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Cardiac Computed Tomography Angiography (CCTA) Predicts Subsequent Cardiac Outcome Events – Results of Visipaque CCTA Registry Study

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ABSTRACTS

Objectives: To evaluate diagnostic performance and predictive value of CCTA on subsequent cardiac outcomes.

Background: CCTA has been suggested as an alternative method to invasive coronary angiography for detection and ruling out coronary artery disease (CAD). However, the value of using CCTA findings to predict patient outcome in routine clinical practice is still uncertain.

Methods: A prospective, multi-center registry study of CCTA with Visipaque Injection 320 mg I/mL (GE Healthcare, Inc., Princeton NJ) was performed in symptomatic patients suspected of CAD as part of their medical care. CCTA findings were used to guide patient management decisions.

Patient cardiac outcomes were followed at 1, 6, and 12 months after the CCTA procedure for occurrence of MACE (cardiac death, nonfatal myocardial infarction, or unstable angina requiring hospitalization). All cardiac outcome events or deaths were independently adjudicated.

Results: Of 874 patients (mean age= 59 years; 51% male) who received Visipaque, 857 were included in the efficacy analysis. Using cardiac outcomes as the endpoint, the sensitivity of CCTA was 96.1%, 95.8%, and 94.7%, specificity 84.5%, 86.6%, and 87.0%, and NPV >99.0% at 1, 6, and 12-months, respectively. At 12 months, the rate of MACE was 5.7% (10/174) in patients with a positive CCTA (one or more ≥50% stenosis) and 0.1% (1/683) patients with a negative CCTA (99.9% MACE free survival rate). The Cox proportional hazards analysis with CCTA outcome, age, gender, reasons for CCTA, and cardiac risk factors as covariates showed a hazard ratio of 87.6 for positive vs. negative CCTA (p=0.0001).

Conclusions: CCTA is a highly accurate, non-invasive tool to detect or rule out subsequent cardiovascular events in patients with intermediate pre-test probability of CAD or an

uninterpretable/equivocal stress test. A positive CCTA finding significantly contributed to the prediction of subsequent MACE while a negative CCTA carried excellent prognostic outcomes at 12 months.

INTRODUCTION

Non-invasive coronary artery imaging has undergone major advances in recent years, the most significant being intravenous contrast-enhanced coronary computed tomography angiography (CCTA). The implementation of 64-multi-detector computed tomography (MDCT) technology has bolstered its perceived usefulness as a reliable diagnostic tool. The improved temporal and spatial resolution plus powerful reconstruction technique and analysis software are instrumental in producing high-quality data sets during peak arterial filling and enhancement and have encouraged hospital adoption of CCTA as a non-invasive coronary artery imaging tool to a degree never before possible.Error: Reference source not found

To date, a number of publications using the criteria have confirmed that 64-MDCT technology has high diagnostic accuracy for coronary artery disease (CAD) with reported sensitivity and specificity between 80% and 95% Error: Reference source not found. More remarkably, most published studies also uniformly reported a very high negative predictive value (NPV) between 95% and 99% Error: Reference source not found]. This is very important, as it suggests that CCTA can reliably "rule out" hemodynamically significant coronary artery stenosis (i.e., ≥50% luminal reduction) in the face of symptoms with low pre-test likelihood of CAD or equivocal functional tests.

However, contrast-enhanced CCTA is considered off-label use because no specific contrast agent has received approval in the United States for this indication. The efficacy and safety of contrast agents used for the procedure have not been demonstrated in well-controlled multi-center clinical trials. The goal of this study is to evaluate the high NPV of CCTA reported in most published studies to understand whether this high NPV could be explained by a selection bias, i.e., a

relatively low prevalence of hemodynamically significant coronary artery stenosis in these study population, or represented the true ability of CCTA to "rule out" hemodynamically significant stenosis. The FDA is also concerned that if subjects who have significant coronary artery obstructions are erroneously sent home based on CCTA results, the consequence may be severe.

