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Targeting computed tomography coronary angiography in acute chest pain

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Abstract

Background: Many patients with suspected acute coronary syndrome in whom myocardial infarction has been ruled out in the Emergency Department remain at risk of cardiovascular events. Whether further investigation reduces this risk is unknown.

Methods: In a multicenter randomized controlled trial, patients were enrolled in the Emergency Department of 14 hospitals across the United Kingdom if myocardial infarction had been ruled out and high-sensitivity cardiac troponin (hs-cTn) testing stratified them as intermediate risk (>5 ng/L). Participants were randomised 1:1 to outpatient computed tomography coronary angiography (CTCA) or standard of care. The primary outcome was myocardial infarction or cardiac death.

Results: Between September 2019 and May 2023, 3170 participants (median age 61 years, 30% female) were randomized to CTCA (n=1587) or standard of care (n=1583). At 90 days, CTCA had been performed in 1462 (92%) in the intervention group versus 35 (2%) in the standard of care group. Seven (0.4%) participants experienced a CTCA-related adverse event. After a median of 3.0 years, at which point the number of events in the standard of care group exceeded the prespecified minimum of 97, the primary outcome occurred in 112 (7.0%) participants in the CTCA group and 116 (7.3%) in the standard of care group (adjusted hazard ratio, 0.95; 95% confidence interval, 0.73 to 1.23; P=0.71).

Conclusion: In patients with suspected acute coronary syndrome in whom myocardial infarction had been excluded, routine CTCA to guide management did not reduce subsequent myocardial infarction or cardiac death. (Funded by the British Heart Foundation; TARGET-CTCA ClinicalTrials.gov number, NCT03952351).

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Patients with acute chest pain account for 5 to 10% of all Emergency Department visits with their assessment placing a substantial burden on healthcare systems and resources.[1-3] Accelerated diagnostic pathways that use high-sensitivity cardiac troponin (hs-cTn) to rule out myocardial infarction at presentation have enabled safe discharge from the Emergency Department and reduced hospital admissions.[4,5] In patients in whom myocardial infarction is ruled out, cardiac troponin provides information regarding subsequent risk and could aid in the identification of patients who would benefit from further investigation, preventative therapies or coronary revascularization.[6,7]

Patients with very low troponin concentrations remain at low risk of myocardial infarction or cardiac death for up to 5 years.[8] In contrast, those stratified as intermediate risk using hs-cTn testing are twice as likely as those with very low troponin concentrations to have coronary artery disease on computed tomography coronary angiography (CTCA)[9] and are 10 times more likely to have a subsequent myocardial infarction or cardiac death at 1 year.[7,10] Consequently, clinical practice guidelines recommend consideration of CTCA or a non-invasive stress imaging test in intermediate risk patients with suspected acute coronary syndrome.[11-13] However, it is unclear what further investigation should be undertaken, and there is currently no evidence that any investigation alters clinical outcomes.

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We designed the present trial to determine whether performing early outpatient CTCA leads to a reduction in subsequent myocardial infarction or cardiac death in patients

with suspected acute coronary syndrome considered to be at intermediate risk in whom myocardial infarction has been excluded.[14]

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Methods

Trial Design and Oversight

The *T*roponin in *A*cute Chest Pain to *R*isk Stratify and *G*uide *E*ffec*T*ive Use of *C*omputed *T*omography *C*oronary *A*ngiography (TARGET-CTCA) trial was a multicenter randomized open-label blinded endpoint (PROBE) event driven trial. The trial design has been published previously.[14] The trial protocol was reviewed and approved by the South-East Scotland Research Ethics Committee (19/SS/0040) and was periodically reviewed by an independent Data Monitoring Committee (DMC). The trial was performed in accordance with the principles of the Declaration of Helsinki and with written informed consent of all participants.

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Trial Participants

Adult patients (≥18 years) presenting to an Emergency Department or acute medical assessment area with suspected acute coronary syndrome were eligible for enrolment. Patients could be included if myocardial infarction had been excluded but they were stratified as intermediate risk based on a maximum cardiac troponin I or T concentration between the low-risk threshold of 5 ng/L[10,15] and the sex-specific 99th centile upper reference limit (***Fig S1***).[16,17] To ensure the trial was inclusive and representative, potential participants who were not approached in hospital were identified using electronic medical records and contacted by telephone. Additional exclusion criteria are listed in the ***Supplementary Appendix*** in ***Table S1***.

