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Original research

Prospective RandOmised Trial of Emergency Cardiac Computerised Tomography (PROTECCT)

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ABSTRACT

Objective Many patients presenting with suspected acute coronary syndrome (ACS) have high-sensitivity cardiac troponin (hs-cTn) concentrations between rule-in and rule-out thresholds and hence need serial testing, which is time consuming. The Prospective RandOmised Trial of Emergency Cardiac Computerised Tomography (PROTECCT) assessed the utility of coronary CT angiography (CCTA) in patients with suspected ACS, non-ischaemic ECG and intermediate initial hs-cTn concentration.

Methods Patients were randomised to CCTA-guided management versus standard of care (SOC). The primary outcome was hospital length of stay (LOS). Secondary outcomes included cost of in-hospital stay and major adverse cardiac events (MACE) at 12 months of follow-up. Data are mean (SD); for LOS harmonic means, IQRs are shown.

Results 250 (aged 55 (14) years, 25% women) patients were randomised. Harmonic mean (IQR) LOS was 7.53 (6.0–9.6) hours in the CCTA arm and 8.14 (6.3–9.8) hours in the SOC arm (p=0.13). Inpatient cost was £1285 (£2216) and £1108 (£3573), respectively, p=0.68. LOS was shorter in the CCTA group in patients with <25% stenosis, compared with SOC; 6.6 (5.6–7.8) hours vs 7.5 (6.1–9.4) hours, respectively; p=0.021. More referrals for cardiology outpatient clinic review and cardiac CT-related outpatient referrals occurred in the SOC arm (p=0.01). 12-month MACE rates were similar between the two arms (7 (5.6%) in the CCTA arm and 8 (6.5%) in the SOC arm—log-rank p=0.78).

Conclusions CCTA did not lead to reduced hospital LOS or cost, largely because these outcomes were influenced by the detection of ≥25% grade stenosis in a proportion of patients.

Trial registration number NCT03583320.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Only two randomised controlled trials (RCTs) of emergency coronary CT angiography (CCTA) have been published during the era of high-sensitivity troponin assays—one including predominantly lower risk troponin negative patients and the other including higher risk patients with non-ST acute coronary syndrome (ACS).

⇒ Patients presenting with suspected ACS, who fall in between the above two risk categories, specifically with intermediate concentration of high-sensitivity troponin on initial blood-draw and non-ischaemic ECG, pose a diagnostic and logistical challenge to clinicians working in emergency department with the need for time-consuming serial troponin/ECG testing, thus contributing to increased hospital stay.

WHAT THIS STUDY ADDS

⇒ The additional use of CCTA did not decrease hospital length of stay (LOS) (CCTA vs standard of care (SOC): harmonic mean (IQR) LOS 7.53 (6.0–9.6) vs 8.14 (6.3–9.8) hours; p=0.13) or inpatient cost (CCTA vs SOC: mean (SD) cost £1285 (£2216) and £1108 (£3573), respectively, p=0.68). On 12 months of follow-up, cumulative major adverse cardiac events did not differ between the two arms—log-rank p=0.78. However, CCTA was associated with significantly reduced outpatient referrals/investigations (p=0.01) and also significantly increased discharge prescription of aspirin (p=0.008).

INTRODUCTION

Acute chest pain is a significant health burden and its accurate and safe assessment in the emergency department (ED) is a key determinant of clinical outcomes and resource utilisation.[1] In recent years, high-sensitivity cardiac troponin (hs-cTn) assays have received approval for clinical use in international practice guidelines for evaluation of patients with suspected acute coronary syndrome (ACS). The European Society of Cardiology guidelines advocate the use of hs-cTn testing to rule-in or rule-out ACS with one blood draw,[2] but a substantial proportion of patients have an equivocal initial result (between rule-out and rule-in thresholds) and therefore serial hs-cTn measurement is required.[3] Furthermore, even after serial hs-cTn measurement, a significant proportion of patients remain between those thresholds (referred to as the observational zone), and this is associated with increased mortality and adverse cardiac event risks compared with patients in the rule-out category.[4–7]

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings complement recent RCTs that have evaluated different cohorts of patients with ACS and together suggest that CCTA may not be useful when managing suspected ACS. However, further research is suggested to evaluate the longer term post-discharge health economic impact of CCTA.

The use of coronary CT angiography (CCTA) in patients with acute chest pain in the era of conventional troponin has been shown to be safe[8] with high sensitivity and negative predictive value for coronary artery disease (CAD)[9–12] and cost-effective with decreased time to diagnosis and earlier discharge from the ED.[8 13] While CCTA may help, there are conflicting data on its utility. On the one hand, the American Heart Association guidelines recommend the use of CCTA in patients with acute chest pain- although this is largely based on evidence gathered during the era of conventional troponin assays.[14–16] On the other hand, two randomised clinical trials carried out in the hs-cTn era suggest that CCTA may not be beneficial.

The Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON) trial, which enrolled a highly selected and relatively low-risk cohort (95% had hs-Tn levels below the reference level), found no difference in the number of patients requiring revascularisation at 30 days.[17] The Rapid Assessment of Potential Ischaemic Heart Disease with computed tomography coronary angiography (RAPID-CTCA) trial enrolled a higher risk cohort (67% had elevated hs-Tn levels, 61% had abnormal ECG) and found that a CCTA (done up to 24 hours following presentation) did not reduce the rate of death or myocardial infarction at 1 year.[18] While these two multicentre trials have advanced our understanding of the utility of CCTA in managing ACS, they leave several pertinent questions unanswered. First, the patients who pose the greatest management challenge, and are also the most frequent presenters to ED with suspected ACS, are those who fall between the ends of the spectrum represented by BEACON and RAPID-CTCA; patients with hs-cTn concentrations above the rule-out threshold (and may be discharged by ED physicians) but lacking ECG changes or rule-in hs-cTn levels (which, if present, would likely end in referral to cardiology). Is there a role for CCTA (performed while the patient is still in ED) in this cohort? Second, if CCTA does (or does not) work, what is the mechanism of this treatment effect?

We hypothesised that, by ruling out obstructive disease (and hence making it unlikely that the presentation is due to ACS), the use of CCTA in the ED for assessment of patients with suspected ACS, intermediate initial hs-cTn concentration but without ischaemic ECG, will reduce time to definitive diagnosis or discharge. We also explored the mechanism of this effect by characterising the standard of care (SOC) group by performing blinded CCTA.

METHODS

Study design

The Prospective RandOmised Trial of Emergency Cardiac Computerised Tomography (PROTECCT) is an open-label, single-centre randomised trial that was conducted at a central London teaching hospital (ClinicalTrials.gov trial registration NCT03583320). Consecutive adult patients presenting to the ED with symptoms suggestive of ACS within 12 hours of symptom onset, in whom an ACS could not be ruled in or ruled out on the basis of biomarkers (those with hs-cTnT concentration between 5 and 50 ng/L on initial blood draw were eligible) or ECG (those with new ischaemic changes were excluded), were enrolled and randomly assigned in a 1:1 ratio to either CCTA+SOC or SOC. Enrolment occurred between 08:00 and 17:00 hours, Monday to Friday. Additional exclusion criteria were haemodynamic instability, atrial fibrillation, a history of obstructive CAD, coronary anomalies or congenital heart disease, previous coronary revascularisation, currently breast feeding or pregnant and unable to undergo CCTA (estimated glomerular filtration rate <30 mL/min, inability to lie flat, inability to hold breath for >10 s and contraindication to beta blockers). Hs-cTnT levels were measured using the Roche Elecsys assay.

All patients provided written informed consent prior to participation in the study. The randomisation sequence was blocked and was prepared by a statistician independent of the study. The conduct of the study was overseen by a trial steering committee and an independent data and safety monitoring committee.

All patients underwent CCTA scans, but clinicians were blinded to results in the SOC arm. In the SOC arm, we ensured that the CCTA was carried out during a time window where patients would normally have been waiting for their serial hs-cTnT blood draw/result and hence hospital length of stay (LOS) would not be affected. In cases with minimal or no atheroma (<25% diameter stenosis), the CCTA report stated that the patient's presentation was unlikely to be due to ACS, but subsequent management (including the need for serial hs-cTnT) in both groups was left to the discretion of the treating physician. In the CCTA arm, scan reports were made available to clinicians involved in patient care in real time. Reports for patients recruited to the SOC arm were only made available to clinicians during the acute hospital setting if the patient was found to have >50% stenosis in the left main stem and/or proximal left anterior descending artery or for serious non-cardiac pathology (such as an acute pulmonary embolism).

CCTA protocol

All CCTA studies were performed using a third-generation dual-source CT (Siemens Healthcare, Forchheim, Germany) with ECG synchronisation. The acquired images were interpreted by readers who had level III certification in CCTA, and reports issued according to the Society of Cardiovascular Computed Tomography guidelines[19]—additional information in online supplemental material.

Outcome measures

The primary outcome was hospital LOS, defined as the time from hospital presentation to hospital discharge or inpatient death. Secondary outcomes included the cost of inpatient stay, rates of invasive coronary angiography (ICA)/revascularisation, confirmed diagnosis of ACS during index hospital visit (as recorded on discharge summary) and rate of planned cardiac outpatient review at discharge. Using the information from the blinded CCTAs as control data, we also aimed to investigate the impact of CCTA reports, classified by the aforementioned 25% stenosis cut-off, on hospital LOS.

The cost of hospital LOS was obtained from the hospital finance department, where the hospital ED and/or inpatient stays were recorded as individualised ED and/or inpatient episode codes. These codes corresponded to the overall cost of hospital stay and included cost of inpatient diagnostics (including haematological/radiology tests, etc) and management of each patient (including medications given, any interventional procedures, etc). The costs of performing CCTA and/or calcium score only were excluded from the healthcare costs evaluation of the SOC arm.

Major adverse cardiac events (MACE), defined as myocardial infarction, coronary revascularisation or all-cause mortality, were assessed at 12 months by a combination of telephone follow-up and electronic patient records linked to UK Office for National Statistics database. Causes of death were ascertained by retrieving death certificates and/or from hospital and primary care health records. The end of the study was defined as 12 months after recruitment of the final patient.

Statistics

Sample size calculations

LOS was expected to be highly skewed and so sample size calculations were based on simulations using the Mann-Whitney U test as follows: data from a random sample of 49 real patients with suspected ACS managed as per-usual SOC and calculated the multiplication factor needed to reduce their median LOS by 1 hour in a putative experimental population; this constant was found to be 0.799. For a given sample size n, 10 000 Monte Carlo simulations were performed by sampling n patients with replacement from each of the two groups, and the p value from a Mann-Whitney U test was calculated for each simulation. The proportion of these 10 000 simulations with a p value below 0.05 was recorded as the power for that sample size n. The sample size was varied until a power of 0.8 was obtained. Based on reported reductions in hospital LOS from previous studies,[14 15 17] we theorised that CCTA may lead to reduction in mean hospital LOS by 20% and this corresponded to a reduction in median LOS of 1 hour. The target sample size was 250 (125 in each arm), which would provide 80% power at a 5% significance level to detect a difference in median LOS of 1 hour.

Analysis

Hospital LOS was compared in the two groups using a two-sample t-test after using an inverse transformation to correct the skewness. LOS results are reported as the harmonic means (IQR) following back transformation. To assess differences in mean cost of hospital LOS between the two arms, we used a generalised linear model (gamma family, identity link) with bootstrapped CIs. Pearson χ^2 test or Fisher's exact test (small frequencies) was used to assess differences in the dichotomous outcomes between the two arms. Kaplan-Meier curves were used to examine cumulative MACE rate and differences between the arms were tested using a log-rank test. The primary analyses were conducted on an intention to treat basis. Analyses were done using SPSS V.26 and Stata V.16.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of this research study.

RESULTS

Study participants

During the period from 11 January 2018 to 4 April 2019, five hundred patients presenting with suspected ACS and a blood draw for hs-cTnT were screened, of whom 250 were recruited (figure 1). Patient characteristics were similar between the two arms (table 1). Seven patients from the SOC arm had CCTAs unblinded during their inpatient hospital stay, including two cases of protocol violation (please see online supplemental material for further details).

Mean (SD) CCTA scanning duration was 12(3.4) min. In the CCTA arm, CCTA versus hs-cTnT mean (SD) turnaround times were similar (from request time to reporting time); 96(11.3) min vs 105(60) min; p=0.28. In the CCTA arm, mean (SD) door to CCTA time was 4.2 (0.99) hours and mean (SD) door to CCTA reporting time was 5.3 (1.06) hours. In the CCTA arm, 31 (26%) out of 118 contrast-enhanced scans were reported before blood draw for second troponin or uploading of the result. Overall mean effective radiation dose was 4.9(2.25) mSv (conversion factor of 0.014 mSv/mGy).

