SUPPLEMENTARY APPENDIX

Early CT Coronary Angiography in Patients with Suspected Acute Coronary Syndrome

A randomised controlled trial

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Figure S1

Time from randomisation to CT coronary angiography

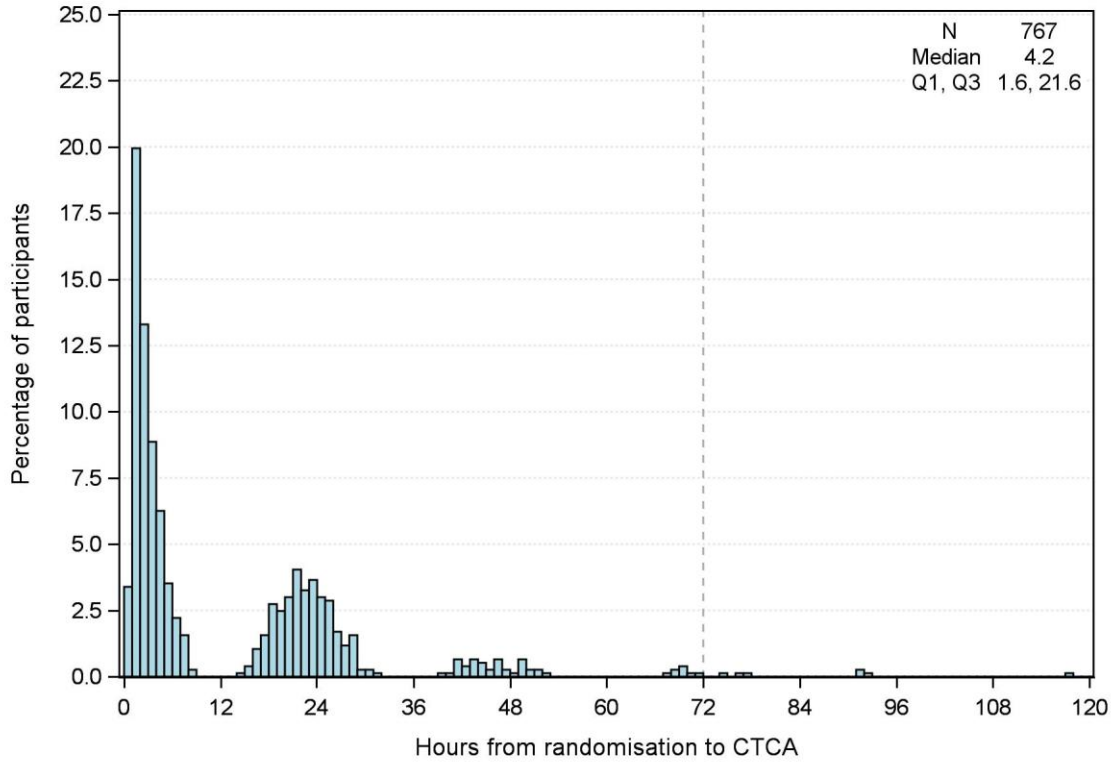
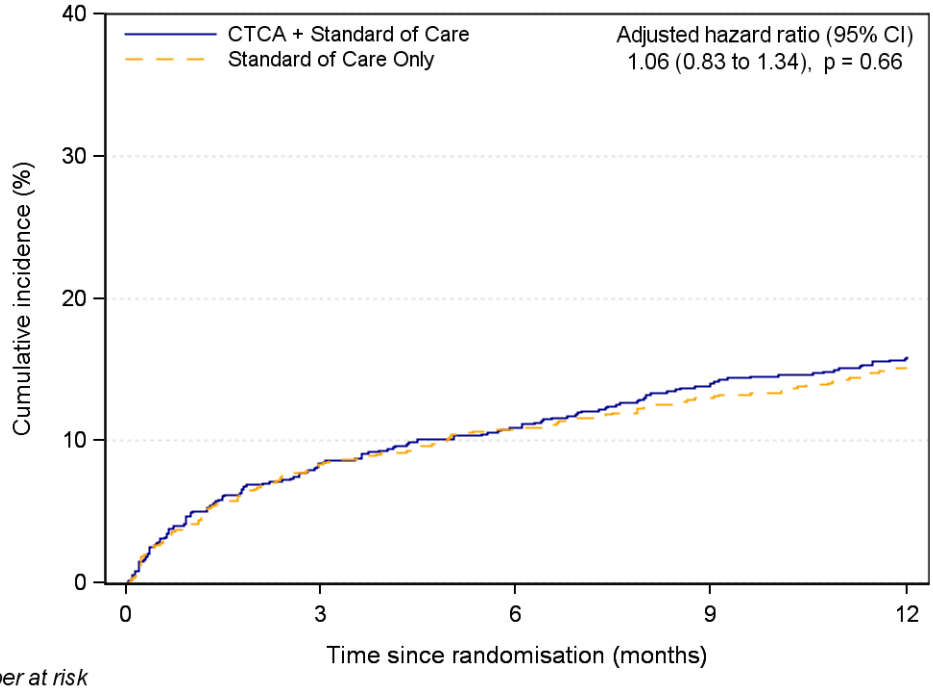


