ABBREVIATIONS

ACS	acute coronary syndrome
CAD	coronary artery disease
CI	confidence interval
CTCA	computed tomography coronary angiography
ED	Emergency Department
ETT	exercise treadmill test
HR	hazard ratio

Introduction

Presentation to the hospital emergency department (ED) with acute chest pain is one of the most frequent occurrences, accounting for around a quarter of all hospital admissions. [1] Most commonly, management is directed towards the exclusion of acute coronary syndromes, using the presence (or absence) of cardiac risk factors, electrocardiographic changes and an appropriate rise or fall in biomarkers. [2] In patients where initial investigation excludes acute coronary syndrome (ACS), with a non-diagnostic ECG and negative cardiac biomarkers, current practice is to offer functional stress testing to elucidate the presence of significant underlying ischemia and provide prognostic information. Despite the improved performance and cost-effectiveness of non-invasive imaging techniques, in the United Kingdom stress testing is most commonly performed using the exercise treadmill (ETT), which provides important prognostic information. [3-6] Despite the widespread availability and use of the ETT, there are a significant proportion of patients who may not be able to undergo this test, for example those with poor exercise tolerance, poor mobility, or resting ECG abnormalities such as left bundle branch block. An inconclusive ETT, or worse, a non-performed one may lead to a dilemma in the subsequent management of the patient, potentially leading to unnecessary invasive coronary angiography.

CT coronary angiography (CTCA) has recently been evaluated as a diagnostic test in patients presenting to the ED with acute chest pain, with encouraging results. [7-9] CTCA has also been shown to be more discriminatory for the diagnosis of ACS than ETT. [10] CTCA has shown prognostic value in this group of patients also for prediction of ACS during the initial admission. [11] Additionally, calcium scoring can also be performed prior to CTCA, which has shown mixed results for prediction of adverse events. [12, 13]

To the best of our knowledge, no study has yet evaluated the prognostic utility of CTCA and calcium scoring beyond the index admission in a cohort of patients unable to undergo a

functional test such as ETT. In this study, we wished to evaluate the prognostic performance of CTCA in this cohort of patients.

Methods

Patient Selection

We prospectively evaluated 246 consecutive patients admitted to our ED with acute chest pain between 2008 and 2012. All patients had non-diagnostic ECGs (non-specific T wave and ST abnormalities) and negative troponin (cardiac troponin I, normal value <0.04 μg/L), thus excluding the diagnosis of ACS. All patients had intermediate pre-test probability of CAD (15-85%) as defined by the current ESC guidelines.[14] All patients were either unable to undergo ETT (the usual standard of care in our unit) or had inconclusive tests and were thus referred for CTCA. ETT was performed using the full Bruce protocol.[15] Inconclusive tests were defined as negative tests at low workload (below 3 Metabolic Equivalent) or with inadequate rise in heart rate (below 80% of max heart rate predicted by age), a positive ECG with resting ECG abnormalities precluding definitive diagnosis of ischaemia, symptomatically positive tests (angina or dyspnoea) with no ECG changes or ischaemic ECG changes with rapid resolution (<60s).[16] We excluded all patients with contrast allergy, impaired renal function (estimated glomerular filtration rate <30ml/min), atrial fibrillation and resting heart rate >70 beats per minute (following adequate rate-limiting medication). Patients with moderately impaired renal function (estimated glomerular filtration rate 30-60ml/min) were hydrated with intravenous fluids before and after CT scanning. . Additionally, nephrotoxic medications such as metformin were withheld for 48 hours either side of the CT contrast administration. These patients were also asked to attend their family practitioner in order to have their renal function checked 1 week after CT. The study was approved by our local ethics committee.

Cardiac CT Examination

All patients were scanned using a 64-slice dual-source CT scanner (Discovery 750 HD, General Electric, Fairfield, CT, USA). All patients received sublingual GTN and oral ± intravenous beta-blocker to reduce heart rate to a target of less than 60 bpm. Patients unable to take beta-blockers were given verapamil for 3 days prior to the day of the CTCA as an alternative.

