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Long-term prognostic performance of low-dose coronary computed tomography angiography with prospective electrocardiogram triggering

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Abstract

Objectives To assess long-term prognosis after low-dose 64-slice coronary computed tomography angiography (CCTA) using prospective electrocardiogram-triggering.

Methods We included 434 consecutive patients with suspected or known coronary artery disease referred for low-dose CCTA. Patients were classified as normal, with non-obstructive or obstructive lesions, or previously revascularized. Coronary artery calcium score (CACS) was assessed in 223 patients. Follow-up was obtained regarding major adverse cardiac events (MACE): cardiac death, myocardial infarction and elective revascularization. We performed Kaplan-Meier analysis and Cox regressions.

Results Mean effective radiation dose was 1.7 ± 0.6 mSv. At baseline, 38% of patients had normal arteries, 21% non-obstructive lesions, 32% obstructive stenosis and 8% were revascularized. Twenty-nine patients (7%) were lost to follow-up. After a median follow-up of 6.1 ± 0.6 years, MACE occurred in 0% of patients with normal arteries, 6% with non-obstructive lesions, 30% with obstructive stenosis and 39% of those revascularized. MACE occurrence increased with increasing CACS ($P < 0.001$), but 4% of patients with CACS = 0 experienced MACE. Multivariate Cox regression identified obstructive stenosis, lesion burden in CCTA and CACS as independent MACE predictors ($P \leq 0.001$).

Conclusion Low-dose CCTA with prospective electrocardiogram-triggering has an excellent long-term prognostic performance with a warranty period >6 years for patients with normal coronary arteries.

Key Points

- *Coronary CT angiography (CCTA) has an excellent long-term prognostic performance.*
- *CCTA can accurately stratify cardiac risk according to coronary lesion severity.*
- *A normal CCTA predicts freedom from cardiac events for >6 years.*
- *Patients with a coronary calcium score of 0 may experience cardiac events.*
- *CCTA allows for reclassification of cardiac risk compared with ESC SCORE.*

Keywords Coronary angiography · Multidetector computed tomography · Coronary artery disease · Event-free survival · Prognosis

Abbreviations

AUC	Area under the curve
BMI	Body mass index
CABG	Coronary artery bypass graft
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CI	Confidence interval
ECG	Electrocardiogram
ESC	European Society of Cardiology
HR	Hazard ratio
IQR	Interquartile range
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event

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MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
ROC	Receiver operating characteristic
SD	Standard deviation
SIS	Summed involvement score
SPECT	Single photon emission computed tomography
SSS	Summed severity score

Introduction

Coronary computed tomography angiography (CCTA) is increasingly used for the non-invasive assessment of suspected or known coronary artery disease (CAD). CCTA has an excellent diagnostic accuracy with outstanding sensitivity and negative predictive value [1, 2], and new methods have been shown to further improve these parameters [3]. Moreover, several meta-analyses [4–6], the large CONFIRM registry [7] and more recent studies [8] demonstrated an excellent prognostic value of CCTA regarding cardiac events. However, the average follow-up duration of these prognostic studies was limited to 2–3 years, which seems short when considering the slowly progressive development of coronary atherosclerosis. Few authors have assessed the ability of CCTA to predict cardiac events in the long term. For this purpose, they used the older electron-beam CT [9] or retrospective electrocardiogram (ECG) gating with tube current modulation [10–13]. The latter technique is no longer the preferred method for CCTA, as it exposes patients to radiation doses of up to 10–20 mSv [14]. More recent long-term studies were focussed on coronary dominance [15], or on specific populations [16, 17].

Prospective ECG triggering was introduced for 64-slice CCTA in 2007 [18]. This technique combines an excellent diagnostic accuracy [19] with a low mean radiation dose of 1.8 mSv [20, 21], which may in turn reduce the potential risk associated with CCTA. We have previously reported on the excellent prognostic performance of CCTA with prospective ECG triggering after 1 year of follow-up [22].

Similarly, coronary artery calcium score (CACS) has been demonstrated to constitute a strong predictor of coronary events [23]. The high negative predictive value of CACS for cardiac events was highlighted in a recent meta-analysis [24], but several authors warned about non-calcified stenoses, which may be associated with increased cardiovascular risk but are not assessed by CACS [25]. Thus, the comparative value of CACS versus CCTA remains a matter of debate. A few studies suggested a superior prognostic value of CCTA over CACS but were mostly limited to short-term follow-up periods of 2-3 years [26, 27].