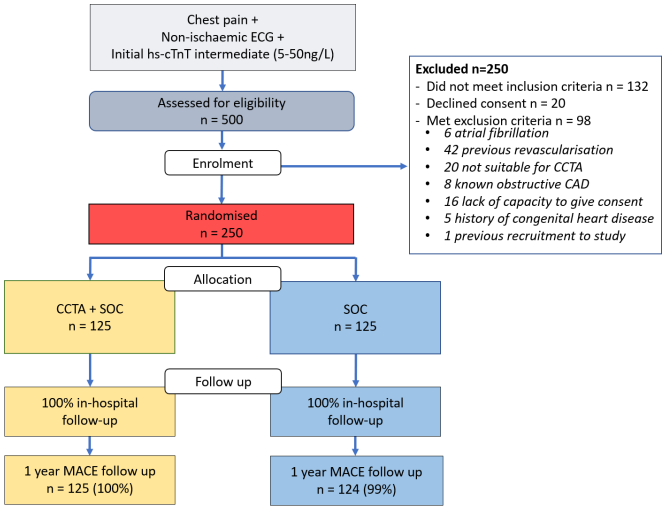

Figure 1 Flow chart of recruitment, randomisation and follow-up of participants. CAD, coronary artery disease; CCTA, coronary CT angiography; hs-cTnT, high-sensitivity cardiac troponin T; SOC, standard of care.

Table 1 Baseline characteristics of study participants

	CCTA arm (n=125)	SOC arm (n=125)
Age mean (SD), years	54.7 (13.3)	56.0 (14.0)
Gender	Male: 93 (74%)	Male: 95 (77%)
Diabetes	24 (19%)	23 (18%)
Hypertension	56 (45%)	59 (47%)
Dyslipidaemia	52 (42%)	50 (40%)
Current or ex-smoker	59 (47%)	63 (50%)
Family history of ischaemic heart disease	35 (28%)	32 (25.6%)
Initial troponin concentration mean (SD), ng/L	11.11 (8.56)	11.52 (7.36)
Initial troponin concentration >99th percentile (14 ng/L) of a healthy reference population	24 (19.2%)	28 (22.4%)
Mean (SD) heart rate (beats/min)	78 (14)	78 (15)
Mean (SD) blood pressure (mm Hg)	–	–
Systolic	141 (21)	143 (22)
Diastolic	85 (15)	86 (14)
Medications	(n=124)	(n=123)
Antiplatelet therapy	16 (13%)	21 (17%)
Statin	29 (23%)	45 (36.6%)
ACE inhibitor	29 (23%)	24 (19.5%)
Angiotensin receptor blocker	14 (11%)	10 (8%)
Beta blocker	13 (10%)	20 (16%)
Calcium channel blocker	30 (24%)	30 (24%)
Diuretic agent	11 (9%)	16 (13%)
Oral diabetic agent	21 (17%)	22 (18%)
Insulin	7 (5.6%)	10 (8%)
Oral anticoagulant agent	7 (5.6%)	6 (5%)
Proton pump inhibitor	22 (18%)	25 (20%)

CCTA, coronary CT angiography; SOC, standard of care.

Table 2 CCTA findings of study participants

	CCTA arm (n=125)	SOC arm (n=125)
Calcium score mean (SD) (CCTA arm: n=110) (SOC arm: n=105)	160.6 (351.4)	158.3 (350.2)
No stenoses on CCTA	46 (37%)	38 (30.4%)
1%–24% stenosis	26 (21%)	29 (23%)
25%–49% stenosis	24 (19%)	19 (15%)
50%–69% stenosis	11 (9%)	15 (12%)
≥70% stenosis	10 (8%)	11 (9%)
Sub-optimal CCTA	1 (1%)	1 (1%)
Calcium score only	7 (5%)	8 (6.4%)
CT scan not carried out	0	4 (3.2%)

CCTA, coronary CT angiography; SOC, standard of care.

Fifteen patients had very high calcium scores (mean (SD) calcium score=1122.82 (606) Agatston units) and did not proceed to a contrast-enhanced study, as these would have yielded suboptimal CCTA results (table 2).

Outcomes

There was no significant difference in the primary outcome between the two arms: the harmonic mean (IQR) LOS was 7.53 (6.0–9.6) hours in the CCTA arm and 8.14 (6.3–9.8) hours in the SOC arm (p=0.13). Median hospital LOS was 7.35 hours in the CCTA arm and 8.05 hours in the SOC arm. In the CCTA arm, LOS for patients with <25% stenoses was significantly shorter than for patients with at least mild (≥25%) stenoses (6.6 (5.6–7.8) hours vs 8.8 (6.5–10.7) hours; p<0.005). LOS in patients with <25% stenoses was significantly shorter in the CCTA+SOC arm, compared with the SOC arm; 6.64 (5.6–7.8) hours vs 7.5 (6.1–9.4) hours; p=0.021, while there was no significant difference in LOS between the two arms among patients with ≥25% stenoses; p= 0.609 (figure 2).

Of patients who had serial hs-cTnT blood draw (n=236), 77 were still found to be in the intermediate or observational zone risk category (n=33 in the CCTA arm vs 44 in the SOC arm). Among this group, we found no difference in LOS—harmonic mean (IQR) LOS was 8.54 (7.1–10.6) hours in the CCTA arm and 9.43 (6.9–12.3) hours in the SOC arm (p=0.36). Based solely on serial second hs-cTnT profiles, 154 patients could be categorised as 'rule-out' (n=78 in the CCTA arm vs 76 in the SOC arm) and again we found no difference in LOS—harmonic mean (IQR) LOS was 7.05 (5.8–8.01) hours in the CCTA arm and 7.5 (6.1–9.2) hours in the SOC arm (p=0.23).

The mean (SD) cost of inpatient hospital stay was not significantly different between the two arms (CCTA vs SOC: £1285 (£2216) vs £1108 (£3573); p=0.68). There were significantly more referrals for cardiology outpatient clinic review and cardiac CT-related outpatient referrals in the SOC arm than the CCTA+SOC arm (60 vs 40; p=0.01). There were no differences between groups in terms of discharge diagnosis of ACS or in the rates of inpatient ICA and revascularisation. There were no inpatient deaths (table 3).

Significantly more patients were prescribed aspirin in the CCTA arm at discharge compared with on admission: n=11 (9%) on admission vs n=26 (21%) on discharge (p=0.008). No such difference was observed in aspirin prescription in the SOC arm: n=18 (15%) on admission vs 25 (21%) on discharge (p=0.23). Furthermore, there were no differences in rates of prescription (between admission and discharge) of other antiplatelet agents or statins in either arm. Medications on discharge are tabulated in the online supplemental material.

Post-discharge 12-month MACE follow-up data were available for 249/250 (99.6%) of patients. Overall, there were seven MACE events in the CCTA+SOC arm and eight in the SOC arm (log-rank p=0.78).

DISCUSSION

We found that a CCTA-guided strategy in ED did not reduce the duration or cost of the in-hospital stay, compared with conventional biomarker-based diagnosis and triage of patients who present with a suspected ACS (figure 2). There are two main reasons why CCTA may have failed to impact on the main outcome events. First, while the finding of little or no CAD gave clinicians the confidence to discharge patients early (as reflected in shorter LOS when the CCTA result was available compared with SOC in these patients), the converse was also true–the finding of at least mild CAD appeared to compound the ambiguity that had arisen from the finding of intermediate initial hs-cTnT concentrations, leading to neither expedited nor delayed discharge. This may have diluted the beneficial impact

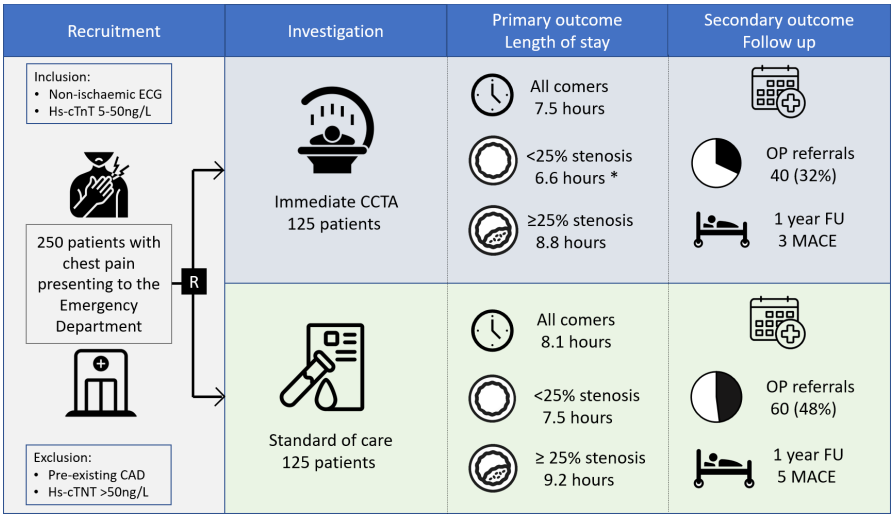

Figure 2 Trial overview. CAD, coronary artery disease; CCTA, coronary CT angiography; FU, follow-up; hs-cTnT, high-sensitivity cardiac troponin T; MACE, major adverse cardiac event; OP, outpatient.

Table 3 Secondary endpoints

Outcomes	CCTA arm (n=125)	SOC arm (n=125)	Difference CCTA-SOC (95% CI)*	P value
Mean (SD) cost of hospital stay	£1285 (£2216) n=124	£1108 (£3573) n=124	£177 (−650 to 1003)	0.68
Cardiac or CCTA-related outpatient referrals (clinic and/or investigations)	40 (32%)	60 (48%)	−16% points (−28% to −4.0%)	0.01
Inpatient invasive coronary angiography	6 (4.8%)	7 (5.6%)	−0.8% points	>0.99
Discharge diagnosis of ACS	5 (4.0%)	4 (3.2%)	0.8% points	>0.99
Inpatient revascularisation	5 (4.0%)	4 (3.2%)	0.8% points	>0.99
Inpatient death	0	0	–	–
Post-discharge ACS events at 12 months	1 (0.8%)	2 (1.6%)	−0.8% points	0.62
Post-discharge revascularisation events at 12 months	2 (1.6%)†	3 (2.4%)‡	−0.8% points	0.68
Post-discharge death events at 12 months	1 (0.8%)	2 (1.6%)	−0.8% points	0.62

*95% CI given where it could be calculated.
†One patient had both ACS and revascularisation (this patient also previously had inpatient ACS and revascularisation).
‡Two patients had both ACS and revascularisation after discharge and one patient also previously had inpatient ACS and revascularisation.
ACS, acute coronary syndrome; CCTA, coronary CT angiography; SOC, standard of care.

of CCTA of patients with little or no disease, and thus contributed to the lack of impact overall.

The second reason may be that the protocol left the interpretation of the CCTA result and subsequent management to the discretion of the clinicians responsible for these patients. While this is reflective of real-world practice, it may have resulted in a lower rate of discharge than might have been achieved with a more didactic protocol. For instance, although 72 (58%) of patients in the CCTA arm had minimal or no coronary disease, only 31 (25%) were discharged early either without the need for serial hs-cTnT testing or without waiting for hs-cTnT results. Investigators of the BEACON trial also left final medical management decision-making to the treating physicians and similarly found that the addition of CCTA was not associated with a reduction in hospital LOS despite the fact that 42% of patients had no detectable CAD on CCTA (the hospital LOS in both arms was 6.3 hours; p=0.80).[17] However, the reasons for this disparity are likely to be pertinent to future pathways and may include the heterogeneity of patient care among physicians, cautious adoption of CCTA in the ED fraternity and the challenging logistics of everyday practice in busy EDs.

Our findings also contrast with clinical trials performed during the era of conventional troponin such as the American College of Radiology Imaging Network-Pennsylvania and Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT II), where the CCTA arms showed significantly reduced hospital LOS.[15 20] However, in both of these trials, the SOC management pathways involved the use of conventional troponin and significantly more inpatient ischaemia testing took place, which likely resulted in more prolonged hospital LOS for SOC pathways. Another reason why a reduction in hospital LOS was not observed with CCTA in our study (and similarly in other CCTA studies involving the use of hs-cTn assays such as BEACON or RAPID-CTCA) may be the faster triage of patients in SOC management with the use of hs-cTn compared with conventional troponin, making it more difficult to observe an improvement in LOS with CCTA.

An important issue for any healthcare system that is considering incorporating CCTA in acute chest pain pathways is the additional cost associated with the use of CCTA compared with a relatively inexpensive biomarker. In our study, healthcare costs were not higher with a CCTA strategy than with SOC, which in turn suggests that the increased cost of CCTA must be offset by other saving, likely reflecting the expedited discharge of patients found to have little or no atheroma. Furthermore, there was a significant reduction in subsequent outpatient investigations and cardiology referrals with a CCTA strategy. This finding is similar to the RAPID-CTCA trial, where CCTA was associated with significantly lower rates of subsequent non-invasive testing for CAD and myocardial ischaemia and possibly reflects the fact that a diagnostic test had already been performed and therefore a subsequent one was not required. Our study was not designed to comprehensively capture the longer term healthcare costs in these patients and so we can only speculate that the cumulative costs on follow-up might have been lower with the use of CCTA in ED. This assertion is supported by the BEACON study, where the CCTA group was associated significantly with lower direct medical costs after 30 days of follow-up. Assessment of healthcare costs of the RAPID-CTCA trial is currently awaiting publication. Another prevalent concern associated with CCTA is the associated ionising radiation. Our mean (SD) effective radiation dose of 4.9(2.25) mSv is lower than values reported in the BEACON trial (7.3(6.6) mSv) and in the ROMICAT II trial (11.3 (5.3) mSv) and is also lower than the reported effective radiation doses of nuclear single-photon emission CT and ICA.[14 21] Technological advancements and research in CT technology may enable further reductions in radiation doses in the future.