For coronary calcium scoring an unenhanced CT was performed with the scan field to cover from the carina to the apex of the heart. CTCA was performed using ECG gating, with prospective acquisition if heart rate was less than 60 bpm and retrospective if greater than 70 bpm. 80-120 ml (according to BMI) of iodinated contrast (Ultravist, Bayer, Germany) was injected into an intravenous cannula at a rate of 5ml/min followed by a bolus of saline. Scanning parameters were as follows: scan parameters: 100–140 kV tube voltage, 370–412 mAs dependent on patient body habitus. Obesity was defined as body mass index >30 kg/m^2.

Cardiac CT Analysis

Post-processing was performed offline on a dedicated workstation. All studies were evaluated by 2 physicians. Images were examined in the axial projection, with curved multiplanar reconstruction and using maximal intensity projection if needed. The coronary arteries were divided into 17 segments as per the AHA/SCCT model.[17] Segments with poor image quality were excluded, as were any with coronary artery diameter <1.5mm.

Calcium scoring was performed using the Agatston evaluation. Areas of calcium were measured using manual planimetry on axial images and the total calcium score was calculated automatically by the computer (Smartscore v 4.0, GE, Fairfield, USA). All 4 main epicardial coronary arteries (including left main) were fully evaluated.

CT coronary angiography images were analysed offline using quantitative analysis on dedicated workstations (CardiQ Express v 2.0, GE, Fairfield, USA). The presence of

obstructive coronary stenosis was defined as the presence of an obstructive plaque ≥70% of the diameter of the reference vessel in two planes (≥50% in the left main coronary artery). Any stenosis of <70% (<50% in the left main) was classified as non-obstructive.

Follow-up

Patients were followed up for a combined primary outcome of death, non-fatal myocardial infarction and late revascularisation (>6 months from index admission) up to June 2014. Patients were followed up by clinic visits where appropriate and computerised record linkage. In case of inability to obtain follow-up data using these methods, the patient's family practitioner was contacted.

Statistical Analysis

All statistical analysis was carried out using SPSS (version 22.0, IBM, Armonk, NY). All normally distributed continuous variables are reported as mean ± SD, while non-normally distributed variables are reported as median with interquartile range in brackets and all categorical data are presented as number and percentage. Comparison between continuous variables was carried out using a two-tailed t-test, while categorical variables were compared using the chi-square test. Outcome analysis was conducted using Cox proportional hazards, and time-to-event curves were drawn using the Kaplan-Meier method. All variables were evaluated using univariate Cox regression analysis to ascertain their prognostic power for prediction of the primary outcome. Hazard ratio and chi-square were obtained. All significant clinical univariable predictors ($p<0.05$) were then entered into a multivariable Cox model to identify significant multivariable clinical predictors.

RESULTS

Baseline Characteristics

Of the 246 patients initially evaluated, 232 had satisfactory image quality to allow coronary artery analysis. Of the 14 patients excluded, 1 had inadequate coronary artery contrast

opacification due to inadequate contrast delivery through the intravenous cannula, 4 had arrhythmias during prospectively-gated scanning leading to unanalyzable segments, 3 had motion artefacts and 6 were unanalyzable due to the presence of heavy calcification.

The majority of patients (59.5%) were referred for CTCA as they were unable to exercise for a sufficient time to reach a diagnostic heart rate. The average age of the cohort was 54.1 years, while the majority of patients were female. Mean heart rate was 57 ± 4 beats/minute, mean radiation dose was 5.5 ± 0.6 mSv. Mean intravenous metoprolol dose given was 17 ± 12 mg. 85% of the studies were performed prospectively while 15% were retrospective. Mean BMI was 27 ± 3 kg/m^2. Mean time from initial presentation to CTCA was 13 ± 6 days. Reasons for referral for CTCA are shown in table 1 while baseline characteristics of the cohort are summarized in table 2.