Visipaque (GE Medical, Milwaukee WI) has been used as the contrast agent for CCTA in both clinical investigations and routine clinical practiceREFERENCES. This registry study was designed to collect subject outcome information in multiple North American institutions in subjects who were clinically referred to undergo a CCTA examination with administration of Visipaque 320 mg I/mL as part of their medical care.

METHODS

Study Design: This was a prospective, multi-center, registry study in symptomatic subjects undergoing CCTA as part of their routine medical care (Figure 1). A total of 17 sites took part in the study. The study was conducted in full accordance with the Declaration of Helsinki, the Good Clinical Practice (GCP), Consolidated Guideline approved by the International Conference on Harmonization (ICH), and any applicable national and local laws and regulations. The subject's willingness to participate in the study was documented in writing in a consent form that was signed by the subject with the date and time of signature indicated. Written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained. The primary inclusion criteria were subjects with chest pain syndrome scheduled to undergo a CCTA examination due to having either intermediate pre-test probability of CAD or an uninterpretable/equivocal stress test (exercise, perfusion, or stress echo), consistent with multi-

societal appropriateness criteria for cardiac computed tomography [1]. Major exclusion criteria included subjects had known CAD as confirmed by previous myocardial infarction, or previous cardiac catheter angiography showing ≥50% obstruction, or previous coronary revascularization, such as PCI, CABG, or stent placement.

Imaging Procedure and Evaluation: Following appropriate preparations, including giving a beta blocker medication to lower down/stabilize patient heart rate to optimize the quality of the exam and placing an intravenous line in an arm vein for contrast administration, the patient underwent a non-contrast coronary calcium scan followed by CCTA procedure according to each institutional protocol with a bolus administration of Visipaque Injection 320 mg I/mL (GEHC, Medical Diagnostics, Princeton NJ). The volume and injection rate of Visipaque 320 mg I/mL was tailored to patient body size but within product allowable limit. CCTA images were processed, reconstructed and evaluated at each site by site experts with regard to the presence and type of plaque, and presence and number of coronary artery stenosis. A positive CCTA was defined as presence of ≥50% coronary stenosis identified at 1 or more coronary segments based on American Heart Association (AHA) 15 coronary artery segmental model.

Clinical Follow-up and Event Adjudication: All subjects received standard clinical care based on their CCTA findings and were followed up at 1 month (± 4 days), 6 months (± 7 days) and 12 months (± 15 days) after the CCTA procedure to obtain cardiac outcomes and relevant information. Cardiac outcomes included MACE defined as cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization, stroke, or acute renal failure; all causes of death; or coronary revascularization, i.e. PCI or CABG. When a subject had an outcome event (i.e., MACE, death or coronary revascularization), the subject was deemed to have completed the study. No subsequent follow-ups were required. All relevant clinical information for the subjects with an outcome event after CCTA was collected for adjudication. The clinical information included, but not limited to, site CCTA report, narratives from the investigator, death certificates and/or autopsy reports (if available), hospitalization discharge summaries, emergency room notes (including physical examination); copies of other diagnostic reports; coronary angiography (CATH) lab reports; operating room surgical notes; consultation notes; local laboratory report; and ECGs. An independent cardiac CT expert who is not associated with any investigational site or the sponsor of the study reviewed all data from case reports forms and relevant clinical information to confirm the following: 1) if CCTA exam was positive or negative in site report and case report form; 2) if a qualified outcome event as reported by the site was identifiable through other source documents.