Intervention and Procedures

Following consent, participants were randomised 1:1 to CTCA plus standard of care or standard of care alone using a web-based computer-generated system to ensure allocation concealment, stratified by site, age (<70 or ≥ 70 years), sex, and the presence or absence of known coronary artery disease. Study participants who were randomized to standard of care had no further study visits. Those randomised to CTCA were invited for an outpatient CTCA using ≥64-multidetector scanner as soon as possible after their initial hospital attendance (ideally within 4 weeks of randomization). Images were reported according to the Society of Cardiovascular Computed Tomography guidelines.[18] Coronary arteries were classified as normal (diameter stenoses <10%), or having mild (10-49%), moderate (50-70%) or obstructive (>70% or >50% stenosis in the left main stem) coronary artery disease. Results including any clinically significant non-cardiac findings were provided to the participant, primary care physician and other healthcare professionals involved in clinical care. The report included a recommendation to commence secondary preventative therapy in those with mild (statin therapy alone) or moderate non-obstructive or obstructive (both antiplatelet and statin therapies) coronary artery disease (***Fig. S2***). Additionally, those with obstructive disease or clinically important non-cardiac findings were offered an outpatient consultation, ideally within two weeks of the CTCA scan result.

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Trial Outcomes

Follow-up data were obtained from medical records at 90 days and annually thereafter, and from participant questionnaires at 90 days and at 1 and 2 years. All participants were followed up until the minimum number of primary outcome events had accrued. The primary outcome was a composite of myocardial infarction or cardiac death.

Myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction[16]. Cardiac death was defined as death resulting from an acute myocardial infarction, sudden cardiac death, or death due to heart failure.[19] All deaths and hospital admissions with suspected acute coronary syndrome and myocardial injury were adjudicated by two independent clinicians blinded to the trial intervention with any discrepancies resolved by a third clinician as described previously.[20] Secondary outcomes included clinical, participant-reported, process and cost-effectiveness outcomes and are listed with definitions in the ***Supplementary Tables S2 and S3***.

Statistical Analysis

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Baseline characteristics are summarized for the study population, and by group. Based on the event rates in a previous trial,[20] and the relative risk reductions observed in a trial of CTCA in stable chest pain,[21] the study was designed to have 90% power to detect a 40% relative risk reduction in the primary outcome between groups. We planned to include 2270 participants to account for a loss to follow up of 5% with at least 97 primary outcome events in the standard of care group required for the study to be conclusive, which was anticipated with a median follow up of 36 months. On April 25, 2022, a blinded assessment of the number of events accrued in the first 1925 participants was undertaken, and the DMC concluded the trial would not reach the required number of events by the planned follow up date of September 2024. This was a consequence of interruptions to recruitment due to COVID-19 with most participants having less than 12 months follow up at this point. To minimize the likelihood that

follow up would need to be extended, the DMC recommended that recruitment continue until 3170 patients had been enrolled.

The analysis was based on the intention-to-treat principle and included all outcomes occurring from randomization to the study end date. Follow up continued until at least 97 primary outcome events were accrued in the standard care group. Outcomes were compared using a Cox proportional hazards model, expressed as a hazard ratio (HR) with corresponding 95% confidence intervals (CI) and a p-value. The model was adjusted for site, age, sex and previous coronary artery disease. The proportional hazards assumption was assessed and confirmed to be satisfied. In a supplementary analysis, a Fine-Gray model was performed taking into consideration competing risks. In a secondary analysis, the effect of intervention on the odds of myocardial infarction or cardiac death at 2 years was evaluated using a logistic regression model adjusting for the same variables. Sensitivity analyses included landmark and per protocol analyses (see ***Supplementary Appendix***). Subgroup analyses were performed by examining the effect of the intervention by subgroup in the adjusted Cox regression model.

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Secondary outcomes were analysed using logistic regression for binary outcomes and linear regression for normally distributed continuous outcomes adjusting for the same variables as for the primary outcome. These outcomes were exploratory in nature with no adjustment made for multiple testing; the 95% CIs thus should not be used in place of hypothesis testing. Survival times were summarized using Kaplan-Meier survival curves. All reported analyses were pre-specified in a Statistical Analysis Plan (which,

along with the protocol, is available at NEJM.org), and performed with SAS software, version 9.4 (SAS Institute Inc.), and R software, version 4.5.2 (R Project for Statistical Computing).

