Diagnostic utility of Computed Tomography Angiography (CTA) in the triage of patients with acute chest pain of suspected cardiac origin: An overview and a critical appraisal of a recently conducted systematic review and meta-analysis

Briefing paper

Original publication:

Samad and colleagues (2012), *A meta-analysis and systematic review of computed tomography angiography as a diagnostic tool for patients with chest pain presenting to the emergency department,* Journal of Nuclear Cardiology, Volume 19, Number 2, 364-376.

Introduction

The current text provides a brief overview and a methodological appraisal of the systematic review and meta-analysis conducted by Samad and colleagues (2012) who assessed the clinical utility and diagnostic accuracy of CTA for the diagnosis of acute coronary syndrome (ACS) in low to intermediate risk patients presenting to the emergency department (ED) with acute chest pain of suspected cardiac origin.[1] In order to assess the methodological quality of the review, we retrieved the original papers[2–10] and carefully examined the primary data and the review process using a number of methodological assessment tools such as the QUADAS 2, the STARD and an adapted version of the PRISMA checklists.[11–13] Here we report on the results from our appraisal and discuss, taking into consideration the findings from previous meta-analyses, whether the presented evidence is sufficient and reliable enough to enable policy decisions and inform changes in the current clinical practice.

Main messages

Despite some methodological quality issues inherent to the original studies and some unreported aspects of the review process that could have potentially biased the results, the overall quality of the systematic review and the meta-analysis conducted by Samad and colleagues (2012) is good, the conclusions reflect the findings and are consistent with those from the two previous meta-analyses. They could, therefore, be used to inform clinical and policy decisions without need for further systematic review and meta-analysis, which was our original proposal.

In patients presenting to the ED with acute chest pain of suspected cardiac origin and initial normal cardiac biomarkers and normal or non-diagnostic resting ECG (low to intermediate pre-test probability), negative CTA scan will effectively rule out the presence of ACS and should allow safe and rapid discharge home:

Pre-test probability for ACS		Negative CT scan		Post-test probability for ACS
10%	⇒	LR-[1] = 0.06	⇒	<1%
29%	⇒	LR- = 0.06	⇒	<2.5%

On the other hand, positive CT scan will increase the pre-test probability for ACS to intermediate level, thus making the case for admission and further testing, but will not be able to definitely rule in ACS:

Pre-test probability for ACS		Positive CT scan		Post-test probability for ACS
10%	⇒	LR+[2] = 7.4	⇒	45%
29%	⇒	LR+ = 7.4	⇒	75%

[1] Negative Likelihood Ratio
[2] Positive Likelihood Ration

Overview of the systematic review conducted by Samad and colleagues (2012)

Background

Acute chest pain in adults is often caused by an ACS, a range of conditions that cover ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). If not treated urgently, such patients have poor prognosis and high mortality rate and, therefore, need emergency care. The main diagnostic priorities for the ED clinicians at this early stage are to differentiate between ACS and other potentially life-threatening causes of chest pain such as pulmonary embolism and aortic dissection; and to risk stratify ACS patients so that appropriate referral and treatment decisions are made.[14]

The current diagnostic and risk stratification algorithms involve, as a first step, a resting ECG and a measurement of the cardiac troponin levels, interpreted in the light of the patient's clinical presentation and history. The results from such investigations are used to identify patients with STEMI, who would benefit from rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy; and to refer patients suspected to have non-ST-elevation ACS (NSTE-ACS) for further observation and testing. The patients in this latter group will be admitted into a chest pain unit (CPU) or an equivalent clinical setting and, following a short (up to 24 hours) period of observation and serial ECG and troponin testing, will be further qualified as patients with non-cardiac causes of chest pain, NSTEMI patients (elevated troponin in the absence of persistent ST-segment elevation) and UAP patients (normal troponin levels but with evidence of myocardial ischaemia). Patients with normal or non-diagnostic ECG and normal troponin levels, in whom the clinical presentation and history suggest ischaemic origin of the chest pain, will undergo a further confirmatory testing, usually an exercise tolerance test (ETT) or some other form of stress test, prior or soon after discharge home.

It has been demonstrated that such diagnostic and stratification algorithm is not very efficient since only 15%-25% of the admitted patients are eventually diagnosed with ACS; and not very effective since up to 2.5% of the patients with ACS are missed.[15–17]

Alternative strategies involving various diagnostic modalities, such as cardiac MRI, nuclear myocardial perfusion imaging and CTA, have been explored as a way of improving the effectiveness and efficiency of the diagnostic process and the risk stratification of patients with ACS. Particularly promising among them is the multi-detector CTA, which allows a rapid non-invasive evaluation of the coronary artery anatomy and, due to its very high negative predictive value (NPV), a safe discharge home of low-risk patients with no significant coronary artery disease (CAD). Additional advantage of the CTA is its ability to rule out, during the same scan, the presence of alternative life-threatening conditions such as aortic dissection and pulmonary embolism ("triple rule-out")[15–21] and to identify significant non-cardiac pathology present in up to 20% of the cardiac CTA scans.[22] Multi-detector CTA is a rapidly evolving technology and many of its former limitations have been overcome with the new generation of scanners, which have a better spatial and temporal resolution, allow imaging at lower radiation dose and could image patients that were difficult to image with the older machines. [23]

A number of studies and three previous meta-analyses were conducted to assess the diagnostic utility of CTA in ruling out ACS in patients with acute chest pain and low to intermediate probability of ACS. They concluded that CTA, with its very high negative predictive value (NPV), could be successfully used to rule out ACS in patients with initial negative or non-diagnostic resting ECG and normal troponin tests.[24–26] The authors of the current systematic review point out, however, that these meta-analyses suffer from some methodological shortcomings such as the inclusion of studies that:

- treated cardiac catheterisation rather than ACS as an end point;
- enrolled patients suspected of causes other than ACS;
- included only patients with established diagnosis of ACS; and,
- failed to include relevant studies and especially the recently published ROMICAT trial.