Figure S2.

Cumulative incidence of representation or recurrent admission to hospital with suspected acute coronary syndrome or recurrent chest pain up to one year



Number at risk

CTCA + Standard of Care	877	796	771	742	715
Standard of Care Only	871	789	767	744	712

Table S1.

Trial inclusion and exclusion criteria.

Inclusion Criteria

Patient ≥18 years with symptoms mandating investigation for suspected or confirmed acute coronary syndrome with at least one of:

1. ECG abnormalities e.g. ST segment depression >0.5 mm;
2. History of ischaemic heart disease (where the clinician assessing patient confirms history based on patient history or available records);
3. Troponin elevation above the 99th centile of the normal reference range or increase in high sensitivity troponin meeting European Society of Cardiology criteria for 'rule-in' of myocardial infarction. Troponin assays varied from site to site; local laboratory reference standards were used.

Exclusion Criteria*

1. Signs, symptoms, or investigations supporting high-risk acute coronary syndrome: ST elevation myocardial infarction; acute coronary syndrome with signs or symptoms of acute heart failure or circulatory shock; Crescendo episodes of typical anginal pain; Marked or dynamic ECG changes e.g. ST depression of >3 mm; Clinical team have scheduled early invasive coronary angiography on day of trial eligibility assessment.
2. Patient inability to undergo CT: Severe renal failure (serum creatinine >250 μmol/L or estimated glomerular filtration rate <30 mL/min/1.73 m^2); Contrast allergy; Beta blocker intolerance (if no alternative heart rate limiting agent available/suitable) or allergy; Inability to breath hold; Atrial fibrillation (where mean heart rate is anticipated to be greater than 75/min after beta blockade);

3. Invasive coronary angiography or CTCA proven obstructive coronary artery disease within last 2, or normal coronary arteries within the last 5 years.
4. Previous recruitment to the trial;
5. Known pregnancy or currently breast feeding;
6. Inability to consent;
7. Further investigation for acute coronary syndrome would not in the patient's interest, due to limited life expectancy, quality of life or functional status;
8. Prisoners.

***** During trial conduct, a further criterion was added to exclude patients where the attending clinician decided that emergent invasive angiography was required as well as increasing the time window for recruitment from hospital presentation to randomisation (from 18 hours to 24 hours).

Table S2.

Treatment guidance based on the CT coronary angiogram (CTCA).

CTCA result	Troponin result	Trial treatment recommendation
Obstructive Disease: Stenosis ≥70%	Positive or Negative	1. ACS and secondary preventative therapies; 2. Invasive coronary angiography ± revascularisation.
Moderate Non-obstructive Disease: Stenosis 50-69%	Positive	1. ACS and secondary preventative therapies; 2. Consider invasive coronary angiography if uncertainty about the presence of obstructive coronary artery disease or functional testing.
Moderate Non-obstructive Disease: Stenosis 50-69%	Negative	1. Secondary preventative therapies; 2. Consider invasive coronary angiography if uncertainty about the presence of obstructive coronary artery disease or functional testing.
Mild Non-obstructive Disease: Stenosis <50%	Positive	1. Consider ACS and secondary preventative therapies; 2. Consider alternative cause of chest pain and troponin rise.
Mild Non-obstructive Disease: Stenosis <50%	Negative	1. Discharge with no further follow up; 2. Consider secondary preventative therapies.
Normal (no evidence of CAD)		Discharge with no further follow up.

