Prognostic performance of low-dose coronary CT angiography with prospective ECG triggering

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Abstract: Objective To assess the prognostic value of low-dose 64-slice coronary CT angiography (CCTA) using prospective ECG triggering in a patient population with known or suspected coronary artery disease (CAD). Design Longitudinal follow-up study. Setting Tertiary referral cardiac imaging centre. Patients 434 consecutive patients who were referred for evaluation of CAD by CCTA. Methods The presence, distribution and severity of coronary lesions (non-obstructive <50% vs obstructive 50% luminal narrowing) were recorded by low-dose prospective ECG-triggered CCTA for each patient. The prognostic value of low-dose CCTA to predict major adverse cardiac events, defined as cardiac death, non-fatal myocardial infarction, or the need for revascularisation, was assessed using multivariate Cox regression analysis. Each person was followed up by telephone interviews and/or on the basis of clinical records. Thirty-eight early revascularised patients were excluded from outcome analysis. Results Completely normal coronary arteries were documented in 171 patients (47%), while exclusively non-obstructive lesions were found in 66 (18%), and obstructive coronary lesions were diagnosed in 130 patients (35%). A mean follow-up of 47±16 weeks was obtained. The first-year event rate was 0% in patients with normal coronary arteries on CCTA but increased to 3% and 26% in patients with non-obstructive and obstructive coronary artery lesions, respectively. In multivariate Cox regression analysis, a significant predictor of events was the presence of obstructive or any coronary lesions. Mean effective radiation dose was 1.8±0.6 mSv. Conclusions These data document an excellent prognostic performance of low-dose CCTA.

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Prognostic performance of low-dose coronary CT angiography with prospective ECG triggering

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Abstract

Objective: To assess the prognostic value of low-dose 64-slice coronary CT angiography (CCTA) using prospective electrocardiogram (ECG) triggering in a patient population with known or suspected coronary artery disease (CAD).

Design: Longitudinal follow-up study.

Setting: Tertiary referral cardiac imaging centre.

Patients: 405 consecutive patients who were referred for evaluation of CAD by CCTA.

Methods: The presence, distribution and severity of coronary lesions (non-obstructive < 50% versus obstructive ≥ 50% luminal narrowing) were recorded by low-dose prospective ECG triggered CCTA for each patient. The prognostic value of low-dose CCTA to predict major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction (MI), or the need for revascularization, was assessed using multivariate Cox regression analysis. Each individual was followed-up by telephone interviews and/or on the basis of clinical records. Thirty-eight early revascularized patients were excluded from outcome analysis.

Results: Completely normal coronary arteries were documented in 171 patients (47%), while exclusively non-obstructive lesions were found in 66 (18%), and obstructive coronary lesions were diagnosed in 130 patients (35%). A mean follow-up of 47±16 weeks was obtained. The first-year event rate was 0% in patients with normal coronary arteries on CCTA but increased to 3% and 26% in patients with non-obstructive and obstructive coronary artery lesions, respectively. In multivariate Cox regression analysis, significant predictors of events were the presence of obstructive or any coronary lesions. Mean effective radiation dose was 1.8±0.6mSv.

Conclusions: The present data document an excellent prognostic performance of

low-dose CCTA.

INTRODUCTION

The advent of multislice coronary computed tomography angiography (CCTA) has provided clinicians with a promising tool for the noninvasive assessment of coronary artery disease (CAD). While the excellent diagnostic accuracy[1] and prognostic performance[2-8] of CCTA have been established, radiation dose exposure has remained an intensely discussed issue and may have in part prevented the widespread use of CCTA in daily clinical routine so far. Early studies with conventional spiral CCTA have reported radiation dose exposures over 20mSv[9] and the introduction of electrocardiographic (ECG) tube current modulation has reduced radiation exposure below 9mSv.[10] The recently introduced scanning protocol using prospective ECG triggering,[11, 12] however, represents a breakthrough with regard to radiation dose reduction in CCTA. In fact, studies using prospectively ECG triggered CCTA have reported radiation doses around 2mSv[11] and below,[13] which proved substantially lower than those obtained from diagnostic invasive coronary angiography (CA) in the first head-to-head comparison.[14] On top of feasibility,[11, 12] accuracy of prospectively triggered CCTA has been reported.[15] However, its prognostic value in an outpatient clinical setting has not yet been established.