They concluded that, as a result, the reported estimates might be biased and conducted a meta-analysis including only those few studies that used ACS as an end point (target condition) and met some specific methodological quality criteria.[1]

Objectives of the review

The main objective of Samad and colleagues (2012) was to produce estimates of the diagnostic accuracy of multi-detector cardiac CTA in confirming or excluding possible ACS in patients with acute chest pain and initial negative or non-diagnostic ECG and normal troponin test (p. 365).[1]

Methodology

Pub Med database, US National Institute of Health, The Cochrane Library and the Cochrane Central Register of Controlled Trials were searched for relevant papers in June 2011. The search was conducted using the key words: “chest pain”, “emergency” and “computed tomography”.

The following inclusion and exclusion criteria were used to select studies for inclusion in the review:

- Prospective studies with ≥ 1-month follow-up
- Use of CTA in the emergency room setting
- Study population with negative ECG and biomarkers on initial evaluation
- Use of ACC/AHA guideline definitions for ACS and major adverse cardiac events (MACE) [27]
- Use of ACS as clinical outcome/end point
- ≥ 30 patients
- Data presented in absolute numbers or sufficient detail to derive these numbers
- Abstracts without peer-reviewed manuscripts were excluded.

Two independent reviewers extracted the data and an appraisal of the methodological quality of the included studies was conducted using the QUADAS 1 assessment tool.[28]

Summary estimates for sensitivity, specificity, negative and positive likelihood ratios (LR— and LR+) were calculated using random effects bivariate model, which takes into account the between-study heterogeneity and the correlation between sensitivity and specificity. Since an indeterminate/non-diagnostic CTA result would lead to a referral for further testing, such results were counted as positive. The presence of a threshold effect was assessed by calculating Spearman correlation coefficient between sensitivity and specificity and conducting a weighted regression of Diagnostic Odds Ratios (DORs). Since the likelihood ratios (LRs) are the test accuracy measures most relevant to clinical decision making, they were assessed for publication bias by visual inspection of the funnel plots and the Egger’s linear regression method.

Results

Selection of studies: The initial search identified 386 studies of which nine studies comprising 1 349 patients met the inclusion criteria and were included in the meta-analysis. Of the excluded studies, 19 studies were excluded because the outcome was different from ACS and 22 studies investigated all-cause chest pain rather than chest pain suspected to be caused by ACS. The reasons for exclusion for some of the excluded studies are detailed in the paper.

Characteristics of studies: One study was a Randomised Controlled Trial (RCT) comparing a CTA-based diagnostic strategy with the standard-of-care diagnostic practice in which nuclear stress imaging was used as a confirmatory test; only the data from the CTA arm was used in the meta-analysis.[6] The remaining studies were prospective observational cohort studies. Studies with retrospective design were excluded from the review.

Six studies stated that patients were evaluated in a consecutive fashion during day time hours on weekdays. Patients in all the studies were in the low to intermediate chest pain risk category with normal initial cardiac biomarkers and no evidence of ischemia on the initial ECG. CTA was generally performed in the ED during the course of evaluation[2,5–7], in the observation unit[9] or immediately upon admission to the hospital[8].

64-slice CT scanners were used in seven studies; one study used 16- and 64-slice scanners[3] and one study used 4- and 16-slice scanners[2]. Five of the nine studies performed initial non-enhanced ECG-gated scan for calcium scoring but did not report these results in sufficient detail to allow further analysis.

Non-diagnostic scans:

- were reported in six studies;[2–4,6,8,9]
- their frequency ranged from 1% to 17%;
- the most cited reasons for non-diagnostic scans were previous stents, obesity, tachycardia and vessel calcification; and,
- they were included in the analysis of diagnostic accuracy in only four studies counted as positive test results.[3,4,6,8]

There was a significant variability across studies with regards to the definition of a positive CTA result, with the main criterion being the level of luminal obstruction:

- ≥50% luminal obstruction (seven studies);
- ≥75% (one study);[2] and,
- In one study the CTA results were stratified into three categories:
    - negative (<25%, immediate discharge home);
    - intermediate (26%-70%) or non-diagnostic scan (referral for a nuclear stress test); and,
    - positive (>70% referral for an invasive coronary angiography).[6]

Only two studies blinded the physicians making the final diagnosis to the results from the CTA.

Characteristics of the patient population: Patients in all studies were in the low to intermediate chest pain risk category with normal initial cardiac biomarkers and no evidence of myocardial ischemia on the initial resting ECG. The characteristics of the included patients and the reasons for exclusion are presented in the tables 1 and 2 below.

Table 1 Characteristics of the pooled patient population

Age	52±2 years
Sex	51% male
The prevalence of cardiac risk factors was as follows:	• 12% diabetics • 42% hypertensive • 35% smokers • 29% with hyperlipidemia
Thrombolysis In Myocardial Infarction (TIMI) score (where reported, in the majority of patients):	<2
History of CAD	7% (although five studies excluded patients with a known history of CAD).