Studies have shown that the vast majority of acute myocardial infarct-related coronary lesions are at least >50% stenotic around the time of patient presentation.[22–24] We selected a more conservative value of <25% stenosis to rule out ACS to further safeguard patient safety. One hundred and thirty-nine patients had either normal or maximal coronary stenoses of <25% (table 2), and among these patients only one had a MACE event at 12 months of follow-up (patient died of disseminated cancer). Notwithstanding the limited power of our study to detect small differences in mortality, it appears that ruling out ACS based on <25% maximal stenosis cut-off on CCTA may be safe. In our study, 12 months of mortality among observational zone patients based on serial hs-cTnT testing, 3/76 (4%) is similar to that reported (3.5%–9.6%) in observational zone cohorts in previous studies.[5 7]

Limitations

First, ours was a single-centre study and hence the results may not be as generalisable as a multicentre study. On the other hand, the enrolment of consecutive patients has meant that we have enlisted a cohort of real-world patients which may therefore be more representative than larger but more highly selected case series. Second, our study was conducted in a large tertiary

hospital during working hours with a dedicated research fellow available to enable a rapid pathway incorporating the use of acute CCTA. This pathway may not be replicable in routine clinical care without such logistical support. Due to the existence of different tariffs for investigations in other regions, the healthcare costs in our study may not be extrapolated to all other healthcare regions, as these differing tariffs may translate to a dissimilar influence on overall healthcare costs elsewhere. It could be queried whether CCTA could have fared better in terms of LOS if it were evaluated among patients found to be still in the observational zone after second hs-cTn rather than among patients with intermediate hs-cTn concentrations on initial blood draw. Here again, we found no significant difference in LOS among these patients. However, our study was not adequately powered to investigate this specifically. The study protocol stated that a scan report would be made available if significant findings were identified in the SOC group. In certain instances, this could have resulted in a 'reassurance bias' because clinicians looking after patients randomised to the SOC arm could have potentially assumed that the lack of unblinding meant that there were no significant findings on the CCTA scans that needed immediate attention. Finally, our study was powered to look at differences in process outcomes rather than clinical events.

CONCLUSION

Performing CCTA in ED to triage and guide management of patients with suspected ACS did not reduce median hospital LOS or inpatient healthcare costs. Further focused research may be of benefit to determine whether the reduction observed in downstream referrals and investigations with CCTA translates to a long-term healthcare economic benefit.

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

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Contributors WA, TR, NB-H, RP, LH, KO'K, RN, MM, RRaz, RRaj and DP contributed to the conception and design of the trial. WA, HM, OMD, AS, TR, RP, SMM, GB, AV, EW and RRaj were involved in the acquisition of data. GC-W, MM and TI were involved in the data and safety monitoring committee. RRaj, RRaz, LH and DP were involved in the trial steering committee. WA, RRaz, TI, DP, NB-H and JP were involved in statistical analyses in the study. All authors participated in the work and reviewed and agreed with the content of the manuscript. DP is responsible for the overall content as guarantor.

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Glossary of Terms and Abbreviations

ACP	Acute Chest Pain
AMI	Acute Myocardial Infarction
ACS	Acute Coronary Syndrome
CAD	Coronary Artery Disease
CD	Compact Disc
CTCA	Computed Tomography Coronary Angiography
cTn	Cardiac Troponin
ECG	Electrocardiogram
ED	Emergency Department
ESC	European Society of Cardiology
FFR	Fractional flow reserve
GSTFT	Guy's and St. Thomas' NHS Foundation Trust
GTN	Glyceryl trinitrate
HU	Hounsfield Unit
hs-cTn	High-sensitivity cardiac troponin
ICA	Invasive Coronary Angiogram
IVUS	Intra-vascular ultrasound
LAD	Left Anterior Descending
LM	Left Main
MACE	Major Adverse Cardiac Events
NPV	Negative Predictive Value
OCT	Optical coherence tomography
OP	Out-Patient
OPD	Out-Patient Department
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value
SCCT	Society of Cardiovascular Computed Tomography
TCFA	Thin Capped Fibroatheroma
WHO	World Health Organization

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10. Finance & Publication Policy

1. Background and Pilot Data

Coronary artery disease (CAD) remains the most common cause of mortality in the world according to the World Health Organization (WHO). Chest pain accounts for a significant healthcare burden representing approximately 700,000 annual visits to the emergency department in England and Wales [1]. Patients with acute chest pain (ACP) suggestive of a cardiac aetiology account for approximately 17% of all emergency department (ED) consultations, but less than 10% of these are eventually diagnosed as having acute myocardial infarction (AMI). On the other hand, the most common reason for patients with a missed diagnosis of AMI has been shown to be non-cardiac chest pain and the discharge of these patients may be associated with increased mortality [2].

Hence a means of evaluating these patients in the emergency department in an efficient manner, whilst ensuring high sensitivity and specificity, is of paramount importance. Cardiac biomarkers e.g. cardiac Troponin (cTn) I or T along with electrocardiogram (ECG) remain the cornerstone in the evaluation of patients with suspected acute coronary syndrome (ACS).

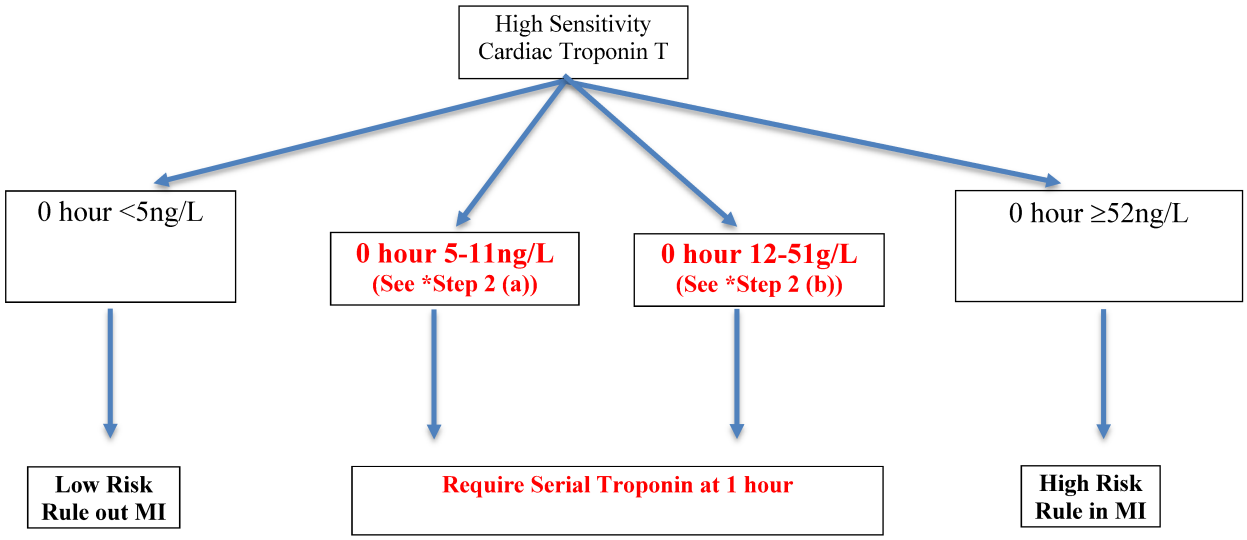
Former generation conventional cardiac troponin (cTn) assays were limited by their inability to detect low levels of cTn. This, coupled with the delayed increase of circulating levels of cTn, meant low sensitivity at the time of a patient's presentation and this would result in the requirement of serial cTn testing for up to 6 hours [3]. The consequent delay in confirming a diagnosis of ACS would potentially lead to complications due to delays in treatment, and delays in excluding the diagnosis would lead to overcrowding in the emergency department and increased cost to the healthcare system.

1.1 Performance of high-sensitivity cardiac troponins

In an effort to address the aforementioned issues with conventional cTn's, high-sensitivity cardiac troponin (hs-cTn) assays have been developed. These assays enable the measurement of cTn at concentrations not detected with the former generation conventional cTn assays. In September 2015 hs-cTn assays were adopted in the

European Society of Cardiology (ESC) guidelines for the management of patients with acute coronary syndrome (ACS) without persistent ST elevation. The proposed algorithms advocate either a single hs-cTn at ED presentation or repeat measurements after 1 or 3 hours and thus enable a more rapid "rule-in" and "rule out" of AMI compared with conventional cTn assays. The cut off values for the different hs-cTn assays are assay specific [4].

The ESC guidelines proposed '*hs-cTnT guided algorithm*' assigns "rule out" status to patients with an hs-cTnT level below 5ng/L (the limit of detection for the assay) at presentation or between 5 and 11 ng/L on initial testing and Δ1 hour of below 3 ng/L. A "rule in" status is assigned to patients with an initial hs-cTnT value of at least 52ng/L or a Δ1 hour of at least 5ng/L on serial testing. The remaining patients would remain in an observational zone (Figure 1.).



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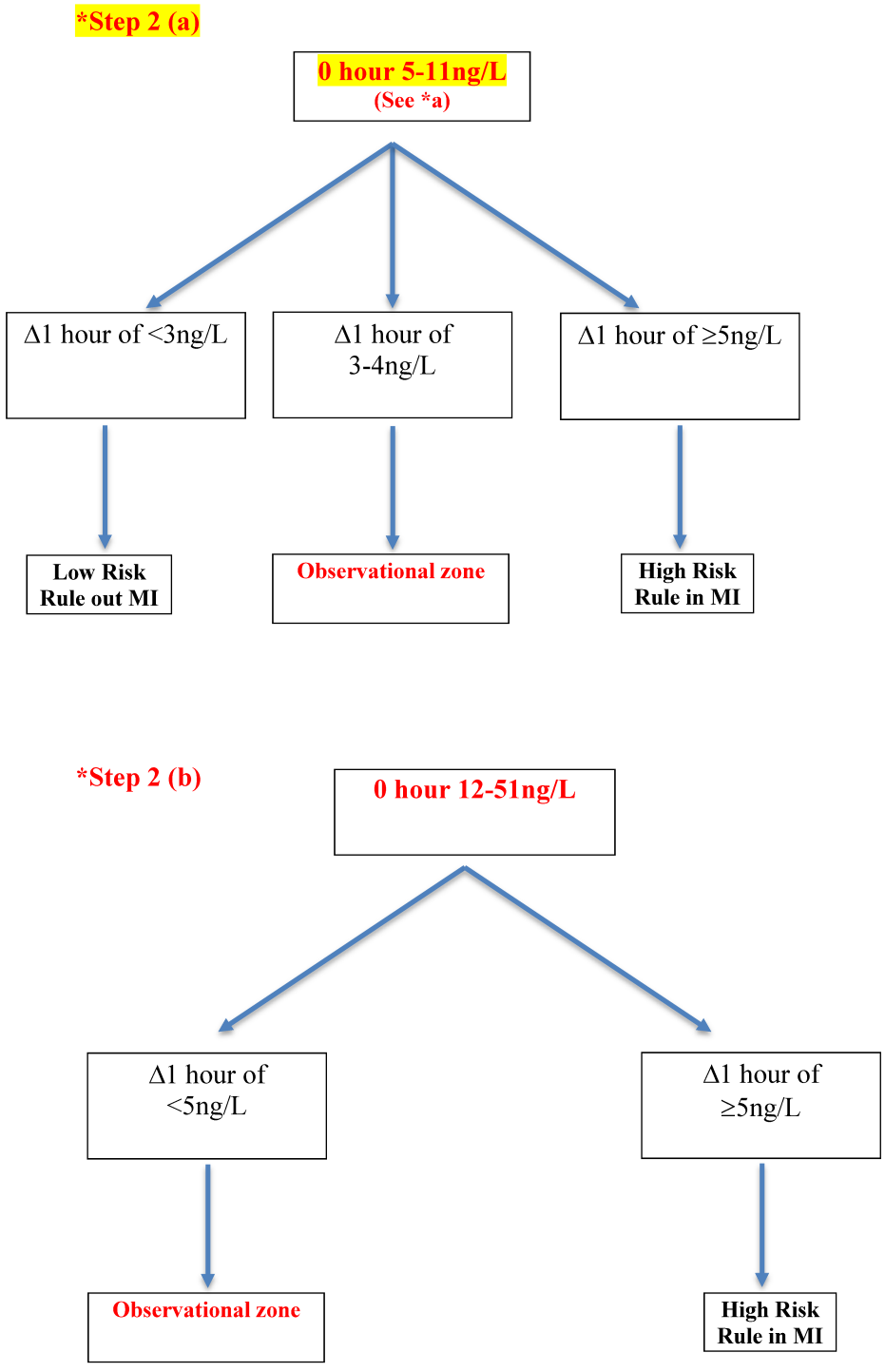

Figure 1.