Therefore, we sought to assess the prognostic performance of 64-slice CCTA at very low radiation dose exposures using prospective ECG triggering.

METHODS

Study protocol and patient selection

This is an observational, retrospective, non-blinded, single-centre follow-up study. We enrolled consecutive patients who underwent a low-dose CCTA (using prospective ECG triggering) for evaluation of suspected or known CAD in the absence of any of the commonly accepted exclusion criteria applied to full-dose spiral CCTA.[16] Thus, none of these patients had irregular heartbeat, known allergy to iodinated contrast agent, contraindications for beta-blocking drugs, renal insufficiency (serum creatinin > 150µmol/l), inability to follow breath hold commands or failure to reach a target heart rate (HR) below 65bpm prior to scanning despite intravenous administration of metoprolol.

Baseline demographic variables, including cardiac risk factors were surveyed at the time of admission. Furthermore, previous cardiac symptoms (angina pectoris, atypical chest pain or dyspnoea) were assessed and the current medication and any history of prior cardiac events (myocardial infarction [MI], percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) as well as previous abnormal test results (pathological ECG, treadmill test or echocardiography) were extracted from physician records within one month of CCTA.

Follow-up data were obtained from telephone interviews with every patient, if possible. Additionally, electronic medical records were retrospectively screened for clinical cardiac events. Primary endpoints were major adverse cardiac events (MACE), defined as the occurrence of cardiac death, non-fatal MI, or revascularization (PCI or CABG). Cardiac death was defined as death caused by acute MI, ventricular arrhythmias, or refractory heart failure. Non-fatal MI was defined on the basis of biomarkers, ECG and symptoms of ischaemia.[17] In one patient where multiple events occurred, the first event was included in the analysis. All patients with revascularization procedures within the first 6 weeks were excluded because during this period revascularization could potentially be directly triggered by the CCTA result, which would introduce a confounder between diagnostic and prognostic value.

The protocol was approved by the institutional review board and each patient provided written informed consent.

CCTA data acquisition and post-processing

Intravenous metoprolol (Beloc, AstraZeneca) up to a maximum dose of 30mg was administered if necessary in order to achieve a target HR below 65bpm. All patients additionally received a single dose of 2.5mg sublingual isosorbiddinitrate (Isoket, Schwarz Pharma) prior to scanning on a LightSpeed VCT XT scanner (GE Healthcare) using prospective ECG triggering with the following scanning parameters as previously reported[11] and validated:[15] slice acquisition 64 × 0.625mm, smallest x-ray window at 75% of the RR-cycle, z-coverage 40mm with an increment of 35mm, gantry rotation time 350ms, body mass index (BMI)-adapted tube voltage and current[18] and an overall z-coverage of 11 to 25cm. Image acquisition with 75±12ml contrast agent (Visipaque 320, GE Healthcare) was initiated 4 seconds after the signal density reached a visually detectable threshold in the ascending aorta (bolus tracking).

Assessement of image quality and coronary lesions

Coronary arteries were subdivided into 16 segments according to a modified model proposed by the American Heart Association[19] with the intermediate artery being defined as segment 16, if present.

Interpretation was performed on axial source images and multiplanar curved reformations. Segments with doubling or discontinuity of the vessel or non-differentiable structures (no clear delineation between vessel and surrounding tissue) were classified as non-evaluative. If a coronary artery segment was non-evaluative, the segment was scored similarly to the most proximal segment which was evaluable.[2] Thus, all segments were scored in all patients, irrespective of image quality.

Non-obstructive coronary lesions were defined as plaques of an area of equal to or greater than $1mm^2$ in orthogonal reconstructions within and/or adjacent to the vessel lumen, not belonging to surrounding tissue. An obstructive lesion was defined as a stenosis with a visual luminal diameter narrowing of equal or greater than 50%.

Effective radiation dose estimation

Values for the effective radiation dose for CCTA were estimated as the product of the dose-length product (DLP) multiplied by a conversion coefficient for the chest. Among the various factors suggested by the European Working Group for Guidelines on Quality Criteria in Computed Tomography[9] we chose 0.014mSv/mGycm as suggested and used in several large multicenter studies on CCTA radiation dose[9, 20] to ensure comparability of the latter with our results.