ACS, acute coronary syndrome; CAD, coronary artery disease.

Table S3.

Trial outcomes

Primary Endpoint

The primary endpoint was all-cause death or subsequent non-fatal type 1 or type 4b myocardial infarction at one year, measured as time to first such event. Myocardial infarction was defined according to the third Universal Definition of Myocardial Infarction[13] and endpoints were adjudicated by two independent cardiologists blinded to the intervention with a third arbitrating where there was disagreement.

Key secondary endpoints up to one year

1. Coronary heart disease death or subsequent non-fatal myocardial infarction;

2. Cardiovascular disease death or subsequent non-fatal myocardial infarction;

3. Subsequent non-fatal myocardial infarction;

4. Coronary heart disease death;

5. Cardiovascular death;

6. All-cause death.

Other Secondary Endpoints up to one year unless otherwise stated

- Coronary heart disease death or subsequent non-fatal myocardial infarction (type 1 or 4b);
- Subsequent non-fatal myocardial infarction (type 1 or 4b);
- Non-cardiovascular death;
- Invasive coronary angiography;
- Coronary revascularisation;

- Percutaneous coronary intervention;
- Coronary artery bypass graft surgery;
- Proportion of patients prescribed acute coronary syndrome therapies during index hospitalisation;
- Proportion of patients discharged on preventative treatment or have alteration in dosage of preventative treatment during index hospitalisation;
- Length of stay for index hospitalisation;
- Representation or rehospitalisation with suspected acute coronary syndrome/recurrent chest pain within 12 months after index hospitalisation;
- Chest pain symptoms up to 12 months;
- Patient satisfaction at 1 month;
- Clinician certainty of presenting diagnosis after CTCA;
- Quality of life, measured by EQ-5D-5L up to 12 months.

Adverse Events and Serious Adverse Events:

- Proportion of patients with alternative cardiovascular diagnoses identified on CTCA;
- Proportion of patients with non-cardiovascular diagnosis identified on CTCA;
- Radiation exposure from CTCA as trial intervention.

* The final change to the trial outcomes are detailed in RAPID-CTCA Protocol version 7 (24/02/2020).

Table S4.

Summary of protocol changes during the trial

Version No	Date	Summary of changes made to the protocol	Date implemented
7	24/02/2020	Updates to primary and secondary endpoints: All decisions made by members of the study team who were blinded to results-to-date split by randomised treatment. Minor update to the primary objective/endpoint with rewording to state 'subsequent' MI instead of 'recurrent' MI as participants will not necessary have had a previous MI so this wording was inaccurate. The secondary endpoints have been clarified to more closely reflect the planned analysis. These have been aligned to provide synergy with secondary endpoints reported for other studies of CTCA in chest pain. 'Key secondary endpoints' have been listed and these will be analysed hierarchically - only moving to the next endpoint if a significant p-value is seen. 'Other endpoints' are then listed which will all be individually analysed. Addition of CTCA scan research repository. Updates to Statistics and Health Economics sections to better reflect SAP and HEAP.	19/06/2020
6	19/07/2018	Changes to sample size and power calculation to reflect extension request.	19/09/2018
5	17/10/2016	Update to allow 24 hours, rather than 18 hours to randomise participants. CTCA delivery section re-worded to clarify the deviation/violation reporting process when high radiation doses are identified. QA Reporting - update to 'experts independent to the trial site'. Updated section 6 and 9.2.1 to include 'alternative heart rate limiting medication (instead of beta blocker)'.	25/11/2016
4	23/05/2016	Primary/secondary endpoints clarified to better reflect proposed statistical analysis:	29/06/2016