Table 2 Reasons for excluding patients from the studies

• atrial or ventricular arrhythmias, • hypotension, • renal insufficiency, • persistent chest pain, • contraindications to beta-blockers or iodine, • asthmatics, and • pregnant women • history of CAD (only in five studies)

Diagnosis of ACS was made in 10% of the cases. There were 30 cases of myocardial infarction in the entire cohort. The 30-day event rate included no deaths and no additional myocardial infarctions. Revascularisation was performed in 21% of patients with positive CTA scans and in 1 patient with a negative CTA scan (13 months after the scan).

Main results: The summary estimates calculated for different test accuracy measures were as follows:

- **sensitivity** was 95% (95%CI 88-100) and was homogeneous across studies;
- **specificity** was 87% (95% CI 83-92) and showed significant heterogeneity (I^2 = 74%);
- **negative likelihood ratio (LR—)** was 0.06 (95%CI 0-0.14); it was homogenous across studies but the funnel plot revealed the presence of publication bias confirmed by the Egger's regression intercept (intercept = —1.3, *P* = .002);
- **positive likelihood ratio (LR+)** was 7.4 (95%CI 4.8-10) and showed significant heterogeneity (I^2 = 71%).

No inverse correlation was established between sensitivity and specificity when different cut-off points for a positive CT result were used.

Discussion and conclusions: The authors discuss the findings from the review in the context of the current clinical practice, the limitations of the CTA and the limitations of the current review.

They point out that the diagnostic protocols currently used to triage patients who present to the ED with acute chest pain are neither efficient nor very effective. In their opinion, there is a significant body of evidence suggesting that the incorporation of cardiac CTA in the triage of low to intermediate risk patients could significantly improve the diagnostic process.

The results from the meta-analysis lead to two main conclusions:

- a negative CT scan can reliably rule out the presence of ACS in patients with low to intermediate probability of ACS and should allow a safe and rapid discharge home with no further testing; thus, a negative likelihood ration of 0.06 will reduce a pre-test probability of 10% to less than 1%, or in other words, in hundred patients tested, less than one out of the ten patients with ACS will be missed. The post-test probability of an ACS with a negative CTA does not exceed 5% until the pre-test probability is ≥57%, which is highly unlikely in patient population selected on the basis of normal cardiac biomarkers and normal or non-diagnostic ECG;
- a positive CT scan significantly increases the probability of an ACS and thus may be helpful in making a timely triage decisions but will not be able to definitely rule in the presence of ACS; thus, a positive CT scan will increase a pre-test probability of 10% to 45% placing the patient in the intermediate risk category but only approximately half of these patients will be eventually diagnosed with ACS.

This means that incorporating the cardiac CTA in the triage of patients with acute chest pain and low to intermediate pre-test probability of ACS could potentially lead to a decrease in the unnecessary hospitalisations by reassuring ED clinicians that patients with negative CT scan can be safely discharged home. Also, it might be able to reduce the time necessary to make diagnostic and referral decisions and hopefully would lead to increased cost effectiveness.

The findings from the review are consistent with and provide strong support to a number of policy recommendations regarding the use of CTA in the triage of patients with acute chest pain such as the recently published NICE guideline on "Chest pain of recent onset: Assessment of recent onset chest pain or discomfort of suspected cardiac origin"[29], the ESC "Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation"[14] and the "2010 Appropriate use criteria for cardiac computed tomography".[30]

Further considerations related to the use of CTA: The following issues need to be considered when making decisions about the use of CTA in the triage of patients with acute chest pain of suspected cardiac origin:

- **Non-diagnostic scans.** Only six studies reported the rate of non-interpretable scans, which ranged from 1% to 17%. Non-interpretable results were mainly due to motion artefacts, previously implanted stents and severe calcification. An uninterpretable CT scan will lead to further testing related to an increased risk to the patient and additional costs. The frequency of non-interpretable scans could be reduced by excluding patients with certain characteristics, such as severe calcification or previous stents, known to predict a high rate of suboptimal images. If appropriate and feasible, such patients could be imaged with the new generation CTA scanners, which have been shown to produce scans with satisfactorily image quality in patients difficult to image with the 64-slice machines.[23]
- **Patient characteristics that preclude the use of CTA.** On top of the characteristics discussed above, further contra-indications for the use of CTA should be taken into consideration (see table 2 above).
- **Patients with known history of CAD.** Including patients with known history of CAD is likely to increase the number of false positives as a result of the increased proportion of patients with pre-existing stenosis unrelated to the current chest pain episode, previously implanted stents and calcification. This will lead to overestimation of sensitivity and underestimation of specificity, implying that in patients with known CAD CTA would be less effective as a rule-out test.[1,8]
- **Incidental findings:** The rate of significant non-cardiac "incidental findings", such as single or multiple pulmonary nodules, is reported to be as high as 23% in some studies.[31] This is the main reason for the recommendation made by the National Imaging Board that cardiac CT scans should be performed by a collaboration of appropriately trained cardiologist and radiologist in order to ensure that both the cardiac and non-cardiac aspects of the scan are correctly interpreted and no significant incidental findings are missed.[22]
- **ACS in the absence of a coronary stenosis:** In some cases (less than 10%), ACS could be caused by a focal spasm of a segment of an epicardial coronary artery (Prinzmetal's angina) or some other form of dynamic coronary obstruction. This issue, however, was not addressed in the current review and needs further investigation.[27]

The focus on diagnostic accuracy and the limited number of predominantly small and heterogeneous primary studies, did not allow many important issues, such as those discussed above, to be thoroughly investigated in the analysis. The authors state that further research needs to take the form of randomised trials that could provide better understanding of real-time performance and address some of the issues not addressed so far:

- The application of CTA in patients with known CAD or high probability of ACS.
- Performance in different patient subgroups, e.g. sex, age etc.
- The downstream costs and effects of incidental findings.
- The issue of ACS in the absence of coronary stenosis.
- Comparison with the current diagnostic practice.