Statistical analysis

We used SPSS 17.0 (SPSS Inc.) for all statistical analysis. Categorical variables are presented as frequencies and continuous variables as mean ± one standard deviation (SD). Variables were compared with chi-square statistics or Fisher's exact test for categoric variables and by Wilcoxon-Mann-Whitney test or independent samples t-test for continuous variables. Follow-up data were analyzed by obtaining cumulative event rates for MACE as a function over time using the Kaplan-Meier function. Event free survival curves were compared using log-rank test. To assess the influence of CCTA findings on clinical endpoints, univariate Cox regression was used. Additionally, stepwise forward multivariate Cox regression was applied to identify possible independent predictors with $p < 0.10$ on univariate analysis. The regression results are presented as hazard ratios and their confidence intervals (CI). A two-tailed p-value of < 0.05 was considered statistically significant.

RESULTS

Patient population

Low-dose CCTA with prospective ECG-triggering was performed in 434 patients who were enrolled in the present outcome study. Twenty-nine patients (6.7%) were lost to follow-up due to invalid contact information (n = 18), refusal to provide follow-up data (n = 1), or migration to a foreign country (n = 10).

Thirty-eight patients that underwent early revascularization (i.e. within 6 weeks after CCTA was performed) were excluded. Thus, final outcome analysis was performed in 367 patients. Baseline characteristics are provided in Table 1.

Table 1 Patient baseline characteristics (n = 367)

Male gender (%)	61
Age (years)	
Mean ± SD	59 ± 12
Range	13 – 85
BMI (kg / m^2)	
Mean ± SD	26 ± 5
Range	18 – 46
Framingham risk score (%)	
Low	77
Intermediate	15
High	8
Cardiovascular risk factors (%)	
Obesity (BMI > 30 kg / m^2)	16
Smoking	35
Diabetes	10
Hypertension	54
Dyslipidaemia	46

Positive family history	40
Clinical symptoms (%)	
Typical angina pectoris	12
Atypical angina pectoris	48
Dyspnoea	13
Asymptomatic	27
Abnormal test results prior to referral (%)	
Electrocardiogram	10
Treadmill test	18
Echocardiography	1
Previous cardiac events (%)	
Myocardial infarction	4
PCI	7
CABG	2

SD = standard deviation, BMI = body mass index, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft

CCTA image quality and findings

In 367 patients, a total of 5023 coronary artery segments (of theoretically 5872 segments in 367 patients with 16 segments) were evaluated. There were 645 segments missing for reasons not related to the technique, i.e. anatomical variants (for example the typically missing intermediate artery).

Normal coronary arteries were documented in 171 patients (47%). Non-obstructive coronary lesions were found in 66 (18%), while obstructive lesions were diagnosed in 130 patients (35%).

Effective radiation dose estimation

Mean DLP for CCTA was 126±43mGycm, resulting in a mean effective radiation dose exposure of 1.8±0.6mSv (range: 0.8 – 3.8mSv).

Follow-up results

During a mean follow-up of 47±16 weeks (range: 26 – 84 weeks), 30 patients (8.2%) reached one of the predefined endpoints. These included 1 (0.2%) cardiac death, 3 (0.7%) non-fatal MI, and 26 (7.1%) revascularization procedures (i.e. 10 CABG and 16 PCI). For 11 MACE no information was available on whether the event occurred in the target vessel with the CCTA finding (1 death without autopsy and 10 patients with multivessel disease referred to CABG in whom no single target vessel could be defined). For the remaining 16 MACE we could assign (angiographically) 14 to the index vessel identified by CCTA, while in 2 patients with angiographic total occlusion the neighbouring artery was revascularized, as origin of collaterals serving the target territory. A tertile analysis revealed that most MACE occurred in the group of patients with the highest amount of coronary lesions, while none occurred in patients in the group with the lowest amount of lesions (Figure 1). An additional 38 patients that underwent early revascularization were excluded from final outcome analysis.

Survival analysis

Patients with normal coronary arteries on CCTA had an excellent event-free survival as opposed to those with abnormal coronary arteries who had a first-year event rate of 20% ($p < 0.001$) (Figure 2).

