Diagnostic accuracy of Cardiac Computed Tomography Angiography for the diagnosis of Acute Coronary Syndrome in Emergency Department patients with working diagnosis of Non-ST-segment Elevation Acute Coronary Syndrome—A systematic review of the literature and meta-analysis

Authors

- Zhivko Zhelev, PhD, Research Fellow, Exeter University Medical School
- Dr. Christopher Hyde, MB BS MRCP FFPH, Professor of Public Health and Clinical Epidemiology, Exeter University Medical School
- Harriet Hunt, MSC, BSC, Associate Research Fellow, Exeter University Medical School
- Morwenna Rogers, Information Specialist, Exeter University Medical School
- Dr. Carl Roobottom, Professor of Radiology, Plymouth Healthcare NHS Trust

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Background

Target condition being diagnosed

Acute coronary syndrome (ACS) is an umbrella term for a spectrum of coronary artery conditions characterised by imbalance in the myocardial blood supply and demand, mainly as a result of highly reduced or interrupted blood flow. It encompasses acute myocardial infarction (AMI), a condition in which heart cells are dying due to insufficient blood supply, and unstable angina (UA), a less severe condition in which a significant reduction in the blood supply causes chest pain and other symptoms associated with ACS but with no evidence of irreversible myocardial damage (Thanikachalam 2005; C. W. Hamm et al. 2011).

The typical presentation of ACS includes ischemic chest pain—constricting discomfort in the chest—which occurs with little or no physical exertion, may radiate to the arms, jaws, neck and back and may be accompanied by nausea, vomiting, dispnea (shortness of breath), diaphoresis (sweating), light-headedness or a combination of these (Achar et al. 2005; NICE 2010; C. W. Hamm et al. 2011). ACS should be distinguished from stable angina (stable chest pain) which is precipitated by physical exertion and relieved by rest or glyceryl trinitrate (GNT) within about five minutes. Atypical presentation, which does not involve typical ischemic chest pain, may occur in up to 40% of the cases subsequently diagnosed with ACS and significantly increases the probability of misdiagnosis and suboptimal treatment (Canto et al. 2000; Valensi et al. 2011).

A number of underlying conditions may cause, separately or in combination, the symptoms associated with ACS, the most common amongst them being those related to coronary artery disease (CAD). CAD is a progressive accumulation of atheromatous plaque on the walls of the coronary arteries which, in its advanced stages, results in a narrowing of the vessels' lumen—the free space in the artery—and affects the coronary blood circulation causing ischemic heart disease (Anderson et al. 2007). CAD is the most

common cause of death in the UK and accounts for 94 000 deaths each year, with approximately one in five men and one in seven women dying from the disease. It is also the most common cause of premature death, causing almost 31 000 premature deaths each year, which is approximately one fifth (19%) of premature deaths in men and one in ten (10%) premature deaths in women (British Heart Foundation 2012).

In the context of CAD, the usual mechanism through which ACS occurs is when atherosclerotic plaque gets ruptured or eroded and, through the processes of thrombogenesis and embolisation, leads to partial or total occlusion of a single or multiple epicardial arteries and the smaller downstream vessels (Thanikachalam 2005; Anderson et al. 2007). In rare cases, ACS may also occur as a result of conditions other than CAD, such as vasospasm, diffuse microvascular dysfunction and spontaneous coronary artery dissection (Krishnamurthy et al. 2004; Anderson et al. 2007; Tanis et al. 2008; Lanza & Crea 2010).
The universal definition for AMI postulates that this term should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. AMI due to a primary coronary event, such as plaque erosion or rupture, is defined as a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia;
- New or presumed new significant ST-segment–T wave changes or new left bundle branch block (LBBB) in the electrocardiogram (ECG);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and,
- Identification of an intracoronary thrombus by angiography or autopsy (Thygesen et al. 2012).

There is no universal definition for UA and it is usually defined as an objective evidence of myocardial ischemia in the clinical context of ACS but without evidence of myocardial necrosis.

Patients with ACS require urgent medical attention as delayed treatment may result in major adverse cardiac events (MACE) and death. Therefore, patients presenting with acute chest pain or other symptoms suggestive of ACS are treated as medical emergency with the initial clinical assessment aiming:

- to differentiate between ACS, other possible life-threatening conditions such as pulmonary embolism and aortic dissection, and conditions that do not require urgent medical attention; and,
- to risk-stratify patients so that appropriate referral and treatment decisions are made.

