# Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials

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| **Background** | Assessment of chest pain patients remains a clinical challenge in the emergency department (ED). Several randomized controlled trials (RCTs) have shown the additive value of coronary computed tomographic angiography (CCTA) compared with standard care. Not all of them, however, had enough power to detect differences in clinical outcomes like revascularization. Therefore, we performed a meta-analysis to test the safety and efficacy of this non-invasive diagnostic approach in low- and intermediate-risk chest pain patients. |
| **Methods** | MEDLINE/PubMed was systematically screened for RCTs comparing CCTA and non-CCTA approaches for ED patients presenting with chest pain. Baseline features, diagnostic strategies, and outcome data were appraised and pooled with random-effect methods computing summary estimates [95% confidence intervals (CIs)]. |
| **Results** | A total of four RCT studies including 2567 patients were identified, with similar inclusion and exclusion criteria. Patients in the CCTA group were more likely to undergo percutaneous or surgical revascularization during their index visit, with an odd ratio of 1.88 (1.21–2.92). Time to diagnosis was reduced with CCTA ($-7.68$ h; $-12.70$ to 2.66) along with costs of care in the ED ($-\$680$; $-1.060$ to $-270$: all CI 95%). |
| **Conclusion** | The present meta-analysis shows that a strategy with CCTA used as first imaging test for low- and intermediate-risk patients presenting to the ED with chest pain appears safe and seems not to increase subsequent invasive coronary angiographies. The approach is cost-effective although limited data and incomplete cost analyses have been performed. CCTA increases coronary revascularizations, with still an unknown effect on prognosis, especially in the long term. |
| **Keywords** | Coronary computed tomographic angiography • Low-risk chest pain • ED |

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# Introduction

Chest pain represents one of the most common reasons for admission to an emergency department (ED), with up to eight million patients with clinical suspicion of acute coronary syndrome (ACS)[1,2] presenting each year in the USA.

These patients present a clinical challenge: up to 85% of them will be shown not to have active cardiac ischaemia, but many of them are admitted to hospital, due to the risk of missing adverse events. Despite new and more sensitive clinical biomarkers, clinical decision rules, and risk scores,[3-8] concerns regarding presentation with atypical symptoms along with the negative consequences of failing to detect ACS drive both ED physicians and cardiologists to take a more cautious approach. While the latter may reduce diagnostic errors, it is certainly time-consuming and more expensive, accounting for up to $10–12 billion annually in the USA.[8] Nonetheless, 2–5% of time-sensitive ACS cases are still missed,[9-11] and underdiagnosed ACS accounts for ~30% of all malpractice judgements.[12]

The definitive way to exclude active ischaemia is demonstration of a disease-free coronary system, as negative coronary angiography engenders a low risk of future cardiac events.[13,14] Coronary computed tomographic angiography (CCTA) is a non-invasive test with a negative predictive value (NPV) of approximately 100% for detection of coronary artery stenosis compared with catheter angiography.[15] It also allows an accurate assessment of the severity of coronary stenosis.[16-19] Clinical application of CCTA has been assessed in several observational studies and has shown good efficacy in terms of detection of coronary disease as well as economic advantages.[20]

Several randomized controlled trials (RCTs) have shown the additive value of CCTA compared with standard care but were under-powered to detect differences in clinical outcomes, like rates of revascularization. Therefore, we performed a meta-analysis to evaluate the safety and efficacy of this non-invasive diagnostic approach in low- and intermediate-risk chest pain patients.

# Methods

## Data sources

The terms 'Coronary computed tomographic angiography or CCTA', 'Emergency Department', and 'chest pain or acute coronary syndrome' were searched across MEDLINE, EMBASE, and Cochrane databases according to optimal search strategies.[20]

Reference lists of included articles were also reviewed. No language restrictions were imposed. The corresponding authors of all short-listed studies were directly contacted for additional data and invited to participate in data analysis and interpretation, as well as suggestions of additional studies.

## Study selection

RCTs comparing a CCTA approach and a non-CCTA approach for patients presenting to the ED with chest pain were included.

