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Clinical Decision Aids and Computed Tomography Coronary Angiography in Patients with Suspected Acute Coronary Syndrome

A secondary analysis of the RAPID-CTCA trial

Running title: Test performance in intermediate-risk ACS

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Abstract

Background

The HEART score, the T-MACS model, and the GRACE score support early decision making for acute chest pain, which could be complemented by computed tomography coronary angiography (CTCA). However, their performance has not been directly compared.

Methods

In this secondary analysis of a multicentre randomised controlled trial of early CTCA in intermediate-risk patients with suspected acute coronary syndrome, *C*-statistics and performance metrics (using the pre-defined cutoffs) of clinical decision aids and CTCA, alone and then in combination, for the index hospital diagnosis of acute coronary syndrome and for 30-day coronary revascularisation were assessed in those who underwent CTCA and had complete data.

Results

Amongst 699 patients, 358 (51%) had an index hospital diagnosis of acute coronary syndrome, for which the *C*-statistic was higher for CTCA (0.80), followed by the T-MACS model (0.78), the HEART score (0.74), and the GRACE score (0.60). The negative predictive value was higher for the absence of coronary artery disease on CTCA (0.90) or a T-MACS estimate of <0.05 (0.83) than a HEART score of <4 (0.81) and a GRACE score of <109 (0.55). For 30-day coronary revascularisation, CTCA had the greatest *C*-statistic (0.80) with a negative predictive value of 0.96 and 0.92 in the absence of coronary artery disease and obstructive coronary artery respectively. The combination of the T-MACS estimates and the CTCA findings was most discriminative for the index hospital diagnosis of acute coronary syndrome (*C*-statistic, 0.88) and predictive of 30-day coronary revascularisation (*C*-statistic,

0.85). No patients with a T-MACS estimate of <0.05 and normal coronary arteries had acute coronary syndrome during index hospitalisation or underwent coronary revascularisation within 30 days.

Conclusions

In intermediate-risk patients with suspected acute coronary syndrome, the T-MACS model combined with CTCA improved discrimination of the index hospital diagnosis of acute coronary syndrome and prediction of 30-day coronary revascularisation.

Keywords

Acute coronary syndrome, clinical decision aid, computed tomography coronary angiography.

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What is already known on this topic

- Clinical decision aids—the HEART score, the T-MACS model, and the GRACE score—and computed tomography coronary angiography (CTCA) have been adopted into clinical practice to risk stratify patients with acute chest pain.

- Their performance for diagnosis and prognosis in intermediate-risk patients with suspected acute coronary syndrome has not previously been directly compared.

What this study adds

- The HEART score, the T-MACS model, and CTCA were more discriminative for the index hospital diagnosis of acute coronary syndrome than the GRACE score, and CTCA was most predictive of 30-day coronary revascularisation.

- The combination of the T-MACS estimates and the CTCA findings had the best diagnostic and prognostic performance for acute coronary syndrome during index hospitalisation and coronary revascularisation within 30 days.

How this study might affect research, practice, or policy

- The T-MACS model combined with CTCA could be used to assist diagnosis, guide management, and improve prognostication in patients with intermediate-risk chest pain due to suspected acute coronary syndrome.

- This may expedite the patient journey in the emergency department and facilitate patient selection for invasive coronary angiography.

Introduction

Acute chest pain is one of the leading reasons for seeking emergency care. The aims of initial clinical assessment are to 'rule out' or to 'rule in' acute coronary syndrome and to differentiate other life-threatening diagnoses like acute aortic syndrome or pulmonary embolism from other less time-sensitive conditions.[1] To support early decision making in this heterogeneous patient population, multiple clinical decision aids have been developed.

The contemporary European Society of Cardiology clinical decision aids are based on serial high-sensitivity cardiac troponin testing and can 'rule out' and 'rule in' myocardial infarction in approximately 60% and 15% of all patients presenting to emergency departments respectively.[2] This leaves 1 in 4 patients assigned to the 'observe' pathway or the 'intermediate risk' category.[3, 4] in which the spectrum of final diagnoses could range from an undetermined aetiology to myocardial infarction. Their distinction has therapeutic implications, as preventative treatment and coronary revascularisation are more likely to benefit those with coronary artery disease.