CTCA results are shown in table 3. The post-test prevalence of CAD was fairly low. The majority of patients had either no CAD or non-obstructive CAD, while 24 patients (10.3%) had obstructive CAD. 27 patients (11.6%) had left main stem or triple vessel CAD, while the median number of segments with any CAD was 1 (interquartile range 0-3). An example of CTCA findings is shown in figure 1.

Predictors of the Primary Outcome

Follow-up was available for all patients. Patients were followed up for a mean duration of 2.5 ± 0.9 years. The combined primary outcome occurred in 26 patients (11.2%). There were 2 deaths, 4 myocardial infarctions, 14 readmissions with unstable angina and 6 percutaneous coronary revascularisations. The only significant univariable baseline clinical predictor of the primary outcome was being of male sex (HR 2.38; 95% CI 1.08-5.24, p=0.032).

Both coronary artery calcium scoring and CT coronary angiographic features were significant univariable predictors of the primary outcome (Table 4). For every 100 Agatston unit increase

in calcium score there was a significant increase in the risk of adverse outcome (HR 1.16; 95% CI 1.02-1.31, p=0.023). A high-risk calcium score (>400) was also associated with adverse outcome in univariable analysis (HR 3.08; 95% CI 1.16-8.17, p=0.024). The absence of coronary artery calcium was not significantly associated with a reduction in adverse events (HR 0.83; 95% CI 0.38-1.79, p=0.63). The presence of both non-obstructive (HR 4.52; 95% CI 1.30-15.73, p=0.018) and obstructive coronary artery stenoses (17.00; 95% CI 4.60-62.85, p<0.001) were significant predictors of the primary outcome (figure 2). Additionally, although the presence of non-calcified (mixed) plaque was not a predictor of adverse outcome, the presence of more than 3 segments with non-calcified plaque did predict adverse events (HR 3.30; 95% CI 1.24-8.76, p=0.017).

In multivariable analysis the presence of coronary artery stenosis was the only significant predictor of adverse outcome with a worse outcome being predicted by the severity of the stenosis (non-obstructive HR 4.17; 95% CI 1.19-14.60, p=0.026; obstructive HR 12.43; 95% CI 3.17-48.80, p<0.001) (table 5).

After exclusion of revascularisations and admissions for angina (leaving only “hard outcomes” of death and MI), age, beta-blocker use and the presence of 3 or more segments with non-calcified plaque remained significant predictors of death/MI in both univariable and multivariable analysis (table 6).

Non-Coronary Diagnoses

In total, 31 patients also had non-coronary diagnoses incidentally made during CT scanning, outlined in table 7. Several of these CT diagnoses lead to a change in management, including one early detection of a bronchial malignancy amenable to treatment, 4 diagnoses of pneumonia with radiological consolidation, one diagnosis of pulmonary fibrosis, one left atrial appendage thrombus requiring anticoagulation and one pericardial effusion.

DISCUSSION

In this study we have added to the evidence that suggests that both CT calcium scoring and CT coronary angiography can be used in the early assessment of patients attending the emergency department with acute chest pain and negative troponins. Additionally, we have shown that the presence of both obstructive and non-obstructive coronary artery stenoses identified using CT coronary angiography are strong independent predictors of adverse outcome within this cohort of patients, and could be used when other methods such as exercise tolerance testing are not feasible or yield inconclusive results. Finally, CTCA may also provide an alternative diagnosis in this group and lead to changes in management beyond treatment of coronary artery disease.

In the majority of patients presenting to hospital with acute chest pain, initial investigation is directed towards the exclusion of acute coronary syndromes (ACS). This involves a combination of clinical features, the resting electrocardiogram, and cardiac biomarkers. With the advent of high-sensitivity troponin, ACS can potentially be excluded within 6 hours of presentation to hospital. It is usual however, once ACS is excluded, to further risk stratify patients who are pain-free prior to discharge from hospital. The absence of significant ischemia on a pre-discharge ETT portends an excellent long-term prognosis. [5, 6] Because of this, and its widespread availability, excellent safety profile and ease of use, the pre-discharge ETT remains the most common modality for risk stratification in this group of patients and is recommended in both the European and American guidelines. [2, 18]

Despite the plethora of evidence for the use of the ETT, there are a number of patients who are unable to achieve a diagnostic test, while many others may be unable to undergo the test at all, either due to immobility or resting ECG abnormalities that may preclude evaluation of the test such as left bundle branch block.[19, 20] Given this, it would be useful to have an alternative risk-stratification strategy in this group of patients.