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The performance of these algorithms (involving hs-cTn) has been evaluated in multiple studies. Ruling out AMI based on undetectable levels of hs-cTn at presentation has been shown to be very safe with high negative predictive values. A prospective multicenter study by Gimenez et al looked at ruling out AMI using undetectable levels of hs-cTn (I and T) at presentation. With hs-cTnT, AMI was ruled out in 26.5% of cases with a sensitivity of 98.2% and negative predictive value (NPV) of 98.6%. Among three different hs-cTnI assays which were studied, the NPV ranged from 98.8% to 100%. No patient with undetectable levels of hs-cTnT died during the first 30 days and only 0.4% had died (2 patients not due to AMI) at 24 months' follow-up. Among the three hsc-TnI assays, mortality at 24 months' follow-up ranged from 0 to 2.4% with only one death due to AMI (which occurred in the first 30 days). In contrast, mortality was significantly higher among patients with detectable levels of hs-cTn [5].

Although the more rapid risk-stratification with these algorithms (on the first sample of hs-cTn) helps in reduced time to rule-in or rule-out AMI there remains, however, (between the initial "rule-in" and "rule-out" categories) an intermediate "observational zone" category of patients, who do require a serial troponin test at 1 hour for further risk-stratification. With the adoption of these ACS management algorithms, pilot data by Marjot et al have shown that, after initial hs-cTnT testing on presentation, there are a significant proportion of patients (54%) who would require further troponin testing after 1 hour as they were stratified in an intermediate category (neither rule in nor rule out) on the initial troponin test. Despite the mandated repeated troponin at 1 hour, Marjot et al also showed that in real world practice, the mean time to repeat troponin was still 2.9 hours and that after training and implementation of the algorithm for 3 months, over 65% of patients still had their troponin taken at least 90 minutes after the first [6]. Similarly, in a sub-study of the ROMICAT II trial, Ferencik et al also found that a substantial 86.9% of patients had intermediate hs-cTn levels on initial testing and the addition of a second or third hs-cTn level did not improve risk stratification [7]. A study involving hs-cTnI (in a 2-hour algorithm) by Lindahl et al showed that, after having ruled out / ruled in AMI based on a 1st troponin test on presentation, 47.1% remained in the observational zone. After a repeat troponin 2 hours later, 25.5% of patients, still remained in the observational zone [8]. This

presents an opportunity for a possible alternative means of further evaluating the initial intermediate category cohort of patients in a more efficient manner.

Other studies that have investigated/validated the approach involving a repeat hs-cTn at 1 to 2 hours to rule-in or rule-out have also shown high sensitivities and NPV's (see table 1).

Author	HsC-Tn assay type/Time to repeat	Sensitivity	Specificity	PPV	NPV	Mortality in "rule-out" group
Lindahl et al [8] (2016)	HsC-TnI (2 hours)	97.7%	95.2%	74.5%	99.4%	0% at 30 days
Jaeger et al [9] (2016)	HsC-TnI (1 hour)	100%	96%	70%	100%	1.7% at 360 days
Mueller et al [10] (2015)	HsC-TnT (1 hour)	96.7%	96.1%	77.2%	99.1%	0.7% at 365 days
Reichlin et al [11] (2015)	HsC-TnT (1 hour)	99.6%	95.7%	78.2%	99.9%	0% at 30 days

Table 1.

However as is evident in Table 1, the excellent negative predictive value to rule-out AMI comes at a cost of a modest reduction in the positive predictive value to rule-in AMI. This is contributed to by the ability of hs-cTn's to detect concentrations at <99th percentile for at least 50-95% of healthy individuals and due to possible other causes of elevated troponin e.g. renal dysfunction, tachy- and brady-arrhythmias, pulmonary embolism etc.

Furthermore, multiple aforementioned studies (Table 1) also showed that, even after repeat serial 1-hour troponin, a significant proportion of patients remain in the intermediate "observational zone" category and this is associated with mortality and

adverse cardiac event risks. Suggestions for further management of these patients is not standardized and in fact is very individualized and guided by possible further repeat troponin and/or invasive or non-invasive cardiac imaging [4]. In a recent prospective international multicenter trial, Mueller et al found that 22.5% of patients remained in the observational zone and cumulative mortality for this cohort was 0.7% at 30 days but increased substantially to 9.6% at 365 days. This was in comparison to "rule out" and "rule in" mortalities of 0.1 and 2.7% at 30 days and 0.7% and 8.9% respectively at 365 days. An adjudicated diagnosis of acute myocardial infarction (AMI) was found in 22.5% of patients in the observational zone [10]. Similarly, in an international multicenter validation study of the 1-hour troponin algorithm, Reichlin et al found that 24.1% of patients were found to be in the observational zone. In this cohort, the prevalence of acute MI was 18.6% and the cumulative mortality was 1.6% at 30 days, rising to 16.5% at 2 years' follow-up (versus cumulative mortality of 1.1% and 13.4% for rule-in and rule-out categories at 2 years) [11]. Mokhtari et al evaluated major adverse cardiac events (MACE) at 30 days in a prospective observational study where the 1-hour hs-cTnT algorithm supplemented by patient history and ECG ("extended algorithm") was compared with an algorithm using hs-cTnT alone (troponin algorithm). Despite the addition of patient history and ECG, the proportion of patients remaining in the observation zone was not significantly different between the two algorithms and was found to be of the order of 25-27%. In the extended algorithm, the 30-day MACE event rate including unstable angina was 10.1% in the observational zone cohort versus 0.5% for "rule out" and 62.3% for "rule in" [12]. The aforementioned study by Jaeger et al (involving a similar 0/1hour algorithm using hs-cTnI) showed that 33% of patients remained in the observational zone and the cumulative mortality was found to be 0.6% at 30 days and 3.55 at 360 days [9]. These studies aptly demonstrate the presence of a significant cohort of patients who remain in the observational zone despite the use of the most up to date and sensitive means available to safely rule-out and rule in AMI with the use of serial hs-cTn's. Thus, again there is a pressing need to clarify risk stratification and further clinical management in order to reduce the proportion of patients who end up languishing in the observational zone.

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1.2 Possible role for computed tomography coronary angiography

The use of computed tomography coronary angiography (CTCA) in patients with acute chest pain has been shown to be safe [13], with high sensitivity and negative predictive value for coronary artery disease [14-17] and cost-effective with decreased time to diagnosis and earlier discharge from the emergency department [13, 18]. The finding of coronary artery disease on CTCA has been shown to predict prognosis, with significantly worse MACE for patients with obstructive stenosis (>50%), compared to those with results ranging from normal coronaries to non-obstructive stenosis (<50%) (Figure 2) [19-21]. The ACRIN-PA study by Litt et al, found that none of the patients who were discharged (after having been found to have <50% stenosis on CTCA) had AMI or death at 30 days' follow-up [22]. In the CT-STAT trial, patients in the CTCA arm who had <25% stenosis were discharged and authors noted that no patients died or had late ACS at 6 months' follow-up [18]. In the observational ROMICAT I trial, absence of significant CAD (defined as >50% stenosis) had a NPV of 98% for ACS and 100% when CTCA showed no plaque disease. However, sensitivity for ACS was 77% when using <50% stenosis cut off, as 7 patients with <50% stenosis had ACS [17]. Historically 10% of patients with clinical Non-ST-elevation myocardial infarction (NSTEMI) on conventional troponin analysis were found to have unobstructed (<50% stenosis) coronary arteries on invasive coronary angiography. Subsequently it has been shown that approximately only 10% of these patients have actual evidence of subendocardial infarction when investigated on late-gadolinium enhanced cardiac MRI (CMR) [23]. Hence in our proposed research clinical pathway (detailed in section **Experimental details and design of proposed investigation**), we have selected the conservative value of <25% stenosis to rule out AMI.

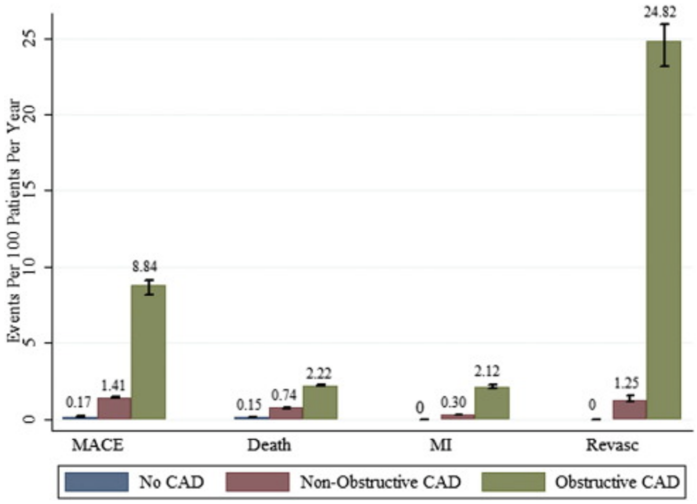


Figure 2. (Source: Hulten et al [21])

The above studies involving CTCA in patients with acute chest pain demonstrate that the main strength of CTCA lies in its ability to more rapidly and safely rule out coronary artery disease (and thus ACS) compared with conventional acute chest pain algorithms involving the use of slow release troponin assays. In more recent times, the ability of hs-cTn's to more rapidly "rule in" or "rule out" ACS with one blood test has obviated the previous need for prolonged observation with serial troponin testing. However as stated previously, a significant number of patients still remain in the intermediate observational zone after both first and second serial hs-cTn. Also of importance is the fact that despite mandating a repeat serial second hs-cTn at 1 hour post initial troponin, in real world practice, it can take at least than 90 minutes for the serial blood test to take place [6]. Modern day CTCA procedural time makes it a feasible investigation modality to be carried out during the time the patient is waiting to have their serial second hs-cTn taken.

Thus far, very few studies have examined the possible role of CTCA in the era of hs-cTn's. The aforementioned observational sub-study of the ROMICAT II trial by Ferencik et al, showed that CTCA, with advanced plaque assessment, significantly decreased the proportion of patients who had been classified in the intermediate category on initial hs-cTn from 43.8% to 24.4%. The study concluded that CTCA, with high-risk plaque assessment following hs-cTn, led to improvements in diagnostic

accuracy of patients with suspected ACS, compared with conventional slow release troponin and traditional CTCA assessment (based on luminal stenosis alone). However, drawbacks of the study included the observational design and the unlimited time for CT interpretation. Thus, one can call into question whether advanced plaque features could be assessed in the real world setting of a busy emergency department to make rapid decisions regarding admission or discharge [7].

The prospective randomized BEACON study compared the use of CTCA in addition to hs-cTn with a conventional management strategy involving hs-cTn alone. The authors concluded that the CTCA supplemented strategy did not meet the primary endpoint of identifying more patients with significant CAD requiring revascularization. In contrast to previous studies, the use of CTCA also did not shorten hospital stay nor allow for more direct discharge from the emergency department, despite 48% of patients having no identifiable CAD and serial troponin testing being carried out at 3-6 hours. The main benefits of CTCA included significantly lower direct medical costs and less out-patient testing. However, duration of hospital stay was not the primary endpoint and the exclusion criteria did not include a specified lower limit for hs-cTn for ruling out AMI [24]. Given the drawbacks of these studies, there is potential for further research with regard to the role of CTCA in the era of hs-cTn's in a prospective randomized manner, in order to clarify how it may influence hospital length of stay as the primary endpoint.

Therefore, in acute chest pain patients, there is a compelling need to compare the performance of a management strategy involving hs-cTn supplemented by CTCA in a direct prospective randomised fashion, with usual standard of care involving serial hs-cTn alone, in the cohort of patients deemed to be in the intermediate observational zone according to the initial hs-cTn result. This is to determine its effect on hospital length of stay as the primary endpoint and also to determine safety, further risk category, aid in clinical decision making, and to evaluate for clinical outcomes.

1.3 FFR-CT

Fractional flow reserve (FFR), measured with aid of an intracoronary pressure wire under maximal hyperemia during invasive coronary angiography, is the gold standard in terms of identifying lesion specific ischemia. An FFR value of 0.80 or less (i.e. a

drop in maximal blood flow of 20% or more caused by a coronary stenosis) indicates the potential of the stenosis to induce myocardial ischemia. Optimal medical therapy, along with percutaneous coronary intervention (PCI) guided by objective evidence of ischemia, in patients with stable coronary artery disease, has been shown to have better outcomes compared with optimal medical therapy alone in two important trials: COURAGE nuclear sub-study and FAME II, which employed the use of invasive FFR [25, 26].