Clinical decision aids, such as the HEART score,[5] the T-MACS model,[6] and the GRACE score,[7] have been developed as risk stratification tools that are less constrained by the requirement of high-sensitivity cardiac troponin testing and repeated sampling for cardiac troponin. However, they are not specifically designed to address the uncertainty in patients at intermediate risk, who often have multiple cardiovascular risk factors, pre-existing atherosclerotic disease, or an ischaemic electrocardiogram (ECG).[8, 9] This can lead to the requirement for additional investigations to refine clinical decision making.[10]

Whilst discriminating myocardial infarction and unstable angina is essential during initial clinical assessment, identifying the presence of coronary artery disease continues to be vital for clinical decision making. This can be readily assessed by computed tomography coronary angiography (CTCA), which clarifies the need for interventional treatment and out-patient review, thereby improving future prognosis.[11, 12] Nevertheless, the effectiveness of clinical decision aids and CTCA in diagnosis, management, and prognostication of patients with suspected acute coronary syndrome has never been directly compared. The combined strength of the estimated clinical risk and the knowledge of coronary artery anatomy could potentially have synergistic benefits.

The Rapid Assessment of Potential Ischaemic Heart Disease with CTCA (RAPID-CTCA) trial evaluated the effectiveness of early CTCA in intermediate-risk patients with suspected acute coronary syndrome and has reported that early CTCA did not further improve 1-year clinical outcomes.[13] In this secondary analysis, we aimed to assess the diagnostic and prognostic performance of the HEART score, the T-MACS model, the GRACE score, and CTCA, alone and then in combination, for the index hospital diagnosis of acute coronary syndrome and 30-day coronary revascularisation.

Method

Trial overview

The RAPID-CTCA trial (ClinicalTrials.gov identifier, NCT02284191) was a prospective randomised open-label blinded endpoint trial conducted at 37 sites across the United Kingdom between March 2015 and June 2019. Patients presenting to an emergency department or hospital admission facilities with intermediate-risk chest pain due to suspected acute coronary syndrome, defined by having either a history of coronary artery disease, an

abnormal ECG, or an elevated cardiac troponin concentration, were randomised to receive early CTCA in addition to standard of care or standard of care only.

The trial was conducted with the approval of the South East Scotland Research Ethics Committee (14/SS/1096). All patients gave written informed consent.

Clinical gestalt and cardiac troponin testing

Before randomisation, treating physicians were asked to use a 3-point Likert scale to grade their perceived probability of acute coronary syndrome of every patient during initial clinical assessment.

Cardiac troponin was measured in local accredited clinical biochemistry laboratories according to standard clinical practice at each site, where assays and local laboratory reference standards varied. The overall cutoffs according to manufacturers were used to standardise the level of cardiac troponin in the current study (Supplementary Table 1). Because not all patients underwent repeated cardiac troponin testing or had the complete profile of serial cardiac troponin measurements recorded, we only used their cardiac troponin concentration at presentation.

Study design

The current study population included individuals who underwent CTCA with a complete dataset for CTCA and the three selected clinical decision aids, as we wished to compare these tools individually and in combination.

Clinical decision aids

The scores of clinical decision aids were retrospectively calculated using data prospectively collected as part of the original trial (Supplementary Tables 2, 3, and 4). The HEART score was developed based on clinical experience and medical literature.[5] The T-MACS model was developed using a logistic regression model,[6] and the original model was used because it has been validated for both cardiac troponin T and I.[14] Various GRACE scores were developed to assess immediate and intermediate outcomes in patients with confirmed acute coronary syndrome. The original GRACE score was used, as it is recommended by the European Society of Cardiology guidelines,[15] and a very early invasive strategy was shown to improve clinical outcomes in a subtest of patients with a GRACE score of >140.[16]

Study outcomes

The outcomes of interest for the current study were: 1) acute coronary syndrome, including myocardial infarction and unstable angina, during index hospitalisation; and 2) coronary revascularisation within 30 days. Although the diagnosis of acute coronary syndrome and the nature of coronary revascularisation were not centrally adjudicated, the validity of the diagnosis and the necessity of the treatment were determined by treating physicians based on clinical assessment, ECG findings, and results of cardiac troponin testing or other objective investigations.