The primary aim of the present study was to assess the long-term prognostic performance of low-dose CCTA with prospective ECG triggering on major adverse cardiac events. The secondary aim was to compare the prognostic performance of CACS and low-dose CCTA. We hypothesized that low-dose CCTA can predict cardiac events in the long term and may have a higher prognostic performance than CACS.

Material and methods

Study protocol and patient selection

We performed an observational, retrospective, non-blinded, single-centre cohort follow-up study. We retrospectively included all consecutive patients undergoing low-dose 64-slice CCTA with prospective ECG triggering to evaluate suspected or known CAD from September 2007 to December 2008 in our centre. None of these patients had any of the routine exclusion criteria for CCTA, such as irregular heartbeat, contraindications for β-blocking drugs, failure to reach a heart rate <65 beats/min (bpm) despite intravenous β-blocking drugs, inability to follow breath-hold commands, known allergy to iodinated contrast agent or renal insufficiency (serum creatinine >150 μmol/L) [20]. Patients undergoing CCTA for other indications, including left atrial assessment before electrophysiological procedures or evaluation of congenital heart disease, were not included. The study population was shared with a previous report on short-term outcome after CCTA [22].

At baseline, we recorded demographic variables, traditional cardiovascular risk factors, cardiac symptoms (typical or atypical angina pectoris, dyspnoea) and cardiac medication. Furthermore, we extracted previous cardiac events (myocardial infarction [MI], percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) from clinical records.

Follow-up was performed using telephone interviews with patients and referring physicians. Additionally, electronic medical records were searched for cardiac events. Patients lost to follow-up were excluded from the study. Primary endpoints were major adverse cardiac events (MACE), defined as cardiac death, non-fatal MI or elective revascularization by PCI or CABG. Cardiac death was defined as either sudden death with probable cardiac origin or death caused by acute MI, ventricular arrhythmias or refractory heart failure. Non-fatal MI was defined on the basis of symptoms, ECG and biomarkers of ischaemia [28]. Revascularization procedures within the first 6 weeks after CCTA were excluded because they may have been directly triggered by the CCTA findings per se [13]. This avoids an important confounder between the diagnostic and the prognostic value of the test. However, patients with such early revascularizations remained in the study and the next MACE was considered as the first event. The protocol was approved by the local ethics committee (KEK-ZH-No. 2013-0585) and the need for written informed

consent was waived. Our study complied with the Declaration of Helsinki.

CCTA data acquisition

Patients were pre-treated with intravenous metoprolol (Beloc, AstraZeneca, London, UK) up to 30 mg if necessary to achieve a target heart rate <65 bpm, and with 2.5 mg sublingual isosorbide dinitrate (Isoket, UCB Pharma, Brussels, Belgium). Scanning was performed on a LightSpeed VCT XT scanner (GE Healthcare, Milwaukee, WI, USA) using prospective ECG triggering with validated scanning parameters [18, 20, 29]: slice acquisition 64 x 0.625 mm, smallest x-ray window at 75% of the RR cycle, z-coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, body mass index-adapted tube voltage and current, and an overall z-coverage of 11–25 cm. Image acquisition with 75 ± 12 ml iodixanol (Visipaque 320, GE Healthcare) was initiated 4 s after the signal density reached a visually detectable threshold in the ascending aorta (visual bolus tracking). The effective radiation dose for CCTA was estimated as the dose-length product multiplied by a conversion coefficient for the chest (0.014 $mSv \cdot mGy^{-1} \cdot cm^{-1}$) [14].

CACS data acquisition and measurement

Unenhanced CT for CACS was performed with a 64-slice CT scanner (LightSpeed VCT XT, GE Healthcare) in patients ≥45 years old [30] and those undergoing hybrid imaging with either single photon emission computed tomography (SPECT) or positron emission tomography (PET) using CT-based attenuation correction [31]. Scan parameters for CACS were as follows: prospective ECG triggering, 2.5-mm slice thickness, 120 kV tube voltage and 200 mA tube current [30, 31]. Calcium scoring was performed on a dedicated workstation using a commercially available semi-automatic software package (SmartScore, GE Healthcare). All voxels with attenuation above a threshold of 130 Hounsfield units (HU) were automatically colour marked and lesions were manually selected. The software then calculated the CACS (i.e. Agatston score) [31].