Statistical Analysis: Statistical analyses were performed by two different Contract Research Organizations (i3 Statprobe and H20). Summary statistics consisted of the number and percentage of responses in each level for categorical variables, and the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values for continuous variables. Diagnostic efficacy of CCTA was analyzed for sensitivity, specificity, accuracy, and positive and

negative predictive values (PPV & NPV) using patient cardiac outcomes. To ascertain diagnostic and predictive values of CCTA, the stroke and acute renal failure were excluded. Cox propositional hazards model was employed for multivariable analyses for MACE, all-cause mortality, coronary revascularization, and all cardiac events with CCTA outcome, age, gender, primary indications for CCTA, and cardiac risk factors as covariates. Kaplan-Meier survival analyses were explored for MACE, all-cause mortality, coronary revascularization, and any cardiac events.

Statistical significance for the Cox proportional hazards analyses was set at $p<0.05$.

RESULTS

Patient Population: A total of 885 subjects were enrolled across 17 investigational sites in the US and Canada from September 2008 with completion of 12 month follow-up for all subjects in September 2010. Of these, 874/885 (99%) received administration of Visipaque 320 mg I/mL (mean volume ±SD = 91 ± 20.5 mL with a median of 95 mL). The efficacy analyses included 857/885 (97%) subjects with 28 excluded for the following reasons 1) did not have an interpretable CCTA images (14 subjects); 2) did not complete any follow-up visit and no outcome event (9 subjects); protocol violation with known history of CAD (5 subjects). The demographic and baseline characteristics of these subjects are summarized in Table 1.

Diagnostic Efficacy of CCTA: A total of 857, 853, and 843 patients completed follow-up at 1 month, 6 months, and 12 months with 51 (6%), 71(8%), and 76 (9%) of them developed 1 or more cardiac outcomes, respectively. The sensitivity of Visipaque-enhanced CCTA for detection of subsequent outcome events using patient cardiac outcomes as the endpoint was 96.1%, 95.8%, and 94.7% at the 1-month, 6-month, and 12-month follow-up periods,

respectively. The specificity was 84.5%, 86.6%, and 87.0% at the 1-month, 6-month, and 12-month follow-up periods, respectively. The PPV was low at all 3 follow-up points, 28.2% for the 1-month follow-up, 39.3% for the 6-month follow-up, and 41.9% for the 12-month follow-up due to a high number of positive CCTA findings but no subsequent cardiac event, which were considered as false positives. In contrast, NPV was over 99.0% at all 3 follow-up periods. The diagnostic efficacy of Visipaque -enhanced CCTA in terms of sensitivity, specificity, percentage agreement, PPV and NPV is presented in Table 2.

Survival Analysis: Kaplan-Meier survival analysis was performed for MACE, death due to all cause, coronary revascularization, and any cardiac events after CCTA, stratified by CCTA outcome. The MACE (i.e., cardiac death, non-fatal myocardial infarction, or unstable angina requiring hospitalization) rate was 5.7% (10/174) in subjects with a positive CCTA finding at the 12-month follow-up versus 0.1% (1/683) in subjects with a negative CCTA finding. The lone CTA event in a negative CCTA was a death that occurred 10 months after the CTA was performed. The survival rate was 94.3% (164/174) for subjects with a positive CCTA finding and 99.9% (682/683) for subjects with a negative CCTA finding (Figure 2). For coronary revascularization, i.e., PCI or CABG, following CCTA, the Kaplan-Meier survival analysis showed that 39.7% of subjects (69/174) with a positive CCTA finding underwent a revascularization procedure by the 12- month time point; this compared to only 0.6% of those subjects (4/683) with a negative CCTA finding. Similarly, the Kaplan-Meier survival analysis demonstrated a rate of 41.4% (72/174)for any cardiac event, i.e., MACE, all-cause mortality, or coronary revascularization, at the end of follow-up for subjects with a positive CCTA finding (i.e. presence of ≥50% coronary stenosis), compared to 0.6% (4/683) for subjects with a negative CCTA.