The outcomes of interest were (a) safety outcomes including rates of coronary angiography and of revascularization during index visit and (b) efficacy outcome including time to diagnosis, rates of direct discharge from the ED, and costs of ED care.

Three investigators (G.B.Z., E.C., and F.D.A.) independently appraised titles, abstracts, and the full texts to determine whether studies met inclusion criteria. Conflicts between reviewers were resolved through re-review and discussion, *Figure 1*.

## Data extraction and quality assessment

Three authors (G.B.Z.; E.C.; F.D.A.) independently abstracted data on study design, setting, CCTA protocol, and control group protocol. Age, gender, cardiovascular risk factors, and clinical presentations were also evaluated. In-hospital outcomes were: direct discharge from ED, time to diagnosis, rates of coronary angiography, of revascularization (both percutaneous and surgical), and costs of care. The follow-up outcomes were the rates of ED re-admissions.

The quality of included trials was assessed according to Cochrane, PRISMA, and QUORUM statements[21,22]; methods to obtain sample size, selection bias (allocation and random sequence generation), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), and attrition bias (incomplete outcome data) were assessed and graphically described.



**Figure 1** Review's profile.
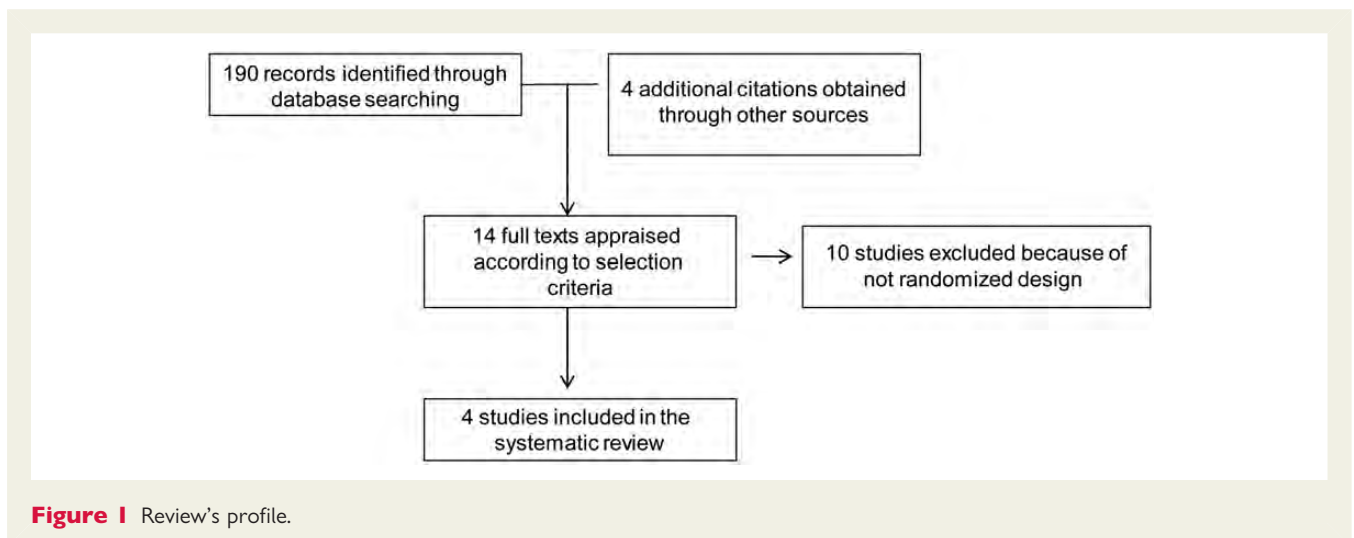
The Jadad Scale[23] was used to appraise the methodological quality of the included studies.

## Data synthesis and analysis

Random-effects models were used to compute dichotomous comparisons. Fixed effects models were also tested and their results reported only if different from random effect. RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q-test, with $I^2$ values of 25, 50, and 75% representing mild, moderate, and extensive statistical heterogeneity, respectively. A funnel plot analysis was performed to identify small study bias.

