude ACS.⁴ Although invasive coronary angiography (ICA) is the "gold standard" for CAD detection, it is not appropriate for extensive use because it is invasive, not routinely available, and has high cost and increased risk of complications. Furthermore, the immediate and future probability of cardiac events in patients without CAD or with minimal CAD is low for patients with chest pain in the ED.^{5,6}

Systematic reviews (SR) are studies with the highest level of evidence (higher in the hierarchy of evidence-based research) and rigorous methodological quality.⁷ Due to the rapid expansion of the literature and the presence of a relatively high number of SR on this topic, the purpose of this study was to conduct an overview of meta-analyses to compile evidence from multiple SR related to the diagnostic and prognostic value of CCTA in the assessment of acute chest pain in the ED.

Methods

Literature search

The search was conducted from January 2005 (the first year of published studies from 64-slice scanners) to July 2015. The strategy was developed through the Medical Subject Heading (MeSH) terms: "coronary artery disease", "computed tomography", "chest pain" and "emergency department". The electronic databases researched were MEDLINE and COCHRANE LIBRARY. This overview included SR on the diagnostic and prognostic value of CCTA in the ED. Only studies reported in English were eligible and had their references checked.

We analyzed all studies of SR, excluding duplicates, performed with CCTA < 64 channels, with at least 30 patients. In the presence of more than one study with the same database, the oldest was deleted.

Ethics approval was not required for this overview.

Quality assessment

All eligible SR were assessed using the PRISMA quality assessment tool (Preferred Reporting Items for Systematic Reviews and Meta-Analysis),⁸ and those scoring $\geq 80\%$ were approved.

Data extraction

Two authors independently extracted data using a standardized data extraction form including study characteristics (design, inclusion and exclusion criteria), characteristics of the intervention (at least 64-slice computed tomography, use and timing of cardiac enzymes relative to CCTA, follow-up duration), patients characteristics (age, sex, cardiac risk factors), outcomes [death, nonfatal myocardial infarction (MI), repeated ED chest pain evaluation, repeated hospitalization for ACS, ICA, revascularization by percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG)], hospital length of stay (LOS), and cost. Disagreements were resolved by consensus or consultation with a third individual.

Data synthesis and statistical analysis

Numerical variables were described as mean and standard deviation and categorical variables, as simple and relative frequencies. The sensitivity and specificity were described as estimates with 95% confidence interval (CI), rounded to the nearest integer. Using true positive (TP), false positive (FP), true negative (TN), and false negative (FN), we derived sensitivity, specificity, positive and negative likelihood ratios (posLR and negLR, respectively), and positive and negative predictive values (VP+ and VP-, respectively) for each study.

Spearman correlation test was used to analyze the correlation between sensitivity and the ratio of FP. Chi-square test (χ^2) was used to assess the heterogeneity of sensitivity and specificity and, in both cases, the null hypothesis was the same (or homogeneity). Potential heterogeneity among studies was assessed using the Cochran's Q test or Higgins and Thompson statistical I^2 . Cochran's Q test calculates a measure of

the overall variation among the studies, stating, as the null hypothesis, that the studies that make up the meta-analysis are homogeneous. The I^2 evaluates the estimate of the variance due to heterogeneity, rather than chance, and is based on traditional statistical variance defined as Cochran's Q .⁹ Significant heterogeneity was set to $I^2 > 50\%$. Data were used with a significance level of 95%. Data analysis was performed with R-package "mada" for meta-analysis (R Core Team, 2015) that presents some approaches for diagnostic studies, such as descriptive statistics and graphs. In the data analysis, in 2×2 tables, cells with zeros often lead to statistical artifacts, since certain reasons can 'not exist'; so the package "mada" uses the value of 0.5 as a correction of continuity "standard". This package does not calculate the aggregated value of sensitivity and specificity. It is not appropriate analytical indicator.¹⁰

In presence of publication bias, the funnel plot, method known to assess publication bias, is unlikely to be useful to detect the effect of sample size because these parameters will vary depending on the cut-off values and random error.¹¹ Meta-regression was not performed, since its purpose is to evaluate the causes of heterogeneity and the diagnostic odds ratio (DOR) was homogeneous.

Results

The literature search generated a total of 4 SR that evaluated the diagnostic and prognostic value of CCTA ≥ 64 channels in the ED,²⁵⁻²⁸ containing 91 primary studies. From these, 13 articles meeting the inclusion criteria were included in the qualitative analysis. Due to absence of quantitative dates, only 10 studies were used in the meta-analysis. The main reasons for exclusion of the primary studies were: not performed in the ED; duplicated studies; and CCTA of 4 or 16 channels. Figure 1 shows a flow chart of study exclusion.

A total of 4831 patients were included (mean age of 54 ± 6 years, 51% male), of whom 46% were hypertensive, 32% had dyslipidemia, 13% had diabetes and 26% had a family history of premature CAD. The primary studies included and their clinical characteristics are outlined in Table 1. In general, patients with atrial fibrillation, ventricular arrhythmias, enzymatic changes, renal failure, hemodynamic instability, allergy to contrast, and pregnant women were excluded from studies.

The studies were conducted in patients at low and intermediate risk for CAD (except Ueno et al.,¹⁹ 2009, that

includes high-risk patients) with normal cardiac enzymes and nonischemic initial ECG.

In the meta-analysis, 9 studies defined positive CCTA when in the presence of luminal lesions $\geq 50\%$, while 1 study defined it when luminal lesion $\geq 70\%$. A total of 1655 patients were included. Descriptive statistics for diagnostic test (CCTA) performance are described in Tables 2 and 3. The study by Rubinstein et al.¹⁶ reported the highest sensitivity ($S = 98\%$), while the study by Johnson et al.²² reported the highest specificity ($E = 100\%$). The largest study was that by Hollander et al.,¹⁸ 2009, which included 568 patients, and reported a 94% sensitivity and a 92% specificity.