		All decisions made by members of the study team who were blinded to results-to-date split by randomised treatment. Clarification of primary endpoint with update from "Primary end-point will be one-year all-cause death or recurrent type 1 or type 4b MI at one year and time to such event" to "Primary end-point will be all-cause death or recurrent non-fatal type 1 or type 4b MI at one year measured as time to first such event." Secondary endpoint updated from "Proportion of patients prescribed ACS therapies and/or discharged on secondary prevention treatment or have alteration in dosage of secondary preventive treatment during index hospitalisation" and instead split into two endpoints "Proportion of patients prescribed ACS therapies during index hospitalisation" and "Proportion of patients discharged on prevention treatment or have alteration in dosage of prevention treatment during index hospitalisation. Updated number of sites to ~35 rather than 30. Clarification now a deviation if participants randomised to have a CTCA do not receive the scan within 72 hours. Clarification to ambulatory scan process. CTCA radiation dose protocol deviations now recorded/reported in DLP not mSV. Update of Management Guidelines to include functional testing as a suggested treatment.	
3	13/11/2015	Update to primary and secondary endpoints for planned statistical analysis of the study. All decisions made by members of the study team who were blinded to results-to-date split by randomised treatment. Primary endpoint updated from "The primary end-point will be all-cause death or recurrent non-fatal type 1 or type 4b myocardial infarction." to "The primary end-point will be all-cause death or recurrent non-fatal type 1 or type 4b MI at one year and time to first such event." Secondary endpoint updated from "Proportion of patients prescribed ACS therapies and/or discharged on secondary prevention treatment during index	15/01/2016

		hospitalisation" to "Proportion of patients prescribed ACS therapies and/or discharged on secondary prevention treatment or have alteration in dosage of secondary preventive treatment during index hospitalisation" "Proportion of patients with alternative e.g. aortic dissection or incidental but potentially concerning e.g. malignancy or pulmonary nodules" updated to two separate endpoints: "Proportion of patients with alternative diagnoses that relates to presentation on CTCA e.g. aortic dissection" and "Proportion of patients with incidental finding but potentially concerning on CTCA e.g. malignancy or pulmonary nodules" "Total average radiation exposure in each arm during index hospitalisation" updated to "Total average radiation exposure from CTCA in the intervention arm during index hospitalisation." New secondary endpoint added "Clinician certainty of presenting diagnosis after CTCA" Inclusion/Exclusion updates: Troponin rise now included definition - increase in high sensitivity troponin meeting European Society of Cardiology criteria for 'rule-in' or myocardial infarction; Invasive coronary angiography only exclusion if on day of trial eligibility assessment; Beta blocker intolerance now only exclusion if no alternative heart rate limiting agent available. Exclusions: Atrial fibrillation now only exclusion if mean heart rate is *anticipated* to be greater than 75 beats per minute after beta blockade. Update to clarify the timeline in which the scan can be completed.	
2	09/12/2014	Secondary endpoints clarified. "Proportion of patients assigned to CTCA with normal or non-diagnostic imaging" updated to "Proportion of patients assigned to CTCA with normal or mild non-obstructive disease" "Total radiation exposure in each arm" updated to "Total average radiation exposure in each arm during index hospitalisation." Screening process clarified.	At study start

1	27/10/2014	N/A - first draft	Never used - study started on version 2

Table S5.

Discharge diagnosis for index hospitalisation

	CT Coronary Angiography + Standard of Care (N = 877) n (%)	Standard of Care Only (N = 871) n (%)	Overall (N = 1748) n (%)
NSTEMI	350 (39.9)	339 (38.9)	689 (39.4)
Chest pain - no clear diagnosis	208 (23.7)	218 (25.0)	426 (24.4)
Unstable angina	81 (9.2)	70 (8.0)	151 (8.6)
Stable angina	64 (7.3)	64 (7.3)	128 (7.3)
Musculoskeletal pain	36 (4.1)	35 (4.0)	71 (4.1)
Other gastrointestinal pain	29 (3.3)	21 (2.4)	50 (2.9)
Pericarditis/myopericarditis	20 (2.3)	28 (3.2)	48 (2.7)
Arrhythmia	19 (2.2)	20 (2.3)	39 (2.2)
Cardiomyopathy	4 (0.5)	15 (1.7)	19 (1.1)
STEMI	9 (1.0)	8 (0.9)	17 (1.0)
Oesophageal pain	9 (1.0)	7 (0.8)	16 (0.9)
Pneumonia/pleurisy	9 (1.0)	5 (0.6)	14 (0.8)
Pulmonary embolism	5 (0.6)	6 (0.7)	11 (0.6)
Heart failure	5 (0.6)	5 (0.6)	10 (0.6)
Anxiety	6 (0.7)	3 (0.3)	9 (0.5)
Syncope	3 (0.3)	5 (0.6)	8 (0.5)
Coronary artery spasm	3 (0.3)	4 (0.5)	7 (0.4)
Costochondritis	2 (0.2)	3 (0.3)	5 (0.3)
Valvular heart disease	1 (0.1)	2 (0.2)	3 (0.2)
Acute aortic syndrome	2 (0.2)	0 (0.0)	2 (0.1)
Symptomatic anaemia	0 (0.0)	2 (0.2)	2 (0.1)
Other	12 (1.4)	11 (1.3)	23 (1.3)

NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

Table S6.