Fractional flow reserve derived from CT (FFR-CT) is one of the latest developments in coronary assessment by CTCA to identify hemodynamically significant coronary stenoses. FFR-CT measurements are calculated using computer software, which combines mathematical calculations involving computational fluid dynamics and an anatomical model of the coronary arteries, derived from CTCA. It can be calculated at each point in the coronary tree under simulated maximal hyperemic conditions without the need for additional image acquisition/ionizing radiation or medication. A number of studies have evaluated the performance of FFR-CT. In the DISCOVER-FLOW trial involving 103 patients, the investigators found that on a per-vessel basis, the sensitivity, specificity, positive predictive value, and negative predictive value were 87.9%, 82.2%, 73.9% and 92.2% respectively, when compared with the reference standard of invasive FFR [27]. Also, in the landmark multicenter NXT trial involving 254 patients, (using invasive FFR as the reference standard), the addition of FFR-CT to traditional CTCA assessment was shown to improve diagnostic accuracy and specificity for the detection of ischemia, and therefore hemodynamically significant CAD on both per-patient and per-vessel basis when compared with CTCA stenosis assessment alone. In this trial, 93% of patients had intermediate (30-70%) stenoses and the investigators found that the per-vessel sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FFR-CT (84%, 86%, 61% and 95% respectively) were improved compared with that of CTCA alone (83%, 60%, 33% and 92% respectively) [28]. A sub-study of the NXT trial by Norgaard et al further showed that FFR-CT provided high diagnostic performance compared with standard CTCA assessment even in high coronary calcium score quartiles (121 to 1703 Agatston units) [29]. In the landmark PLATFORM trial, investigators showed that FFR-CT worked as an effective gatekeeper for patients intended for invasive coronary angiography (ICA), with significantly fewer rates of

no obstructive CAD found on ICA when selection was guided by FFR-CT (73.3% in the ICA arm and only 12.4% in the FFR-CT guided arm). This resulted in the cancellation of 61% of ICA's and none of these patients had adverse clinical events. It also showed that there was no statistically significant difference in the finding of no obstructive CAD found on ICA when selection was guided by FFR-CT or usual non-invasive testing e.g. stress testing (including stress echo, nuclear myocardial perfusion, CTCA etc.). It would have been interesting to see the performance of FFR-CT/CTCA against stress testing alone in the non-invasive arm. The inclusion of CTCA (with its high negative predictive value for CAD) in 60% of cases may have improved the rate of the primary end-point in the non-invasive testing arm [30]. Indeed, the PROMISE trial showed that anatomic testing with CTCA was associated with significantly fewer catheterizations showing no obstructive CAD compared to functional stress testing [31]. The FFR-CT RIPCORD study by Curzen et al showed that after disclosure of FFR-CT data there was a change in the allocated management strategy on the basis of CTCA alone in a substantial 36% of cases [32].

However, it is important to note that, to date, the above-mentioned studies involving FFR-CT have been carried out in stable chest pain populations and its evaluation in the acute chest pain patients who have corresponding hs-cTn results remains yet to be investigated.

2. Study Objectives and Design

2.1 Aim of the study

In patients with ACP requiring serial hs-cTn testing, to perform a head-to-head comparison of a management strategy involving serial hs-cTn supplemented by CTCA versus the conventional standard of care management guided by serial second hs-cTn alone in a randomized prospective trial. To the best of the author's knowledge this study will provide the first prospective and randomized data in the use and outcomes of CTCA on this ACP cohort (with an intermediate observational zone category on initial hs-cTn) results presenting to the emergency department in a tertiary hospital (see Study 1 below).

It will also provide further data on the influence of more advanced CTCA diagnostics (e.g. FFR-CT, advanced plaque characterization) in clinical decision making, incremental to that provided by hs-cTn based care alone in patients with acute chest pain (see Study 2 below).

2.2 Original hypothesis

The use of CTCA will lead to improvements in hospital length of stay and risk stratification and clinical management of patients in the intermediate/observational zone category on initial hs-cTn when compared with standard of care involving serial hs-cTn alone.

2.3 Experimental Details and Design of the Proposed Investigation

The proposed work is divided into two clinical studies:

Study 1: Prospective, randomized single-center trial to compare hospital length of stay, patient clinical management and outcomes between standard of care supplemented by CTCA versus standard of care alone, in ACP patients deemed to be in the intermediate observational zone category on initial hs-cTn in an acute hospital setting.

An unselected cohort of adult patients who attend the Accident and Emergency Department of St. Thomas' Hospital with acute chest pain, who have been found to be in the intermediate observational zone on initial hs-cTn and who require serial hs-cTn, will be identified for potential recruitment. The times for recruitment will be from 8am to 4pm, Mondays to Fridays (inclusive). If clinically, it is felt that there is a need for serial hs-cTn, the patients will be randomized to undergo either (Arm A): early CTCA along with a serial second hs-cTnT; or (Arm B): undergo standard of care involving serial hs-cTnT alone. Patients in both arms will be consented to have CTCA. However, Arm B (standard of care arm) will be blinded from CTCA findings and will have standard of care based clinical management according to serial hs-cTn. The CTCA data in Arm B will be used for Study 2 (see below).

Arm A: CTCA assessment will be carried out in Arm A while the patient would normally be waiting to have their repeat serial hs-cTn taken or waiting for the blood test result. The CTCA image interpretation followed by reporting will be carried out as early as possible in the acute hospital setting, while the patient is an in-patient. The CTCA will be interpreted and reported by an experienced Radiologist or Cardiologist with a minimum of Level II certification in cardiac CT angiography. Angiograms will be reported using the standard 15 segment model [33]. A stenosis will be graded in severity according to the following classification, as described in the Society of Cardiovascular Computed Tomography (SCCT) Guidelines [34]:

(a) Normal: 0%
(b) Minimal: 1-24%
(c) Mild: 25-49%
(d) Moderate: 50-69%
(e) Severe: 70-99%
(f) Total Occlusion: 100%

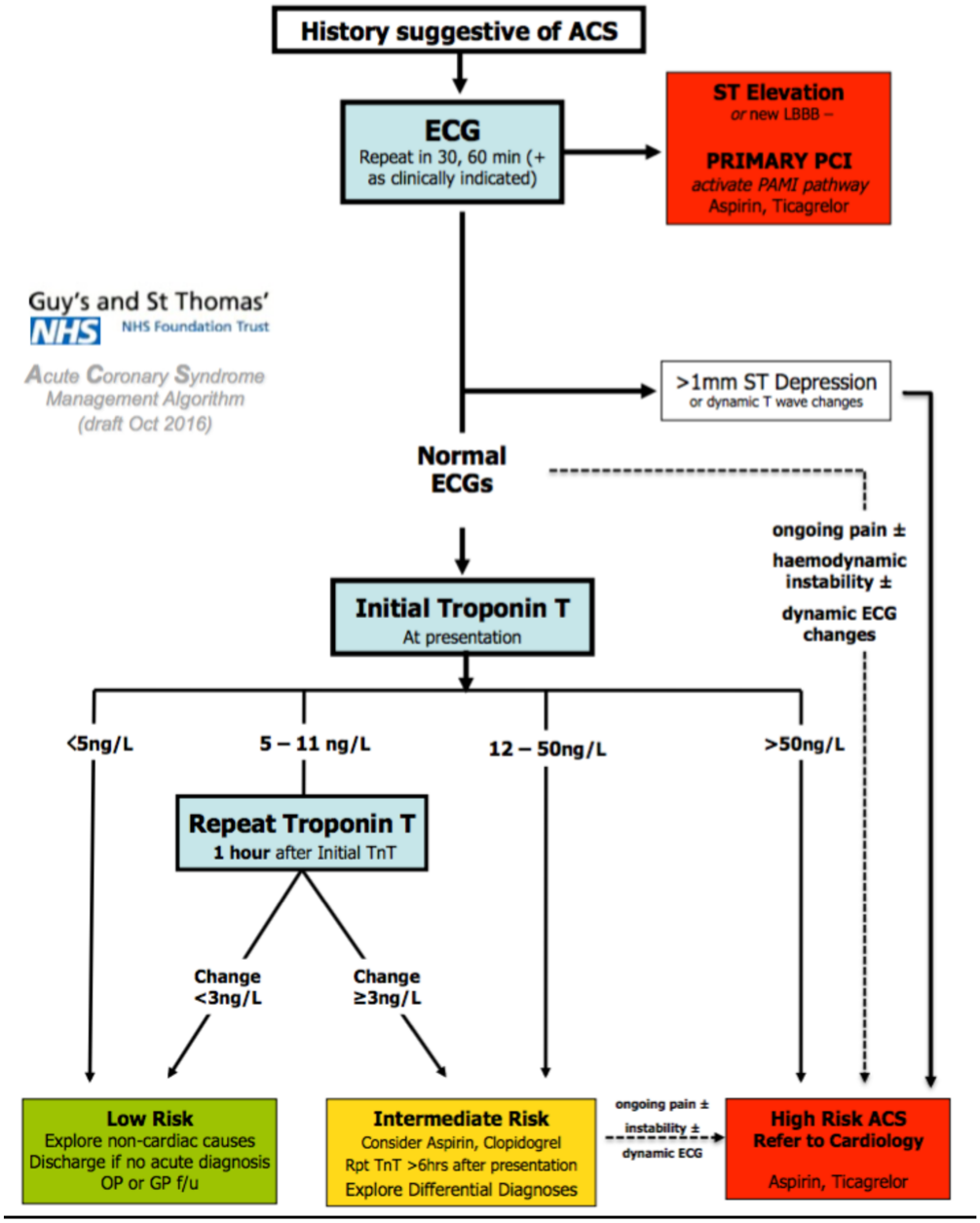
Patients with <25% stenosis will have AMI ruled-out. The reason for selection of this cut off (<25%) has been discussed previously but, to summarize, multiple studies have shown that <50% stenosis on CTCA corresponds with a favorable prognosis compared with >50% stenosis and also <50% stenosis has been shown to not be associated with AMI at 30 days' follow-up. Therefore, we have selected a more conservative value of <25% stenosis on CTCA to rule out AMI [19-22]. Patients with <25% stenosis may be considered for discharge or alternative reasons for their troponin rise may be investigated by the hospital care team e.g. renal failure, myocarditis, pulmonary embolism etc.

The results of these CTCA scans will be made available to the patients' clinical care team and further management decisions will be left to their discretion.

Arm B: Patients in this arm will be managed according to standard of care, which includes serial hs-cTn testing. As stated, these patients will also have CTCA carried out, but the CTCA assessment will not form part of the patients' clinical management as this arm will be blinded to CTCA findings. Furthermore, unlike Arm A, CTCA image interpretation will not take place in the acute hospital setting. It will be carried

out in the following days, again by an experienced Radiologist or Cardiologist with a minimum of Level II certification in CTCA. The whole CTCA procedure will be carried out **after** the patient has had their hs-cTn taken and while the patient is waiting for their hs-cTn result (as we would not like the CTCA to delay the staff members from taking the blood test). Should the CTCA on a patient in Arm B, be found to have significant high risk CAD e.g. >50% stenosis in the left main (LM) coronary artery, and/or >50% stenosis in the proximal left anterior descending (LAD) coronary artery, they will be un-blinded, taken out of the study and kept in a separate registry. Data collected up to that point will be kept by the research team. Their results will be discussed with the hospital care team and if they have not had any invasive coronary imaging during the preceding hospital admission, an urgent cardiology out-patient referral will be made to enable further clinical management.

Standard of Care Acute Chest Pain Management Algorithm at Guy's and St. Thomas' (Arm B)



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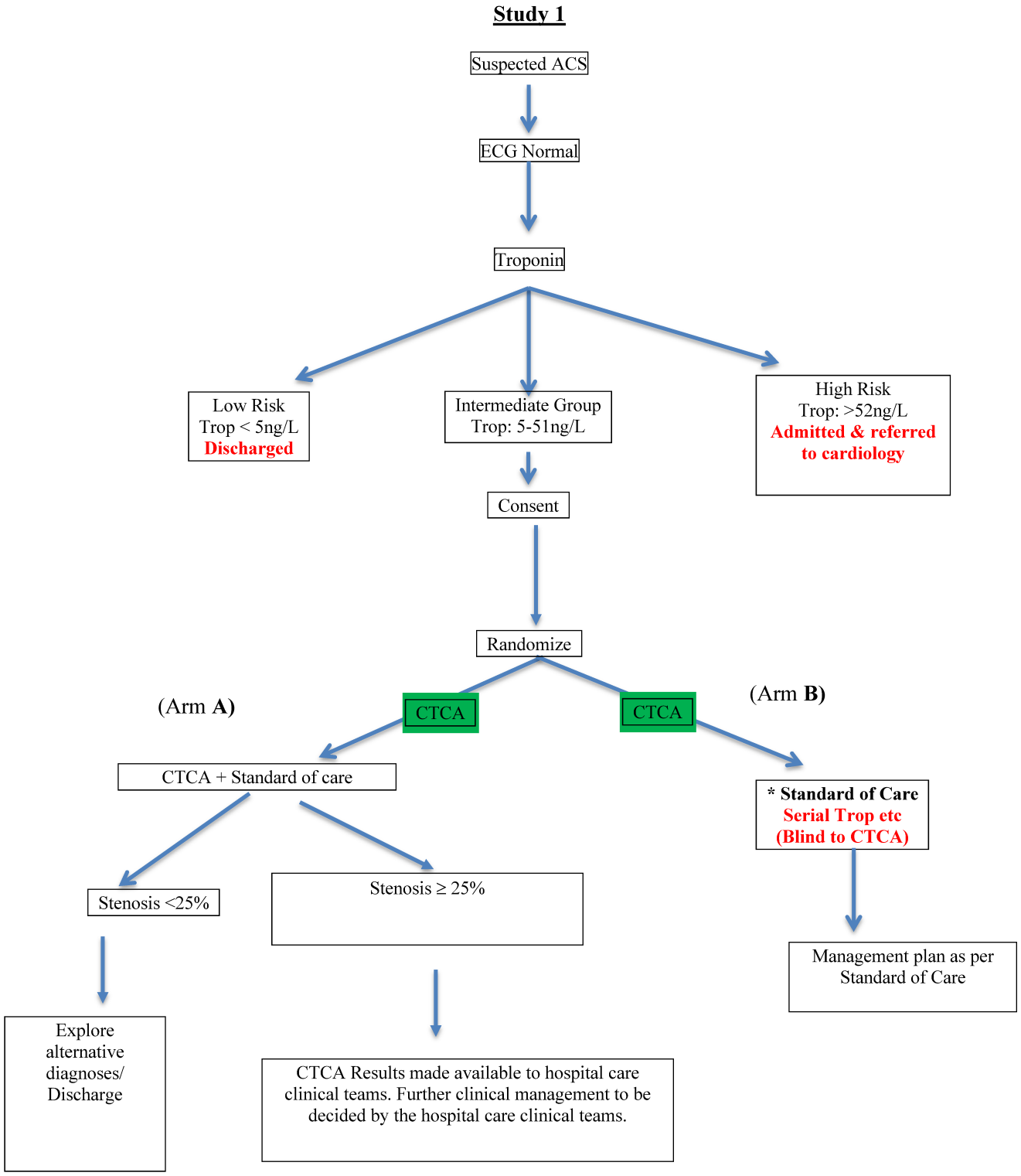

