Early computed tomography coronary angiography in adults presenting with suspected acute coronary syndrome: the RAPID-CTCA RCT

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Scientific summary

The RAPID-CTCA RCT

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Scientific summary

Background

Acute chest pain is an extremely common complaint in patients presenting to the emergency department (ED). Such patients are evaluated for acute coronary syndrome with urgent diagnostic investigation, including a 12-lead electrocardiogram (ECG) and cardiac troponin level measurement, so that those with or at risk of acute coronary syndrome receive prompt treatment with therapies such as antiplatelet agents and coronary revascularisation. These interventions may reduce the risk of progressing to or recurrence of myocardial infarction and improve longer-term clinical outcomes.

The lack of clarity on optimal diagnostic work up has led to the development of clinical decision tools and risk scores that not only can 'rule in' or 'rule out' acute coronary syndrome but also quantify the risk of underlying coronary artery disease and guide further investigation with functional or anatomical testing. Recent international guidelines have proposed that patients at low or intermediate risk of coronary artery disease should undergo further investigation if acute coronary syndrome is suspected, including stress testing and non-invasive [computerised tomography coronary angiography (CTCA)] or invasive coronary angiography.

Several North American trials have explored the role of CTCA in patients with low-risk chest pain presenting to the ED. These studies showed that CTCA increased the rates of hospital discharge and resulted in shorter lengths of stay. However, trial participants were at low risk of coronary heart disease (CHD) and had extremely low rates of cardiovascular events, leading some to suggest that non-invasive testing was unnecessary and only simple clinical evaluation was required.

To the best of our knowledge, the strategy of early CTCA in patients with intermediate-risk acute chest pain has not been investigated or established. Such a strategy could allow identification of patients who would benefit from additional therapeutic interventions, thus improving clinical outcomes. In patients without disease, CTCA may reduce the need for invasive coronary angiography, shorten hospital stay and avoid recurrent hospitalisations. This may be of benefit in hospitals without on-site invasive coronary angiography facilities or for patients who do not have obstructive or actionable coronary artery disease. However, if CTCA does not influence patient investigations, treatments and outcomes, it may increase the cost and patient risk without any clinical benefit.

Aims and objectives

This study aimed to investigate the effect of early CTCA in patients with suspected or provisionally diagnosed acute coronary syndrome presenting to the ED, acute medicine or cardiology services on interventions, event rates and health-care costs in a pragmatic clinical trial and an economic evaluation up to 1 year after the trial intervention.

The primary objective was to investigate the effect of the intervention by comparing all-cause death or subsequent non-fatal type 1 or type 4b myocardial infarction at 1 year.

The secondary objectives aimed to investigate the effect of early CTCA on:

- the use of cardiovascular treatments during index hospitalisation and the use of preventative therapies on hospital discharge
- the proportion of patients undergoing invasive coronary angiography and revascularisation

- the length of stay for index hospitalisation
- the proportion of patients reattending or readmitted to hospital with suspected acute coronary syndrome or recurrent chest pain, for up to 1 year
- the use of NHS resources, including hospitalisation and other investigations and interventions, for up to 1 year
- the proportion of patients with symptoms and morbidity and mortality rates, for up to 1 year
- quality of life, for up to 1 year
- the incremental cost per quality-adjusted life-year (QALY) gained by providing CTCA compared with current standard practice.

Methods

Trial design

A prospective, multicentre, open, parallel-group randomised controlled trial (RCT) with blinded primary end-point adjudication.

Setting

The trial was delivered in 37 UK regional and district hospitals, with participants recruited in EDs, acute medical services and cardiology departments.

Eligibility, recruitment and randomisation

Patients were eligible to participate if they were aged ≥ 18 years with symptoms mandating investigation for acute coronary syndrome, with at least one of the following:

- history of coronary artery disease
- cardiac troponin level elevation above the 99th centile of the normal reference range
- ECG abnormalities, such as ST segment depression of > 0.5 mm.

Patients were excluded if they met any of the following criteria:

- They exhibited signs, symptoms or investigations supporting high-risk acute coronary syndrome.
- They were unable to undergo CTCA.
- They had had invasive coronary angiography or CTCA within the last 2 years and the previous investigation revealed obstructive coronary artery disease or they had had either investigation within the last 5 years and the result was normal.
- They had previously been recruited to the trial.
- They were known to be pregnant or were currently breastfeeding.
- Inability to consent.
- Further investigation for acute coronary syndrome would not be in the patient's interest, owing to limited life expectancy, quality of life or functional status.
- They were prisoners.

Trial intervention

Electrocardiogram-gated calcium scores and contrast-enhanced CTCAs were conducted using ≥ 64-slice scanners. All centres were encouraged to use radiation and heart rate reduction techniques and sublingual glyceryl trinitrate. CTCAs were reported at each recruiting centre in accordance with the Society of Cardiovascular computerised tomography guidelines and the American Heart Association coronary artery segment model. Standard care was at the discretion of the attending clinician.