- The implications of using initial non-enhanced ECG-gated scans for calcium scoring.
- Cost-effectiveness and clinical patterns.
- Radiation exposure.

Limitations of the review: The authors of the review point to a number of potential sources of bias and limitations to the applicability of the results stemming mainly from the methodological shortcomings of the original studies:

- study design: mostly non-randomised studies;
- potential selection bias: even consecutively enrolled patients were enrolled during work hours and on weekdays only; one study enrolled patients only two days in the week;[3]
- lack of blinding: only two studies blinded the physicians making the final diagnosis to the CTA results but since the results were very similar to the rest of the studies, no significant impact on the effect size was anticipated;[3,4]
- non-interpretable scans: poor reporting and inconsistent handling of the non-diagnostic scans;
- a lack of patient level data precluded the investigation of the variation in test accuracy between different subgroups;
- use of CT scanners with different number of detectors: one study used 4- and 16-sliced scanners on all the included patients; excluding this study from the meta-analysis improved the summary sensitivity to 98.1% but the specificity remained essentially unchanged (84.9%); this means that a negative result from a higher resolution scanner may lead to even greater reduction in the probability of ACS (summary LR— = 0.02, 95% CI 0—0.10);
- presence of publication bias in the negative likelihood ratio: publication bias was identified in the negative likelihood ratio, most probably due to the relatively small number of cases with ACS;
- significant level of heterogeneity in the specificity and the positive likelihood ratio;
- wide confidence intervals around the positive likelihood ratio;
- inclusion of patients with known history of CAD: five studies enrolled patients with known history of CAD, which may have led to overestimation of sensitivity and underestimation of specificity.

Methodological appraisal of the review

Background, objectives and rational: The decision-making problem addressed by the review is well presented in the paper and a rational supported by critical examination of previously conducted systematic reviews on this topic is provided. The review question specifies index test, target condition and patient description, as recommended in the Cochrane Handbook for DTA Reviews.[32]

Methods: Although the authors provided information on the design and conduct of the review, details about some important aspects are not given:

- the procedures used to screen the initially identified studies, such as the number of reviewers, the method of resolving discrepancies and a measure of agreement;
- the procedures and criteria used in the assessment of the methodological quality of the included studies; and,
- an explicit definition of acceptable reference standard.

The **search strategy**, as detailed in the paper, appears to be relatively limited, including only four databases, two of which index only RCTs and systematic reviews (The Cochrane Library and Cochrane Central Register of Controlled Trials). No hand search of relevant journals or additional search methods are mentioned. It is, therefore, possible that relevant studies were missed and not included in the review.

The lack of information about the **screening process** makes its evaluation difficult. Although the number of initially identified papers was relatively small, only 386 studies, relevant studies could have been missed if no adequate screening procedures were put in place to ensure that all of the studies that met the inclusion criteria were selected. Independent screening by two reviewers using a piloted list of criteria is the gold standard for screening and any deviation from this procedure could potentially lead to bias.

In order to check whether relevant studies were missed by Samad and colleagues (2012), we retrieved some of the studies not included in this review but included in the previous meta-analyses and especially in the systematic review conducted by Takakuwa and colleagues (2011), which was not mentioned in the paper[24–26] We identified one study that met the inclusion criteria set out by Samad and colleagues but was not included in their review. [33] This demonstrates the limitations of their search strategy and/or selection process and suggests that relevant studies could have been missed from their review.

The data extraction, on the other hand, is well reported. It was conducted independently by two investigators and the discrepancies were resolved by a third reviewer or global consensus. Even though no piloting of the data extraction form is mentioned, it appears that the process was rigorous and the relevant data were extracted.

The authors state that "the included studies adhered to the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) guidelines" (p. 365). However, there is no structured summary of the results from this assessment and the information provided in the paper suggests that many of the studies suffered serious methodological shortcomings. For instance, the authors acknowledge that three of the studies used convenience sampling and only in two studies the physicians who made the final diagnosis were blinded to the results from the CT scans. We identified the following issues with regards to the conduct of the methodological quality assessment:

- First, judging by the provided reference, the authors used the old version of the QUADAS tool, QUADAS 1, rather than its updated version QUADAS 2, which prompts reviewers to assess both the risk of bias and the applicability of the primary data to the review question.[11]
- Second, the QUADAS tool provides only a framework for methodological quality assessment of diagnostic accuracy studies. Its effective application, however, depends on the tailoring of the tool to the specific needs of the given systematic review. An effective assessment process would involve developing and piloting a list of explicitly defined criteria and independent assessment of the included studies by at least two reviewers. Neither such adaptation of the tool nor a list of the definitions used in the assessment is provided or referenced in the paper.

The target condition is broadly defined as ACS including myocardial infarction and unstable angina and the readers are referred to the 2007 ACC/AHA guidelines for the specific definitions of these conditions. With regards to the reference standard, the authors only state that "the main analysis was performed using ACS as the gold standard" (p. 365) and no explicit definition of acceptable reference standard is provided.