Statistical analysis

Descriptive data were summarised with median (interquartile range) for continuous variables and frequency (percentage) for categorical variables, and differences were compared with the Mann–Whitney *U* test and the Fisher's exact test as appropriate.

The receiver operating characteristic analysis was conducted, and *C*-statistics of clinical decision aids, CTCA, alone and then each clinical decision aid in combination with CTCA, were compared using the nonparametric method. The performance of clinical decision aids and CTCA in subgroups by age and by sex was explored.

Apart from the overall discrimination and prediction, the performance measures, such as the sensitivity, the specificity, and the negative and the positive predictive value, of each clinical decision aid and CTCA were derived from a two-by-two confusion matrix using cutoffs reported by previously published studies (<4 and >6 for the HEART score, <0.05 and >0.95 for the T-MACS model, <109 and >140 for the GRACE score, and coronary artery anatomy for CTCA). Comparisons were made using the exact McNemar's test (for sensitivities and specificities) or the weighted generalised score statistics (for negative predictive values and positive predictive values) as appropriate.

A *post hoc* sensitivity analysis using the classification tree analysis, which included all three clinical decision aids and CTCA for tree building, was conducted for both study outcomes. The tree model was developed based on recursive partitioning using the Chi-square automatic interaction detection algorithm (alpha of 0.05 for splitting with the Bonferroni correction) and a 10-fold cross-validation for overfitting control. Nodes with a size of ≥10% of the study population size were considered.

This study was exploratory with no adjustment for multiplicity applied. All analyses were performed by the complete-case approach using SAS software, version 9.4 (SAS institute, Cary, NC, USA).

Patient and public involvement

The Sheffield Emergency Care Forum (a patient and public representative group that provides independent advice on emergency care related research) provided valuable feedback about the patient perspective throughout the trial, which helped guide the decision making of the trial team. Patients and the public were not directly involved in this secondary analysis.

Results

Study population

Amongst 1748 patients enrolled in the RAPID-CTCA trial, 974 (56%) were excluded due to the lack of CTCA data, and 75 (4%) were further excluded due to incomplete data for calculation of the three selected clinical decision aids (Figure 1). The study population comprised of 699 patients whose baseline characteristics were similar to those excluded from the analysis (Table 1). At presentation, 155 (22%) patients had a history of myocardial infarction or coronary revascularisation, 283 (40%) had an abnormal ECG, and 404 (58%) had an elevated cardiac troponin concentration.

The median HEART score was 5 (15%, 57%, and 27% had a score of <4, 4–6, and >6), the median T-MACS estimate was 0.26 (19%, 51%, and 30% had an estimate of <0.05, 0.05–0.95, and >0.95), and the median GRACE score was 106 (55%, 32%, and 13% had a score of <109, 109–140, and >140). In addition, 163 (23%), 200 (29%), and 336 (48%) patients had normal coronary arteries, non-obstructive coronary artery disease, and obstructive coronary artery disease respectively.

Diagnostic performance for the index hospital diagnosis of acute coronary syndrome

At hospital discharge, 358 (51%) patients had a final diagnosis of acute coronary syndrome. The GRACE score had the lowest discriminative ability for the index hospital diagnosis of acute coronary syndrome, whereas the HEART score, the T-MACS model, and CTCA had better discriminative ability (Figure 2), and the results were comparable across age and sex subgroups (Supplementary Table 5). The T-MACS model (difference in *C*-statistic, 0.03; 95% confidence interval, −0.00 to 0.07; p=0.053) and CTCA (difference in *C*-statistic, 0.06; 95% confidence interval, 0.01 to 0.10; p=0.011) were both more discriminatory than the HEART score.

To further determine the diagnostic performance of the clinical decision aids and CTCA as a 'rule-out' tool using the pre-defined 'low-risk' threshold, the negative predictive value of CTCA (0.90; 95% confidence interval, 0.84 to 0.94) appeared to be similar to that of the T-MACS model (0.83; 95% confidence interval, 0.76 to 0.89) (p=0.114) but was higher than that of the HEART score (0.81; 95% confidence interval, 0.72 to 0.88) (p=0.032). The T-MACS model (19%) and CTCA (23%) would have excluded acute coronary syndrome in a greater proportion of patients than the HEART score (15%) (p=0.026 and p<0.001 respectively) (Table 2). When being used as a 'rule-in' tool with the pre-defined 'high-risk' threshold, the positive predictive values of the HEART score, the T-MACS model, and CTCA were similar, and CTCA would have identified a higher proportion of patients with acute coronary syndrome (Supplementary Table 6).