All studies showed high positive likelihood ratio (the highest in the study by Johnson et al.,²² 2008), and low negative likelihood ratio (the lowest in the study by Rubinstein et al.,¹⁶ 2007).

To assess the effect of different cut-offs for "significant" luminal obstruction on analysis, we performed diagnostic threshold analyses. We found a Spearman correlation coefficient of 0.045, $p > 0.05$ (95% CI -0.602 to 0.656), which means 'very weak' correlation or no significant correlation.

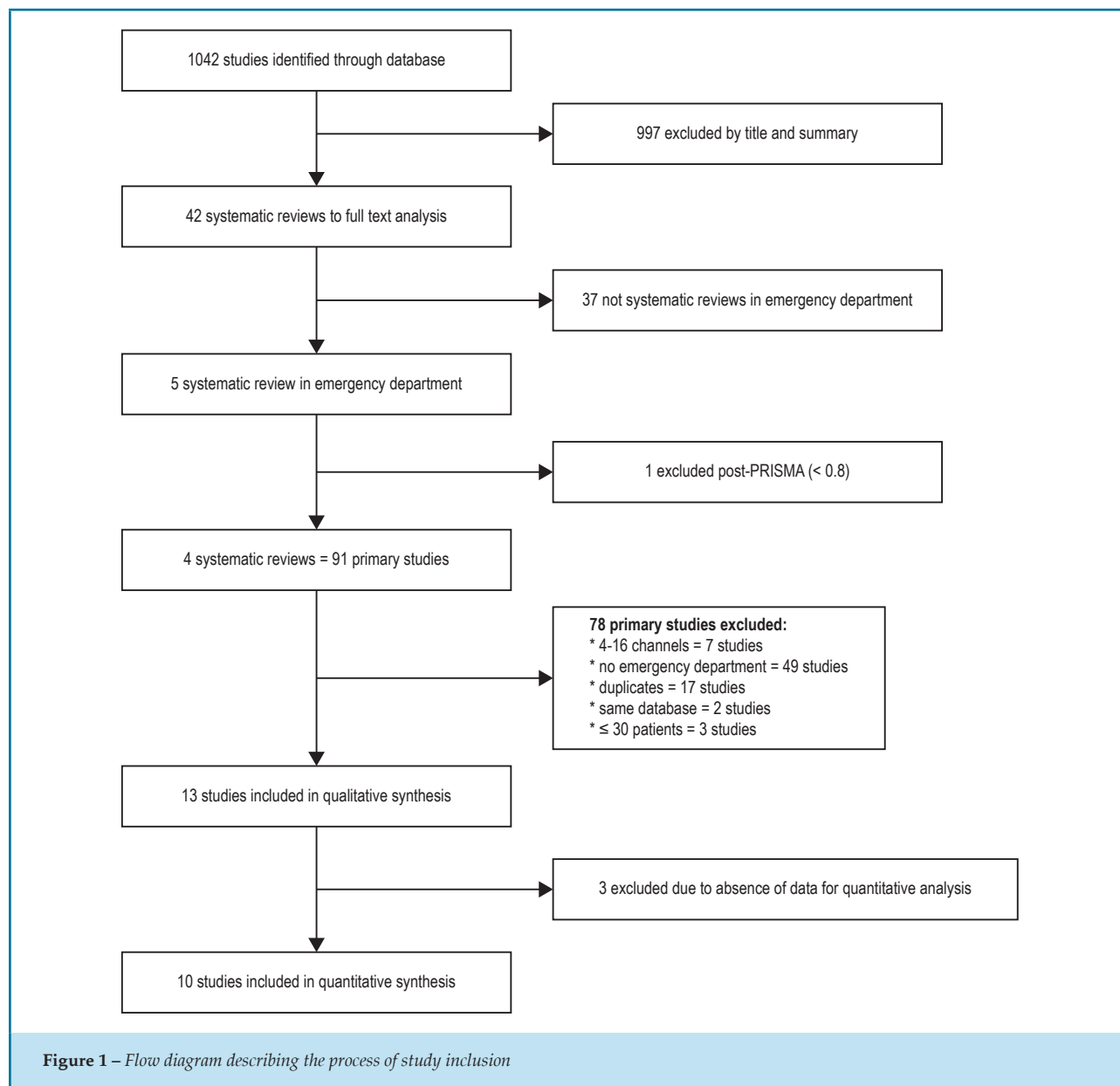
The equality test for sensitivity showed homogeneity across studies [$\chi^2 = 8.4$ (df = 9), $p = 0.5$] and heterogeneity for specificity [$\chi^2 = 55.5$ (df = 9), $p < 0.001$], confirmed with the forest plot (Figures 2 and 3).

The univariate analysis showed homogeneity of DOR [$Q = 8.5$ (df = 9), $p = 0.48$ and $I^2 = 0\%$]. Figure 4 shows estimate of the synthesis.

The χ^2 test did not reject the hypothesis of homogeneity for the model [$\chi^2 = 10.14$ (df = 1), $p = 0.34$, θ (theta) = 0.018 (CI_{95%}: 0.0014 to 0,0246)] and so we opted for the fixed effects model. The area under the curve (AUC) was 0.982 (95% CI: 0.967-0.999).

As for the events, there was great variability between studies in the outcomes assessed. A summary of the compound events in all studies, with their specific characteristics, is described in Table 4. In most studies, the events investigated were death, MI, CABG and ICA. Others evaluated the diagnosis of ACS, and, in three studies, the technique of "triple rule-out" was used (in addition to investigating CAD, pulmonary embolism and aortic dissection).