## Results

The abstracts of 194 studies were initially appraised. Many of them were excluded for not meeting the inclusion criteria. In total, 10 further studies[9,15,24–31] were excluded because of non-randomized design.[32–35]

Finally, we included four randomized control trials with a total of 2567 patients (*Tables 1–3*); their median age was 50 years (49.751.25), about half of them (48%; 47–50) were male, 39% (38–45) suffered from hypertension, 34% (31–35) were hyperlipidemic, and 11% (9–13) diabetic. The median thrombolysis in myocardial infarction (TIMI) risk score was 1.01 (0.07–1.24).

The inclusion and the exclusion criteria were similar; briefly the selected studies randomized patients presenting with chest pain to the ED, without ischaemic ECG changes or raised cardiac biomarkers, and not reporting a history of coronary artery disease (CAD).

With regard to in-hospital outcomes, patients in the CCTA group were more likely to undergo percutaneous or surgical revascularization during their index visit, with an odds ratio (OR) of 1.88 (1.21–2.92). Time to diagnosis was significantly reduced

(−7.68 h; −12.70 to 2.66), along with costs of care in the ED (−$680; −1.060 to −270: all confidence interval (CI) 95%), while rates of direct discharge were lower, although not significant (OR 1.53; 0.51–4.63).

Follow-up duration was of 6 months in 2 studies, and 2 months in the two remaining: no differences were reported in ED re-attendance (OR 0.94; 0.67–1.32) (see *Figures 2–7*).

The risk of bias of included RCTs (evaluated both with JADAD scale and Cochrane) was low, especially regarding blinding and selection bias (Supplementary data online, *Figure SA* and *Table SA*).

## Discussion

This systematic review and meta-analysis showed that CCTA is a safe and efficacious strategy for low and intermediate risk patients presenting with chest pain to the ED.

CCTA offers the chance to exclude CAD safely in many ED patients, having also the potential to lead to additional diagnostic testing and therapeutic interventions. Although previous studies report good sensitivity and NPV,[36–39] rates of false-positive results are still a concern. Some authors have suggested that this may lead to additional and unwarranted testing[40,41] and therapies and to unnecessary and potentially hazardous procedures with an increased health care expenditures. In our meta-analysis, both diagnostic paths appear to generate the same rates of angiographic procedures even if we recorded an increased rate of percutaneous or surgical revascularization in the CCTA group during the index visit. It is possible that a coronary lesion detected with CCTA imaging could influence the operator in the choice to perform the angioplasty, much more than if patients are selected for angiography by a positive-stress test with or without imaging. More generally, the impact on survival of non-ischaemia provoking coronary lesions in patients with atypical chest pain is still undefined,[42]

**Table 1** Main features of included studies

| Study | Number of patients | Location | Follow-up (months) | CCTA protocol | Control group protocol |
|---|---|---|---|---|---|
| Goldstein, JACC 07 | 99 vs 98 | USA | 6 | Imaging was performed on a 64-slice MSCT scanner. Sensation 64 Cardiac, Siemens Medical Systems, Forchheim, Germany). An initial non-enhanced electrocardiogram-gated can was acquired for calcium scoring | Patients underwent serial electrocardiograms and cardiac biomarkers at 4 and 8 h after their baseline studies and standard same-day rest-stress myocardial perfusion SPECT imaging |
| Goldstein, JACC 11 CT-STAT | 361 vs 338 | USA | 6 | Imaging was performed on CCTA scanners available at each institution including 64320-slice scanners. Contrast-enhanced images were obtained using 60–100 mL Ultravist 300 (Bayer HealthCare, Montville, NJ, USA) model | Stress testing was done only if the resting studies were normal; these included symptom-limited standard exercise treadmill or pharmacological (adenosine or dipyridamole) |
| Hoffmann 12, ROMICAT II | 501 vs 499 | USA | 1 | CCTA | Standard care |
| Litt, NEJM 12 | 908 vs 462 | USA | 1 | CCTA was performed with the use of a 64-slice or greater multi-detector CT scanner that could be used to perform ECG-synchronized cardiac studies | The patient's health care provider decided which tests, if any, were to be performed |