Coronary calcium scoring provides a marker of risk which correlates well with the extent of atherosclerosis. The absence of coronary artery calcium (Agatston score = 0) has predicts a very low long-term risk of adverse events, particularly in patients with stable angina. [21] Additionally, a high calcium score is known to be a strong predictor of mortality. [22]

Nevertheless, it is increasingly recognised that in many patients it is not calcified plaques that cause ACS, but so-called non-calcified plaques which might not be picked up by calcium scoring. [23] This may explain our finding that calcium scoring was not a significant multivariable predictor of adverse outcome. Our results extend the findings of those recently reported in a substudy of the ROMICAT II trial, in which the authors found that calcium scoring did not have any added value over and above CTCA in acute chest pain presentations. [24] We have now extended this to provide prognostic information on calcium scoring, again finding that it is not as powerful a predictor of events as CTCA.

CTCA has been shown to have excellent diagnostic and prognostic value in stable angina patients. The large, multi-centre SCOT-HEART trial showed the value of CTCA in assessment of patients with suspected stable angina referred to a rapid access chest pain clinic. [25] In this study we demonstrated that CTCA provided diagnostic and prognostic information. This potentially might allow the clinician to select patients who more targeted invasive investigation. Although several studies have shown the diagnostic accuracy of CTCA in acute chest pain, very few have specifically examined its prognostic benefit. 2-year outcome data from the original ROMICAT cohort showed that there were no adverse events in patients with no coronary artery disease. [11] This is very similar to the findings in our study, where we also found that the presence of CAD was the strongest predictor of adverse outcome. Our study also showed a trend towards the importance of plaque characterisation for the prediction of adverse events, with the presence of a significant burden of non-calcified plaque being associated with adverse outcome. This reflects recent data from a substudy of the ROMICAT-II trial which also showed the prognostic value of plaque characterisation.[26]

While the presence of non-calcified plaques in our study was not a significant multivariable predictor of adverse outcome, this may have been because of a relative lack of events in follow-up, which in itself is due to the low risk nature of the cohort. Interestingly however, the presence of more than 3 of non-calcified plaques was a strong predictor of "harder" outcomes (death and myocardial infarction). This may be a reflection of recent data which has shown that non-calcified plaques are more likely to be associated with death and acute coronary syndromes than calcified plaques regardless of stenosis severity.[27, 28]

CTCA has been shown to be a valid alternative to ETT, and indeed may be more cost-effective. [10] Our study suggests that CTCA could be used in patients in whom ETT is not possible, and indeed could potentially be utilized as a first-line alternative if available. An anatomical non-invasive imaging technique could potentially be a useful alternative to a functional imaging strategy as it is increasingly recognized that the presence coronary plaque seen on CT is predictive of adverse outcome, in particular acute coronary syndrome. [23, 29, 30] Potentially, the identification of coronary artery disease using CTCA could lead to improved risk stratification and intensified preventative therapy.

Our study has some limitations. Firstly, it was a single centre study with a relatively low event rate, although this was mitigated by a fairly substantial follow-up period. Our event-rate also compares well with that of the large ROMICAT prognostic data (11.2% vs. 9.5%).[11] The addition of functional techniques such as CT fractional flow reserve or CT perfusion may also have provided further information. Nevertheless, as a relatively small observational study design this can only be viewed as a hypothesis-generating addition to the already published literature. This also limited our ability to look at the significance of CTCA in prediction of individual endpoints. Particularly, it limited our ability to perform a detailed multivariable analysis including only hard endpoints (death/myocardial infarction). In order to mirror typical "real-world" reporting practices and make our results more relevant to general cardiologists, we only used a simple measure of lesion severity (the presence of obstructive

CAD). There are however several other measures of CAD severity that we did not evaluate which may also be of prognostic importance in this group of patients such as the segment involvement score, Duke prognostic index and segment stenosis score. Further larger, randomised trials are warranted in order to investigate important parameters such as cost implications, optimal timing of scanning and potential benefits and complications of a CTCA-guided management strategy in this group of patients.