Assessment of coronary lesions

Coronary arteries were divided into 16 segments according to a modified version of the American Heart Association model [32] with the intermediate branch defined as segment 16, if present. CCTA image interpretation was performed by two independent readers with at least 2 years of experience in CCTA derived from 64-slice CT scanners from axial source images, multi-oblique and multi-planar curved reformations, maximum intensity projections and volume-rendered images, as recommended [33]. Disagreement between readers was solved by consensus. Segments with doubling or discontinuity of the vessel, or non-differentiable structures (no clear delineation between vessel and surrounding tissue) were classified as non-evaluable. For lesion severity, non-evaluable segments were scored as the more proximal evaluable segment of the respective vessel [7]. Thus, all segments were scored in all patients. Coronary lesions were defined as plaques of ≥1 mm^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 ≥50%. Patients were stratified according to coronary lesions documented by CCTA: normal coronary arteries, non-obstructive lesions (luminal narrowing <50% or eccentric wall calcifications), obstructive stenosis (luminal narrowing ≥50%) or revascularized patients (previous PCI or CABG). Additionally, a segment involvement score (SIS: 1 point for each coronary segment with any luminal narrowing) and segment severity score (SSS: total of all segments scored according to lesion severity with 0 = no lesion, 1 = narrowing <50%, 2 = stenosis 50–69%, 3 = stenosis ≥70%) was calculated for each patient [11]. Readers interpreting CCTA had access to patient data, such as symptoms, age, risk factors or previous events. However, the reading was performed immediately after scanning. Thus, readers were unaware of any subsequent invasive coronary angiography or MACE.

Statistical analysis

We used SPSS Statistics 22 (IBM, Armonk, NY, USA) and MedCalc Statistical Software 15.8 (MedCalc Software, Ostend, Belgium) for statistical analyses. Categorical variables are presented as frequencies with percentages and continuous variables as mean ± standard deviation (SD) or median ± interquartile range (IQR), as appropriate. Categorical variables were compared using the χ^2 or Fisher's exact test and continuous variables by Student's t-test or the Mann-Whitney U-test, as appropriate. We performed Kaplan-Meier event-free survival analysis using the time to the first MACE of each patient. Event-free survival curves were compared between groups based on coronary lesions and CACS levels using the log-rank test. Moreover, the annual MACE rate was compared using the Mann-Whitney U-test and Kruskall-Wallis test. In patients without previous revascularization, we assessed the influence of baseline characteristics and CCTA findings on MACE occurrence using univariate Cox proportional hazard regression. Then, multivariate Cox regression was performed in a forward stepwise conditional manner with entry at $P \leq 0.05$ and removal at $P \geq 0.10$ to identify independent predictors of MACE. Cox regression results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Furthermore, receiver operating characteristic (ROC) curves were generated to compare the prognostic performance of CCTA and CACS regarding MACE in patients who underwent both examinations. Areas under the curves (AUCs) with 95% CI were compared using the method of DeLong et al. [34]. Finally, we calculated the cardiovascular risk according to the SCORE algorithm of the European Society of Cardiology (ESC) [35] in a subset of patients with appropriate data to assess the reclassification rate after CCTA. Two-sided P values <0.05 were considered statistically significant. We reported our results according to the STROBE guidelines for observational studies [36].

Results

Patient population

We enrolled 434 patients who underwent low-dose CCTA with prospective ECG triggering. Among them, 29 (7%) were lost to follow-up due to invalid contact information or migration to a foreign country. Thus, 405 patients were included into the final statistical analysis. Baseline characteristics are presented in Table 1.

CCTA and CACS findings

In 405 patients, a total of 5,781 coronary segments were evaluated. We noted 699 missing segments due to anatomical variations, such as the often missing intermediate branch. Normal coronary arteries were observed in 153 patients (38%), non-obstructive lesions in 87 patients (21%) and obstructive stenosis in 131 patients (32%), whereas 34 patients (8%) were previously revascularized. Mean dose-length product of CCTA scanning was 123 ± 42 mGy·cm, resulting in an effective radiation dose of 1.72 ± 0.59 mSv.

Mean SIS and SSS were 0 for patients with normal coronary arteries, but both 0.91 ± 1.21 with non-obstructive lesions. (This value is slightly <1, because of minimal eccentric wall calcifications without luminal narrowing.) In patients with obstructive stenosis, mean SIS was 3.62 ± 2.23 and mean SSS 7.35 ± 5.28.