**Table 2** Inclusion and exclusion criteria

| Study | Inclusion | Exclusion |
|---|---|---|
| Goldstein, JACC07 | Chest pain or angina equivalent symptoms compatible with ischaemia during the past 12 h; age > 25 years; prediction of a low-risk of infarction and/or complications | Known CAD; electrocardiograms diagnostic of cardiac ischaemia and/or infarction (significant Q waves, ST-segment deviations of >0.5 mm, or T-wave inversion); elevated serum biomarkers including creatine kinase-MB, myoglobin, and/or cardiac troponin I on initial, and 4-h testing; previously known cardiomyopathy, with estimated ejection fraction <45% contraindication to iodinated contrast and/or beta-blocking drugs; atrial fibrillation or markedly irregular rhythm; renal insufficiency (creatinine > 1.5 mg/dL) |
| Goldstein, JACC11 CT-STAT | Chest pain suspicious for angina based on an ED physician's history taking and physical examination; age > 25 years; time from onset of chest pain to presentation>12 h; time from ED presentation to randomization >12 h; normal or non-diagnostic rest ECG at the time of enrolment, without ECG evidence of ischaemia (i.e. ST-segment elevation or depression <1 mm in 2 or more contiguous leads, and/or T-wave inversion>2 mm TIMI risk score <4 for unstable angina or non−ST-segment elevation myocardial infarction | Known CAD; elevated serum biomarkers including creatine kinase−myocardial band, myoglobin, and/or troponin I ischaemic ECG changes, as denoted in the preceding text; previously known cardiomyopathy, with an estimated ejection fraction of <45%; contraindication to iodinated contrast and/ or beta-blocking drugs; atrial fibrillation, or markedly irregular rhythm; elevated serum creatinine levels (creatinine > 1.5 mg/dL) |
| Hoffman 12, ROMICAT II | >5 min of chest pain or equivalent in the last 24 h 40−74 years of age sinus rhythm | New diagnostic ischaemic ECG changes troponin elevation documented or self reported history of CAD >6 h since presentation with pain impaired renal function clinical instability contraindication to CT |
| Litt, NEJM 12 | Patients 30 years of age or older with signs or symptoms that were consistent with a possible ACS were eligible if the treating physician determined that they would require admission or objective testing to rule out an ACS the electrocardiogram (ECG at presentation did not reveal acute ischaemia, and if the patient had an initial thrombolysis in myocardial infarction risk score of 0−2). | Symptoms that were clearly non-cardiac in origin had a coexisting condition that necessitated admission regardless of whether they might have an ACS had had normal findings on CCTA or invasive angiography in the previous year contraindications to CCTA |

**Table 3** Clinical features of patients presenting with chest pain at ED

| | Age (years) | Male Gender (%) | Hypertension (%) | Hyperlipidemia (%) | Diabetes (%) | Median TIMI risk score |
|---|---|---|---|---|---|---|
| Goldstein, JACC 07 | 50 | 45 | 39 | 34 | 11 | 1.27 |
| Goldstein, JACC 11 CT-STAT | 50 | 47 | 37 | 35 | 7 | 1.01 |
| Hoffman 12, ROMICAT II | 55 | 53 | 54 | 45 | 17 | – |
| Litt, NEJM 12 | 49 | 49 | 51 | 27 | 14 | 0.98 |

potentially representing the aetiology of the ED presentation or merely an incidental finding. A feasible solution to this diagnostic challenge is the use of fractional flow reserve (FFR), which has a role in reducing unnecessary percutaneous coronary intervention and possibly rates of adverse cardiac events.[43] Recently, non-invasive FFR[44] derived from CCTA images has demonstrated encouraging results, but this technique has still to be investigated and validated in larger settings. CCTA may therefore represent the first step to detect atherosclerosis, allowing physicians to suggest appropriate lifestyle modification and pharmacological therapies, while percutaneous transluminal coronary angioplasty guided by FFR may avoid unnecessary stenting.

Both diagnostic strategies enable ED physicians to discharge a similar rate of patients, while the major advantage of CCTA is its ability to rule out any CAD rapidly, thereby facilitating the diagnosis and improving cost-effectiveness.