The current practice of triaging ED patients suspected to have ACS involves, as a first step, combining information from the patient's history and clinical examination, resting ECG and cardiac biomarkers. Upon admission to the ED patients undergo initial resting ECG and a blood sample is drawn to measure the level of cardiac troponins. Based on the results from the ECG, clinical examination and history patients are assigned to one of the following working diagnoses:

- ST-segment elevation ACS (ST ACS);
- Non-ST-segment elevation ACS (NSTE ACS); and
- Probably not ACS.

Persistent ST-segment elevation is indicative of a total or nearly total occlusion of a coronary artery and most of the patients with STE ACS will eventually develop ST-segment elevation myocardial infarction (STEMI). Such patients benefit from urgent reperfusion therapy and will be immediately admitted to hospital. Patients assigned to the NSTE ACS group may undergo further testing to rule in or rule out the diagnosis of ACS. Eventually, they will be diagnosed as having:

- Non-ST-segment elevation myocardial infarction (NSTEMI) if the level of cardiac troponins is elevated indicating the presence of myocardial necrosis;

- UA if the troponin level is normal but there is sufficient evidence of myocardial ischemia that explains the current symptoms; or,
- Non-ACS diagnosis.

Since none of the first line diagnostic tests, or a combination of them, are accurate enough to confirm or exclude the diagnosis of ACS in the early hours of the diagnostic process, patients suspected to have ACS but with initial normal or non-diagnostic ECG and normal troponin levels will be admitted to hospital for a short period of clinical observation and will undergo serial ECG and troponin measurement. If these tests are negative or non-diagnostic, patients may need to undergo further testing, before discharge or soon after that, to rule out the presence of myocardial ischemia (Mant et al. 2004; NICE 2010; C. W. Hamm et al. 2011).
This diagnostic algorithm, though allowing for reliable exclusion of ACS as the cause of the initial symptoms (Farkouh et al. 1998; Achar et al. 2005; J.A. Goldstein et al. 2007), is highly inefficient since only about 20% of all patients with working diagnosis of NSTE ACS admitted for clinical observation and serial testing are ultimately diagnosed with ACS (Pope et al. 2000; Goodacre et al. 2005; Bragulat et al. 2007; Pitts et al. 2008). As a result, significant pressure is put on the healthcare system, since acute chest pain and other symptoms suggestive of ACS are one of the most common reasons for emergency department visits and account for approximately 5% of all visits to the ED and up to 40% of the emergency hospital admissions in the UK (NICE 2010b).

In order to increase the efficiency of the diagnostic process, alternative diagnostic strategies have been devised, taking advantage of the new developments in cardiac imaging and biomarkers that allow faster triage of low risk patients presenting to the ED with chest pain or other symptoms suggestive of ACS (Wackers & J 2009; Than et al. 2011; James A. Goldstein et al. 2011; Reichlin 2012; Hoffmann et al. 2012). Amongst them, the use of CCTA early in the diagnostic process is particularly promising as this imaging modality allows direct visualisation of the coronary vasculature and is, therefore, able to rule out the presence of significant CAD; has a very high negative predictive value (NPV); is widely available; and is constantly evolving with the new scanners having better spatial and temporal resolution and allowing imaging at a lower radiation dose (Mowatt et al. 2008; Dewey et al. 2009; H. Alkadhi et al. 2010; Von Ballmoos et al. 2011; Samad et al. 2012).

Index test: CCTA

CCTA is a non-invasive computed tomography technique which uses x-rays to visualise the coronary artery tree, thus allowing examination of the coronary arteries for the presence or absence of CAD. A number of studies and meta-analyses have demonstrated that CCTA has a very high sensitivity (approaching 100%) for detecting significant stenosis when compared to invasive coronary angiography (ICA), the current gold standard for CAD (Vanhoenacker, Heijenbrok-Kal, et al. 2007; Mowatt et al. 2008; M. Westwood et al. 2011).

Since the absence of a significant coronary stenosis effectively rules out ACS secondary to CAD, the diagnostic utility of CCTA as a rule-out test in ED patients suspected to have ACS has been investigated in a number of studies. The focus was on patients with low to intermediate probability of ACS, who had initial normal or non-diagnostic ECG and normal troponin levels. Three meta-analyses (table 1) have shown that in this group of patients CCTA has a very high sensitivity and NPV and that a negative CCTA result effectively rules out the presence of ACS and reliably predicts the absence of MACE for at least one month after the scan.