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Study 2: Sub-analysis of CTCA + biomarkers arm (Arm B): The study also contains an observational arm to evaluate the influence of advanced CTCA diagnostic information on clinical risk categories and clinical decisions, incremental to the original risk category and clinical management plan based on hs-cTn alone. Retrospective analysis of the CTCA data-sets will be carried out (at a later date) including, FFR-CT (see below) and plaque characterization (see below). Thereafter this information will be revealed to a select group of clinicians, who will be asked (in a virtual setting) to comment on possible changes to their original (hs-cTn based) clinical management plans in the light of the retrospective information gleaned from the existing CTCA datasets. From existing CTCA luminal stenosis data, the cardiology clinicians will be asked to comment on any changes to their clinical management plan if they were given the following information:

(i) hs-cTn + CTCA stenosis

(ii) CTCA stenosis + FFR-CT

(iii) CTCA stenosis + CT plaque characterisation

(iv) A combination of the above

We will also make a comparison between these virtual plans of action and actual course of action among patients who undergo invasive coronary angiogram +/- invasive FFR assessment as part of their routine care.

The rationale behind the use of FFR-CT has been discussed previously (Section 1.3). The CTCA DICOM data-sets will first be anonymized and subsequently couriered to Heartflow (Redwood City, California, USA) on an encrypted external hard drive for full post hoc processing to derive FFR-CT values. A research collaboration will need to be agreed between Guy's and St. Thomas' Hospital, King's College London and Heartflow in this regard. From preliminary data, we believe that out of 250 recruited patients, for Study 1, we would potentially require FFR-CT analyses on approximately **85 cardiac CT cases in total** (who would have at least ≥ 25% stenosis). The FFR-CT analysis will be carried out on retrospectively on patients already recruited to the trial and prospectively on patients that have yet to be recruited.

The rationale behind CTCA plaque characterization will be discussed below.

CT-Plaque Characterization

AMI results from sudden coronary luminal thrombosis, which can occur from any of three underlying pathological lesions: plaque rupture, plaque erosion and calcified nodules. Plaque rupture represents the majority of the underlying pathologies for AMI and the precursor coronary lesion is known as thin capped fibroatheroma (TCFA). These tend to be composed of a large lipid-rich necrotic core, thin and intact fibrous cap, spotty calcium, inflammation due to infiltration by macrophages and some smooth muscle cells [35].

Imaging with modern cardiac CT scanners enables the identification of coronary lesions with features of TCFA which could be prone to rupture and hence AMI. The high risk morphological features of TCFA on CTCA plaque assessment include: (a) napkin ring sign (b) positive remodeling (c) spotty calcification and (d) low attenuation.

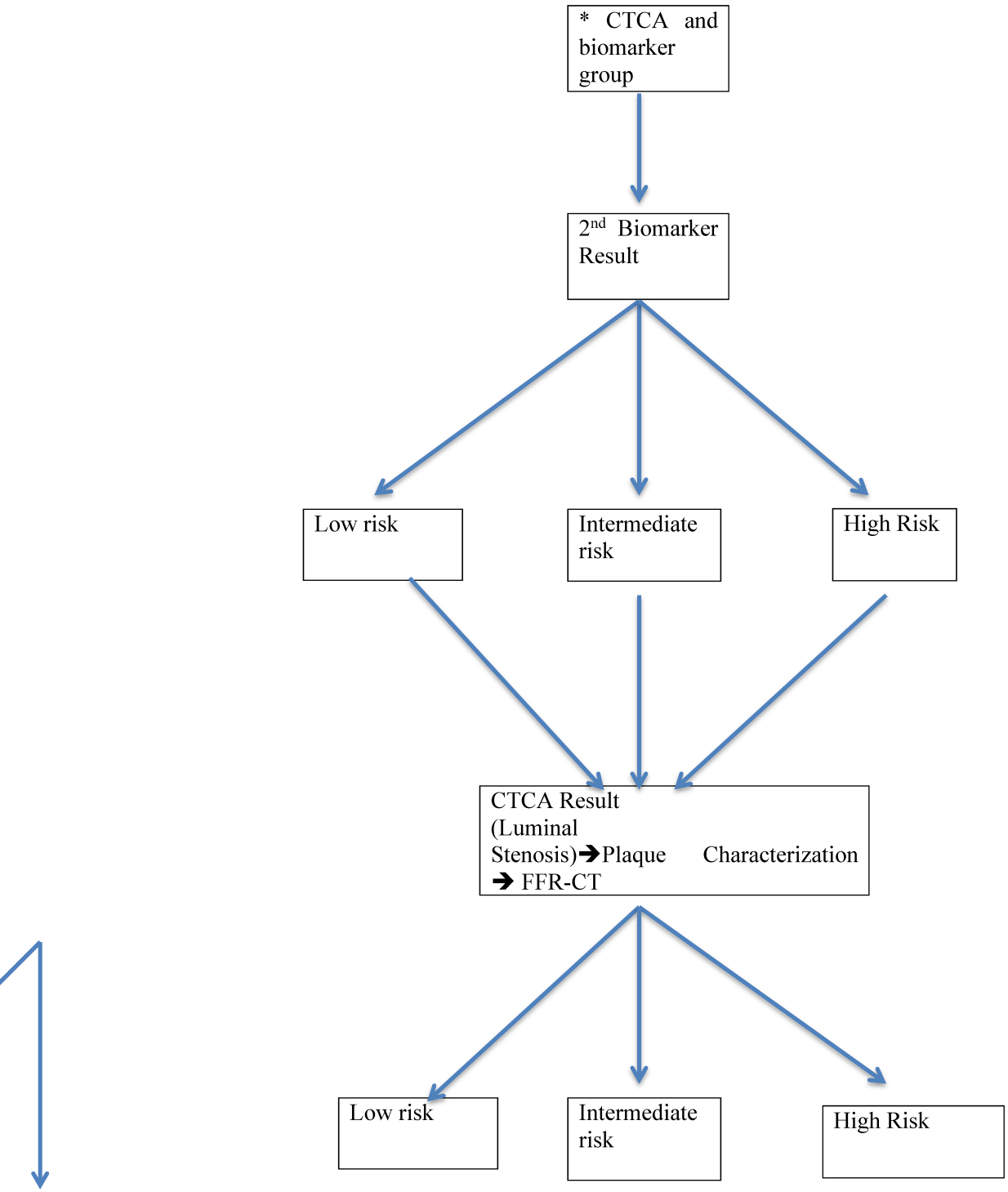
(a) Napkin Ring Sign: A term used to describe the CTCA appearance of non-calcified plaque with a central area of low CT attenuation and an outer ring-like higher attenuation plaque. It has been shown to have a high specificity in identifying TCFA (94.1%) [36], and also to be strongly associated with future ACS events, independent of other high-risk coronary CTCA features like positive remodelling, and low attenuation [37].

(b) Positive Remodelling: This describes the preservation of the vessel luminal area despite the presence of compensatory enlargement of the vessel wall due to atherosclerosis. Lesions with positive remodelling on CTCA compared to lesions without positive remodelling, have been shown to possess a significantly larger percentage of necrotic core and a higher prevalence of TCFA when assessed with virtual histology intra-vascular ultrasound (IVUS) [38]. In a study by Motoyama et al, the authors found positive remodelling was found to be significantly more frequent in patients with ACS compared to those with stable angina (87% vs12% $p < 0.0001$) [39].

(c) Spotty Calcification: Coronary artery calcification always indicates underlying coronary atherosclerosis and has been shown to be associated with poor clinical outcomes even in asymptomatic patients [40, 41]. Spotty calcification is the presence of small dense calcified plaque (>130HU) deposit(s) surrounded by non-calcified plaque and these can be classified according to size into small (<1mm), intermediate (1-3mm) and large (>3mm). On IVUS examination, the finding of small spotty calcification has been found to be significantly more frequent among coronary lesions with high percentage necrotic core and plaques. Furthermore, lesions with small spotty calcification were also shown to have the highest percentage of TCFA compared with large spotty or dense calcifications [42]. In multiple studies the presence of spotty calcification has been shown to be associated with ACS as compared with lesions found in stable angina [39, 43, 44].

(d) Low attenuation: On CTCA, low attenuation has been seen to be a consistent feature of lipid-rich plaque. In a multimodality imaging study by Ozaki et al, the authors found that among culprit lesions causing acute coronary syndrome (ACS), 71% had ruptured fibrous caps and the remainder had intact fibrous caps, whereas all patients with stable angina had intact fibrous caps, when imaged by optical coherence tomography (OCT) coronary imaging. CTCA imaging of these patients revealed that low-attenuation plaques (defined as <30 HU) were significantly more frequent (88%) among patients with ruptured fibrous caps/ACS compared with intact fibrous caps/stable angina (18%). They also found that positive remodelling and spotty calcification were significantly more frequent among patients with ruptured fibrous caps than stable lesions. However, these features (low attenuation, positive remodelling or spotty calcification on CTCA) were unable to differentiate between stable lesions and intact fibrous cap lesions associated with ACS [43].

Study 2. Sub-analysis of CTCA + biomarkers arm (Arm B):



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Study 2: Sub-analysis of CTCA + biomarkers arm in more detail (Arm B):

1. How would the addition of CTCA luminal stenosis reclassify (upgrade or downgrade) patients into low, intermediate and high risk groups compared with biomarkers risk category?

    a. How would this information change management?
    b. Clinical outcomes of patients in each risk category (rates of death, MI, unstable angina, hospital readmissions, coronary revascularisation)
    c. Which findings on CT were associated with clinical outcomes?

2. How would the addition of plaque characteristics to luminal stenosis reclassify patients into low, intermediate and high risk groups compared with biomarkers risk category?

    a. How would this information change management?
    b. Clinical outcomes of patients in each risk category (rates of death, MI, unstable angina, cardiac related hospital readmissions, coronary revascularisation)
    c. Which findings on CT were associated with clinical outcomes?

3. How would the addition of FFR-CT to luminal stenosis reclassify patients into low, intermediate and high risk groups compared with biomarkers risk category?

    a. How would this information change management?
    b. Clinical outcomes of patients in each risk category (rates of death, MI, unstable angina, cardiac related hospital readmissions, coronary revascularisation)
    c. Which findings on CT were associated with clinical outcomes?

4. How would the combination of these factors affect influence risk category/management?

5. Correlation of serial high-sensitivity cardiac troponin levels and diagnoses of MI/unstable angina with CTCA e.g. across various degrees of stenosis (<25%; 25%-49%; 50%-69%; >70%), high risk plaque features and FFR-CT?

2.4 Primary Endpoint (Study 1)

The primary objective will be to compare median hospital length of stay in each arm.

2.5 Secondary Endpoints (Study 1)

- Number of admissions in each arm;
- Number of discharges in each arm;
- Time taken to arrive at decision for admission or discharge;
- Number of additional investigations during hospital stay (if admitted);

- Proportion of patients with completeness of diagnosis on discharge;
- Rates of OPD referrals at discharge;
- Rates of OP cardiac testing referrals at discharge
    - Rates of ICA referrals in each arm
    - Rates of negative ICA
- Number of cardiac out-patient clinic visits during 1 year;
- Time taken for completeness of diagnosis in each arm;
- Number of cardiac related AE revisits in each arm over 1 year;
- Number of cardiac related hospital re-admissions in each arm over 1 year.

Patient Experience
Patient Satisfaction/QoL at baseline, 1, 2, 3, 6, 9, and 12 months.

Safety
Differences in terms of radiation dose in each arm.

Health Economics
Cost of ED visit.
Total healthcare cost in each arm at 6 months and 1 year.
Total hospital admission costs in each arm.

Clinical Endpoints: Rates of death, ACS, revascularization at 30 days, 6 months, 12 months.