CCTA reduces costs of care in the ED, which are one of the growing concerns in modern health care. Over the last two decades, studies concerning acute chest pain management have demonstrated the usefulness of imaging techniques, with significant reductions in hospital admission rates,[43,45−47] but only limited data on CCTA are currently available. Although only 3 of the 4 selected studies performed financial analysis,[33−35] we have estimated a significant overall reduction in the cost of care with CCTA in the ED.
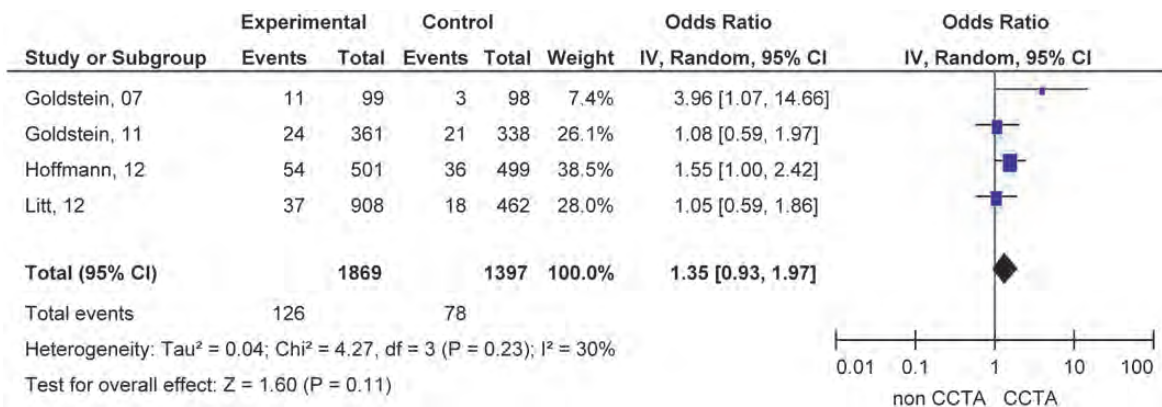
| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Goldstein, 07 | 11 | 99 | 3 | 98 | 7.4% | 3.96 [1.07, 14.66] |
| Goldstein, 11 | 24 | 361 | 21 | 338 | 26.1% | 1.08 [0.59, 1.97] |
| Hoffmann, 12 | 54 | 501 | 36 | 499 | 38.5% | 1.55 [1.00, 2.42] |
| Litt, 12 | 37 | 908 | 18 | 462 | 28.0% | 1.05 [0.59, 1.86] |
| Total (95% CI) | | 1869 | | 1397 | 100.0% | 1.35 [0.93, 1.97] |
| Total events | 126 | | 78 | | | |

Heterogeneity: Tau² = 0.04; Chi² = 4.27, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 1.60 (P = 0.11)

**Figure 2** Rates of patients undergoing coronary angiography during index access to ED.

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Goldstein, 07 | 5 | 99 | 1 | 98 | 4.2% | 5.16 [0.59, 44.99] |
| Goldstein, 11 | 13 | 361 | 8 | 338 | 24.5% | 1.54 [0.63, 3.77] |
| Hoffmann, 12 | 29 | 501 | 18 | 499 | 54.1% | 1.64 [0.90, 3.00] |
| Litt, 12 | 23 | 908 | 4 | 462 | 17.2% | 2.98 [1.02, 8.66] |
| Total (95% CI) | | 1869 | | 1397 | 100.0% | 1.88 [1.21, 2.92] |
| Total events | 70 | | 31 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)