Outcomes

The primary end point was all-cause death or subsequent type 1 (spontaneous) or type 4b (stent thrombosis) myocardial infarction at 1 year, measured as time to first such event.

Key secondary end points included (1) CHD death or subsequent non-fatal myocardial infarction, (2) cardiovascular disease death or subsequent non-fatal myocardial infarction, (3) subsequent non-fatal myocardial infarction, (4) CHD death, (5) cardiovascular death and (6) death from any cause.

Safety was measured by reporting (1) adverse events and serious adverse events, (2) the proportion of patients with alternative cardiovascular diagnoses identified on CTCA, (3) the proportion of patients with non-cardiovascular diagnosis identified on CTCA and (4) radiation exposure from CTCA in the CTCA arm during index hospitalisation.

Cost-effectiveness was measured by estimating the lifetime incremental cost per QALY gained.

Data collection for primary, secondary and safety clinical outcomes

Data were collected from NHS records or trial-specific documentation and included the following categories: eligibility criteria, consent and baseline demographics, comorbidities, regular treatment, ECG results, vital signs, blood results, admission and discharge diagnoses, relevant investigations or interventions, length of stay, repeat hospitalisations and adverse events. Data were also collected on the trial intervention, including timing, procedural details, radiation dose, reporting clinician, incidental findings and any intervention-related adverse events.

Collection of cost and health outcome data

The length of stay, and major adverse cardiac events were recorded from NHS records and telephone contact with patients, and deaths were recorded from the central registry office or equivalent. At baseline and 1, 6 and 12 months, quality of life and angina symptoms were measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and World Health Organization ROSE angina questionnaires by direct patient interview, postal survey or e-mail survey, with telephone follow-up for non-responders after two mailings 2 weeks apart.

Sample size

The original aim was to recruit 2424 evaluable patients (1212 patients per arm) to have 90% power to detect a 20% compared with a 15% difference in 1-year death or subsequent type 1 or type 4b myocardial infarction rate (20% in standard-care arm compared with 15% in CTCA arm), two-sided $p < 0.05$. After a review of the first 716 participants, the overall event rate was 6.8% [95% confidence interval (CI) 5.2% to 8.9%]. Given this and trial progress, we recalculated the sample size to be 1735 participants to detect a 3.4% absolute risk reduction at a revised primary event rate of 6.8%, with 80% power and two-sided $p < 0.05$. The revised sample size was calculated to recruit at least 1720 patients (not allowing for missing data), at least 1735 with expected loss to follow-up rates, which would provide the trial the opportunity to detect a 3.4% absolute risk reduction at the primary event rate of 6.8%, with 80% power and two-sided $p < 0.05$.

Clinical effectiveness and cost-effectiveness analysis

The trial was reported on an intention-to-treat basis. The primary outcome was defined as the first event of all-cause death or subsequent type 1 (spontaneous) or 4b (stent thrombosis) myocardial infarction. Time to primary outcome was defined as the time from randomisation to the primary outcome. Patients discontinuing the study prior to reaching the primary outcome had their time to primary outcome censored at the last contact date. The relationship between the intervention and the primary outcome was analysed using Cox proportional hazard regression adjusted for study site (used to stratify the randomisation), baseline Global Registry of Acute Coronary Events (GRACE) score and previous coronary artery disease. In the within-trial cost-effectiveness analysis, incremental cost per QALY gained by using CTCA compared with standard care was estimated by calculating the area under the curve for health utility using the EQ-5D-5L scores and health service costs for up to 1 year. We updated an existing decision-analytic model and used it to estimate the costs and QALYs for patients surviving beyond 1 year, and, therefore, estimate the lifetime incremental cost per QALY gained by using CTCA compared with standard care.

Results

Trial population

Between 23 March 2015 and 27 June 2019, we recruited 1749 patients, with 1748 participants available for analysis. The mean age of the participants was 62 years [standard deviation (SD) 13 years] and 1114 (63.7%) were male. At recruitment, 601 (34.4%) participants had prior CHD, 1004 (57.4%) had elevated cardiac troponin levels and 1064 (60.9%) had an abnormal ECG. Chest pain was the primary complaint in 1549 (88.7%) participants, with 857 (49.0%) having an acute coronary syndrome diagnosis (myocardial infarction or unstable angina) at discharge from their index hospitalisation. The mean GRACE score was 115 (SD 35), with 410 (23.5%) participants having a GRACE score of > 140. Baseline characteristics, enrolment, randomisation and follow-up were well matched between trial arms.