2.6 Study Statistics

We will first inspect the normality of the distribution of the outcome variable. If it appears as though the distribution is not normal as expected, then we will use non-parametric tests (Mann-Whitney U test); differences between groups will be constructed using 10,000 bootstrap simulations on the difference in medians, and derive associated confidence intervals and p-values. If there are any significant imbalances in any covariate(s) between the two groups, then we will also perform quantile (specifically median) regression analysis on the difference between median length of stay between the two groups, adjusted for these covariate(s). To estimate the standard errors for the difference in medians, 10,000 bootstrap simulations of this quantile regression will be performed. If there are any significant imbalances, then the adjusted analysis will be considered the main analysis, otherwise the univariate analysis will be taken to be the main analysis. If the data are Normally distributed then standard regression techniques will be used.

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2.7 Cost and Economic Analysis

The cost and cost-effectiveness analyses will assess whether the addition of CTCA within the Emergency Department setting to the conventional clinical pathway without acute imaging will produce any changes in terms of total costs and/or cost-effectiveness analyses. For the purposes of the secondary objectives of cost analyses and economic evaluations (consistent with secondary outcomes) quality of life and symptoms will be measured using the EQ-5D-5L questionnaire at baseline after the ED episode and then monthly for the first three months and three monthly thereafter. All relevant costs from an NHS and Personal Services perspective will be considered using a top-down costing strategy (consistent with GSTFT finance data).
Cost-effectiveness will be estimated in terms of the incremental cost per quality-adjusted life year (QALY) of comparing both clinical pathways (with and without the use of CTCA in acute setting). This ratio will be calculated using the area under the curve for health utility using the EQ-5D-5L and health service costs up to one year. Sensitivity analyses will explore the potential impact of major adverse events upon lifetime costs and QALYs as well as the adoption of a societal perspective.
Existing published models will constitute the base for long-term modelling of both clinical pathways. Lifetime QALYs and costs of surviving patients will be estimated from published sources of life expectancy, annual costs and corresponding annual utilities. It is hypothesised that patients in whom coronary artery disease is identified, will adhere better to strategies that include primary and secondary prevention. This means that the early use of CTCA might hold benefits in the short-term) as well in the medium and long-term.

2.8 Timeline

In our internal audit, patients who presented with acute chest pain to the ED at GSTFT, and were found to be in an intermediate grey zone on initial troponin analysis and who required a second troponin amounted to 26 patients per week (Monday to Sunday), which works out to be over 3 patients per day. As we are going to recruit patients Monday to Friday from 8am to 4 pm, it is anticipated that we may able to

recruit 4-5 patients per week in total. Given the target of 250 patients in the study, recruitment is likely to take approximately 12-15 months to achieve.

Follow up Procedures

Patients will be followed up at 1, 2, 6, 9 and 12 months following the hospital visit, in order to capture all relevant costs and outcomes.

In the event of patient death or failure to comply with study requirements, he/she will be excluded from the study. It is estimated that 30% of participants enrolled in the study may be lost to follow-up.

Data collection

General and study specific data

Data will be collected by the research team from routinely collected NHS records and will include several categories, such as: baseline demographics, co-morbidities, ECG results, admission and discharge diagnoses, cardiology and other relevant investigations or interventions, repeat hospitalizations and adverse events. Study specific data will also be collected such as: radiation dose per CTCA scan, timing of interventions, report of incidental findings and any adverse events.

Patient diaries and questionnaires

Patients will receive a call (at 1, 2, 3, 6, 9 and 12 months) to collect key information around resource use, patient quality of life and patient satisfaction. All patients will be provided with **a diary** in the registration pack after the initial episode at the ED. In these patient diaries, patients should record all hospital and GP visits, community care, medications and investigations. Quality of life will be assessed using a standard questionnaire (EQ-5D-5L questionnaire). Patient satisfaction will be evaluated using a 0-10 scale.

3. CTCA Procedures and findings

3.1 CTCA Procedure

The CTCA exam will be performed on a new generation CT scanner, i.e. a multi-detector dual-source CT scanner. This CT scanner will be used for both clinical and research purposes. Given the need for possible 1 scan per day, we do not anticipate logistic difficulties in completing the CT scans. Only GSTFT standardized

prospective ECG-gated protocols will be used to perform the CTCA exam. This will significantly reduce the overall radiation dose to below 9 mSv per CTCA scan. This dose assessment is based on the dose for a typical patient as there will be normal variation around the average dose due to individual subjects' body habitus and heart rate. If, for some reason, the use of prospective ECG-gated protocols is not possible, the CTCA scan will not be carried out, and therefore the patient will not enter the study. Female patients of potential child bearing age will be screened for the possibility of pregnancy according to the local Guy's and St. Thomas' Radiology protocols.

We will try to ensure optimum CTCA images by attempting to minimize coronary and chest wall motion artefact through reducing heart rate to below 63 beats per minute (bpm) and by getting the patients to practice breath holding for 10 – 12 seconds. If the heart rate is above 63 bpm and the systolic blood pressure (BP) is above 100 mmHg, intravenous beta-blockers (e.g. metoprolol 5-30mg) will be given to achieve the target heart rate. In order to further optimize coronary images, sublingual glyceryl trinitrate (GTN) will be given if the systolic BP is above 90 mmHg. A small dose of oral diazepam may also be given to improve heart rate control in patients who may be anxious. Pre-CTCA renal function will be available from routine bloods samples that are taken as part of standard of care work-up of patients presenting to the ED with acute chest pain of suspected cardiac origin.

As stated previously, CTCA assessment will be carried out in Arm A while the patient would normally be waiting to have their repeat serial hs-cTn taken or waiting for the blood test result. This is in contrast to Arm B, where the CTCA procedure will be carried out after the patient has had their hs-cTn taken and while the patient is waiting for their hs-cTn result (as we would not like the CTCA to delay the staff members from taking the blood test).

3.2 CTCA Image Interpretation and Reporting

The CTCA will be interpreted and reported by an experienced Radiologist or Cardiologist with a minimum of Level II certification in cardiac CT angiography. Angiograms will be reported using the standard 15 segment model [33]. A stenosis will be graded in severity according to the following classification:

(a) Minimal: 0-24%

(b) Mild: 25-49%
(c) Moderate: 50-70%
(d) Severe: >70%
(e) Total Occlusion: 100%

Patients with <25% stenosis will have AMI ruled-out. The reason for selection of this cut off (<25%) has been discussed previously but briefly the reasons are that multiple studies have shown that <50% stenosis on CTCA corresponds with favorable prognosis compared with >50% stenosis and also <50% stenosis has been shown to not be associated with AMI at 30 days' follow-up. Therefore, we have selected a more conservative value of <25% stenosis on CTCA to rule out AMI [19-22].

3.3 CTCA Results

For Arm A, CTCA image interpretation followed by reporting will be carried out as early as possible in the acute hospital setting, while the patient is an in-patient. The results will be made available to the patients' clinical care team and further management decisions will be left to their discretion.

As stated previously, patients in Arm B will also have CTCA carried out but the CTCA assessment will not form part of the patients' clinical management as this arm will be blinded to CTCA findings. Furthermore, unlike Arm A, CTCA interpretation followed by reporting will not necessarily take place in the acute hospital setting and therefore will be carried out in the following three weeks. Should the CTCA be found to have significant high risk CAD e.g. >50% stenosis in the left main (LM) coronary artery, and/or >50% stenosis in the proximal left anterior descending (LAD) coronary artery, they will be un-blinded and kept in a separate registry. Their results will be discussed with the hospital care team and if they have not had any invasive coronary imaging during the preceding hospital admission, an urgent cardiology out-patient referral will be made to enable further clinical management.

3.4 CTCA Incidental Findings

Pooled studies show: (i) an incidental extra-cardiac finding in 44% of patients undergoing CTCA; and (ii) the diagnosis of a major finding in 16% of the CTCA exams [45]. Incidental findings on CTCA will be documented in the CTCA report. In the case of Arm A (Study 1), the clinical care team will be made aware of the finding

through the report. In Arm B (where the CTCA images will be evaluated at a later date), any clinically significant findings e.g. cancers and/or prognostically significant coronary artery disease will be notified as a Radiology alert to the clinical care team and the patient's general practitioner.

4. Sample Size, Selection and Withdrawal of Subjects

4.1 Sample Size

Waiting times often exhibit a skewed distribution, and so the sample size calculation was based on the difference in median waiting time.

To estimate the sample size needed to observe a one-hour reduction in median hospital length of stay, normal techniques based on standard deviation estimates are not valid. We therefore used a random sample of 49 patients undergoing the current pathway as the control 'population', and created an equivalent treatment 'population' by multiplying the waiting times of the 49 sampled patients by a constant such that the median was reduced by one hour; this constant was found to be 0.799.

For a given sample size n, 10,000 Monte Carlo simulations were performed by sampling n patients with replacement from each of the two groups, and the p-value from a Mann-Whitney U test was calculated for each simulation. The proportion of these 10,000 simulations with a p-value below 0.05 was recorded as the power for that sample size n. The sample size was varied until a power of 0.8 was obtained, and was found to be **250** patients in total (**125** patients in each arm of the study).

Patient drop-out is anticipated to be minimal as all patients, by definition of the primary outcome, will be in hospital for the length of their hospital stay, and therefore their length of stay will be recorded.

4.2 Inclusion Criteria

1. Patients above 18 years of age with ischaemic sounding chest pain prompting visit to the emergency department (suspected ACS).

2. No-ischaemic ECG changes (i.e. no ST-segment elevation or depression ≥ 1mm in 2 or more contiguous leads, and/or T-wave inversions).
3. Episode of chest pain within last 12 hours.
4. Initial troponin in the intermediate range (5-50ng/L).

4.3 Exclusion Criteria

1. STEMI.
2. Initial troponin < 5ng/L or >50ng/L.
3. Signs and symptoms of acute heart failure and/or haemodynamic instability.
4. Dynamic ischaemic ECG changes.
5. Patient not suitable to undergo CTCA
    a. Inability to breath hold for 10 seconds
    b. Severe renal impairment (eGFR <30 mL/min)
    c. Contraindication to beta-blockers
6. Atrial Fibrillation on ECG.
7. Patients with known significant obstructive coronary artery disease (>50% stenosis) on previous invasive or CT coronary angiogram.
8. Patients with previous PCI/CABG revascularisation.
9. Patients with a history of congenital heart disease.
10. Patients with known coronary artery anomalies.
11. Patients who lack capacity to give consent or participate in the study.
12. Previous recruitment to the present study.
13. Known pregnancy or patients who are currently breast feeding.
14. Prisoners.
15. Patients involved in current or a recent (within the last 4 months) CTIMP trial.

4.4 Criteria for Premature Stopping of the Trial

If 5 consecutive participants are randomised to Arm A of the study (Cardiac CT + standard of care), and cardiac CT is not available within the required time-frame.

5. Study Procedures

5.1 Screening Procedures

Patients with suspected ACS eligible for the study will enter GSTFT via the ED at St Thomas' Hospital. As part of their standard care, all patients will be clinically assessed on arrival by the routine clinical care team. Subsequently, if the initial ECG shows no ischemic changes and the initial hs-cTn result cannot rule in or rule out ACS, and there is a need for a serial hs-cTn test, the patient will be identified as a potential recruit to the study. Subsequently if the patient meets at least one of the inclusion criteria (and none of the exclusion criteria), a trained member of staff will be responsible for taking written signed informed consent from the patient.

A screening log must be maintained by the site and kept in the Investigator Site File. This must record all potentially eligible patients approached about the study and the reasons why they were not registered in the study if this is the case.

5.2 Consenting Participants

Once a potential participant is identified by the routine care team, the patient will be approached by research staff, to discuss the study with the patient. The Investigator, or a person appropriately trained and delegated by the Investigator (as documented in the site delegation log) is responsible for obtaining and documenting informed consent (either verbal or written as abovementioned) from each subject prior to any participation/study specific procedures. This procedure will be supported by a patient information sheet that appropriately explains the aims, methods, anticipated benefits and potential hazards of the study.

Following agreement between Heartflow and GSTFT/KCL, for purposes of FFR-CT analysis, patients who have already been recruited in Study 1 will be consented retrospectively for the FFR-CT analysis by being contacted via a phone call. Following agreement, all future patients (if any have yet to be recruited) will be consented for potential FFR-CT in the hospital setting.