Figure 7 shows the main events: 29 (0.6%) MI, 92 (1.9%) CRM, and 312 (6.4%) ICA. There was no death. The diagnosis of ACS occurred in 7.3% of the 1655 patients included in the meta-analysis.



Although analyzed heterogeneously, the four randomized clinical trials (RCTs) also evaluated the hospital LOS and costs. Compared to usual care, the use of CCTA reduced the hospital LOS in all studies, and the costs, in three studies.

Discussion

This study had the purpose to evaluate the diagnostic and prognostic value of CCTA in the evaluation of acute chest pain in the ED. We included 4 SR, totaling 13 studies. After primary analysis of the exclusion criteria, we used 10 studies for quantitative analysis (meta-analysis).

We found that CCTA has high sensitivity and specificity for CAD detection in patients with chest pain in the ED in all studies, and showed high positive likelihood ratio and low negative likelihood ratio. The distribution of sensitivity was homogeneous, while that of specificity was heterogeneous. We found weak correlation on the effect of the different cut-offs for the diagnosis of significant luminal obstruction. The DOR was homogeneous and significant. There was variability on the number and type of events between the studies. The clinical trials reported decreased LOS and costs.

Table 1 – Primary studies included and their clinical characteristics

Authors	Type of study	Year	Type of CCTA (Channels)	Centers	Patients (N)	Age (Mean ± SD)	Men (%)	BMI, (kg/m ² ± DP)	HTN N (%)	HL N (%)	DM N (%)	FH of premature CAD N (%)	Smoker N (%)
Goldstein et al. ¹²	RCT	2007	64	Single center	197	50 ± 12	50	29 ± 5	75/38	70(36)	20(10)	82(42)	35(18)
CT-STAT ¹³	RCT	2011	64 a 320	Multicenter	699	50 ± 10	46	28 ± 5	259/37	234(33)	48(7)	212(30)	157(22)
ACRIN-PA ¹⁴	RCT	2012	≥ 64	Multicenter	1370	49 ± 9	47	-	695/51	367(27)	194(14)	394(29)	447(33)
ROMICAT II ¹⁵	RCT	2011	64	Single center	1000	54 ± 8	53	29 ± 5	541/54	454(45)	173(17)	271(27)	492(49)
Rubinstein et al. ¹⁶	Cohort	2007	64	Single center	58	56 ± 10	64	-	33/57	32(55)	12(21)	9(16)	22(38)
Gallagher et al. ¹⁷	Cohort	2007	64	Single center	85	49 ± 11	53	-	31(36,5)	23(27)	8(9)	50(59)	22(25,9)
Hollander et al. ¹⁸	Cohort	2009	64	Single center	568	47 ± 9	44	-	251(44)	108(19)	77(14)	104(18)	200(35)
Ueno et al. ¹⁹	Cohort	2009	64	Single center	36	66 ± 12	53	-	17(47)	19(53)	9(25)	8(22)	13(36)
Hoffmann et al. ²⁰	Cohort	2009	64	Multicenter	368	53 ± 12	61	29 ± 6	145(39)	135(37)	40(11)	-	180(49)
Johnson et al. ²¹	Cohort	2007	64	Single center	55	67 ± 10	64	-	-	-	-	-	-
Johnson et al. ²²	Cohort	2008	64	Single center	109	63 ± 14	72	-	-	-	-	-	-
Takakuwa et al. ²³	Cohort	2008	64	Single center	197	49 ± 11	72	-	92(46,7)	53(26,9)	29(15)	62(31)	62(31,5)
Hansen et al. ²⁴	Cohort	2010	64	Single center	89	56 ± 9	63	-	35(39)	37(42)	7(8)	29(33)	39(44)

CCTA: coronary computed tomography angiography; SD: standard deviation; BMI, body mass index; HTN: hypertension; HL: hyperlipidemia; DM: diabetes mellitus; FH: family history; CAD: coronary artery disease; RCT: randomized clinical trial

Table 2 – Test performance characteristics of CCTA in the studies included

Year	Authors	N	TP	FN	FP	TN	S	IC _{95%}	E	IC _{95%}
2007	Goldstein et al. ¹²	99	8	0	24	67	0.94	0.63 - 0.99	0.73	0.64 - 0.81
2007	Rubinstein et al. ¹⁶	58	20	0	3	35	0.98	0.81 - 1.00	0.91	0.78 - 0.97
2007	Gallagher et al. ¹⁷	85	6	1	3	72	0.81	0.47 - 0.96	0.95	0.88 - 0.98
2009	Hollander et al. ¹⁸	568	7	0	47	508	0.94	0.60 - 0.99	0.92	0.89 - 0.94
2009	Ueno et al. ¹⁹	36	11	1	4	20	0.89	0.62 - 0.97	0.82	0.63 - 0.92
2009	Hoffmann et al. ²⁰	368	24	7	44	293	0.77	0.60 - 0.88	0.87	0.83 - 0.90
2007	Johnson et al. ²¹	55	16	1	3	35	0.92	0.71 - 0.98	0.91	0.78 - 0.97
2008	Johnson et al. ²²	109	13	0	0	96	0.96	0.73 - 1.00	1.00	0.95 - 1.00
2008	Takakuwa et al. ²³	197	6	1	16	174	0.81	0.47 - 0.96	0.91	0.87 - 0.95
2010	Hansen et al. ²⁴	89	3	0	1	85	0.88	0.40 - 0.99	0.98	0.93 - 1.00

CCTA: coronary computed tomography angiography; TP: true positive; FN: false negative; FP: false positive; TN: true negative; S: sensibility; CI: confidence interval; E: specificity.