Table 1 Summary estimates of CCTA for the diagnosis of ACS

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)
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			SDOR = summary diagnostic odds ratio CI = confidence interval			

However, CCTA has a number of limitations that merit careful consideration in policy and clinical decisions:

- **Coronary lesions with unclear functional significance.** CCTA often identifies coronary lesions with unclear functional significance or unrelated to the current episode of chest pain. This has an impact on the specificity of the test and is reflected in its relatively lower positive predictive value, making it less useful as a rule-in test, especially in patients with history of CAD (Ueno et al. 2009; Samad et al. 2012). Positive test result in low to intermediate risk patients will significantly increase the probability for ACS, thus placing low probability patients into the intermediate category, but will not be sufficient to rule in the diagnosis of ACS. Therefore, patients with a positive CT scan may have to undergo further testing to confirm the diagnosis. The unclear functional significance of the intermediate range of coronary lesions is reflected in the varying definitions of a positive CCTA result adopted in different studies. Although most studies defined a positive CT scan as 50% luminal obstruction, in some studies higher cut-off values were used (Sato et al. 2005; J.A. Goldstein et al. 2007) and intermediate lesions (51%—70% stenosis) were considered of unclear functional significance leading to further testing (J.A. Goldstein et al. 2007).
- **Non-diagnostic scans.** Non-diagnostic CT scans can happen for a number of reasons and will lead to further imaging tests involving more radiation or invasive angiography which carries a small but non-insignificant risk of bleeding and myocardial infarction. In the most recent systematic review conducted by Samad and colleagues (2012) the proportion of scans with inadequate image quality ranged from 1% to 17% across the included studies, the most common reasons being motion artefacts, previous stent placement and severe calcification (Samad et al. 2012).
- **Patient-based contraindications.** CCTA is contraindicated in a number of conditions such as pregnancy; atrial fibrillation, arrhythmia, inability to receive beta-blockers; contrast-related factors such as allergy to the contrast medium, hyperthyroidism, metformin use and renal insufficiency; and obesity. In the ROMICAT I trial the proportion of patients excluded because of contraindications to CCTA was 57% of all patients presenting to the ED with chest pain lasting >5 min (Hoffmann et al. 2009; Hendel & Dahdah 2011). At similar results arrived the retrospective study conducted by Hamid and colleagues (2010) who found that 51% of all ED patients admitted to a chest pain unit were unsuitable for CCTA (Hamid et al. 2010). A study conducted by Litt and colleagues reported significantly lower percentage of exclusions—16% of all patients randomised to the CCTA arm—but the reported data is insufficient to determine whether patients with contradictions to CCTA had not been excluded prior to randomisation (Litt et al. 2012).
- **Coronary calcium score (CCS).** Contrast-enhanced CCTA is usually preceded by a non-enhanced CT scan for cardiac calcium scoring to determine whether or not the patient should undergo contrast-enhanced CCTA which involves a higher radiation dose. Patients with severe coronary calcification are considered unsuitable for CCTA as this often results in non-diagnostic scans (Samad et al. 2012). In the current NICE guidelines, patients with CCS zero are considered CAD-negative, while patients with severe coronary calcification (CCS >400 Agatston U) should be referred directly for invasive coronary angiography (NICE 2010). The results from the recent multi-centre CONFIRM

trial showed, however, that 13% of the patients with CCS of zero had non-obstructive stenosis; 3.5% had ≥50% stenosis and 1.4% had ≥70% stenosis. Among 8,907 patients with follow-up for MACE, 3.9% with CCS of zero and ≥50% stenosis experienced an event (hazard ratio: 5.7; 95% confidence interval: 2.5 to 13.1; p <0.001) compared with 0.8% of patients with a CCS of 0 and no obstructive CAD. This shows that in symptomatic patients with CCS score zero the incidence of stenotic disease and MACE is significant and should not be ignored (Villines et al. 2011). Studies investigating the accuracy of CCTA not always report sufficient details on CCS and this information is not included in the previous meta-analyses, which may have had an impact on the reported diagnostic accuracy estimates (Samad et al. 2012).

- **Radiation.** Another issue that needs to be considered when incorporating this technique into the routine diagnostic practice is the significant level of radiation exposure involved in the CCTA scans. One multicentre study estimated the median radiation dose at 12 mSv, which is the equivalent of approximately 600 conventional chest x-rays. Significant variation in the radiation dose was found across study sites, CT systems, years of operator experience, volume of institutional cases, tube voltage, presence of sinus rhythm and scan length. Strategies to reduce radiation dose were available but some of them were not frequently used (J. Hausleiter et al. 2009). A recent study, more indicative of the current practice, has demonstrated that a significantly lower radiation dose could be achieved by using prospective ECG-gated CCTA. The median effective dose in this study was 4.5 mSv (inter-quartile range 3.5—5.4) (Gosling et al. 2010).