CACS was performed in a subpopulation of 223 patients (56%). Median CACS was 61 ± 508.

Follow-up results

During a median follow-up of 6.1 ± 0.6 years, 116 MACE occurred in 101 patients (25%). Of these events, we excluded 50 elective revascularizations within 6 weeks of CCTA. Thus, we studied 66 MACE occurring in 55 patients (14%). These events were 7 cardiac deaths, 9 non-fatal myocardial infarctions, 38 elective PCI and 12 elective CABG. Furthermore, 16 patients died of non-cardiac causes: 4 of infection, 4 of cancer, three of suicide, two of haemorrhage, two after surgery and one of multiple diseases. These results are detailed by group in Table 2.

Table 1 Patient baseline characteristics (n = 405)

Clinical characteristics	
Male gender, n (%)	259 (64%)
Age (years), mean ± SD	59.4 ± 11.4
BMI (kg/m^2), mean ± SD	26.2 ± 4.5
Cardiovascular risk factors, n (%)	
Arterial hypertension	219 (54%)
Diabetes mellitus	41 (10%)
Dyslipidaemia	190 (47%)
Positive family history	168 (42%)
Smoking	143 (35%)
Clinical symptoms, n (%)	
Typical angina	51 (13%)
Atypical angina	187 (46%)
Dyspnoea	51 (13%)
Other symptoms	47 (12%)
Asymptomatic	69 (17%)
Previous cardiac events, n (%)	
Myocardial infarction	18 (4%)
PCI	31 (8%)
CABG	6 (1%)
Pathological test results prior to CCTA, n (%)	
Electrocardiogram	39 (10%)
Treadmill test	73 (18%)
Echocardiography	4 (1%)
LVEF (%), mean ± SD	65.1 ± 10.2

SD standard deviation, *BMI* body mass index, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *LVEF* left ventricular ejection fraction, *CCTA* coronary CT angiography, *CACS* coronary artery calcium score, *IQR* interquartile range

Survival analysis

Event-free survival was excellent in patients with normal coronary arteries, but decreased among patients with non-obstructive lesions, and decreased further with obstructive stenosis as diagnosed by CCTA and in previously revascularized patients (all pairwise P ≤ 0.003, except not significant for obstructive vs. revascularized; Fig. 1). Similarly, event-free survival decreased with increasing CACS (P for trend < 0.001) (Fig. 2). Of note, no MACE occurred among patients with normal coronary arteries according to CCTA, whereas 4% of patients with a CACS of 0 experienced MACE. Annual MACE rates stratified

Table 2 Events by group according to coronary lesions in CCTA (n = 405)

Event	Normal arteries (n = 153)	Non-obstructive lesions (n = 87)	Obstructive stenosis (n = 131)	Previous PCI or CABG (n = 34)	P-value
Non-cardiac death	6	1	7	2	0.423
Total MACE	0	6	45	15	<0.001
Cardiac death	0	1	6	0	0.021
Non-fatal MI	0	1	5	3	0.008
PCI*	0	4	24	10	<0.001
CABG*	0	0	10	2	<0.001

P-values were calculated using the χ^2 test

* Elective revascularizations >6 weeks after CCTA

CCTA coronary computed tomography angiography, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *MACE* major adverse cardiac events, *MI* myocardial infarction

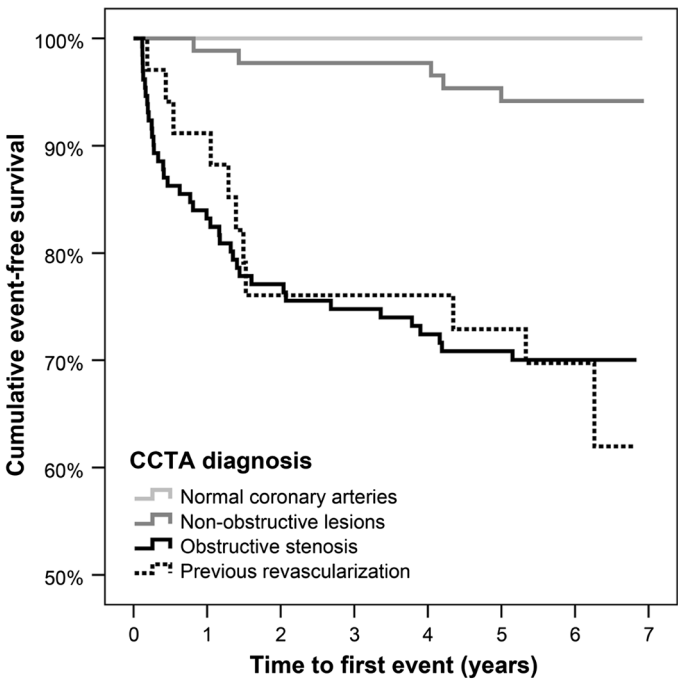
according to CCTA findings and to CACS levels are given in Figs. 3 and 4.