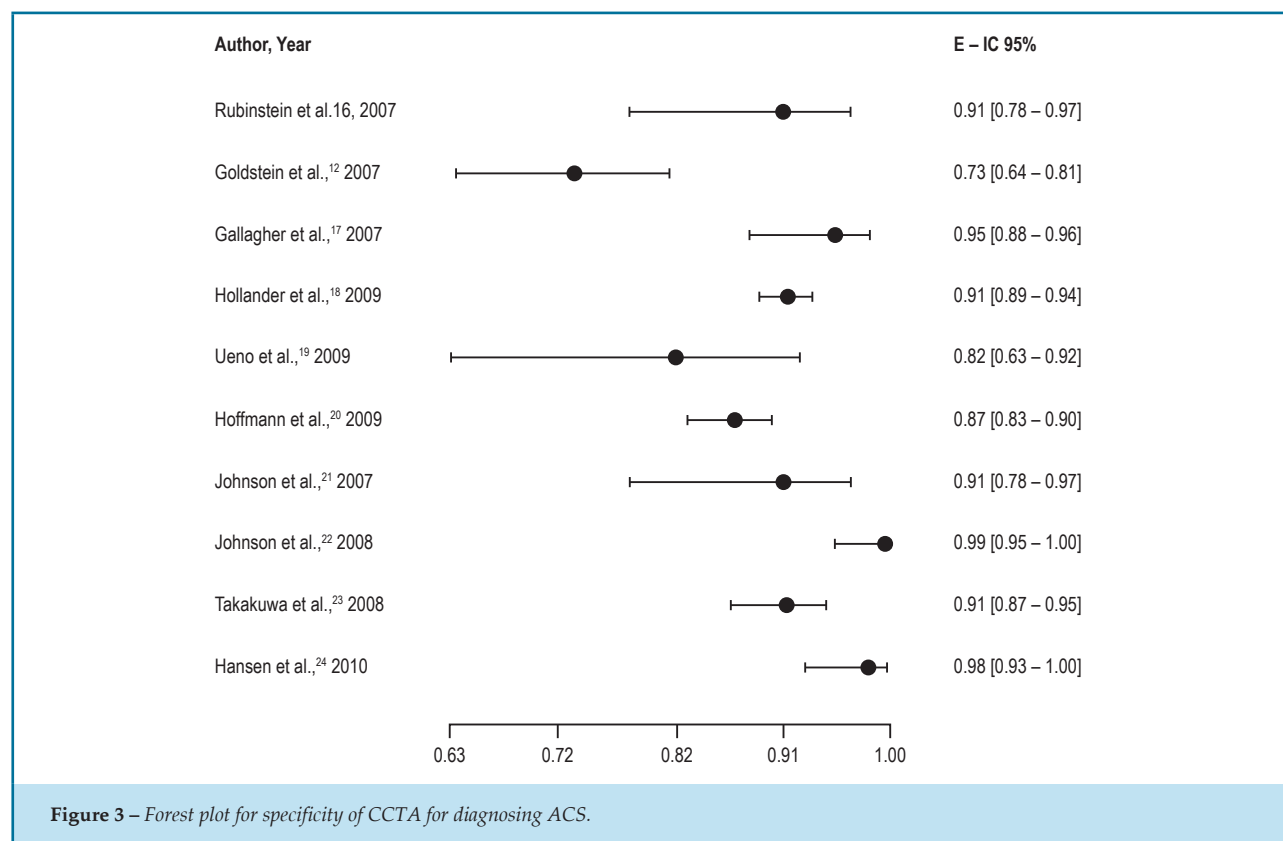
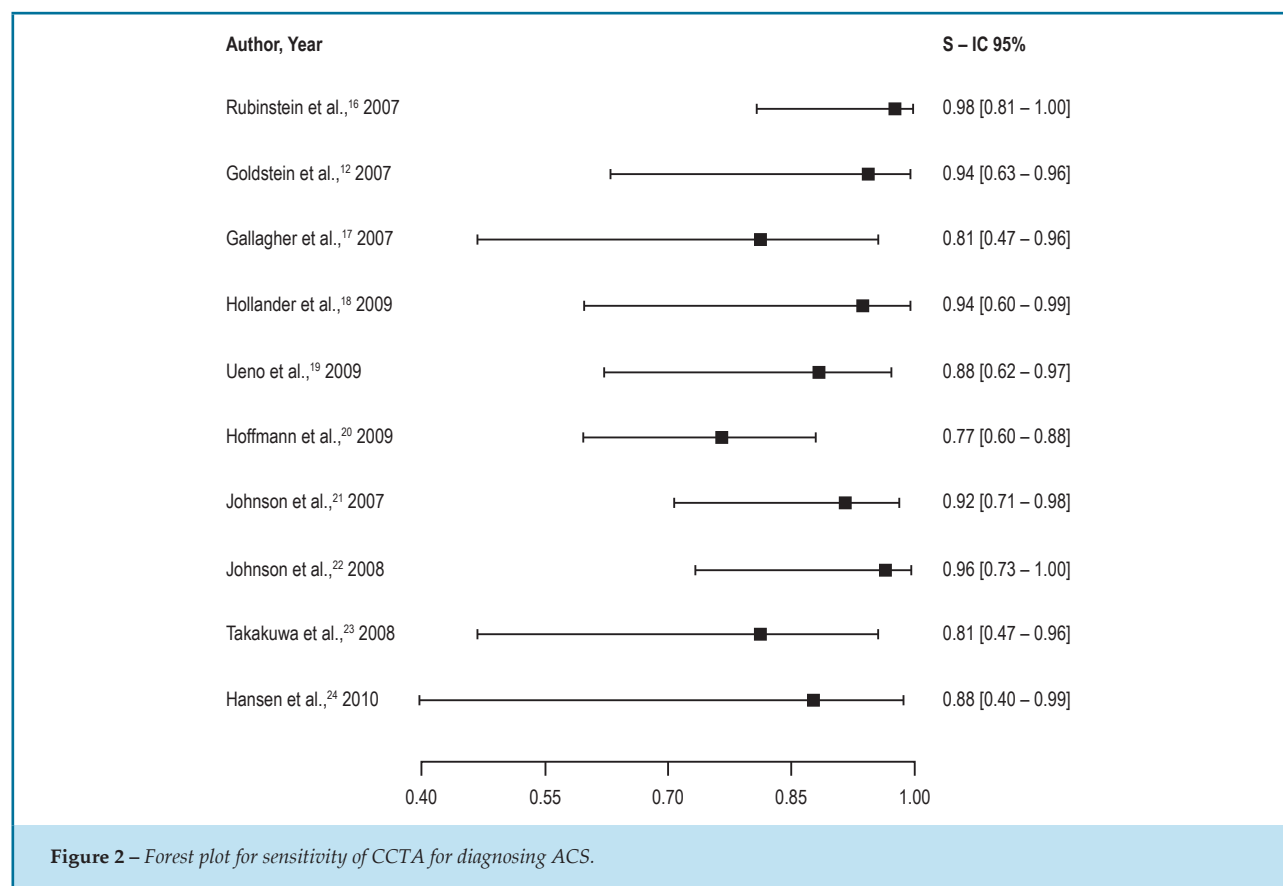
Table 3 – Descriptive analysis of the likelihood ratio