In the Cox proportional hazards analyses, the risk of MACE, revascularization, or any cardiac event was significantly higher for subjects with a positive CCTA finding with hazard ratios of 87.6 (95% CI: 8.98 to 854.84, p=0.0001), 82.5 (95% CI: 29.62 to 229.55, p<0.001), and 84.5 (95% CI: 30.45 to 234.34, p<0.001), respectively. For male gender, the hazard ratio to undergo a coronary revascularization or to have a cardiac event was 2.8 (95% CI: 1.55 to 5.11, p=0.0007) and 2.5 (95% CI: 1.41 to 4.35, p=0.0016), respectively, compared to female gender. Similarly, for in subjects with obesity, the hazard ratio for MACE was 18.4 (95% CI: 2.96 to 114.48, p=0.0018) (Table 3).

Adverse Events: Overall, 17 (2%) subjects experienced a total of 27 AEs. The most common AEs were hypersensitivity (7 events in 2 subjects), followed by angina pectoris (4 events in 4 subjects), CAD (3 events in 3 subjects), and coronary artery stenosis (3 events in 2 subjects). Five 5 (1%) subjects with AEs were considered related to Visipaque 320 mg I/mL administration. There were 10 SAEs reported for 8 (1%) subjects. None of the SAEs were considered related to Visipaque administration.

DISCUSSION

Introduction of multi-detector CT (MDCT) scanners in recent years, coupled with advanced reconstruction technique and analysis software, has taken non-invasive CT coronary artery imaging to a higher level. Compared to conventional ICA, CCTA is less invasive and costly, and a more patient-friendly procedure. Contrast material is injected into a peripheral vein rather than a catheter inserted into an artery, and the CCTA procedure takes a few minutes to complete versus an hour or more for ICA. Patients often have CCTA on an out-patient basis without the need for hospital admission, as is necessary for ICA.

The diagnostic performance of CCTA has improved steadily over time as evidenced in multiple, meta-analysis publications Error: Reference source not found. The high sensitivity (97% to 100% with 64-detector MDCT) and high NPV (95% to 100%) indicate that CCTA is capable of detecting and ruling out clinically-significant CAD in appropriate clinical situations [10-14]. The current study was a prospective, multi-center, real-life registry in symptomatic subjects undergoing CCTA as part of their routine medical care. The study achieved similar diagnostic efficacy results to those published literatures Error: Reference source not found]. At the 12-month follow-up, the sensitivity of CCTA images was approximately 95% for detection of ≥50% coronary artery stenosis at the patient level, while the NPV was > 99% for CVD outcomes.

It has been a general debate point whether the CCTA results may carry any predictive value on subsequent cardiac events and impact patient care. In this study, all subjects were followed at several time points for occurrence of cardiac outcome events, such as MACE, coronary revascularization, or any cause of death after CCTA. Kaplan-Meier survival analysis at 12 month follow-up has been very encouraging. The rate of MACE was 5.7% (10/174) in patients with a positive CCTA (one or more ≥50% stenosis) and 0.1% (1/683) patients with a negative CCTA (implying 99.9% MACE free survival rate). Meanwhile, 39.7% of subjects with a positive CCTA (vs 0.6%) had coronary revascularization, and 41.4% (vs 0.6%) had any cardiac event. Similarly, in the analyses using the Cox proportional hazards model, the risk of MACE, revascularization, or any cardiac event was significantly higher for subjects with a positive CCTA finding with hazard ratios of 87.62 ($p=0.0001$), 82.45 ($p<0.0001$), and 84.47 ($p<0.0001$), respectively. While the study did not directly evaluate the potential benefit of CCTA imaging as a triage tool for clinical management, these results suggest that in appropriately selected patient populations, the

CCTA procedure could potentially alter unnecessary need of ICA or additional treatment, particularly for those with a negative CCTA finding.