Patients with non-obstructive coronary artery lesions showed an only slightly elevated first-year event rate of 3% ($p < 0.05$ versus patients with normal coronary arteries), while patients with obstructive coronary artery lesions presented with a substantially higher event-rate of 26% ($p < 0.001$ versus patients with normal coronary arteries and patients with non-obstructive coronary lesions) (Figure 3 and 4).

CCTA predictors of events

The results of univariate Cox regression analysis for clinical characteristics, patients' symptoms, cardiovascular risk factors, and CCTA findings are given in Table 2. The presence of an atherosclerosis as evidenced by any non-obstructive or obstructive lesion was a strong predictor of MACE (hazard ratio = 74.3, $p < 0.001$). The presence of non-obstructive lesions was a moderate but significant predictor of MACE (hazard ratio = 7.1, $p = 0.04$). Conversely, patients with obstructive CAD (Figure 5) were at substantially higher risk for MACE on follow-up (hazard ratio 58.6, $p = 0.002$).

Table 2 **Univariate cox regression proportional hazard analysis** (n = 367)

Variable	**Hazard ratio (95% CI)**	**p-value**
Clinical characteristics		
Age	1.04 (1.01 – 1.08)	0.014
Male gender	2.11 (0.91 – 4.92)	0.077
History of myocardial infarction	2.57 (0.78 – 8.48)	0.082
History of PCI		NS
History of CABG		NS
Cardiovascular risk factors		
Obesity	4.01 (1.96 – 8.55)	0.001
Smoking		NS
Diabetes	2.33 (0.95 – 5.70)	0.045
Hypertension	2.52 (1.12 – 5.67)	0.021
Dyslipidaemia	1.98 (0.94 – 4.16)	0.054

Positive family history	3.23 (1.24 – 8.45)	0.011
Medication		
Aspirin use	2.38 (1.15 – 4.95)	0.015
Betablocker use		NS
ACEI/ARB use		NS
Statin use		NS
Nitrate use	5.99 (2.45 – 14.67)	0.001
Symptoms		
Typical angina pectoris	4.59 (2.18 – 9.66)	0.001
Atypical chest pain	0.38 (0.17 – 0.86)	0.014
Dyspnoea	2.73 (1.21 – 6.13)	0.012
Asymptomatic		NS
Abnormal test results		
Electrocardiogram		NS
Treadmill test	1.98 (0.91 – 4.33)	0.071
Echocardiography		NS
CCTA findings		
Normal coronary arteries	0.01 (0.01 – 0.26)	0.001
Abnormal coronary arteries	74.31 (3.91 – 1413.18)	0.001
Number of abnormal segments	1.42 (1.28 – 1.58)	0.001
Non-obstructive coronary lesions	7.07 (0.96 – 51.93)	0.037
Number of non-obstructive segments		NS
Obstructive coronary lesions	58.60 (7.98 – 430.30)	0.002
Number of obstructive segments	1.49 (1.35 – 1.64)	0.001

CI = confidence interval, NS = non significant, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, ACEI = angiotensin-converting enzyme-inhibitor, ARB = angiotensin receptor blocker, CCTA = coronary computed tomography angiography

The results of multivariate Cox regression analysis corrected for baseline characteristics are given in Table 3.

Table 3 **Multivariate Cox Proportional Hazard Analysis** (n = 367)

Variable	**Hazard ratio (95% CI)**	**p-value**
Abnormal coronary arteries	73.97 (3.89 – 1405.84)	0.004
Number of abnormal segments	1.41 (1.25 – 1.59)	0.001
Obstructive coronary lesions	50.45 (6.80 – 374.27)	0.001
Number of obstructive segments	1.52 (1.35 – 1.71)	0.001

CI = confidence interval

DISCUSSION

The present data demonstrate the excellent prognostic value of prospectively ECG triggered CCTA with a mean effective radiation dose below 2mSv. Absence of atherosclerotic findings in CCTA was an excellent predictor of event-free survival. Similarly, patients with exclusively non-obstructive lesions had only a slightly reduced event-free survival. By contrast, patients with obstructive lesions had a massive reduction in event-free survival. Furthermore, the extent of obstructive coronary artery disease (i.e. the amount of segments with obstructive lesions) correlated with an adverse cardiac outcome. First-year event rate was 0% for patients without any evidence of atherosclerosis, 3% for patients with non-obstructive lesions, and 26% for patients with obstructive lesions.