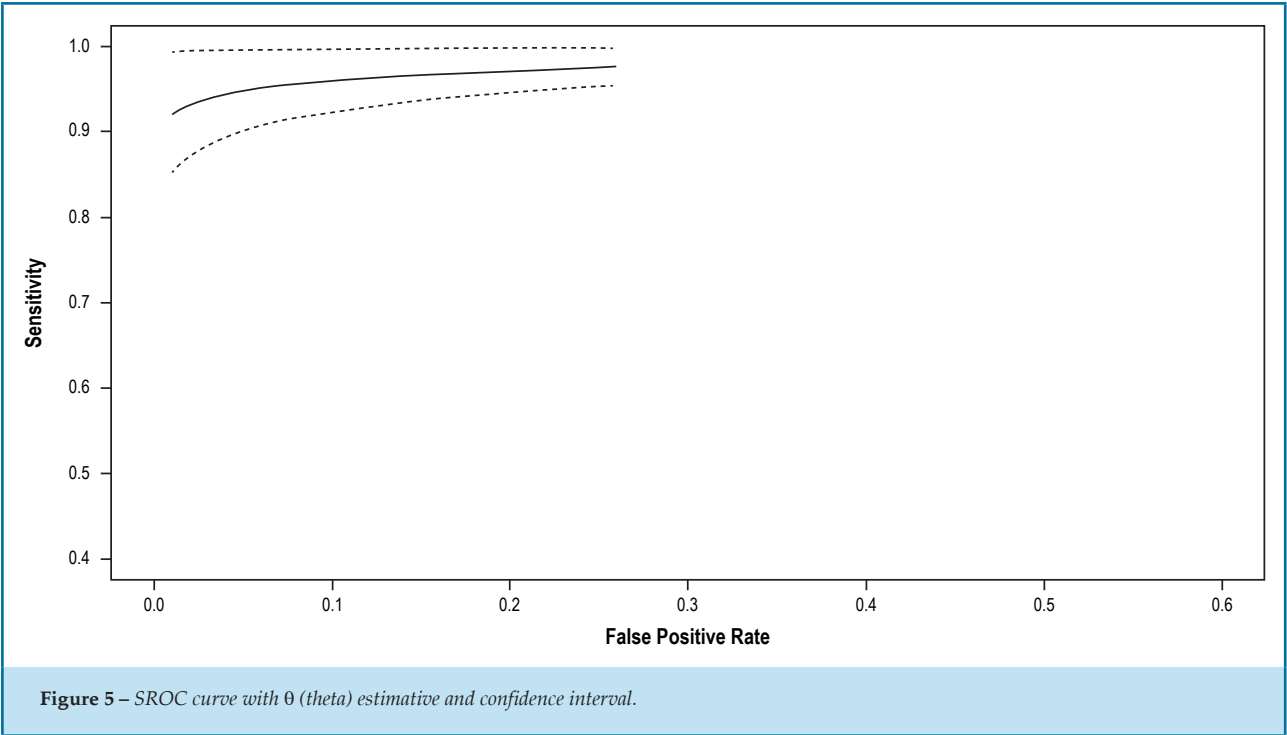
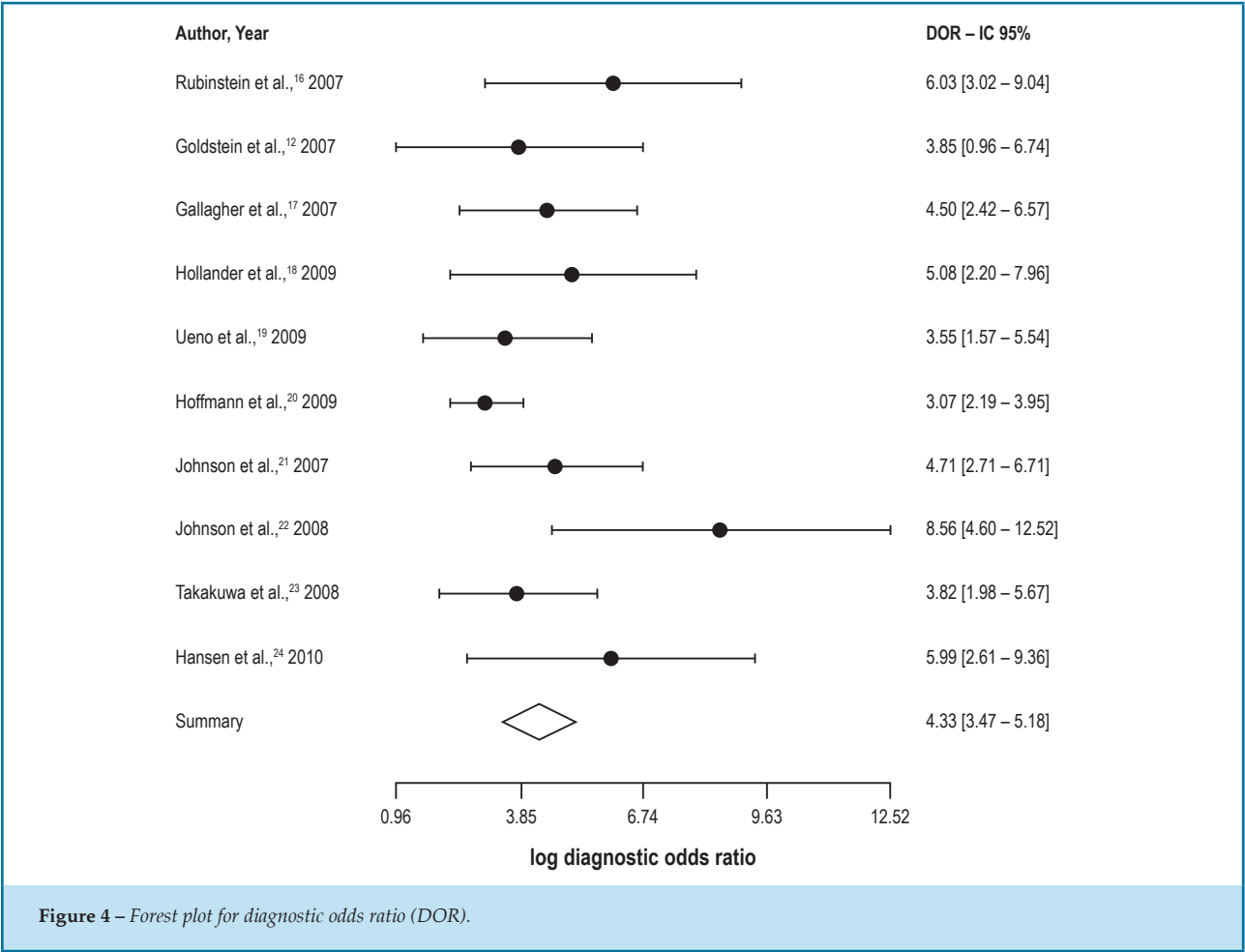
Year	Authors	posLR	Minimum	Maximum	negLR	Minimum	Maximum
2007	Goldstein et al. ¹²	3.546	2.439	5.157	0.076	0.005	1.123
2007	Rubinstein et al. ¹⁶	10.878	3.995	29.620	0.026	0.002	0.405
2007	Gallagher et al. ¹⁷	17.643	6.015	51.746	0.197	0.046	0.832
2009	Hollander et al. ¹⁸	10.974	7.925	15.196	0.068	0.005	1.001
2009	Ueno et al. ¹⁹	4.915	2.081	11.607	0.141	0.031	0.641
2009	Hoffmann et al. ²⁰	5.815	4.163	8.123	0.270	0.144	0.506
2007	Johnson et al. ²¹	10.214	3.723	28.022	0.092	0.020	0.425
2008	Johnson et al. ²²	187.071	11.763	2974.950	0.036	0.002	0.546
2008	Takakuwa et al. ²³	9.405	5.325	16.611	0.205	0.048	0.869
2010	Hansen et al. ²⁴	50.750	9.952	258.792	0.127	0.010	1.700