There were some limitations to this study. First of all, according ACR Manual on Contrast Media, delayed adverse reactions, particularly skin reactions, may occur one week following contrast material exposure. In this registry trial, we monitored occurrence of only unexpected AEs or SAEs for 48 hours following CM administration, and other type or additional events may have been reported if the period of patient monitoring had been extended. On the other hand, review of the reported AEs revealed that most of them were actually not unexpected AEs, but rather all types of AEs. No SAE was deemed to be related to Visipaque administration in this study. Therefore, despite comprehensive safety data collection, the safety results are indicative that Visipaque is safe to be used in a CCTA procedure. Secondly, CCTA images in this study were evaluated by individual sites as usual clinical practice and results were used for patient clinical managements. There were no central evaluations of images performed. While this reflects the real-world clinical practice, diversifications of imaging reading experience might affect study outcome. Moreover, while all patients with a positive cardiac outcome event were verified by an independent adjudicator, those without cardiac outcome events were only verified by a study monitor in selected samples of 15% of patients. Finally, there is no cost analysis performed in this study, which is considered as an important component of healthcare delivery. Future studies should be designed to include this component.

We did not compare the results of CCTA to CAC testing. The CAC score has been shown as the strongest predictor of incident coronary events in asymptomatic persons, and recommended in the ACC/AHA guidelines from both 2010 and 2013 [15,16,17,18]. However, appropriate use

criteria suggest CAC is inappropriate for symptomatic persons, while suggesting CCTA to be highly appropriate for multiple indications [1,14].

In summary, this prospective, multi-center registry study demonstrates that CCTA is a highly accurate, non-invasive imaging modality to detect or rule out subsequent cardiovascular events in patients with chest pain with intermediate pre-test probability of CAD or an uninterpretable/equivocal stress test (exercise, perfusion, or stress echo) undergoing CCTA as part of their routine medical care. A positive CCTA finding significantly contributed to the prediction of subsequent MACE, coronary revascularization and any cardiac events while a negative CCTA carried excellent prognostic outcomes at 12 months. Multicenter studies have demonstrated a prognostic utility for individuals with CCTA-identified CAD, with an increasing risk of event with increasing extent and severity of CCTA-identified CAD.[19-20] This study was concordant with the existing literature, showing increasing extent of CAD was associated with increased MACE risk.

The results of this study imply that CCTA is a highly reliable non-invasive imaging modality to triage patients with chest pain with intermediate pre-test probability of CAD or an uninterpretable/equivocal stress test (exercise, perfusion, or stress echo).

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FIGURE LEGENDS

Figure 1. Flow diagram of the Visipaque CCTA registry study procedures. CCTA = Cardiac computed tomography angiography**;** AHA = American Heart Association; MACE = Major Adverse Cardiac Event.

Figure 2. Kaplan-Meier Survival Curves for MACE Stratified by CCTA Outcome (positive vs. negative).