These results are consistent with previous studies reporting up to 40% first year event rates in patients with obstructive CAD.[2-5] The latter studies, however, used spiral CT techniques which are associated with relatively high effective radiation dose exposure to the patients ranging between 8 and 25mSv per scan. By contrast, the effective radiation dose in the present study averaged 1.8±0.6mSv as we used prospective ECG triggering to obtain low-dose CCTA. As radiation safety issues have evoked a vivid discussion on the risk to benefit ratio of CCTA,[21] reduction of radiation dose is essential. This is particularly true for patient populations commonly referred for CCTA as their cardiac event risk is typically low. Furthermore, in such a population the bars seem to be very high to justify the risk of any diagnostic or interventional procedure, as further improvement of prognosis may be difficult to achieve. Therefore, the massive reduction in effective radiation dose by introduction of prospective ECG triggering is important, as it contributes to shift the risk to benefit ratio towards the favourable side of the balance.

After demonstrating the feasibility[11, 12] and diagnostic accuracy[15] and its confirmation in a growing body of literature from many different centres,[22-25] the present study is the first to establish the prognostic performance of low-dose CCTA. This refinement, merely the successful reduction of radiation dose exposure by an order of magnitude from introduction of spiral CCTA with over 20mSv[9] to prospective triggered CCTA with 2mSv[11, 13] or even scanning in the submillisievert range[26] has allowed CCTA to rapidly evolve from a premature technique to a reliable and valuable clinical tool in daily routine.

Indeed, repeat CCTA scanning for sensing the transition of atherosclerosis into clinically and prognostically relevant CAD or for the monitoring of CAD treatment may no longer be considered prohibitive for radiation concerns.

Limitations

It may be perceived as a potential limitation of the present study that despite the above mentioned improvements in CCTA technique, there is still a small percentage of patients with non-interpretable coronary segments.[12] Latest generation scanners[27, 28] may contribute to further decreasing non-interpretable studies.

Furthermore, it may be perceived as a limitation that coronary interventions were included as events in the present study. In fact, all previous studies assessing the predictive value of spiral CCTA for MACE have included these endpoints. In order to ensure meaningful comparability of our results with prospectively triggered CCTA versus spiral CCTA we followed the design of these previous studies including all revascularization procedures during the entire follow-up period. However, the fact that we have – in contrast to previous studies – excluded all patients revascularized within the first 6 weeks constitutes a strength of the present study, as this period ensures that all procedures triggered by CCTA itself had been excluded from outcome analysis.

Finally, the CCTA studies were analyzed visually without quantification of anatomic lesion severity. However, this corresponds to current clinical practice[1] as no validated software offering a quantitative algorithm is available as of today.

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Competing interests The University Hospital Zurich holds a research contract with GE Healthcare.

Patient consent Obtained.

Ethics approval The protocol was approved by the institutional review board.