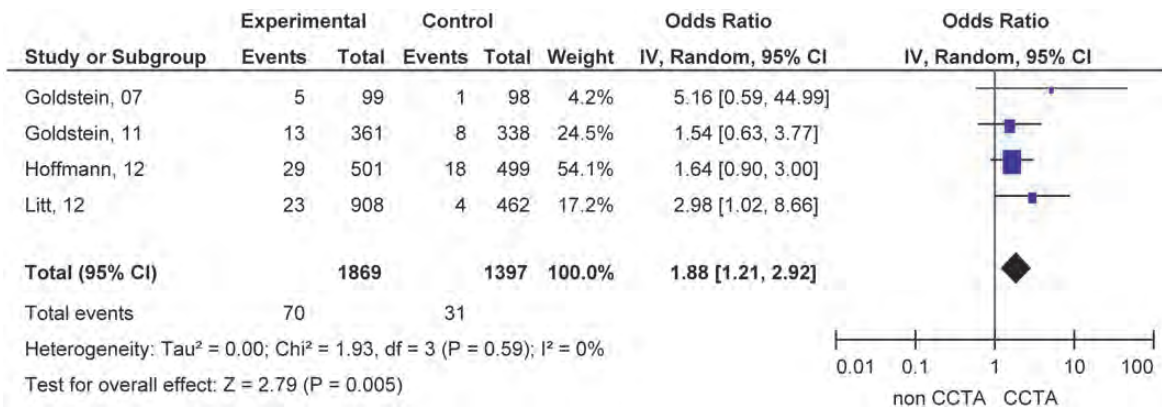**Figure 3** Rates of patients undergoing coronary revascularization (both percutaneous and surgical) during index access to ED.

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Goldstein, 07 | 88 | 99 | 95 | 98 | 19.8% | 0.25 [0.07, 0.94] |
| Goldstein, 11 | 262 | 361 | 271 | 338 | 26.6% | 0.65 [0.46, 0.93] |
| Hoffmann, 12 | 233 | 501 | 62 | 499 | 26.7% | 6.13 [4.46, 8.43] |
| Litt, 12 | 450 | 908 | 105 | 462 | 26.9% | 3.34 [2.59, 4.30] |
| Total (95% CI) | | 1869 | | 1397 | 100.0% | 1.53 [0.51, 4.63] |
| Total events | 1033 | | 533 | | | |

Heterogeneity: Tau² = 1.17; Chi² = 102.25, df = 3 (P < 0.00001); I² = 97%
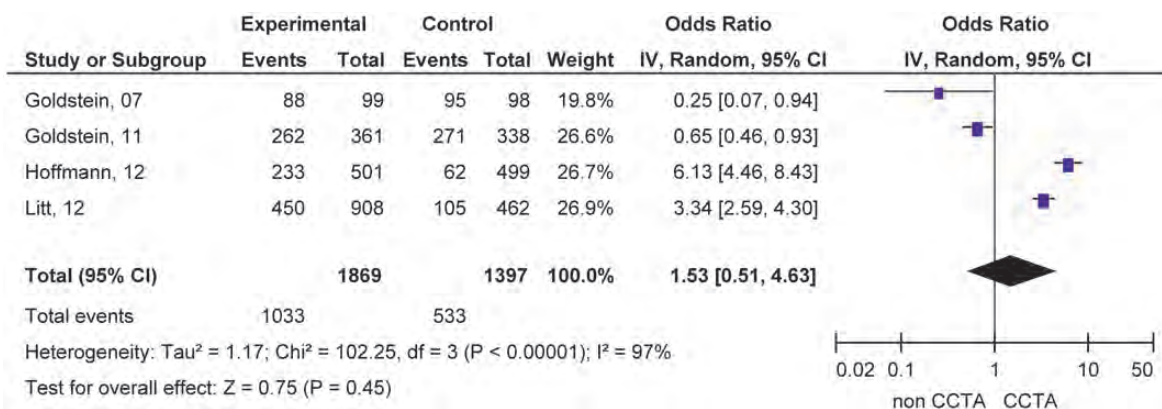Test for overall effect: Z = 0.75 (P = 0.45)