FIGURES

Figure 1 Visipaque CCTA registry Study Scheme

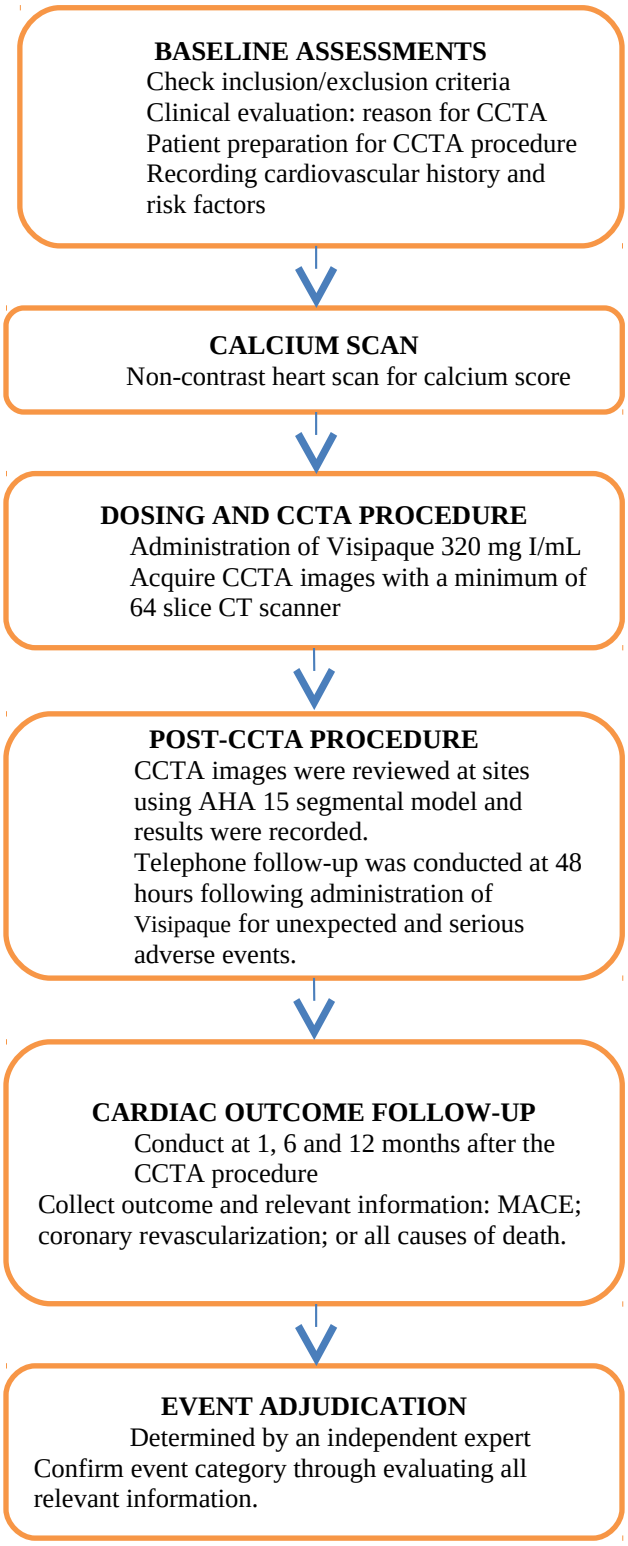
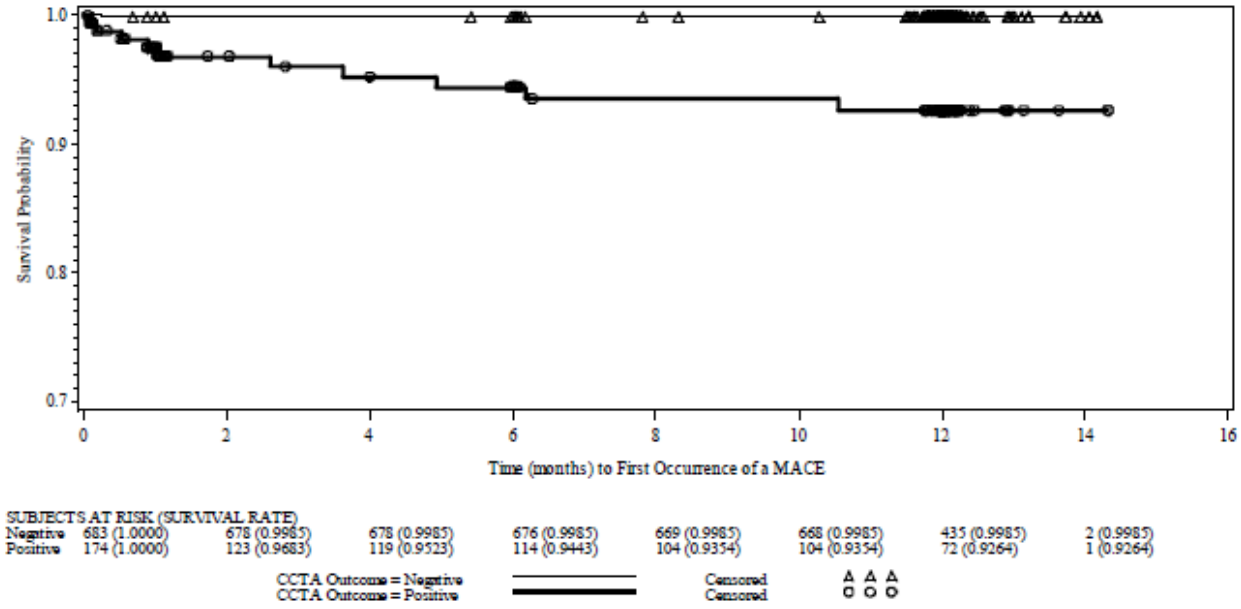