Reasons for non-adherence with the trial intervention of computed tomography coronary angiography

	n
Total	**110**
CT scanner unavailable	26
Clinician decision not to proceed with scan	16
Patient deterioration	13
High coronary artery calcium score	13
Heart rate issue	13
Patient non-compliant in scan	6
Radiologist not available	6
Cannula issue	5
Patient declined scan	5
Exclusion criterion identified after randomisation [a]	4
Death	1
Other reason [b]	2

[a] Patient unable to undergo CT coronary angiogram due to allergy to contrast (n=2), eGFR too low for local radiology guidelines (n=1), or CT coronary angiogram within last 5 years (n=1).

[b] Patient transferred to another hospital before CT coronary angiogram could be completed (n=1), and CT coronary angiogram not performed as it was incorrectly thought patient had been randomised to standard of care only arm (n=1).

Table S7.

Other secondary cardiovascular outcomes

Outcome within 12 months	CT Coronary Angiography + Standard of Care (N = 877)	Standard of Care Only (N = 871)	Estimate	Hazard Ratio (95% Confidence Interval)	P-value
Coronary heart disease death or non-fatal myocardial infarction (type 1 or 4b)	43 (4·9%)	43 (4·9%)	Unadjusted	0·99 (0·65 to 1·51)	0·95
			Adjusted	0·97 (0·63 to 1·48)	0·88
Non-fatal myocardial infarction (type 1 or 4b)	35 (4·0%)	38 (4·4%)	Unadjusted	1·03 (0·69 to 1·55)	0·88
			Adjusted	1·02 (0·67 to 1·53)	0·94
Non-cardiovascular disease death	7 (0·8%)	9 (1·0%)	Unadjusted	1·03 (0·69 to 1·54)	0·88
			Adjusted	1·01 (0·68 to 1·52)	0·95

Table S8.

Chest pain symptoms reported on WHO Rose angina questionnaire

	CT Coronary Angiography + Standard of Care (N = 877) n (%)	Standard of Care Only (N = 871) n (%)
Symptoms at one month		
No chest pain	213 (34.1)	205 (35.2)
Non-exertional chest pain	180 (28.8)	152 (26.1)
Chest pain on exertion	232 (37.1)	226 (38.8)
	n = 625	n = 583
Symptoms at six months		
No chest pain	278 (45.8)	264 (47.3)
Non-exertional chest pain	142 (23.4)	119 (21.3)
Chest pain on exertion	187 (30.8)	175 (31.4)
	n = 607	n = 558
Symptoms at twelve months		
No chest pain	287 (48.9)	248 (47.2)
Non-exertional chest pain	121 (20.6)	107 (20.4)
Chest pain on exertion	179 (30.5)	170 (32.4)
	n = 587	n = 525

Table S9.

Quality of life as measured by mean utility values from EQ-5D questionnaire

	CT Coronary Angiography + Standard of Care (N = 877)	Standard of Care Only (N = 871)
Number of participants included in analysis	764	713
Baseline	0.765	0.768
One month	0.739	0.738
Six months	0.758	0.769
Twelve months	0.761	0.765

The quality of life analysis excluded the 113 participants in the CTCA + standard of care arm and 158 participants in the standard of care only arm without any follow-up utility values, i.e. they did not respond to any of the EQ-5D-5L questionnaires at one, six, and twelve months. Of the 764 participants in the CTCA + standard of care arm who responded to at least one of the EQ-5D-5L questionnaires at one, six, and twelve months there were 72, 102, and 130 who did not respond to the questionnaires at one, six, and twelve months respectively. Similarly, of the 713 participants in the standard of care only arm who responded to at least one of the EQ-5D-5L questionnaires at one, six, and twelve months there were 92, 117, and 143 who did not respond to the questionnaires at one, six, and twelve months respectively. Multiple imputation techniques were employed to impute these missing utility values at one, six, and twelve months. The imputed values were used in the calculation of the mean utility values.