**Figure 4** Rates of direct discharge from ED.
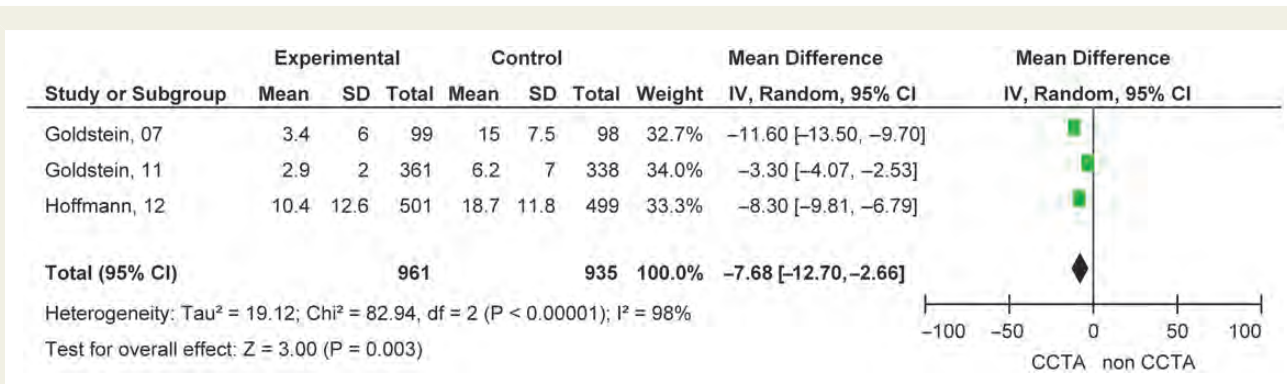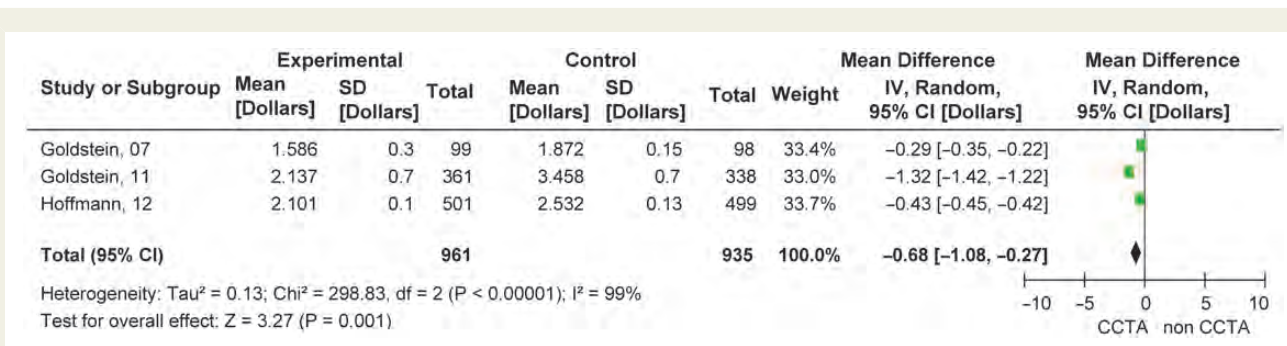
**Figure 5** Time to diagnosis.