CONCLUSIONS

Our study suggests that CT coronary angiography provides important prognostic information in patients attending hospital with troponin negative acute chest pain. CT coronary angiography could be used as an alternative strategy in patients unable to undergo exercise tolerance testing.

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Table 1. Reasons for non-diagnostic ETT

Reason	**Number (%)**
Poor mobility	73 (31.5)
Fatigue (unable to achieve predicted heart rate)	65 (28.0)
Borderline ST segment changes	30 (12.9)
Symptoms but no ischemia at high workload	23 (9.9)
Bundle-branch block on resting ECG	22 (9.5)
Ischemia but no symptoms at high workload	19 (8.2)

Table 2. Baseline Characteristics of the Cohort.

Characteristic	**All Patients (n=232)**	**Suffered Primary Outcome (n=26)**	**Did Not Suffer Primary Outcome (n=206)**	**p value**
Age (years)	54.1 ± 10.9	56.9 ± 10.1	53.7 ± 11.0	0.14
Male	98 (42.2)	16 (61.5)	82 (39.8)	**0.035**
Diabetes Mellitus	17 (7.3)	1 (3.8)	16 (7.8)	0.70
Hypercholesterolaemia	124 (53.4)	13 (50.0)	111 (53.9)	0.65
Hypertension	96 (41.4)	15 (57.7)	81 (39.3)	0.08
Smoker	31 (13.4)	3 (11.5)	28 (13.6)	0.75
Previous MI/Angina	13 (5.6)	2 (7.7)	11 (5.3)	0.64
Family history of CAD	52 (22.4)	8 (30.8)	44 (21.4)	0.27
Obesity	107 (46.1)	13 (50.0)	94 (45.6)	0.66
Aspirin/clopidogrel	30 (12.9)	4 (15.3)	26 (12.6)	0.71
Statin	114 (49.1)	12 (46.2)	103 (50.0)	0.69
ACE Inhibitor	64 (27.6)	9 (34.6)	55 (26.7)	0.39
Beta-blocker	49 (21.1)	7 (26.9)	42 (20.4)	0.43

Table 3. CT Coronary Angiography Results

Characteristic	**All Patients (n=232)**	**Suffered Primary Outcome (n=26)**	**Did Not Suffer Primary Outcome (n=206)**
Calcium Score (Agatston units)	0 (0-116.8)	0 (0-114.0)	0.5 (0-359.0)
No CAD	99 (42.7)	3 (3.0)	96 (97.0)
Non-obstructive CAD	109 (47.0)	14 (12.8)*	95 (87.2)*
Obstructive CAD	24 (10.3)	9 (37.5)*	15 (62.5)*
Left Main Stem/Triple Vessel Disease	27 (11.6)	7 (26.9)$^{+}$	20 (9.7)
Number of segments with any plaque	1 (0-3)	1 (0-3)	1 (0-2)
Number of segments with calcified plaque	0 (0-2)	0 (0-1)	0 (0-2)
Number of segments with non-calcified plaque	0 (0-1)	0 (0-2)	0 (0-1)

**p<0.05 compared to patients with no CAD; $^{+}$p<0.05 compared to patients who did not suffer the primary outcome*

Table 4. Univariable Predictors of the Primary Outcome.