Trial intervention

Of those randomised to receive CTCA, 767 (87.4%) underwent CTCA. The median time from randomisation to CTCA was 4.2 hours (interquartile range 1.6 to 21.6 hours). The CTCA scan was of diagnostic quality in 700 (91.3%) participants, and CTCA delivered a median effective radiation dose of 3.1 mSv (interquartile range 1.9–5.5 mSv) (0.014 mSv/mGy/cm conversion factor) and was associated with four related adverse events (one readmission with a possibly related non-cardiac condition and three non-serious adverse events related to the intravenous cannula). A small number of participants in the standard-care arm (48, 5.5%) underwent CTCA within 30 days of randomisation: 33 cases within the first 3 days.

Computerised tomography coronary angiography identified normal coronary arteries in 178 (23%) participants, non-obstructive disease in 222 (29%) participants and obstructive disease in 359 (47%) participants. Greater severity of coronary artery disease was associated with increasing age, male sex, prior CHD, troponin level elevation and GRACE score, as well as the use of invasive coronary angiography and subsequent revascularisation.

Primary and key secondary outcomes

The primary outcome of all-cause death or non-fatal myocardial infarction (type 1 or 4b) within 12 months occurred in 51 (5.8%) out of the 877 participants in the early CTCA arm and 53 (6.1%) out of the 871 participants in the standard-care arm [adjusted hazard ratio (HR) 0.91, 95% CI 0.62 to 1.35; $p = 0.65$]. For the prespecified subgroup analysis for the primary outcome, there was no statistically significant heterogeneity for any comparison. Key secondary outcomes related to causes of death (all-cause, CHD, cardiovascular death) and non-fatal myocardial infarction were also similar. There was no evidence of a difference between allocated treatment arms for any of the comparisons.

Patient treatment and satisfaction

Participant satisfaction (rated excellent or very good on a five-point Likert scale) was higher in the early CTCA arm than in the standard-care arm (83.3% vs. 79.7%). The attending clinician reported increased diagnostic certainty following CTCA: mean increase of 1.4 points (SD 2.2 points) on a scale from 0 to 10 points (from 7.1 to 8.5 points, with 10 points being the most certain). Fewer participants in the CTCA arm than in the standard-care arm received invasive coronary angiography: 474 (54.0%) compared with 530 (60.8%), respectively (adjusted HR 0.81, 95% CI 0.72 to 0.92; $p = 0.001$). Despite fewer invasive coronary angiograms in the CTCA arm than in the standard-care arm, there was no evidence of a difference in the rates of coronary revascularisation by trial allocation (adjusted HR 1.03, 95% CI 0.87 to 1.21; $p = 0.76$). Overall, there was no evidence of a difference in the in-hospital prescription of medications for acute coronary syndrome treatment [adjusted odds ratio (OR) 1.06, 95% CI 0.85 to 1.32; $p = 0.63$]. At hospital discharge, the change in prescription of preventative therapies was similar between trial arms (adjusted OR 1.07, 95% CI 0.87 to 1.32; $p = 0.52$). The median length of hospital stay was longer in the CTCA arm than in the standard-care arm: 2.2 days (95% CI 1.1 to 4.1 days) compared with 2.0 days (95% CI 1.0 to 3.8 days), respectively (Hodges–Lehmann estimator of location shift 0.21 days, 95% CI 0.05 to 0.40 days; $p = 0.009$). There was no difference in the discharge diagnosis of acute coronary

syndrome (myocardial infarction or unstable angina) between trial arms: 50.2% in the CTCA arm compared with 47.9% in the standard-care arm. Subsequent hospital attendances with chest pain were similar (adjusted HR 1.06, 95% CI 0.83 to 1.34; $p = 0.66$). The mean total health-care costs over 1 year appeared to be higher in the CTCA arm than in the standard-care arm: £7418 (95% CI £6877 to £8031) compared with £6857 (95% CI £6347 to £7379), respectively.

Conclusions

Routine early CTCA does not have a demonstratable beneficial impact on the management or prevention of subsequent clinical outcomes in intermediate-risk patients with suspected or provisionally diagnosed acute coronary syndrome presenting to the ED or other acute hospital facilities. Given the lack of clinical effectiveness and cost-effectiveness, the routine use of early CTCA is unlikely to be of benefit in patients with intermediate-risk acute chest pain. However, given the increased diagnostic certainty and reduced need for invasive coronary angiography, CTCA may have a role in selected patients in whom there is a low probability of obstructive coronary artery disease or who have limited access to invasive cardiac catheterisation facilities, although this needs further prospective evaluation.

The research recommendations are as follows:

- a RCT of CTCA in patients presenting with acute chest pain and an intermediate cardiac troponin level using a high-sensitivity assay, such as between the rule-out and the rule-in thresholds
- a RCT of CTCA in patients with modest elevations in cardiac troponin levels (between the 99th centile and three-fold the upper reference limit) and a low (< 109) or intermediate (109–140) GRACE score
- a RCT of CTCA before interhospital transfer for invasive coronary angiography in patients with provisionally diagnosed acute coronary syndrome at sites with no on-site invasive angiography facilities.

Trial registration

This trial is registered as ISRCTN19102565 and Clinical Trials NCT02284191.

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