The paper provides a full description of the statistical methods used in the meta-analysis.

Results: The characteristics of the included studies are well presented and a detailed description of the patient population is provided, thus making it possible to understand the clinical context to which the results from the review could be generalised. The authors discuss some of the limitations of the studies, such as the study design (mostly observational cohort studies), the selection of patients (convenience sampling in three studies and enrolment of participants limited to working hours on weekdays), the lack of blinding to the CTA results (in seven studies) and the variability in the definition of abnormal CTA result. Limited information is provided, however, on the possible risk of bias that stems from the interpretation of the CTA scans and the risk of bias related to the reliability and conduct of the reference standard.

Using the QUADAS 2 and the STARD checklists, we explored some aspects of the primary studies that might have led to potentially biased results but were not discussed in the paper.[11,12]

Index test:

- **Test review bias:** Test review bias occurs when the interpretation of the index test is affected because the readers are aware of the results from the reference standard.[12] In most of the included studies, CTA (index test) was done prior to the reference tests, thus precluding biased interpretation of the CT scans as a result of knowing the final diagnosis.
- **Variability in the interpretation of the CT scans:** Previous studies have demonstrated that the interpretation of test results, especially in the field of imaging, is often characterised by significant inter-reader variability.[12,34–36] Most of the studies included in this review did not report data on inter-reader variability. The CT scans were interpreted by one clinician in four studies; by two clinicians, jointly, in four studies and independently in one study. This latter study reported Cohen's kappa of 0.92 which indicates a high level of agreement between the image readers. Most studies were conducted at university hospitals and the scans were interpreted by highly experienced clinicians whose level of expertise may differ from that of clinicians working in an ordinary ED setting. This means that the same level of test accuracy may not be achievable in the usual ED practice.[12]
- **Clinical review bias:** Providing image readers with additional clinical information has been shown to increase the accuracy of interpretation thus affecting the final test accuracy results.[12,37–39] Test accuracy evaluations should try to create conditions similar to those in practice, so that the calculated test accuracy indices are relevant to the clinical context in which they would be applied. In the current review, physicians reading the scans were blinded to the clinical data in five of the included studies and this may have affected the accuracy of their reading.

Reference standard: ACS comprises a range of conditions including myocardial infarction and unstable angina, characterised by an imbalance between myocardial oxygen supply and demand. The most common cause of ACS is a narrowing or a complete occlusion of a coronary artery segment caused by a thrombus that developed on a disrupted atherosclerotic plaque, although other mechanisms, such as dynamic obstruction or severe narrowing without spasm or thrombus, are also possible.[27] The presence of significant CAD is highly correlated with ACS and the probability of ACS happening in the absence of significant coronary stenosis is low. Therefore, some previous test accuracy evaluations have used ICA—the gold standard for CAD—as a reference test for establishing the presence or absence of ACS.[40,41] ICA, however, is an invasive procedure associated with rare but serious procedure-related adverse events, such as bleeding and myocardial infarction, and its use in low risk patients who, following a negative CT scan, are very unlikely to have a clinically significant stenosis is unjustified.[9,42,43]

- **Composite reference standard:** The current review excluded studies using ICA as the sole reference test and included only evaluations that used the diagnostic criteria set out in the 2007 American College of Cardiology/American Heart Association Guidelines. According to these criteria the diagnosis of ACS should be based on the results from the history and clinical examination combined with those from a range of diagnostic tests, the most important ones being ECG and cardiac biomarkers. More specifically, patients presenting with symptoms suggestive of ACS, in which the resting ECG shows persistent ST-segment elevation are diagnosed with STEMI if the diagnosis is confirmed by elevated cardiac troponin. Elevated troponin in patients without ST-segment elevation but symptoms and/or ECG results suggestive of ACS leads to the diagnosis of NSTEMI, while patients with symptoms and/or objective evidence of myocardial ischemia (e.g. from a stress test or imaging) but without elevated cardiac biomarkers are diagnosed with UAP.[27] The diagnosis of UAP is particularly challenging since neither the clinical symptoms nor the non-invasive tests

used to diagnose myocardial ischemia are perfectly accurate and there is always the possibility of an error and some level of subjectivity in the diagnosis.[9,44,45]

In diagnostic accuracy evaluations, when no gold standard is available or could be used in all patients, a composite reference standard is constructed, using a combination of diagnostic tests and procedures to verify the presence and absence of the target condition. The use of a composite reference standard, however, is associated with possible misclassifications and this should be taken into account in the design and appraisal of test accuracy evaluations.[46] In the included studies, the combination and sequence of reference tests and diagnostic procedures, such as expert panel decisions, used to verify positive and negative CTA results showed significant variability. In order to improve the reliability of the reference standard and to obtain prognostic information on the CTA results, the authors of the review included only studies that had at least one month follow up for MACE. This, however, added another source of variability, since the follow-up period across studies ranged from one to fifteen months.