Figure 2 **Kaplan-Meier Survival Curves for MACE Stratified by CCTA Outcome (Efficacy Population**



TABLES

Table 1. Summary of Demographics and Baseline Characteristics (Safety Population)

Variables	Overall (N=874)
Demographics	
Age	
Mean (SD)	58.8 (12.0)
< 65 years, n (%)	568 (65)
≥ 65 years, n (%)	306 (35)
Gender	
Male, n (%)	443 (51)
Female, n (%)	431 (49)
Race, White, n (%)	684 (78)
Body Mass Index (kg/m^2), Mean (SD)	29.7 (6.4)
Reasons for CCTA	
Chest pain, n (%)	715 (82)
Shortness of breath, n (%)	304 (35)
Dyspnea on at exertion, n (%)	178 (20)
Post myocardial perfusion imaging, n (%)	308 (35)
Stress ECG, n (%)	98 (11)
Stress echocardiography test, n (%)	56 (6)
Others, n (%)	173 (20)
Risk Factor	
Subjects with at least 1 risk factor, n (%)	834 (95)
Hyperlipidemia, n (%)	538 (62)
Hypertension, n (%)	522 (60)
Positive Family History of CAD, n (%)	426 (49)
Smoking - Ex, n (%)	272 (31)
Sedentary Lifestyle, n (%)	251 (29)
Obesity, n (%)	244 (28)
Diabetes, n (%)	166 (19)
Smoking - Current, n (%)	112 (13)

Note: Each subject may have multiple reasons for CCTA or risk factors.

Table 2 Diagnostic Efficacy of CCTA for detecting cardiac events

Follow-up Period	Statistics				
	Sensitivity (95% CI)	**Specificity (95% CI)**	**Percent Agreement (95 % CI)**	**PPV (95% CI)**	**NPV (95% CI)**
1 month	49/51	681/806	730/857	49/174	681/683
	96.1% (86.5, 99.5)	84.5% (81.8, 86.9)	85.2% (82.6, 87.5)	28.2% (21.6, 35.5)	99.7% (98.9, 100.0)
6 month	68/71	677/782	745/853	68/173	677/680
	95.8% (88.1, 99.1)	86.6% (84.0, 88.9)	87.3% (84.9, 89.5)	39.3% (32.0, 47.0)	99.6% (98.7, 99.9)
12 month	72/76	667/767	739/843	72/172	667/671
	94.7% (87.1, 98.5)	87.0% (84.4, 89.3)	87.7% (85.3, 89.8)	41.9% (34.4, 49.6)	99.4% (98.5, 99.8)

PPV = Positive Predictive Value; NPV = Negative Predictive Value; CI = Confidence Interval.

Table 3 Results of cox Proportional Hazards Model for Positive vs. Negative CCTA on Cardiac Outcomes Categories

Event Category	N	Number of Events		Hazard Ratio (95% CI)	p value
		n	%		
MACE	857	11	1.3	87.6 (9.0 – 854.8)	0.0001
Coronary Revascularization	857	73	8.5	82.5 (29.6 – 229.6)	<0.001
Any Cardiac Event	857	76	8.9	84.5 (30.4 – 234.3)	<0.001

CCTA= Coronary computed tomography angiography; MACE= Major adverse cardiac event; CI = Confidence Interval.