Prognostic performance for 30-day coronary revascularisation

The proportion of patients with coronary artery disease on CTCA increased with the estimated risk by clinical decision aid (Supplementary Figure 1). At 30 days, 225 (32%) patients had undergone coronary revascularisation, for which CTCA had the highest *C*-

statistic (0.80; 95% confidence interval, 0.77 to 0.83) (Figure 3). Moreover, the results were comparable across age and sex subgroups (Supplementary Table 7). With either the 'low-risk' or the 'high-risk' threshold, all three clinical decision aids and CTCA had a modest positive predictive value, ranging between 0.26 and 0.58 (Supplementary Table 8). CTCA had the numerically highest negative predictive value—0.96 (95% confidence interval, 0.92 to 0.99) and 0.92 (95% confidence interval, 0.89 to 0.95) in the absence of coronary artery disease and obstructive coronary artery disease respectively, followed by the T-MACS model by the cutoff of 0.05 (0.89; 95% confidence interval, 0.83 to 0.94).

Performance of clinical decision aids combined with CTCA

When incorporating each clinical decision aid with CTCA, the diagnostic and prognostic performance of all clinical decision aids improved (Figure 4 and Supplementary Table 9). The combination of the T-MACS model with CTCA was numerically most discriminative for the index hospital diagnosis of acute coronary syndrome and predictive of 30-day coronary revascularisation.

Using the optimal thresholds (a negative predictive value ≥0.99 for 'rule-out' and a positive predictive value ≥0.70 for 'rule-in') proposed by the European Society of Cardiology, a T-MACS estimate <0.05 and normal coronary arteries on CTCA would have classified 41 (6%) patients 'rule-out' for the index hospital diagnosis of acute coronary syndrome, with none having acute coronary syndrome during index hospitalisation or undergoing coronary revascularisation within 30 days. In addition, a T-MACS estimate of ≥0.05 and obstructive coronary artery disease on CTCA or a T-MACS estimate >0.95 and non-obstructive coronary artery disease on CTCA would have classified 299 (43%) patients and 42 (6%) patients 'rule-in' for the index hospital diagnosis of acute coronary syndrome respectively. Of these

patients, 280 (82%) actually had acute coronary syndrome during index hospitalisation, and 196 (57%) underwent coronary revascularisation within 30 days (Supplementary Table 10).

Sensitivity analysis

The classification tree analysis identified the T-MACS estimates and the CTCA findings as the two most important features that discriminated the index hospital diagnosis of acute coronary syndrome (Supplementary Figure 2). The classification algorithm based on the combination of the T-MACS model and CTCA had a negative predictive value of 0.90 (95% confidence interval, 0.85 to 0.93). Similarly, the T-MACS model and CTCA were the two most important risk stratification tools that predicted 30-day coronary revascularisation (Supplementary Figure 3), and the algorithm had a positive predictive value of 0.68 (95% confidence interval, 0.61 to 0.75).

Discussion

In this secondary analysis of the RAPID-CTCA trial including only a pre-defined group of patients with intermediate-risk chest pain due to suspected acute coronary syndrome, we demonstrated that the T-MACS model and CTCA had similar but better discriminative ability for the index hospital diagnosis of acute coronary syndrome, compared with the HEART score and the GRACE score. In addition, CTCA, as a single test, was most predictive of 30-day coronary revascularisation. The combination of the T-MACS estimates and the CTCA findings had the best diagnostic and prognostic performance for the index hospital diagnosis of acute coronary syndrome and 30-day coronary revascularisation.

When managing undifferentiated acute chest pain, clinical assessment of presenting symptoms, medical history, and physical examination remain relevant. Experts advocate a

sequential approach whereby clinical assessment and ECG findings assist with guiding the appropriate clinical pathway.[17] Whilst clinician judgement continues to be crucial in selecting low-risk patients for early discharge,[18, 19] our findings underline that the structuralised assessment using clinical decision aids or CTCA can be helpful in identifying and managing intermediate-risk patients with suspected acute coronary syndrome.