- **Differential verification bias:** If the positive and negative outcomes from the index test are verified using different reference tests this may result in a differential verification bias since the different reference tests are unlikely to have the same test accuracy.[12,46,47] In the included studies positive and negative CTA results were verified using different diagnostic algorithms combining a number of diagnostic tests and procedures. Typically, a positive CT scan was verified by increased troponin, SPECT or ICA[2,7,10], while the verification of a negative CT scan ranged from simply discharging patients home and following them up for at least one month[7,9,10] to ICA and a follow-up period. [2] The incorporation of a follow-up period increases the reliability of the reference standard, especially in terms of providing reassurance that patients with a negative CTA result could be safely discharged home.
- **Incorporation bias:** Physicians who interpreted the reference tests and made the final diagnosis were blinded to the results from the CTA in only two studies. In these studies, a panel of experts blinded to the CTA results reviewed all patient data and made the final diagnosis, resolving disagreements by consensus and arbitration.[3,4] In the remaining studies, no blinding to the results from the CTA was present and, therefore, these studies are at increased risk of incorporation bias. Incorporation bias occurs when the interpretation of the reference standard is affected by the results from the index test and most often results in overestimation of test accuracy.[48–50]

Statistical analysis: Statistical analysis appears to be well conducted. The test accuracy results from the individual studies were given in a table (sample size, sensitivity, specificity and predictive values presented as proportions and percentages) and as forest plots of sensitivity, specificity, negative and positive likelihood ratios.

Summary estimates of sensitivity, specificity and positive and negative likelihood ratios were presented with 95% CI and assessed for heterogeneity. Significant heterogeneity was identified in the estimates for specificity and positive likelihood ratio, while sensitivity and negative likelihood ratio were homogenous across studies. The effect of different cut-off points for “significant” luminal obstruction was also assessed and no inverse correlation between sensitivity and specificity was found. Diagnostic performance, as assessed by the diagnostic odds ratio using random effects, was not affected by the threshold for sensitivity and specificity. Publication bias was identified in the negative likelihood ratio (which reflects the sensitivity) due to the low number of patients with coronary events.

We found a minor mistake in the way in which the results from one of the studies were included in the meta-analysis. In their study, Goldstein and colleagues[6] stratified the results from the CTA into three categories: normal (<25% luminal obstruction), intermediate (26-70%) and abnormal (>70%). Patients with intermediate results were referred for a nuclear stress test and, in the case of a positive test result, underwent an ICA. Thus, out of all 24 patients with intermediate results, three patients had positive stress scans and underwent ICA, which confirmed significant stenosis. Despite this, in the meta-analysis all 24 intermediate results were included as false positives, although three of them were, in fact, true positives. This, however, is a minor inaccuracy and is unlikely to have

affected the calculation of the final test accuracy estimates. Also, from the paper it is not clear whether 25% or 70% luminal obstruction was considered to be the cut-off point used to differentiate a positive and negative CT scan. In the original study positive result was defined as >70% luminal obstruction but in the meta-analysis positive and intermediate results were combined and all treated as positive. This means that for the purposes of the meta-analysis 25% luminal obstruction was considered to be the cut-off point used to differentiate a positive from a negative CT scan.

Discussion and conclusions: The conclusions made by the authors, namely that "ACSs may be excluded with high sensitivity in low to intermediate risk patients with chest pain presenting to the ED if there is no coronary disease on CTA" and that "a positive CTA significantly increases the probability of an ACS and may thus be helpful in making a timely triage decisions" (p. 370), seem appropriate and reasonable, and grounded in the findings from the review. The authors discuss the appropriate context for the application of the review results—namely patients presenting to the ED with acute chest pain of suspected cardiac origin and initial negative or non-diagnostic ECG and cardiac troponin. They also point out that even though the results concur with the recently published 2010 appropriateness criteria for cardiac computed tomography[30] they are derived from a limited number of small and heterogeneous studies and should be treated with caution.

Conclusions

The systematic review and meta-analysis conducted by Samad and colleagues (2012) focused on the diagnostic accuracy of CTA when used to establish the presence and absence of ACS in ED patients with acute chest pain of suspected cardiac origin and initial negative ECG and cardiac biomarkers. In order to achieve more precise and clinically relevant estimates of test accuracy the authors included only studies that used the 2007 ACC/AHA criteria[27] for the diagnosis of ACS and followed up the patients for at least one month after their discharge.

Only nine studies were included in the review most of which were small and suffered from significant methodological shortcomings such as convenience sampling; a lack of independent reading of the CT scans by at least two readers; differences in the clinical information available to the CT scan readers (clinical review bias); use of different reference tests to verify the positive and the negative results from the index test (differential verification bias); incorporation of the results from the index test into the final diagnosis (incorporation bias); and not reporting/ excluding the indeterminate test results. The small number of studies precluded a sub-group analysis and the impact of different study characteristics on the final results is not clear.

At systematic review level, some minor methodological issues were identified: limited search strategy and a lack of detail about the screening process which may have resulted in omitting some relevant studies; a lack of detail about the methodological quality assessment of the included studies; and minor inaccuracies in the handling of the primary data. Despite these minor issues, the systematic review and meta-analysis conducted by Samad and colleagues (2012) appear to be of good quality and their conclusions take into account the limitations inherent to the primary studies.

Moreover, the test accuracy estimates produced by Samad and colleagues (2012) are consistent with those from the previous meta-analyses (see table 3 below) and re-enforce the main message coming from research, namely that CTA could be used in the ED setting to rule out safely the presence of ACS in patients with acute chest pain and initial negative cardiac biomarkers and ECG results.