Characteristic	**Hazard Ratio (95% CI)**	**p value**
Age	1.03 (0.99-1.06)	0.16
Male	2.38 (1.08-5.24)	**0.032**
Diabetes Mellitus	0.46 (0.06-3.40)	0.45
Hypercholesterolaemia	0.86 (0.40-1.86)	0.71
Hypertension	1.95 (0.90-4.25)	0.09
Smoker	0.82 (0.25-2.75)	0.75
Previous MI/Angina	1.43 (0.34-6.06)	0.63
Family History of CAD	1.68 (0.73-3.88)	0.22
Obesity	1.17 (0.54-2.53)	0.68
Aspirin/clopidogrel	1.14 (0.39-3.32)	0.81
Statin	0.88 (0.41-1.90)	0.74
ACE Inhibitor	1.37 (0.61-3.06)	0.45
Beta-blocker	1.38 (0.58-3.27)	0.48
Calcium Score (per 100 Agatston units)	1.16 (1.02-1.31)	**0.023**
Calcium Score ≥400	3.08 (1.16-8.17)	**0.024**
Calcium Score = 0	0.83 (0.38-1.79)	0.63
Presence of any coronary artery stenosis	6.34 (1.90-21.11)	**0.003**
Presence of non-obstructive coronary artery stenosis	4.52 (1.30-15.73)	**0.018**
Presence of obstructive coronary artery stenosis	17.00 (4.60-62.85)	**<0.001**
Presence of ≥1 non-calcified plaque	0.9 (0.43-2.10)	0.95
Presence of ≥2 non-calcified plaques	1.67 (0.70-3.94)	0.25

Presence of ≥3 non-calcified plaques	3.30 (1.24-8.76)	**0.017**

Table 5. Multivariable Predictors of the Primary Outcome

Characteristic	**Hazard Ratio (95% CI)**	**p value**
Male	1.59 (0.71-3.60)	0.26
Calcium Score (per 100 Agatston units)	1.07 (0.92-1.24)	0.37
Presence of non-obstructive coronary artery stenosis	4.08 (1.16-14.32)	**0.028**
Presence of obstructive coronary artery stenosis	12.00 (3.05-47.19)	**<0.001**
Presence of ≥3 non-calcified plaques	2.09 (0.76-5.76)	0.15

Table 6. Predictors of Death or Myocardial Infarction

Characteristic	**Univariable Hazard Ratio (95% CI)**	**p value**	**Multivariable Hazard Ratio (95% CI)**	**p value**
Age	1.07 (1.00-1.06)	**0.047**	1.11 (1.00-1.23)	**0.047**
Male	1.54 (0.31-7.67)	0.60		
Diabetes Mellitus	2.23 (0.26-19.13)	0.46		
Hypercholesterolaemia	0.88 (0.18-4.37)	0.88		
Hypertension	2.88 (0.53-15.73)	0.22		
Smoker	1.27 (0.15-10.85)	0.83		
Previous MI/Angina	1.43 (0.34-6.06)	0.63		
Family History of CAD	0.04 (0-174.45)	0.44		
Obesity	1.15 (0.23-5.71)	0.86		
Aspirin/clopidogrel	3.39 (0.40-29.02)	0.26		
Statin	0.52 (0.10-2.86)	0.45		
ACE Inhibitor	1.29 (0.24-7.02)	0.77		
Beta-blocker	7.36 (1.34-40.21)	**0.021**	14.45 (1.95-106.87)	**0.009**
Calcium Score (per 100 Agatston units)	1.21 (0.95-1.53)	0.12		
Calcium Score ≥400	2.53 (0.30-21.70)	0.40		
Calcium Score = 0	0.42 (0.08-2.29)	0.32		
Presence of any coronary artery stenosis	55.57 (0.08-41068.83)	0.23		
Presence of ≥3 non-calcified plaques	13.74 (2.77-68.20)	**0.001**	60.78 (6.68-552.71)	**<0.001**

Table 7. Non-coronary Diagnoses Made During CT Scanning

Diagnosis	**Number**
Lung nodule	15
Pneumonia	4
Liver cyst	4
Pericarditis/pericardial thickening	2
Pericardial effusion	1
Bronchial Carcinoma	1
Pulmonary fibrosis	1
Splenic cyst	1
Left atrial appendage thrombus	1
Mediastinal lymphadenopathy	1