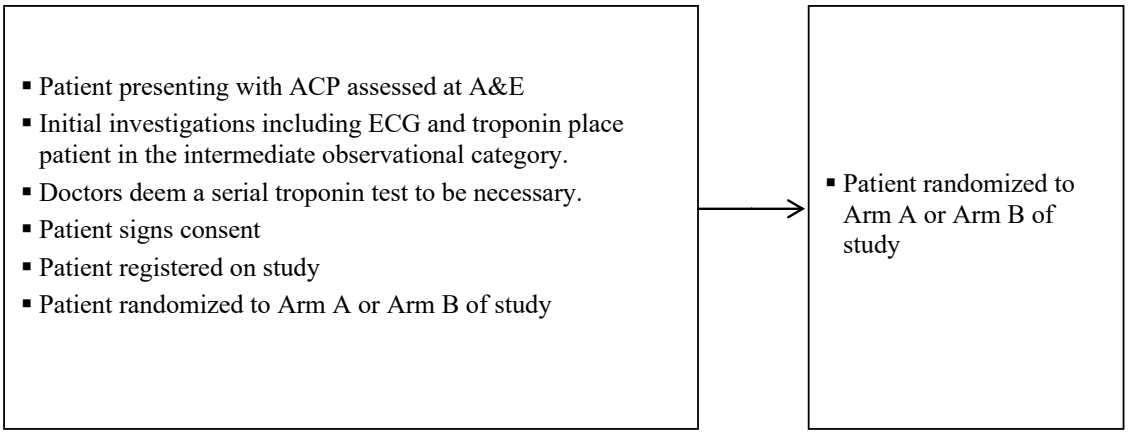
It is anticipated that the consent process will take no longer than 15 minutes.

If the patient shows no interest in taking part in the study, he/she will not be included in the study. If the patient shows interest in taking part in the study, the patient information sheet will be given to the patient and discussed with him/her. Potential

risks and benefits should be discussed with the patient (and their accompanying relative/companion, if present and appropriate). It will be explained to the patient that it is his/her right to ask to be withdrawn from the study at any point in time.

During these discussions, the current approved patient information sheet for the study will be discussed with the patient (and, if present and appropriate, their accompanying relative). The recruitment process and initial tasks to be performed, both for the Pathway 1 and Pathway 2 clinical pathways, are illustrated in the flowchart below in Figure 4 and Figure 5, respectively.

Summary of Consent Process



Potentially eligible participants who are willing to take part in the study will be asked to provide informed consent. Written informed consent on the current approved version of the consent form for the study will be obtained before any study-specific procedures are conducted, and a copy will be given to the patient and kept in the patient's medical notes. The discussion and consent process must be documented in the patient notes and will be obtained by a trained member of the clinical team or a member of the research team.

The patient's capacity will be assessed by trained and delegated clinical/research staff who have completed study specific training and have been delegated this responsibility by the Principal Investigator (PI).

GSTFT staff are responsible for:

- Assessing the patient's capacity to provide informed consent.
- Checking that the current approved version of the information sheet and consent form are used.

- Checking that information on the consent form is complete and legible and the patient has completed/initialled all relevant sections and signed and dated the form.
- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient.
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.).
- Following registration:
    - Adding the patient study number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file.
    - Giving the patient a copy of their signed consent form and patient information sheet.
- Respecting the right of the patient to refuse to participate in the study without giving reason as all patients are free to withdraw at any time.

5.3 Randomization Procedures

Once patients consent to participate in the study, they will be randomized into the intervention group (i.e. with CTCA) or the control group (i.e. hs-cTn based standard of care) on a 1:1 ratio. For purposes of Study 2, the control group of patients will also be consented to undergo CTCA. However, CTCA will not form part of their in-patient clinical management as the clinical teams will be blinded from CTCA findings (except for cases of prognostically significant coronary disease e.g. 50% stenosis of the LM and/or proximal LAD coronary arteries).

Randomization will be carried out via the use of opaque sealed envelope block randomization method. Both the block randomization list and the sealed envelopes will be produced by the statistician. Each block will contain 5 envelopes, which would translate to 50 blocks. 25 blocks will contain 3 envelopes for Arm A and 2 envelopes for Arm B. The remaining 25 blocks will contain 3 envelopes for Arm B

and 2 envelopes for Arm A. Each block will also be randomly arranged. The sealed opaque envelopes/blocks used to assign patients to either arm will be prepared by an individual external to the study. The recruiter will not be able to identify which arm a potential participant is going to be randomized to until **after** he/she has received informed signed consent from the potential participant.

Once randomized onto the study, the patient will be given a study number. This will be documented in the enrolment log.

5.4 Radiology Assessments

Radiological assessments will be used in the both arms of Study 1. However, the clinical pathway as outlined in Study 1 is likely to increase the radiation burden as CTCA is an imaging modality which uses ionizing radiation. In order to decrease the overall radiation burden, and the risks associated, several processes are going to be respected:

- The clinical pathway outlined in Study 1 will only consider the use of prospective CTCA scanning protocols on a new generation CT scanner. This will lead to low radiation doses (below 9 mSv) while maintaining the image quality and high diagnostic performance.
- If, for some reason, (e.g. patients with elevated heart rate despite the use of oral and/or intravenous beta-blockers) it is not possible to use prospective CTCA scanning protocols, the patient will not undergo the CTCA examination and therefore will not enter the study.

Given the potentially life threatening condition under review, it is considered that the **potential benefits of using CTCA outweigh the potential risks**.

5.5 End of Study Definition

For regulatory purposes the end of the study will be 12 months after recruitment of the final patient at which point the 'declaration of end of study' form will be submitted to ethical committees, as required.

6. Assessment of Safety

A serious adverse event is any untoward medical occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Other important medical events**.

Notes:

*The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Other events may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.1 Ethics reporting

A serious adverse event (SAE) occurring to participant would be reported to the REC that gave a favorable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs would be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form.

All related AEs that result in a patient's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs. It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment due to what he, or she, perceives as an

intolerable AE. If either of these occurs, the patient would undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

7. Study Steering Committee

The Study Steering Group will be chaired by _____who is acting as an external advisor to this study. The Study Steering Group will meet at fixed points during the study and will include patient representatives.

All GSTT clinical governance protocols will be respected during the conduction of the present trial.

Data Monitoring and Ethics Committee (DMEC) functions will be embedded in the Study Steering Committee. The Study Steering Committee will have access to unblinded comparative data. The committee will monitor data collection methods and make recommendations regarding whether there are any ethical or safety reasons why the study should not continue.

8. Ethics & Regulatory Approvals

East Midlands Leicester South Research Ethics Committee

9. Data Handling

9.1 Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant identification (ID) number. This ID number will be coded in such a way that participants cannot be identified. All documents will be stored securely and only accessible by study staff and authorised personnel.

Different sources of data will be collected by trained staff at different points in time (as illustrated in Figure 3 and Table 1). If an external organisation is to capture data on behalf of the study team such as follow-up data through automated systems (i.e. automated text message systems) this needs to be previously agreed with the GSTFT governance team and a formal agreement will be be established under GSTFT terms of data protection policies.

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As previously mentioned, the participant identification (ID) number will be provided as soon as feasible, during the initial procedure of registration in the study immediately following the informed consent signature.

No patient identifiable data will be transferred outside the EU.

9.2 Case Report Form

Trained staff (as per the delegation log) will be responsible for the completion of the CRF.

9.3 Record Retention and Archiving

At the end of the study, GSTFT will archive securely all centrally held study related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the study held at site are retained for a minimum of 5 years after the end of the study, in accordance with national legislation and for the maximum period of time permitted by GSTFT.

9.4 Compliance

The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so and no non-anonymised data will be used for the purposes of the study or subsequent study publication.

9.5 Clinical Governance Issues

All GSTFT clinical governance protocols will be respected during the conduction of the present study.

9.6 Non-Compliance

GSTFT may require a report on the incident(s). If GSTFT staff are unsure whether a certain occurrence constitutes a deviation from the protocol, the GSTFT study team can be contacted immediately to discuss (via email - ACPint-toheti@kcl.ac.uk – or phone on 0207 188 9529). .

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GSTFT will use an organisation's history of non-compliance to make decisions on future collaborations.

10. Finance and Publication Policy

The study is fully funded by a grant secured from Guy's and St Thomas' Charity. The contact details are listed below:

- Name and address of funder:
- Name: Guy's and St Thomas' Charity
- Address:

  Guy's and St Thomas' Charity

  Second Floor, Francis House

  9 King's Head Yard

  London

  SE1 1NA
- Telephone: 020 7089 4550
- Fax: 020 7089 4585
- Email: grants@gsttcharity.org.uk

Authorship Policy

All data collected as part of the study will reside with the research team. Once the study is completed, all study data will be analysed and documented. The authors of this document are listed in the first pages of this protocol.

Publication

The present study is aimed at publishing and presenting data to peer reviewed journals and scientific meetings. If successfully completed, it is anticipated the main paper from this project will be published in leading medical journals.

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CCTA Protocol

A combined automated tube potential selection software (CAREkV, Siemens Healthineers) and current selection algorithm (CAREDose 4D, Siemens Healthineers) was utilized with a reference peak tube voltage of 120 kV and reference mA of 280. Intravenous metoprolol in 5 mg incremental doses was used where required to achieve a heart rate of ≤60 bpm and 800mcg sublingual glyceryl trinitrate was administered to all patients. All scans were prospectively acquired using an axial-sequential scan mode extending from the carina to the inferior aspect of the heart upon an inspiratory breath hold with a gantry rotation time of 250 ms. The ECG pulsing and padding range was automatically determined by the scanner with arrhythmia rejection enabled (Adaptive Cardio Sequential). In all cases Omnipaque 370 mg/ml was injected at a rate of 5-6 mls/second followed by a 75 mls mixed bolus of contrast: saline (35%:65%) and a 25 mls saline chaser. Bolus tracking was used with the scans triggered once a minimum of 110 Hounsfield Units was achieved in the thoracic descending aorta. All images were reconstructed using ADMIRE strength 2 (Advanced Modelled Iterative Reconstruction, Siemens Healthineers) using a medium-smooth dedicated heart kernel (Bv40 d).

Unblinded participants from SOC arm

Overall, 7 patients from the SOC arm had CCTAs unblinded during their in-patient hospital stay:

- 4 had >50% stenosis in the proximal LAD of whom:
  - 1 had an in-patient ICA and PCI to LAD;
  - 1 was referred for out-patient ICA,
  - 1 was referred for a non-invasive functional test and
  - 1 referred for cardiology out-patient review),
- 1 had an acute pulmonary embolism and
- 2 were protocol violations whereby CCTA results were inadvertently released:
  - In one patient, CCTA reported severe (70-99%) stenosis in the mid LAD, diagonal branch, and proximal RCA and mild (25-49%) stenosis in the proximal LCX. The patient subsequently underwent in-patient ICA which showed a chronic total occlusion of a non-dominant RCA; severe distal LCX disease and,

moderate to severe mid and distal LAD disease. This was not felt to be amenable to percutaneous or surgical revascularisation.

- Another patient's CCTA reported severe (70-99%) stenosis in the mid LAD. Subsequent in-patient ICA showed pressure wire negative moderate mid LAD disease and severe disease in a small calibre 2nd diagonal branch. The patient subsequently underwent PCI to the 2nd diagonal branch.

The 2 unblinded patients who underwent in-patient revascularisation are included in the 4 patients overall, who underwent in-patient revascularisation in the SOC arm (Table 3).

Medications on discharge

	CCTA Arm (n= 124)	**SOC Arm (n=122)**
Antiplatelet therapy	37 (30%)	32 (26%)
Statin	40 (32%)	51 (42%)
ACE Inhibitor	32 (26%)	23 (19%)
Angiotensin receptor blocker	13 (10.5%)	9 (7%)
Beta-blocker	20 (16%)	27 (22%)
Calcium channel blocker	26 (21%)	31 (25%)
Diuretic agent	9 (7%)	16 (13%)
Oral diabetic agent	20 (16%)	22 (18%)
Insulin	7 (5.6%)	10 (8%)
Oral anti-coagulant agent	8 (6.5%)	7 (6%)
Proton-pump inhibitor	25 (20%)	30 (24.6%)

Times from (i) hospital presentation and (ii) from patient randomisation to (a) CCTA completion and (b) CCTA report

	CCTA Arm Harmonic Mean (IQR)	SOC arm Harmonic Mean (IQR)
Presentation to CCTA completion	4.13 (3.68 – 5) hours	4.6 (3.98 – 5.4) hours
Randomisation to CCTA completion	0.67 (0.55 – 0.92) hours	0.74 (0.62 – 1.02) hours
Presentation to CCTA report	5.13 (4.6 -5.9) hours	n/a
Randomisation to CCTA report	1.33 (1.3 – 2.1) hours	n/a

In-patient investigations of patients in the SOC arm

Excluding 7 patients from the SOC arm that were unblinded, the remaining 118 patients underwent the following investigations:

- 113 (96%) underwent chest radiographs
- 3 (2.5%) underwent transthoracic echocardiograms
- 4 (3%) underwent invasive coronary angiography
- 1 (1%) underwent CT pulmonary angiogram
- 1 (1%) underwent doppler ultrasound scans of the lower limbs

Example of breakdown costs of Patient 1 who was discharged early and also of Patient 2 who had a substantially longer in-patient hospital stay

	Cost Patient 1 (GBP)	Cost Patient 2 (GBP)
ED Department	348	269
Pathology	77	537
Clinical Coding and Informatics	2	45
Patient Administration	2	8
Patient Support	7	149
CCTA	364	364
Chest X-Ray	37	37
Pharmacy Department (including drugs)	-	381
Infection Control	-	14
Cath Lab	-	1262
Surgical Theatres	-	3044
Critical Care	-	2810
Wards	-	3330
Clinical Department costs (includes Staffing)	-	3060
Total:	**837**	**15310**