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Results

Trial Participants

From September 18, 2019, to May 11, 2023, a total of 3170 participants (median 61 [interquartile interval 53 to 70] years, 30% female) were enrolled at 14 sites ***(Table S4)***: 1587 were randomly assigned to the CTCA group and 1583 to the standard of care group a median of 6 (3 to 9) days following presentation (***Fig S3***). On December 4, 2025, 97 primary outcome events had been accrued in the standard care group, and sites were asked to complete an end of study review. Following database lock, the trial concluded on May 25, 2026, providing a median follow up of 3.0 [interquartile interval 3.0 to 4.0] years.

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Overall, the two groups were balanced (***Table 1*** and **Table S5**) and were representative (**Table S6**). The presenting complaint was chest discomfort in 2809 (89%) participants with 553 (17%) and 478 (15%) having a previous diagnosis of myocardial infarction or angina, respectively. The mean (standard deviation) of the HEART score was 3.5 (1.4) with 1566 (49%) classified as intermediate or high-risk with a score >3.[22,23] At randomization, 921 (29%) and 1373 (43%) were taking an anti-platelet agent and a statin, respectively.

Trial Intervention

In the group randomized to CTCA, 1462 (92%) participants underwent CTCA with imaging performed a median of 22 [interquartile interval 13 to 36] days following randomisation. Normal coronary arteries were identified in 465 (32%), non-obstructive

coronary artery disease in 622 (42%), and obstructive coronary artery disease in 331 (23%) (***Table 2***). Non-cardiac findings were reported in 617 (42%) of participants undergoing the study CTCA with 157 (25%) of these considered to be clinically significant (***Table S7***).

In the group randomized to standard care, a non-study CTCA was performed in 35 (2%) participants within 90 days and in 103 (7%) participants by the end of study. Invasive coronary angiography was performed in 177 (11%) participants in the CTCA group and 137 (9%) participants in standard care with non-invasive stress testing performed in 133 (8%) and 153 (10%) participants, respectively.

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Management

At 90 days after randomization, 665 (42%) and 994 (63%) participants in the CTCA group were on anti-platelet or statin therapy respectively, compared to 515 (33%) and 760 (48%) in the standard of care group (***Table 2*** and ***Table S8***). Percutaneous or surgical coronary revascularization was performed in 26 (2%) and 15 (1%) participants in the CTCA and standard of care groups at 90 days, respectively, and in 98 (6%) and 77 (5%), respectively, by the end of study.

Primary and Secondary Outcomes

During the follow-up period, the primary outcome occurred in 112 (7.0%) participants in the CTCA group and 116 (7.3%) in the standard of care group (adjusted hazard ratio, 0.95; 95% confidence interval, 0.73 to 1.23; P=0.71; ***Table 3***, ***Figure 1 and Table S9***). No difference in the primary outcome was observed between groups when adjusting for

competing risks, at 2 years, or in landmark, per protocol or *post hoc* sensitivity analyses (***Table S10***). In the CTCA group, the primary outcome occurred in 10 (2%) participants without coronary artery disease, and in 40 (6%) and 38 (11%) with non-obstructive and obstructive coronary artery disease, respectively. There were no missing data for the primary outcome, and the time-to-event analysis was therefore performed using complete outcome data for all participants.

The effect of the trial intervention on the primary outcome appeared generally consistent across prespecified subgroups (**Figure 2**), as well as those performed *post hoc* (**Fig. S4**). Analysis of the subgroup stratified by the HEART score appeared to favor CTCA-guided care in low-risk participants.

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There were no apparent differences in most secondary outcomes, including myocardial infarction, cardiac death, or cardiovascular death (***Table 3***). All-cause death occurred in 73 (4.6%) participants in the CTCA group and 97 (6.1%) participants in the standard of care group (aHR, 0.74; 95% CI, 0.54 to 1.00); ***Table 3*** and ***Fig. S5***); non-cardiovascular deaths accounted for 41 and 64 of these, respectively (aHR, 0.63; 95% CI, 0.43 to 0.93). However, secondary and subgroup analyses were not adjusted for multiplicity, precluding causal conclusions.