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Figures

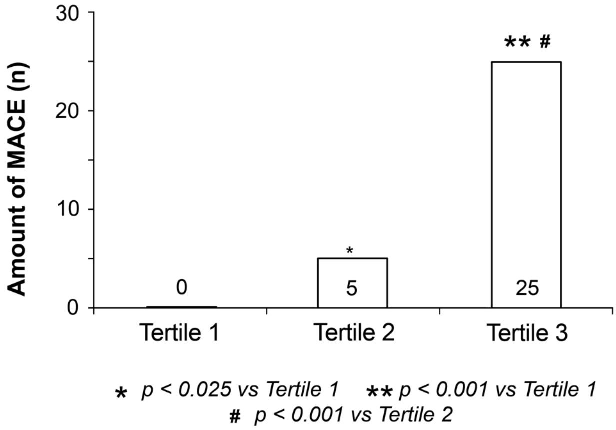
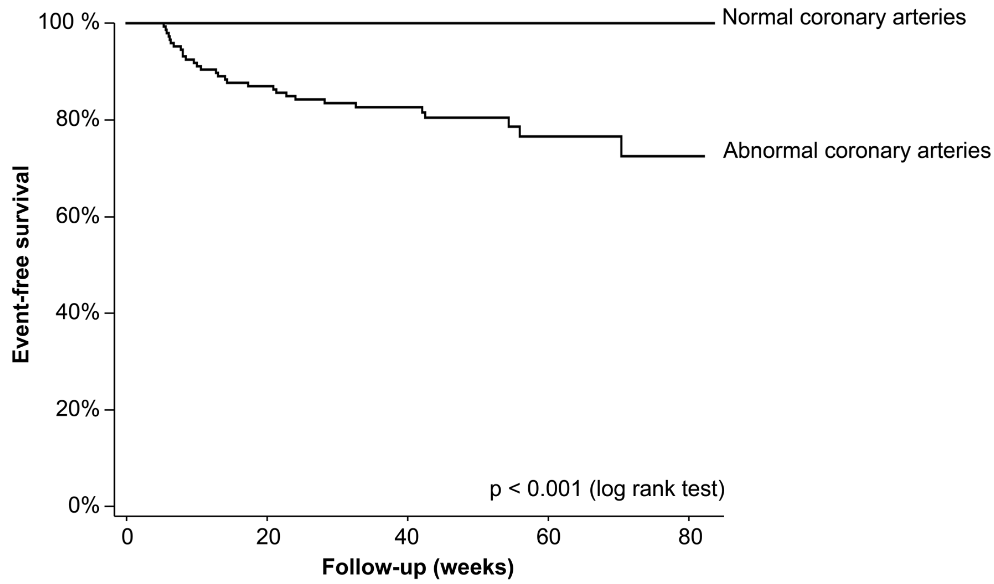


Figure 1

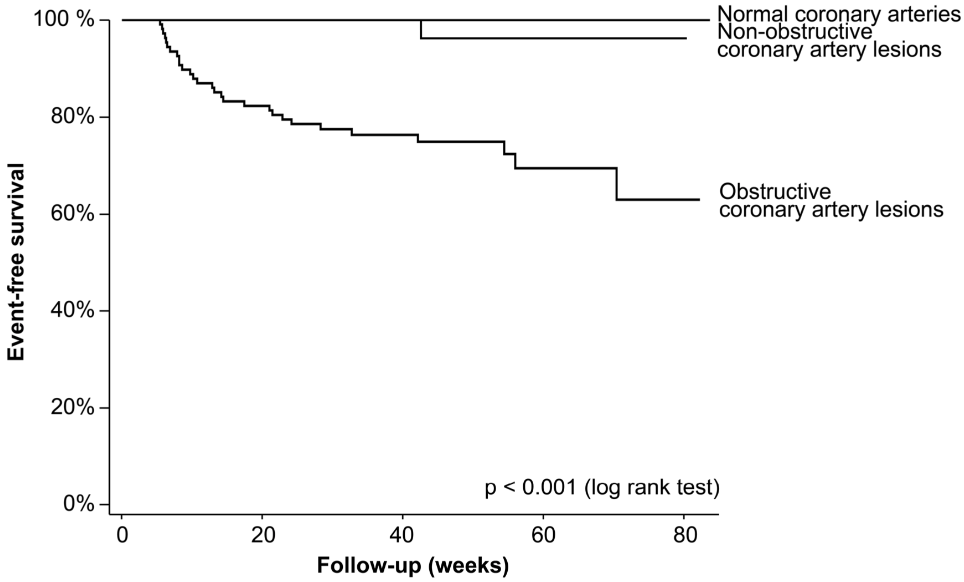
Tertile analysis relating the amount of coronary plaque burden (i.e. the amount of coronary lesions) to the incidence of major adverse cardiac events (MACE).



Patients at risk for events	367	286	154	48	3
Normal coronary arteries	190	150	78	25	1
Abnormal coronary arteries	177	136	76	23	2

Figure 2

Kaplan-Meier cumulative event-free survival curves for patients with normal or abnormal (non-obstructive and/or obstructive lesions) coronary arteries. Patients with normal coronary arteries on CCTA had an excellent event-free survival as opposed to those with abnormal coronary arteries who had a first-year event rate of 20% ($p < 0.001$).