Zhivko Zhelev,

Peninsula College of Medicine and Dentristry

Table 3 Comparison of test accuracy estimates produced by different meta-analyses

Review/Study	Studies/ Patients	Sensitivity	Specificity	LR-	LR+	SDOR
Vanhoenacker et al 2007	9 studies, 566 patients	0.95 (95% CI, 0.90-0.98)	0.90 (95% CI, 0.87-0.93)	0.12 (95% CI, 0.06-0.21)	8.60 (95% CI, 5.03-14.69)	131.81 (95% CI, 50.90 – 341.31)
Athappan et al 2010	16 studies, 1119 patients	0.96 (95% CI, 0.93-0.98)	0.92 (95% CI, 0.89-0.94)	0.09 (95% CI, 0.06-0.14)	10.12 (95% CI, 6.73-15.22)	190.80 (95% CI, 102.94 – 353.65)
Takakuwa et al 2011	9 studies, 1559 patients	0.93 (95% CI, 0.88 – 0.97)	0.90 (95% CI, 0.88 – 0.91)	**PPV: 48.1% (95% CI, 42.5 – 53.8)**	**NPV: 99.3% (95% CI, 98.7 – 99.6)**	102.4 (95% CI, 51.8 – 207.6)
Samad et al 2012	9 studies, 1349 patients	0.95 (95% CI, 0.88-1.00)	0.87 (95% CI, 0.83-0.92)	0.06 (95% CI, 0.00-0.14)	7.4 (95% CI, 4.8-10.00)	

LR- = negative likelihood ratio
LR+ = positive likelihood ration
PPV = positive predictive value
NPV = negative predictive value
SDOR = summary diagnostic odds ratio
CI = confidence interval

Bibliography

1. Samad Z, Hakeem A, Mahmood SS, et al. A meta-analysis and systematic review of computed tomography angiography as a diagnostic triage tool for patients with chest pain presenting to the emergency department. *Journal of Nuclear Cardiology: Official Publication of the American Society of Nuclear Cardiology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22322526. Accessed March 9, 2012.

2. Sato Y, Matsumoto N, Ichikawa M, et al. Efficacy of Multislice Computed Tomography for the Detection of Acute Coronary Syndrome in the Emergency Department. *Circulation Journal*. 2005;69(9):1047–1051.

3. Hoffmann U, Nagurney JT, Moselewski F, et al. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation*. 2006;114(21):2251–2260.

4. Hoffmann U, Bamberg F, Chae CU, et al. Coronary Computed Tomography Angiography for Early Triage of Patients With Acute Chest Pain: The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) Trial. *Journal of the American College of Cardiology*. 2009;53(18):1642–1650.

5. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation*. 2007;115(13):1762–1768.

6. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *Journal of the American College of Cardiology*. 2007;49(8):863–871.

7. Hollander JE, Litt HI, Chase M, et al. Computed Tomography Coronary Angiography for Rapid Disposition of Low-risk Emergency Department Patients with Chest Pain Syndromes. *Academic Emergency Medicine*. 2007;14(2):112–116.

8. Ueno K, Anzai T, Jinzaki M, et al. Diagnostic capacity of 64-slice multidetector computed tomography for acute coronary syndrome in patients presenting with acute chest pain. *Cardiology*. 2009;112(3):211–218.

9. Gallagher MJ, Ross MA, Raff GL, et al. The Diagnostic Accuracy of 64-Slice Computed Tomography Coronary Angiography Compared With Stress Nuclear Imaging in Emergency Department Low-Risk Chest Pain Patients. *Annals of Emergency Medicine*. 2007;49(2):125–136.

10. Hollander JE, Chang AM, Shofer FS, et al. Coronary Computed Tomographic Angiography for Rapid Discharge of Low-Risk Patients With Potential Acute Coronary Syndromes. *Annals of Emergency Medicine*. 2009;53(3):295–304.

11. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* 2011;155(8):529–536.

12. Bossuyt PMM. STARD Statement: Still Room for Improvement in the Reporting of Diagnostic Accuracy Studies. *Radiology*. 2008;248(3):713–714.

13. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Reprint—Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Physical Therapy*. 2009;89(9):873 –880.

14. Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32(23):2999–3054.

15. Haidary A, Bis K, Vrachliotis T, et al. Enhancement performance of a 64-slice triple rule-out protocol vs 16-slice and 10-slice multidetector CT-angiography protocols for evaluation of aortic and pulmonary vasculature. *J Comput Assist Tomogr*. 2007;31(6):917–923.

16. Gallagher MJ, Raff GL. Use of multislice CT for the evaluation of emergency room patients with chest pain: the so-called 'triple rule-out'. *Catheter Cardiovasc Interv*. 2008;71(1):92–99.

17. Schertler T, Frauenfelder T, Stolzmann P, et al. Triple rule-out CT in patients with suspicion of acute pulmonary embolism: findings and accuracy. *Acad Radiol*. 2009;16(6):708–717.

18. Takakuwa KM, Halpern EJ, Gingold EL, Levin DC, Shofer FS. Radiation dose in a 'triple rule-out' coronary CT angiography protocol of emergency department patients using 64-MDCT: the impact of ECG-based tube current modulation on age, sex, and body mass index. *AJR Am J Roentgenol*. 2009;192(4):866–872.

19. Furtado AD, Adraktas DD, Brasic N, et al. The triple rule-out for acute ischemic stroke: imaging the brain, carotid arteries, aorta, and heart. *AJNR Am J Neuroradiol*. 2010;31(7):1290–1296.

20. Rogg JG, De Neve J-W, Huang C, et al. The Triple Work-Up for Emergency Department Patients with Acute Chest Pain: How Often does It Occur? *The Journal of Emergency Medicine*. 2011;40(2):128–134.