The new generation (>64-slice) CT scanners have better spatial and temporal resolution, involve a lower radiation dose and contrast medium and might be able to overcome some of the limitations discussed above, thus making possible the imaging of patients previously considered unsuitable for CCTA, such as obese patients, patients with high heart rates, arrhythmias, intolerance to beta-blockers, patients unable to hold their breath and patients with high levels of coronary calcium and previous stent implantations (M. Westwood et al. 2011; NICE 2012). However, previous meta-analyses that evaluated the diagnostic accuracy of CCTA for ACS in ED patients included only ≤64-slice CT scanners and may have underestimated the diagnostic performance of CCTA in this particular setting (Vanhoenacker, Decramer, et al. 2007; Athappan et al. 2010; Samad et al. 2012).

Rational

Although the diagnostic accuracy of CCTA in ED patients with low-to-intermediate probability for ACS have already been evaluated in three meta-analyses (Vanhoenacker, Decramer, et al. 2007; Athappan et al. 2010; Samad et al. 2012), they included only studies using ≤64-slice CT scanners and failed to conduct subgroup analyses due to poor reporting in the primary studies. Their results, however, may underestimate the performance of the new generation of cardiac CT scanners which have better spatial and temporal resolution and allow the imaging of patients excluded from previous studies as unsuitable for CCTA.

Therefore, we propose to conduct a systematic review with meta-analysis on studies in which ≥64-slice cardiac CT scanners have been used, including studies that compared directly early CCTA with alternative diagnostic strategies in the same patient population. Such review will produce more accurate test accuracy estimates and may be able to comment on the accuracy of CCTA as compared with other diagnostic strategies.

Objectives

Primary objectives

- To determine the diagnostic accuracy of early ≥64-slice CCTA for diagnosing ACS in ED patients with working diagnosis of NSTE ACS.
- To compare the accuracy of early ≥64-slice CCTA with that of alternative diagnostic strategies.

Investigation of sources of heterogeneity

Diagnostic accuracy studies will be examined for the presence of heterogeneity first, through visual inspection of the forest plots of sensitivities and specificities and the ROC plot of the raw data; and second, by calculating the I^2 statistics. The following sources of heterogeneity will be considered:

- Technical characteristics of CCTA scanners such as the number of detectors.
- Differences in the definition of a positive CCTA result.
- Differences in the definition of the reference standard.
- Different comparators.
- Clinical subgroups.
- Methodological quality of the included studies.

Methods

Criteria for considering studies for this review

Type of studies

- Primary diagnostic accuracy studies including prospective case series, cohort studies of consecutive patients and diagnostic RCTs.
- Studies available in English or French.

Participants

Adults presenting to the ED with:

- Symptoms suggestive of ACS; and,
- Working diagnosis of NSTE ACS; and,
- Low to intermediate probability of ACS.

Index test

The index test is CCTA with ≥64 detectors performed early in the triage process following the initial resting ECG but prior to patients being admitted for clinical observation and serial tests.

Comparator

Any diagnostic test or strategy performed in the relevant context.

Target condition

ACS including AMI—according to the third universal definition (Thygesen et al. 2012)—and UA defined as an objective evidence of myocardial ischemia in the clinical context of ACS but without evidence of myocardial necrosis.

Reference standard

Although ICA is considered the gold standard for CAD and was used as a reference standard in earlier diagnostic evaluations of CCTA for ACS, it is an invasive procedure involving small but non-insignificant risk of myocardial infarction and bleeding and, therefore, its application is not justified in low risk patients with no evidence of myocardial ischemia. Contemporary studies use composite reference standard, most often verifying a positive CT scan by ICA and a negative one by additional non-invasive testing and follow-up for at least one month. Since in this clinical setting CCTA is evaluated as a rule-out test, adding a follow-up period provides additional reassurance that none of the patients with ACS will be missed.

For the purposes of the current systematic review, we will accept any reference standard that is consistent with the current definition of ACS and, if possible, will explore the impact that variations in the reference standards has on the study outcomes.

Search methods for identification of studies

Electronic searches

- We will search Ovid MEDLINE, MEDLINE in-process, Ovid EMBASE, Science Citation Index (SCI), Medion database, Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Research Portfolio Online Reporting Tools (RePORT, formally CRISP) and International Network of Agencies for Health Technology Assessment (INAHTA).
- Also, we will perform a cited reference search for forward tracking of relevant articles on Google Scholar.
- Studies available in English or French will be considered.