Patients at risk for events	367	286	154	48	3
Normal coronary arteries	190	150	78	25	1
Non-obstructive lesions	47	40	24	8	1
Obstructive lesions	130	96	52	15	1

Figure 3

Kaplan-Meier cumulative event-free survival curves for patients with normal coronary arteries, non-obstructive coronary lesions, and obstructive coronary lesions. Patients with non-obstructive coronary artery lesions had a first-year event rate of 3% ($p < 0.05$ versus patients with normal coronary arteries), while patients with obstructive coronary artery lesions presented with an event-rate of 26% ($p < 0.001$ versus patients with normal coronary arteries and patients with non-obstructive lesions).

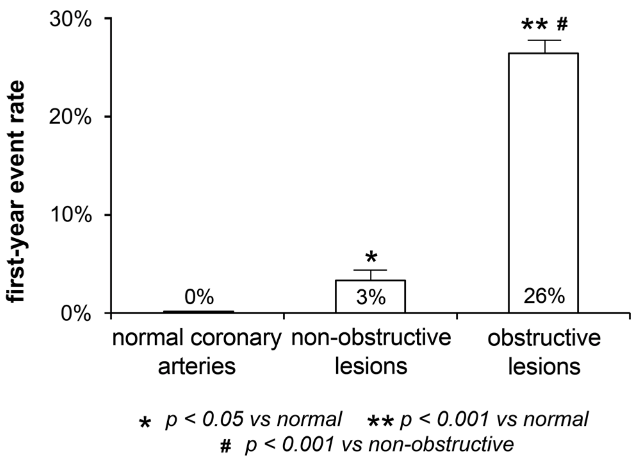


Figure 4

Patients with normal coronary arteries on CCTA had an excellent event-free survival as opposed to those with non-obstructive (3% first-year event rate), or obstructive coronary artery lesions (26% first-year event rate).

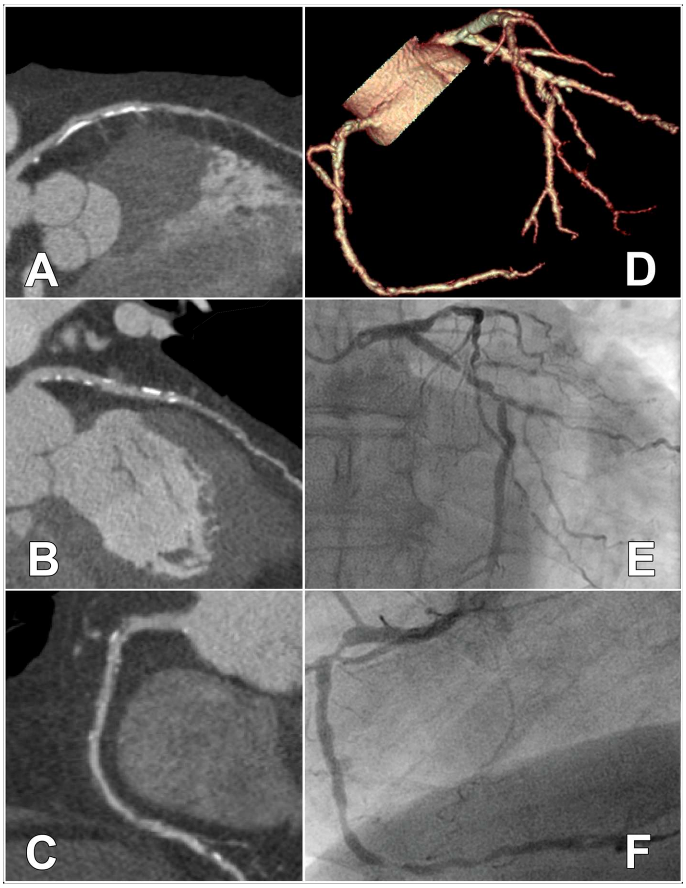


Figure 5

CCTA of a seventy-two year old male patient showed multiple non-obstructive lesions in all three coronary arteries, illustrated in the multiplanar curved reconstructions of the LAD (A), CX (B), and RCA (C), and the volume-rendered vessel tree (D). The patient suffered non-fatal myocardial infarction 56 weeks later with the invasive coronary angiography (E, LAD and CX; F, RCA) now revealing stenoses in all three vessels and the patient being scheduled for emergency coronary artery bypass surgery. CCTA acquisition was performed with 85ml of contrast agent. Radiation dose was 1.9mSv.