Process and participant-reported outcomes did not appear to differ materially between groups (***Table S11*** and ***Table S12***). CTCA-related adverse events were infrequent with 7 (0.4%) participants experiencing an allergic reaction or acute kidney injury to contrast. Three events (presumed allergic reactions) were categorized as serious by site

investigators, but symptoms in all cases were mild and resolved with no intervention (2 cases) or following treatment with an antihistamine (1 case) . (**Table S11**).

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Discussion

In this large prospective multicenter randomized trial of patients with suspected acute coronary syndrome in whom myocardial infarction had been excluded and troponin levels suggested intermediate risk, early outpatient CTCA to guide care did not reduce subsequent myocardial infarction or cardiac death.

Worldwide there is marked variation in the approach to further cardiac investigation in patients with suspected acute coronary syndrome after myocardial infarction has been excluded.[24] Clinical practice guidelines in the United States recommend CTCA in patients with acute chest pain considered to be at intermediate risk (≥1% event rate at 30 days) for exclusion of obstructive coronary artery disease (Level 1A).[13] In Europe, clinical practice guidelines recommend consideration of CTCA or non-invasive stress imaging in patients with suspected acute coronary syndromes where cardiac troponin is not elevated (Level IIa, Class A).[12] These recommendations are based on randomized trials that evaluated the effect of CTCA on length of stay or discharge from the Emergency Department,[25-28] and were performed prior to the widespread adoption of hs-cTn testing for risk stratification within accelerated diagnostic pathways to support the safe discharge of low-risk patients.[4,7,11]

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In our trial, CTCA did not reduce myocardial infarction or cardiac death at 3 years compared to standard care. This is despite enrolling patients known to be at risk of cardiovascular events with intermediate cardiac troponin concentrations[6,10,29,30]. The population was representative (***Table S6***), enrolling participants across 14 hospitals

with 76% of those eligible for inclusion after screening undergoing randomization. The intervention was delivered successfully in 92% of participants with just 2% undergoing a non-study CTCA in the standard care group at 90 days. In the CTCA group, two thirds of participants had coronary artery disease and were established on preventative therapy at 90 days. Our findings appeared consistent across all high-risk subgroups and in those without a prior diagnosis of coronary artery disease who may have been most likely to benefit from investigation.

The FAST-CCTA trial is ongoing and will evaluate whether CTCA targeted to patients presenting to the emergency department with chest pain who have a HEART score >3 reduces the risk of death, myocardial infarction or unstable angina [NCT04748237]. Subgroup analyses in our trial that were stratified according to the HEART score did not suggest greater benefit of CTCA in those with a score >3.

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Rates of all-cause and non-cardiovascular death appeared lower in the CTCA group compared to standard care. We did not control for multiple hypothesis testing, and causal conclusions cannot be made. We did not collect data to inform whether the detection of non-cardiac findings, as occurred in 42% of participants, altered care.

Our trial has some limitations. First, the event rate at one year was lower than projected (2.5% *versus* 3.6%).[4] To mitigate for this and ensure the trial was suitably powered we used an event driven design, and identified more events during follow up than planned. Still, the confidence intervals around the hazard ratio are compatible with as much as a 27% reduction to a 23% increase in the primary outcome. Second, the trial enrolled

patients classified as intermediate-risk using troponin, but only half of participants were classified as intermediate risk using risk scores. Third, most participants in our trial were male. Acute coronary syndrome is less common in women and the female sex-specific 99th centile for troponin is lower ,[17] which results in fewer female patients being classified as intermediate risk. Fourth, a proportion of the trial population were known to have coronary artery disease or were established on preventative therapy and may have had less to gain from the intervention. This could explain the modest differences in the use of preventative medications between groups. Finally, our trial was conducted in the United Kingdom where the proportion of patients undergoing functional or anatomical imaging for coronary artery disease is low.[31] However, this would be expected to increase the probability that CTCA, would impact management and improve outcomes; it seems unlikely that CTCA would be more likely to reduce cardiac events in healthcare systems with higher rates of investigation as the standard of care.