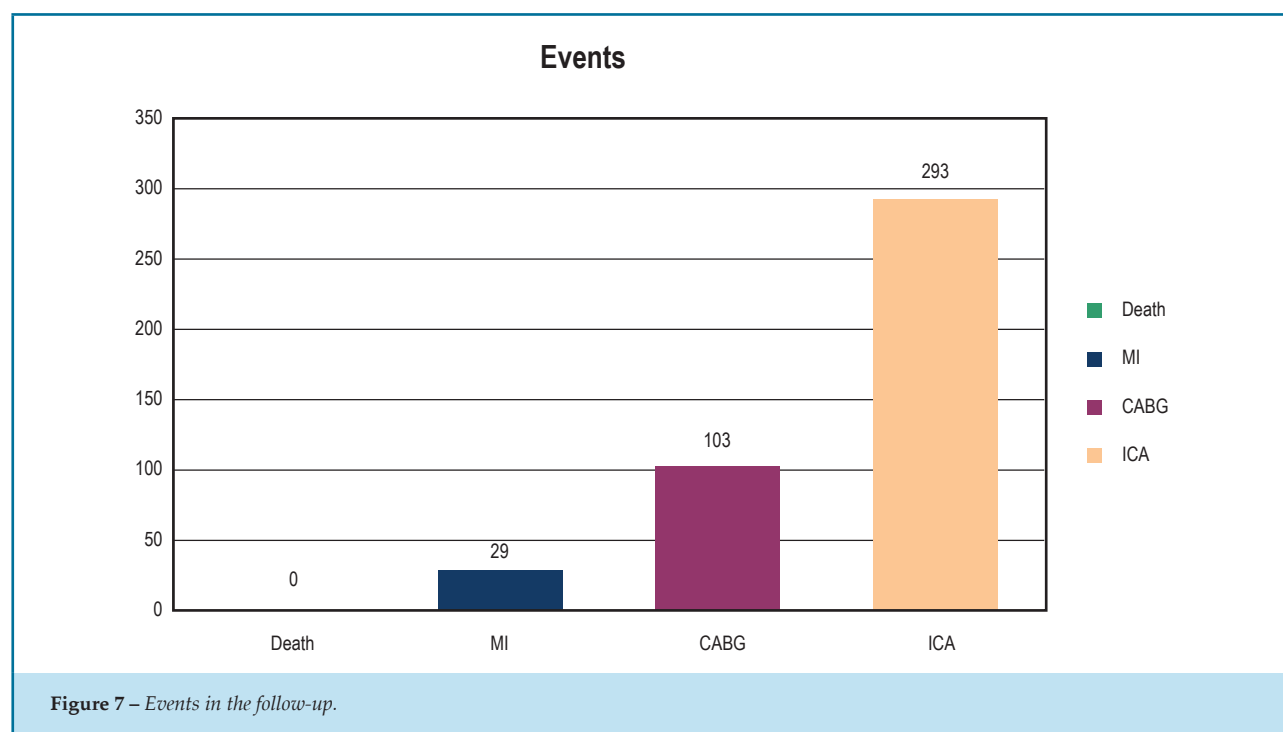
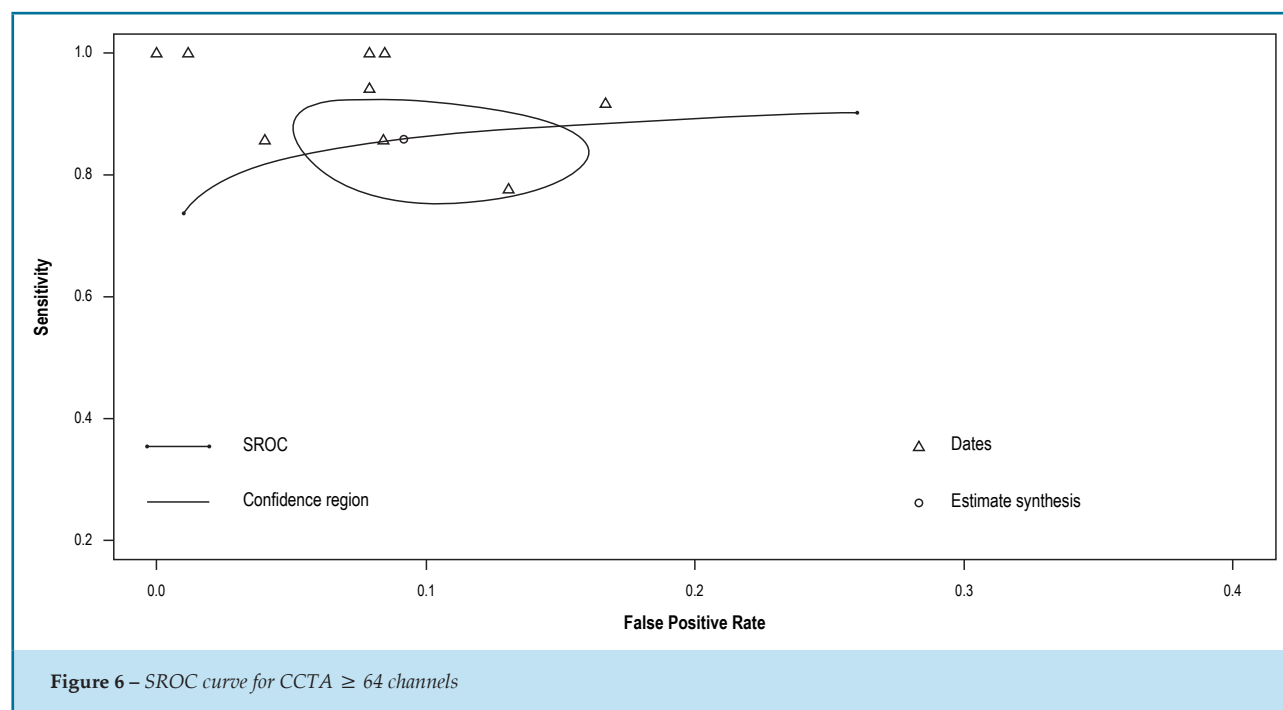
posLR: positive likelihood ratios; negLR: negative likelihood ratios.