Compared to algorithms based on high-sensitivity cardiac troponin testing alone, clinical decision aids factoring in additional clinical information achieved a similar safety benchmark to 'rule out' myocardial infarction.[20] However, two randomised controlled trials evaluating the HEART score-based management have shown that many patients being considered low-risk still underwent ischaemia investigations,[21, 22] suggesting that physicians and patients often seek reassurance from additional diagnostic testing. Whilst physicians realise that they can rule out myocardial infarction using clinical decision aids, they also understand that this does not equate to the exclusion of underlying coronary artery disease. In the current study, a HEART score of <4 or a T-MACS estimate of <0.05 was associated with coronary artery disease in 44% and 69% of patients respectively. A recent study demonstrated that nearly half of patients with suspected acute coronary syndrome and a very low high-sensitivity cardiac troponin concentration had coronary artery disease.[23] This represents a potential missed opportunity to offer preventative treatment and to improve subsequent outcomes. To that end, CTCA provides anatomical clarification of coronary arteries and refines treatment selection.[24, 25]

Previous studies assessing high-sensitivity troponin testing and clinical decision aids have focused on unselected and predominantly low-risk populations, in which the prevalence of acute coronary syndrome was usually under 20%. The RAPID-CTCA trial enrolled an

intermediate-risk patient population, and half of these patients had an index hospital diagnosis of acute coronary syndrome, who represent a real clinical conundrum after initial clinical assessment in terms of whom to select for investigations, invasive coronary angiography, and treatment.[15] We here demonstrated that in the absence of coronary artery disease on CTCA and a T-MACS estimate <0.05, none of these patients had acute coronary syndrome during index hospitalisation or underwent coronary revascularisation within 30 days.

The T-MACS model, compared to the HEART score, tended to have a higher positive predictive value for myocardial infarction,[26] for which further invasive coronary angiography is usually inevitable when trying to establish the diagnosis and guide treatment.[27] On the other hand, CTCA had a high diagnostic accuracy for coronary artery disease,[28] the extent of which remains prognostically important in those with cardiac troponin elevation.[29] Finally, CTCA can identify a new diagnosis that may have not been uncovered by biomarkers or other cardiac imaging.[30]

Limitations

Our study has several limitations which we should highlight. First, cardiac troponin was measured locally at each site using different assays and laboratory reference standards to define myocardial infarction, and follow-up cardiac troponin was tested at the discretion of clinicians, which was not systematically recorded in the trial database. Second, the index hospital diagnoses were made by treating physicians rather than independent adjudication. Results of cardiac troponin testing used in risk metrics of all three clinical decision aids could strongly influence such diagnoses, and both cardiac troponin testing and CTCA might have also impacted selection of patients for further investigations, leading to coronary

revascularisation. Therefore, we cannot exclude the potential for diagnostic misclassification and bias for incorporation and verification. Third, the HEART score and the T-MACS model were devised as part of initial assessment of undifferentiated acute chest pain to identify low risk patients, and the RAPID-CTCA trial enrolled those at intermediate risk after initial assessment. As a result, the number of patients in our current study with a T-MACS estimate of <0.02 was small, reflecting the higher risk of the population studied in the RAPID-CTCA trial, and therefore we had to use a different threshold (<0.05) to risk stratify patients in this study. Moreover, all clinical decision aids were retrospectively calculated, and some variables, such as the presence of worsening angina, were different from the original validated definition, thereby attenuating their discriminative ability. Finally, patients with inadequate image quality will introduce uncertainty regarding coronary artery anatomy.

Conclusion

In intermediate-risk patients with suspected acute coronary syndrome, the T-MACS model and CTCA offered better discrimination for the index hospital diagnosis of acute coronary syndrome, and CTCA provided the best prediction of 30-day coronary revascularisation. Combining the T-MACS estimates with the CTCA findings can enhance diagnosis and management of acute coronary syndrome.

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Contributorship statement

Concept and design: WKL and CT.

Analysis or interpretation of data: WKL, CT, MM, DEN, and AJG.