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In this multicenter trial, the use of CTCA to guide management in patients with suspected acute coronary syndrome in whom myocardial infarction was ruled out did not reduce subsequent myocardial infarction or cardiac death.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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~~Conflicts of Interest~~

~~MCW has received honoraria from Canon Medical Systems and Siemens Healthineers, and consulted for FEOPS, Novartis, Bayer, Elucid and Canon Medical Systems. The other authors have no competing interests to declare.~~

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Author Contributions

The TARGET-CTCA investigators contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. They were involved in

drafting the manuscript and revising it and have given final approval of the version to be published. The TARGET-CTCA investigators are accountable for the work.

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Figure Legends

Figure 1. Primary outcome in Patients Randomized to Standard Care or CTCA-guided Care

Shown are Kaplan-Meier survival curves for the primary outcome of myocardial infarction or cardiac death for patients randomised to standard care (red) or CTCA-guided care (blue).

Figure 2. Primary Outcome in Subgroups of Patients Randomized to Standard Care or CTCA-guided Care

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Shown is a forest plot reporting the adjusted hazard ratio with the 95% confidence interval for the primary outcome assessing subgroups by sex, age (< or ≥70 years), previous diagnosis of coronary artery disease, preventative therapy (anti-platelet agent or statin) at randomisation, high-sensitivity assay (cardiac troponin I or T), sex and assay-specific median maximum cardiac troponin concentrations, and the HEART score (low risk ≤3 or intermediate/high risk >3).

Table 1. Characteristics of Trial Participants at Randomization

	Standard care	CTCA
No. of participants	1583	1587
Age, years	61.0 [53.0-70.0]	61.0 [52.0-69.0]
Female	477 (30%)	479 (30%)
Cardiovascular risk factors		
Body mass index, kg/m^2	29.5±6.1	29.5±6.0
Diabetes mellitus	216 (14%)	237 (15%)
Hypertension	697 (44%)	724 (46%)
Family history of CAD	545 (35%)	626 (40%)
Current cigarette smoker	204 (13%)	210 (13%)
Ex-smoker	605 (38%)	606 (38%)
Past medical history		
Previous myocardial infarction	270 (17%)	283 (18%)
Known angina	242 (15%)	236 (15%)
Coronary revascularization		
Previous PCI	236 (15%)	246 (16%)
Previous CABG	42 (3%)	51 (3%)
Medications at randomisation		
Anti-platelet therapy *	469 (30%)	452 (29%)
Statin	684 (43%)	689 (43%)
Preventative medication †	747 (47%)	760 (48%)
ACE inhibitor or ARB	557 (35%)	610 (39%)
Beta-blocker	372 (24%)	384 (24%)
Presenting complaint		
Chest discomfort	1412 (89%)	1397 (88%)
Electrocardiogram		
Q-waves	52 (3%)	52 (3%)
ST-segment elevation	45 (3%)	44 (3%)
ST-segment depression	25 (2%)	18 (1%)
T-wave inversion	228 (15%)	243 (16%)
Left/right bundle branch block	121 (8%)	123 (8%)
Risk scores		
GRACE score	91±24	91±23
GRACE score ≥109	700 (52%)	722 (53%)
HEART score	3.6±1.4	3.5±1.4
HEART score >3	770 (49%)	796 (50%)
Hematology and clinical chemistry		
Hemoglobin, g/dL	14.4±1.4	14.4±1.4
eGFR, mL/min	63±10	63±10
Maximal hs-cTnI, ng/L	8.0 [6.0-11.0]	8.0 [6.0-11.0]
Maximal hs-cTnT, ng/L	8.0 [7.0-10.0]	8.0 [7.0-10.0]

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Presented as No. (%), mean±SD or median [inter-quartile range]. Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; CTCA= computed tomography coronary angiogram; eGFR = estimated glomerular filtration rate; CABG = coronary artery bypass grafting; EDACS = Emergency Department Assessment of Chest Pain Score; HEART = History, Electrocardiogram, Age, Risk factors, Troponin (range 0-10: low risk ≤3, intermediate risk 4-6, and high risk ≥7); GRACE = Global Registry of Acute Coronary Events (range 0-383; low risk ≤108, intermediate risk 109-140, high risk ≥141); PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction.
* Aspirin or a P2Y12 antagonist, † Any anti-platelet agent or a statin.