Searching other resources

- Specialists in the relevant fields will be consulted and, if recommended, additional sources and publications will be considered.
- The bibliographies of the identified studies will be hand searched for additional publications.

Data collection and analysis

Selection of studies

- The first review author will review all the titles and abstracts to identify relevant articles that will be retrieved for full text review.
- Full text articles will be reviewed independently by two researchers and disagreements will be settled through discussion. If necessary, the study authors will be contacted and asked to provide additional information to resolve the uncertainty. Since the review authors who will conduct the selection process are not familiar with this field, they will not be blinded to study authors, institution, and study results during the selection process. Inter-observer agreement for the selection of articles (Cohen's Kappa) will be calculated.

Data extraction and management

Two review authors will independently extract data using a standardised data collection form developed by taking into account the Standards for Reporting of Diagnostic Accuracy (STARD) checklist (P. M. Bossuyt et al. 2003). The form will be piloted in a small subset of studies and, if necessary, changes will be made. The absolute numbers of observations of true positives, false positives, true negatives, and false negatives must be specified or must be derivable from the available data. Study authors will be contacted

to clarify any uncertainties and to obtain the complete data set. If the absolute number of observations cannot be obtained, despite contacting the authors, then the study will be excluded. Articles reanalysing or republishing data from a study population that has already been included in the review will be excluded.

Data abstracted by the two authors will be compared and any disagreements will be recorded and resolved through discussion or arbitration. The raw test accuracy data will be used to construct 2 x 2 contingency tables and to calculate sensitivity and specificity.

The following additional data will be abstracted:

1. General information: title, journal (including volume and pages), year, institution and country, language, and study design.
2. Population sampling (full description of the referral and selection process; number of participants screened, number enrolled, number completed index test, comparator and reference standard, number and reasons for drop out, description of the clinical setting).
3. Participants' characteristics (mean age; percentage of male patients enrolled; mean heart rate, body mass index, number of patients receiving Beta-blockers; history of CAD, coronary calcium score, risk factors, risk score, reasons for exclusion).
4. Full description of the diagnostic strategies and the included tests such as: manufacturer, model, technical characteristics, protocols, definition of a positive test result, frequency of and reasons for non-diagnostic results, level of expertise and inter-observer agreement between clinicians interpreting test results.
5. Reference standard: protocols and follow up; time period between index test and reference standard; measures of reproducibility.
6. Adverse events from performing the index test and the reference standard.
7. QUADAS 2 items.

Assessment of methodological quality

Adapted version of QUADAS 2 checklist will be used to guide the methodological quality assessment of the included studies (Whiting et al. 2011). The results from the methodological quality assessment will be used in the sensitivity analysis to evaluate the impact of each methodological quality item on the results; and will inform the meta-analysis of the included studies.

Two review authors will independently assess study quality and disagreements will be settled through discussion or arbitration.

Statistical analysis and data synthesis

We will construct 2x2 tables and calculate sensitivity and specificity, with 95% confidence intervals (CI), for each test/strategy, provided sufficient data is available. We will use RevMan 5.1.6 or similar software to create coupled forest plots to evaluate the variation in the estimates of sensitivity and specificity within each subset of data. We will plot the results of studies for each subset of data in a receiver operator characteristic (ROC) space. Sensitivity will be used to define the y-axis, 1 - specificity will define the x-axis, and each point on the plot will therefore represent the proportion of true positives against the proportion of false positives for one particular study. We will construct the ROC plots with each study being represented by a rectangle whose height relates to the number of diseased and whose width relates to the number of non-diseased participants.

If appropriate, we will conduct meta-analyses of study-specific pairs of sensitivity and specificity to create a summary ROC curve in the SROC space using the random-effects hierarchical SROC model of Rutter and Gatsonis (Rutter & C. A. Gatsonis 2001). Covariates will be added as source of heterogeneity.

Sensitivity analysis

In order to assess whether the methodological quality of the included studies influences the results, sensitivity analysis will be carried out using each individual quality item as a covariate in a bivariate regression model.

Assessment of reporting bias

We will contact the authors of those studies that were excluded because they did not report specific outcome measures of interest to inquire whether these data are available but had not been published. If data are available and meet the inclusion criteria, we will include them in our analysis. We will contact the authors of relevant papers to determine if they are aware of existing unpublished data that had not been included in the review. If appropriate, we will assess publication bias qualitatively (Deeks et al. 2005).

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