The quality of cardiac image by CCTA is directly related to the evolution of tomography. Current technical developments of CT scanners and the software are intended to improve the spatial and temporal resolution of cardiac CT images while reducing the radiation dose received from a typical examination. They include wider detector arrays that allow a higher number of simultaneously acquired image slices, faster x-ray tube rotation, and use of alternative image

reconstruction techniques.²⁹ Its use in patients with early biomarkers and negative ECG for myocardial ischemia is already included in the algorithm of chest pain evaluation in several emergency centers, a strategy that is supported by the current Appropriate Use Criteria for Cardiac Computed Tomography³⁰ and Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction.³¹







The CCTA has the unique ability to noninvasively depict the coronary anatomy, not only allowing visualization of the arterial lumen to detect severe stenosis or occlusion responsible for myocardial ischemia, but also allows the assessment of the coronary

artery wall by demonstrating the presence or absence of CAD and characteristics of the plaque (can identify predictors of plaque rupture).³² It may aid in the differential diagnosis of diseases, such as pulmonary embolism, aortic aneurysm, among others.³³

Table 4 – Clinical outcomes of the individual studies

Author	Year	Type of Study	Number of patients	Age (Mean $\pm$ SD)	Male %	CAD Risk	Follow-up (months)	Outcomes
Goldstein et al. ¹²	2007	RCT	99	50 $\pm$ 12	50	Very low	6	CABG and ICA
CT-STAT ¹³	2011	RCT	361	50 $\pm$ 10	46	Low	6	CABG and ICA
ACRIN-PA ¹⁴	2012	RCT	908	49 $\pm$ 09	47	Low and intermediary	1	MI, CABG and ICA
ROMICAT II ¹⁵	2011	RCT	501	56 $\pm$ 10	53	Low and intermediary	1	MI, ICA and PCI
Rubinstein et al. ¹⁶	2007	Prospective cohort	58	54 $\pm$ 8.0	64	Intermediary	15	MI, Death, CABG
Gallagher et al. ¹⁷	2007	Prospective cohort	85	49 $\pm$ 11	53	Low	1	Diagnosis ACS
Hollander et al. ¹⁸	2009	Observational cohort	568	47 $\pm$ 8.9	44	Low	1	Absence of death and MI
Ueno et al. ¹⁹	2009	Prospective cohort	36	66 $\pm$ 12	53	High	1	-
Hoffmann et al. ²⁰	2009	Observational cohort	368	52.7 $\pm$ 12	61	Low and intermediary	6	Chest pain, UAP, readmission
Johnson et al. ²¹	2007	Prospective cohort	55	67 $\pm$ 10	64	Low and intermediary	$\geq$ 5	Focus on further tests and contrast-induced nephropathy
Johnson et al. ²²	2008	Prospective cohort	109	63 $\pm$ 14	71	Low and intermediary	6	Arrhythmia; Pleural effusion (pleurisy); Readmission
Takakuwa et al. ²³	2008	Prospective cohort	197	49 $\pm$ 11	72	Low and intermediary	1	There were no events (not specified which events)
Hansen et al. ²⁴	2010	Prospective cohort	89	56.3 $\pm$ 8.6	63	Low and intermediary	12	There were no events (Death and MI)

SD: standard deviation; CAD: coronary artery disease; CABG: coronary artery bypass graft; ICA: invasive coronary angiography percutaneous; MI: myocardial infarction; PCI: percutaneous coronary intervention; UAP: unstable angina pectoris

The CCTA allows the identification of non-obstructive CAD in patients with acute chest pain improving substantially the therapeutic management in this group of patients by allowing a previous clinical decision, more effectively targeting the treatment.³⁴

In face of the epidemiology of chest pain in the ED, the evaluation of these patients is a major challenge, both from the point of view of diagnosis and the optimization of time (to start treatment or discharge) and in the correct direction of resources. The use of serum biomarkers does not allow a rapid exclusion of myocardial ischemia, resulting in early discharge from the ED. Thus, there are limited tools available for fast triage of patients with chest pain. It is with this idea that the four clinical trials randomized¹²⁻¹⁵ investigated the reduction in hospital LOS and concluded that the use of emergency CCTA in patients at low to intermediate risk of CAD reduces the hospital LOS.

Shreibati et al.³⁵ found in an observational cohort (2005-2008) an increase of costs and incidence of cardiac catheterization using CCTA. Three of the four RCT^{12,13,15} showed a reduction in hospital costs. However, to assess the impact of new technologies on health costs requires the use of specific methodology that allows the evaluation of cost-effectiveness.

There was increased ICA in the group that underwent CCTA as opposed to standard monitoring, but the design of the studies provides no data to assess if there is an excess use of ICA in the group that underwent CCTA or underutilization in the group which did not use it. In the CONFIRM registry,³⁶ during follow-up, the rates of ICA were low in patients with no to mild CAD according to CCTA, revealing that, in clinical practice, physicians are accepting the results obtained by CCTA, and, in this case, the negative predictive value is high.

The rate of major cardiac events among patients involved in the studies was very low, it is concluded that these have excellent prognosis. However, the data is not sufficient to determine whether the use of CCTA brought some benefit in reducing major adverse cardiac events (death and heart attack) compared to standard of care.

The overall prevalence of CAD in most studies was low; therefore, the data cannot be extrapolated to high-risk patients. More studies are necessary to detect differences in clinical outcomes, given the nature of this low-risk population. The evaluation of patients in the ED did not show a fixed standard between studies, contrariwise, there was great

variability in the behavior; in most studies, the attending physician decided the next "step" in the evaluation, even for RCT.

For the exclusion of ACS in patients with known coronary occlusions, the CCTA would have a less useful role as a screening test, since the identification of coronary obstruction in patients with known CAD does not explain the etiology of chest pain.

Limitations

A difficulty found was the heterogeneity of the studies published in the ED. There was a deficiency of standardization in the evidence of the evaluation method, and large differences in follow-up and outcome measures.

Even with a total number of 4831 patients, the "force" to detect differences in clinical events such as heart attack and death is still low, since these are rare in these groups of patients.

All studies may have verification bias, since it is impossible to "blind" the conduct (CCTA or standard of care) for physicians and patients.

The methodology used in diagnostic test accuracy studies is quite different from that of therapeutic/interventional studies and has been developed substantially in recent decades.³⁷

Conclusions

The use of CCTA as a tool for stratification of patients with low or intermediate cardiovascular risk, who are in the ED with chest pain, has high accuracy, safety, reduces hospital LOS and probably the costs, producing an early diagnosis and more effective decision making. To assess the value of CCTA in the prevention of future events, studies with more appropriate design and longer follow-up are necessary.

Author contributions

Conception and design of the research: Tavares IS, Matos CJO, Lyra Júnior DP, Oliveira JLM. Acquisition of data: Tavares IS, Matos CJO, Oliveira JLM. Analysis and interpretation of the data: Tavares IS, Matos CJO, Nunes MAP, Sousa ACS, Lyra Júnior DP, Oliveira JLM. Statistical analysis: Tavares IS, Matos CJO, Nunes MAP, Sousa ACS, Oliveira JLM. Writing of the manuscript: Tavares IS, Matos CJO, Sousa ACS, Oliveira JLM. Critical revision of the manuscript for intellectual content: Tavares IS, Matos CJO, Sousa ACS, Lyra Júnior DP,

Oliveira JLM. Supervision / as the major investigator:
Tavares IS, Matos CJO, Oliveira JLM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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