**Figure 6** Costs of care in ED (expressed as thousands of dollars).
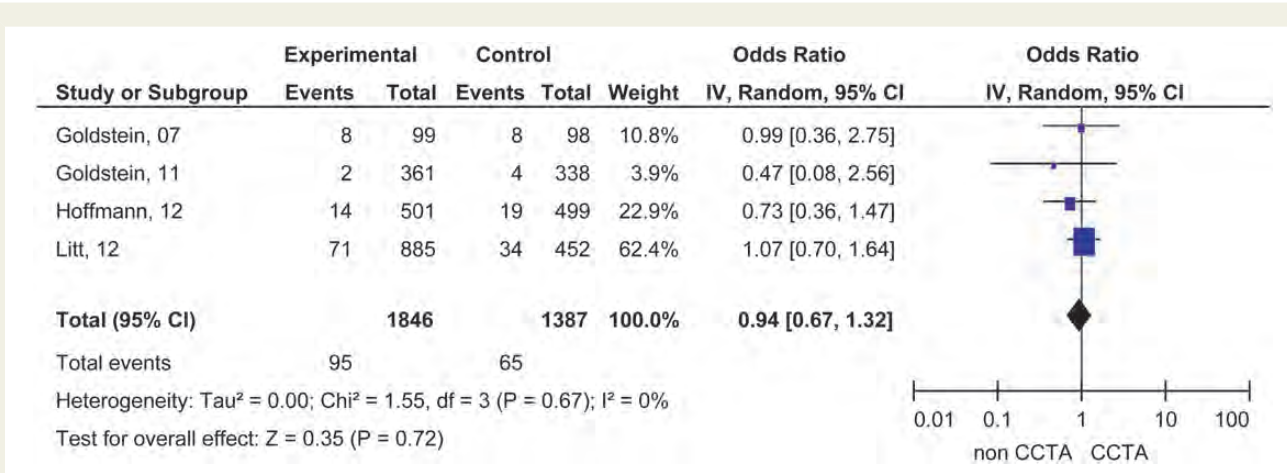


**Figure 7** Rates of ED re-admission after the index one during follow-up a median of 3.4 months (1–6).

Some argue that current studies lack a substantial true cost analysis, (e.g. for increased revascularization) and also fail to consider the large number of patients ineligible for the designed approach and the frequent requirement for additional downstream testing[48]; however, these analyses have not considered the indirect effects of more rapid discharge on ED overcrowding. Moreover in a recent editorial,[49] it was reported that ROMICAT 2 suffered from bias because including patients only during 'weekday daytime hours'; however, a significant reduction in time to diagnosis persisted also after the exclusion of this limitation (OR −7.13; −10.90 to −3–30; all CI 95%).

The CCTA approach shares several important limitations. At least 64-slice devices are now mandatory for optimal diagnostic accuracy, but this expensive equipment is not available in all EDs and

even if available, its use may be limited by time pressures or by lack of appropriately skilled staff.[50] The use of ionizing radiation is another important concern. The often-reported estimated exposure is between 6 and 11 mSv, extending to 16 mSv if functional evaluation is performed; however, recent studies reported newer CT techniques providing lower amount of radiations, also when compared with other technology like single-photon emission computed tomography (SPECT). CCTA may be associated with a considerable x-ray exposure in women, who represent the majority of patients with less than high-risk chest pain seen in the ED (52% in this meta-analysis; also reported as prevalent in young women in a previous study[51]). Unfortunately, a lack of data makes difficult to include a direct comparison between radiation's burden in the different strategies the future goal will be the introduction of novel techniques to minimize the CT dose while preserving an optimal diagnostic accuracy.[52,53]

Beyond the performance of CCTA, other factors may limit its use in ED patients. There may be un-interpretable segments on 64-slice CCTA, excessive cardiac motion, or prominent coronary artery calcification[54–56] that may cause motion artefact preventing accurate interpretation of that segment. The most common reasons for not performing CCTA include renal insufficiency, arrhythmias or beta-blockers intolerance, suspected allergy, and an inability to complete the study because of contrast extravasation or claustrophobia. Overall, these conditions may limit performing CCTA to between 25 and 60% of ED chest pain patients.[57–59] In our work, we could not perform an overall analysis on the percentage of patients undergoing CCTA. Only in the study of Litt *et al.* it was reported that CCTA examination could not be performed in 16% of subjects who were assigned to that group, most commonly as a consequence of elevated heart rate.

Our meta-analysis has some limitations, typical of all reviews'. A low-risk of bias was reported for most of the included studies, inconsistency was <50% for most of the examined outcomes, and no differences were found between random and fixed effects. The most important limitation in this study is the absence of long-term follow-up, which may increase knowledge about safety of CCTA. The other is the absence in one study of economical analysis, and in two, of the overall cost for the two arms, being limited to ED management. Moreover, the control group was based also on an imaging test, like scintigraphy, an approach that may not reflect every-day clinical practice. Another limitation is that the paper of Litt *et al.* reported all-cause re-admissions, while the others reported only 'chest pain': after excluding this paper, however, the significance did not change (OR 0.76 [0.44–1.31]; $I^2 = 0$%). Moreover, under-powered sample size may explain the lack of significance both for rates of angiography and for direct discharge, the latter being influenced also from different definitions. In two studies, indeed, direct discharge was defined as discharge within 6 h.[34,35]

The present meta-analysis shows that a strategy with CCTA used as first imaging test for low- and intermediate-risk patients presenting to the ED with chest pain appears safe and seems not to increase subsequent invasive coronary angiographies. The approach appears cost-effective although limited data and incomplete cost analyses have been performed. CCTA increases coronary revascularizations, with a still unknown long term effect on prognosis.

# Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

**Conflict of interest:** none declared.

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