21. Madder RD, Raff GL, Hickman L, et al. Comparative diagnostic yield and 3-month outcomes of 'triple rule-out' and standard protocol coronary CT angiography in the evaluation of acute chest pain. *J Cardiovasc Comput Tomogr*. 2011;5(3):165–171.

22. Board NI. Cardiac imaging: a report from the National Imaging Board March 2010. 2010. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114380. Accessed April 28, 2012.

23. Westwood M, Al M, Burgers L, et al. Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD: a Diagnostic Assessment Report. *Kleijnen Systematic Reviews Ltd.* 2011.

24. Vanhoenacker PK, Decramer I, Bladt O, et al. Detection of non-ST-elevation myocardial infarction and unstable angina in the acute setting: meta-analysis of diagnostic performance of multi-detector computed tomographic angiography. *BMC Cardiovascular Disorders*. 2007;7(1):39.

25. Athappan G, Habib M, Ponniah T, Jeyaseelan L. Multi-detector computerized tomography angiography for evaluation of acute chest pain–a meta analysis and systematic review of literature. *International Journal of Cardiology*. 2010;141(2):132–140.

26. Takakuwa KM, Keith SW, Estepa AT, Shofer FS. A Meta-analysis of 64-section Coronary CT Angiography Findings for Predicting 30-day Major Adverse Cardiac Events in Patients Presenting with Symptoms Suggestive of Acute Coronary Syndrome. *Academic radiology*. 2011;18(12):1522–1528.

27. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Journal of the American College of Cardiology*. 2007;50(7):e1.

28. Devillé WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Medical Research Methodology*. 2002;2(1):9.

29. NICE. CG95 Chest pain of recent onset: full guideline. *NICE*. 2010. Available at: http://www.nice.org.uk/. Accessed December 21, 2011.

30. Taylor AJ, Cerqueira M, Hodgson JMB, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology*. 2010;56(22):1864.

31. Burt JR, Iribarren C, Fair JM, et al. Incidental findings on cardiac multidetector row computed tomography among healthy older adults: prevalence and clinical correlates. *Archives of internal medicine*. 2008;168(7):756.

32. Anon. Handbook for DTA Reviews | Diagnostic Test Accuracy Working Group. Available at: http://srdta.cochrane.org/handbook-dta-reviews. Accessed November 9, 2011.

33. Hansen M, Ginns J, Seneviratne S, et al. The value of dual-source 64-slice CT coronary angiography in the assessment of patients presenting to an acute chest pain service. *Heart, Lung and Circulation*. 2010;19(4):213–218.

34. Elmore JG, Wells CK, Lee CH, Howard DH, Feinstein AR. Variability in radiologists' interpretations of mammograms. *New England Journal of Medicine*. 1994;331(22):1493–1499.

35. Elmore JG, Feinstein AR. A bibliography of publications on observer variability (final installment). *J Clin Epidemiol*. 1992;45(6):567–580.

36. Brealey S, Scally AJ. Bias in plain film reading performance studies. *British journal of radiology*. 2001;74(880):307–316.

37. Begg CB. Biases in the assessment of diagnostic tests. *Statistics in medicine*. 1987;6(4):411–423.

38. Doubilet P, Herman PG. Interpretation of radiographs: effect of clinical history. *American Journal of Roentgenology*. 1981;137(5):1055–1058.

39. Berbaum KS, Franken Jr EA, Dorfman DD, et al. Tentative diagnoses facilitate the detection of diverse lesions in chest radiographs. *Investigative Radiology*. 1986;21(7):532.

40. Olivetti L, Mazza G, Volpi D, et al. Multislice CT in emergency room management of patients with chest pain and medium-low probability of acute coronary syndrome. *La Radiologia Medica*. 2006;111(8):1054–1063.

41. Meijboom WB, Mollet NR, Van Mieghem CA, et al. 64-Slice CT coronary angiography in patients with non-ST elevation acute coronary syndrome. *Heart*. 2007;93(11):1386.

42. Wyman RM, Safian RD, Portway V, et al. Current complications of diagnostic and therapeutic cardiac catheterization. *Journal of the American College of Cardiology*. 1988;12(6):1400–1406.

43. Chandrasekar B, Doucet S, Bilodeau L, et al. Complications of cardiac catheterization in the current era: a single-center experience. *Catheterization and cardiovascular interventions*. 2001;52(3):289–295.

44. Hollander JE, Blomkalns AL, Brogan GX, et al. Standardized reporting guidelines for studies evaluating risk stratification of emergency department patients with potential acute coronary syndromes. *Ann Emerg Med*. 2004;44(6):589–598.

45. Shaw LJ, Berman DS. Sequential single-photon emission computed tomography myocardial perfusion imaging. *The American journal of cardiology*. 2005;96(8):28–39.

46. Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM. *Evaluation of diagnostic tests when there is no gold standard. A review of methods*. Gray Pub. 2007.

47. Bachmann LM, Jüni P, Reichenbach S, et al. Consequences of different diagnostic 'gold standards' in test accuracy research: Carpal Tunnel Syndrome as an example. *International Journal of Epidemiology*. 2005;34(4):953–955.

48. Mower WR. Evaluating bias and variability in diagnostic test reports. *Ann Emerg Med*. 1999;33(1):85–91.

49. Rutjes AWS, Reitsma JB, Di Nisio M, et al. Evidence of bias and variation in diagnostic accuracy studies. *CMAJ*. 2006;174(4):469–476.

50. Worster A, Carpenter C. Incorporation bias in studies of diagnostic tests: how to avoid being biased about bias. *CJEM*. 2008;10(2):174–175.