FIGURE LEGEND

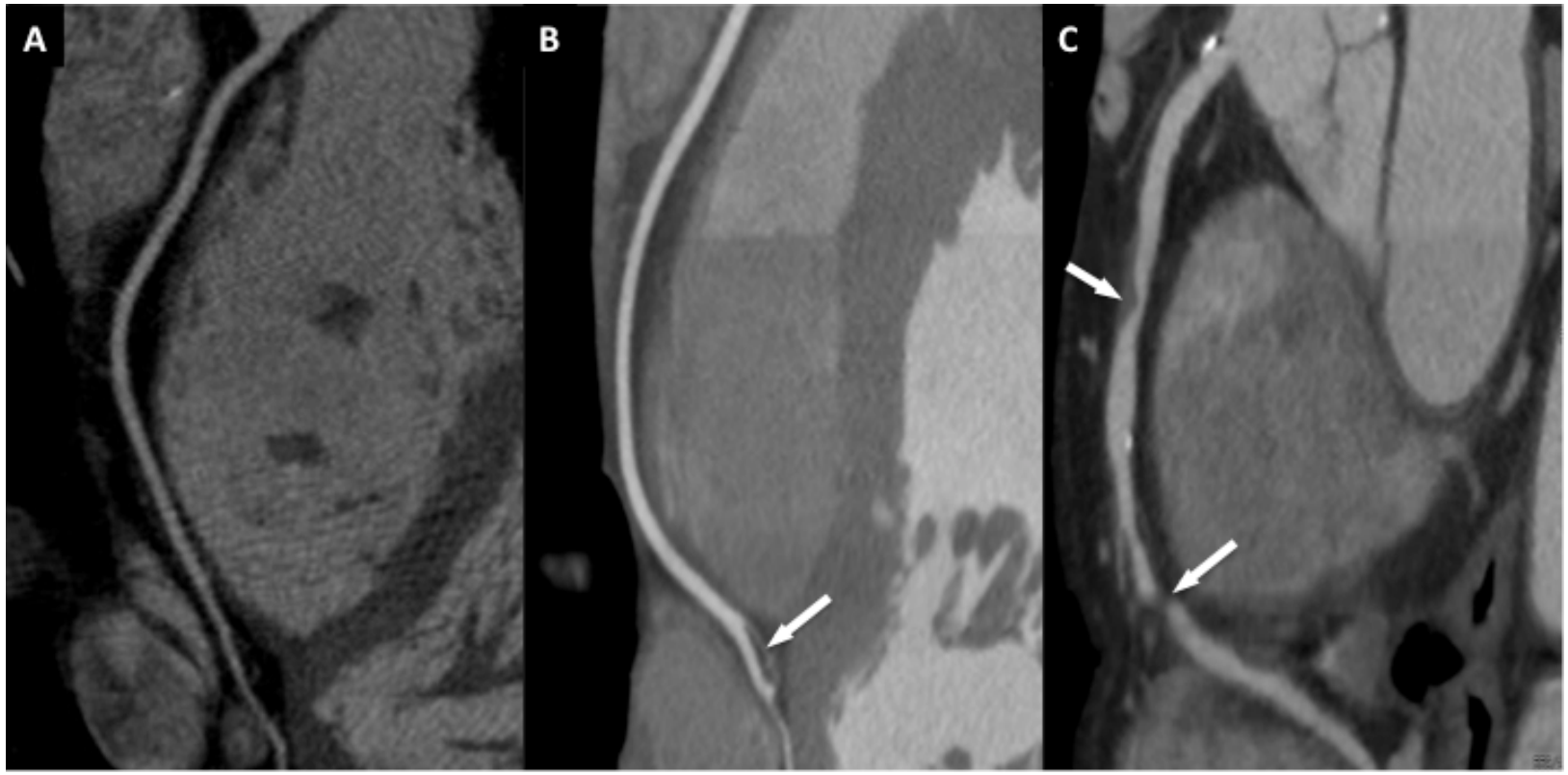
1. Examples of CT Coronary Angiography in the study.