Drafting of the manuscript: WKL, DEN, and AJG.

Critical revision of the manuscript for important intellectual content: CT, MM, RO, KO, LK, RFS, DF, NC, AK, CR, JES, and SG.

Obtained funding: DEN and AJR.

Administrative, technical, or material support: RO and KO.

Supervision: LK, RFS, DF, NC, AK, CR, JES, SG, DEN, and AJR.

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Figure legends

Figure 1. Study flowchart. CTCA, computed tomography coronary angiography; ECG, electrocardiogram.

Figure 2. Receiver operating characteristic analysis for index hospital diagnosis of acute coronary syndrome. CTCA, computed tomography coronary angiography.

Figure 3. Receiver operating characteristic analysis for 30-day coronary revascularisation. CTCA, computed tomography coronary angiography.

Figure 4. Receiver operating characteristic analysis of the combination of clinical decision aids and CTCA for (A) index hospital diagnosis of acute coronary syndrome and (B) 30-day coronary revascularisation. CTCA, computed tomography coronary angiography.

Table 1. Baseline characteristics of patients included in and excluded from the analysis

	Included in analysis (N = 699)	**Excluded from analysis (N = 1049)**	**p value**
Age, years	61 (53 to 71)	61 (52 to 71)	0.924
Female sex	261 (37)	373 (36)	0.447
Diabetes mellitus	115 (16)	203 (19)	0.129
Hypertension	313 (45)	504 (48)	0.187
Dyslipidaemia	285 (41)	409 (39)	0.485
Former or current smoker	416 (60)	645 (61)	0.424
Prior myocardial infarction or coronary revascularisation	155 (22)	268 (26)	0.111
Clinical gestalt for acute coronary syndrome			0.928
Low suspicion	127 (18)	187 (18)	
Moderate suspicion	319 (46)	473 (45)	
High suspicion	253 (36)	389 (37)	

ECG at presentation			0.841
Normal	257 (37)	391 (38)	
Non-ischaemic	159 (23)	242 (23)	
Ischaemic	283 (40)	406 (39)	
Cardiac troponin at presentation			0.684
≤99th centile upper reference limit	295 (42)	380 (41)	
>99th centile upper reference limit	404 (58)	545 (59)	
HEART score	5 (4 to 7)	5 (4 to 6)	0.826
T-MACS estimate	0.26 (0.08 to 0.98)	0.32 (0.08 to 1.00)	0.547
GRACE score	106 (89 to 125)	105 (90 to 124)	0.997
CTCA finding			0.192
Normal coronary arteries	163 (23)	22 (29)	
Non-obstructive coronary artery disease	200 (29)	25 (33)	

Obstructive coronary artery disease	336 (48)	28 (37)

*Values are median (interquartile range) or n (%).

†Non-ischaemic ECG includes other abnormalities, bundle branch block, and left ventricular hypertrophy, and ischaemic ECG includes T-wave inversion and ST-segment deviation.

CTCA, computed tomography coronary angiography; ECG, electrocardiogram.

Table 2. Performance metrics for index hospital diagnosis of acute coronary syndrome using 'low-risk' thresholds

	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Negative predictive value (95% confidence interval)	Positive predictive value (95% confidence interval)	No. considered low risk
HEART score	0.94 (0.92 to 0.97)	0.25 (0.21 to 0.30)	0.81 (0.72 to 0.88)	0.57 (0.53 to 0.61)	106 (15)
T-MACS model	0.94 (0.91 to 0.96)	0.33 (0.28 to 0.38)	0.83 (0.76 to 0.89)	0.59 (0.55 to 0.63)	133 (19)
GRACE score	0.52 (0.47 to 0.57)	0.62 (0.56 to 0.67)	0.55 (0.50 to 0.60)	0.59 (0.53 to 0.64)	382 (55)
CTCA	0.95 (0.93 to 0.97)	0.43 (0.37 to 0.48)	0.90 (0.84 to 0.94)	0.64 (0.59 to 0.68)	163 (23)

*'Low-risk' thresholds are a HEART score of 4, a T-MACS estimate of 0.05, a GRACE score of 109, and coronary artery disease on CTCA.

CTCA, computed tomography coronary angiography.