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Table 2. Investigations and Management Following Randomization

	Standard care	CTCA
No. of participants	1583	1587
CT coronary angiography		
Study	-	1462 (92%)
Non-study (90 days)	35 (2%)	-
Non-study (end of study)	103 (7%)	-
Normal coronary arteries	-	465 (32%)
Non-obstructive coronary artery disease	-	622 (43%)
Obstructive coronary artery disease	-	331 (23%)
Obstructive disease in proximal LAD	-	132 (9%)
Obstructive disease in left main stem	-	11 (1%)
One-vessel obstructive coronary artery disease	-	201 (14%)
Two-vessel obstructive coronary artery disease	-	87 (6%)
Three-vessel obstructive coronary artery disease	-	43 (3%)
CAD-RADS score	-	2.0 (0.0-3.0)
Segment involvement score	-	2.0 (0.0-5.0)
Segment stenosis score	-	2.0 (0.0-7.0)
Non-diagnostic or missing	-	44 (3%)
Non-cardiac findings	-	617 (42%)
Clinically significant non-cardiac findings	-	157 (10%)
Other cardiac investigation		
Invasive coronary angiography	137 (9%)	177 (11%)
Non-invasive stress imaging	153 (10%)	133 (8%)
Outpatient attendance		
Cardiology at 90 days	264 (17%)	424 (27%)
Other specialty at 90 days	84 (5%)	91 (6%)
Cardiology at end of study	598 (38%)	799 (50%)
Medical therapy		
Anti-platelet agent at 90 days *	515 (33%)	665 (42%)
Anti-platelet agent at end of study *	462 (32%)	619 (42%)
Statin at 90 days	760 (48%)	994 (63%)
Statin at end of study	813 (56%)	1,024 (69%)
Preventative medication at 90 days †	820 (52%)	1,046 (67%)
Preventative medication at end of study †	854 (58%)	1070 (72%)
Coronary revascularisation		
PCI or CABG at 90 days	15 (1%)	26 (2%)
PCI or CABG at end of study	77 (5%)	98 (6%)

Presented as No. (%), mean±SD. Abbreviations: CABG = coronary artery bypass grafting; CTCA= computed tomography coronary angiogram; PCI = percutaneous coronary intervention.
* Aspirin or a P2Y12 antagonist † Any anti-platelet agent or a statin

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Table 3. Primary and Secondary Outcomes

	Standard care	CTCA	Adjusted Hazard Ratio or Odds Ratio (95% CI)	P-value
No of participants	1583	1587		
Primary outcome				
Myocardial infarction or cardiac death	116 (7.3%)	112 (7.0%)	aHR 0.95 (0.73–1.23)	0.71
Secondary outcomes*				
Myocardial infarction	100 (6.3%)	93 (5.8%)	aHR 0.92 (0.69–1.22)	
Cardiac death	27 (1.7%)	23 (1.4%)	aHR 0.83 (0.48–1.45)	
All cause death	97 (6.1%)	73 (4.6%)	aHR 0.74 (0.54–1.00)	
Non-cardiovascular death	64 (4.0%)	41 (2.6%)	aHR 0.63 (0.43–0.93)	
Cardiovascular death	33 (2.1%)	32 (2.0%)	aHR 0.95 (0.58–1.54)	
Myocardial infarction or cardiovascular death	121 (7.6%)	121 (7.6%)	aHR 0.99 (0.77–1.27)	
Reattendance with suspected ACS	602 (38.0%)	640 (40.3%)	aOR 1.11 (0.96-1.28)	
Unscheduled coronary revascularisation	42 (2.7%)	38 (2.4%)	aOR 0.90 (0.58-1.41)	
Major bleeding (BARC 3-5)	3 (0.2%)	6 (0.4%)	aOR 2.02 (0.50-8.08)	

Presented as No. (%), mean±SD or median [inter-quartile range]. Abbreviations: ACS = Acute Coronary Syndrome; aHR = adjusted hazard ratio with adjustment for site, age, sex and previous coronary artery disease; aOR = adjusted odds ratio with adjustment for site, age, sex and previous coronary artery disease; BARC= Bleeding Academic Research Consortium definition of bleeding; CTCA= computed tomography coronary angiogram. *95% CIs for secondary outcomes were not adjusted for multiplicity and should not be used in place of hypothesis testing.

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