   CTCA images in the right coronary artery (RCA) of 3 different patients. Patient A has no evidence of coronary artery disease (CAD) with a smooth RCA. B shows a patient with non-obstructive CAD in the distal RCA (arrows) while patient C has obstructive CAD in both the proximal and mid RCA (arrows).

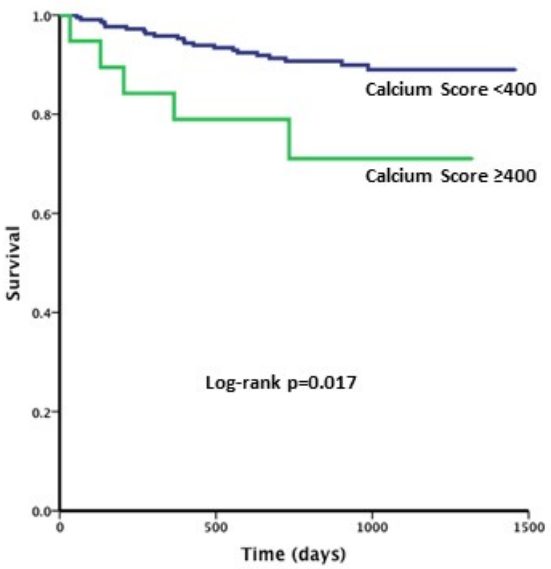
2. Kaplan-Meier Curves of the Primary Outcome.

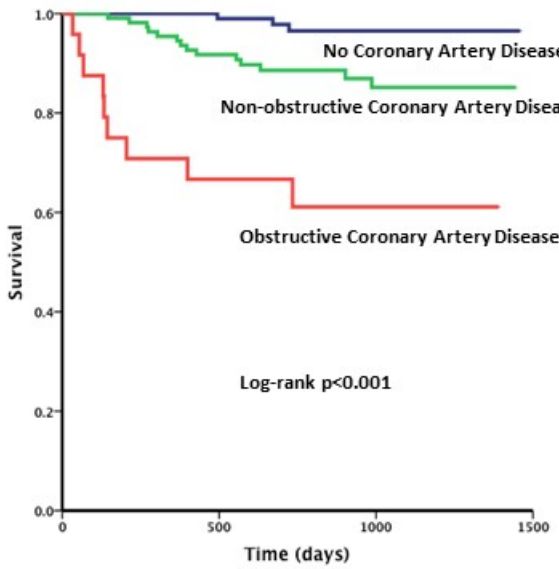
   Time to event curves of the primary outcome using calcium scoring (A), CTCA (B) and the number of segments with non-calcified (mixed) plaques (C).

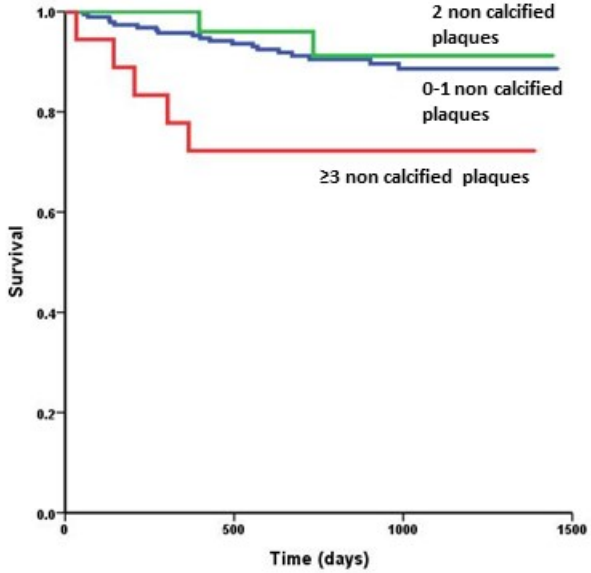
1.



2.







Calcium Score			
<400	212	190	94
≥400	20	14	9

No CAD	101	98	50
Non-obstructive CAD	108	95	46
Obstructive CAD	23	14	8

0-1 non calcified plaques	188	168	86
2 non calcified plaques	25	22	10
≥3 non calcified plaques	18	12	5