Predictors of MACE

Results of univariate Cox regression analysis for demographics, cardiovascular risk factors, symptoms, previous events, CACS and CCTA findings are given in Table 3. In multivariate Cox regression analysis adjusted for demographics, cardiovascular risk factors, symptoms and previous cardiac events, CCTA findings of obstructive stenosis, SIS and SSS remained strong independent MACE predictors (all P ≤ 0.001) (Table 4).

CCTA versus CACS

In the subgroup of patients who underwent a CACS scan (n = 223), CACS was a strong independent MACE predictor in multivariate Cox regression analysis (P < 0.001). However,



Patients at risk for events	405	379	363	354	347	331	208	0
Normal coronary arteries	153	153	153	150	147	142	84	0
Non-obstructive lesions	87	86	85	84	84	79	55	0
Obstructive stenosis	131	109	100	96	92	87	54	0
Previous revascularization	34	31	25	24	24	23	15	0

Fig. 1 Kaplan-Meier cumulative event-free survival according to CCTA diagnosis. Log-rank test showed significant differences in cardiac events for all pairwise comparisons between groups (all P ≤ 0.003), except for obstructive stenosis versus previous revascularization (P = 0.82). *CCTA* coronary CT angiography

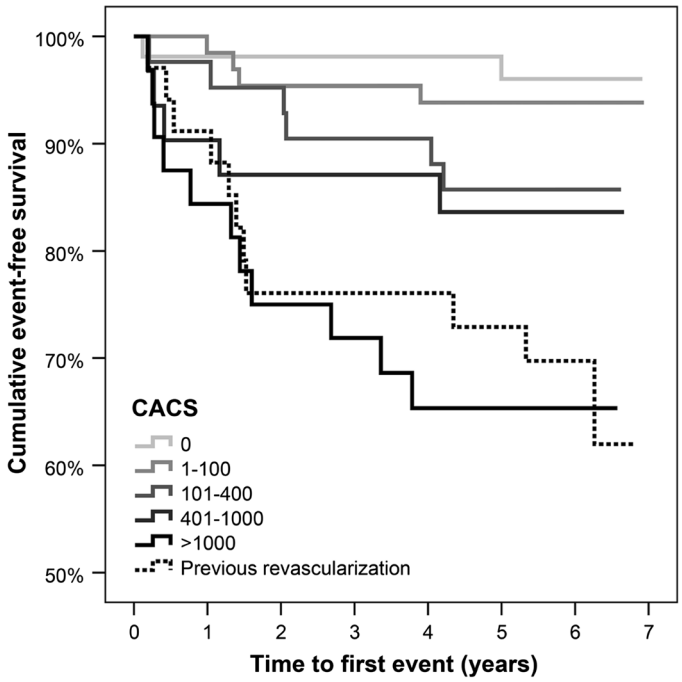


Fig. 2 Kaplan-Meier cumulative event-free survival according to CACS. Test for trend was significant for a shorter event-free survival with increasing CACS ($P < 0.001$). *CACS* coronary artery calcium score

Patients at risk for events	257	243	229	223	218	207	135	0
CACS 0	53	52	52	51	50	46	29	0
CACS 1-100	65	64	62	62	61	60	41	0
CACS 101-400	42	41	40	38	38	35	24	0
CACS 401-1000	31	28	26	25	25	24	18	0
CACS >1000	32	27	24	23	20	19	8	0
Previous revascularization	34	31	25	24	24	23	15	0

CCTA findings of obstructive stenosis, SIS and SSS remained independent MACE predictors even after adding CACS to the multivariate Cox regression model (all $P \leq 0.01$; Table 5). A head-to-head comparison of the prognostic performance of

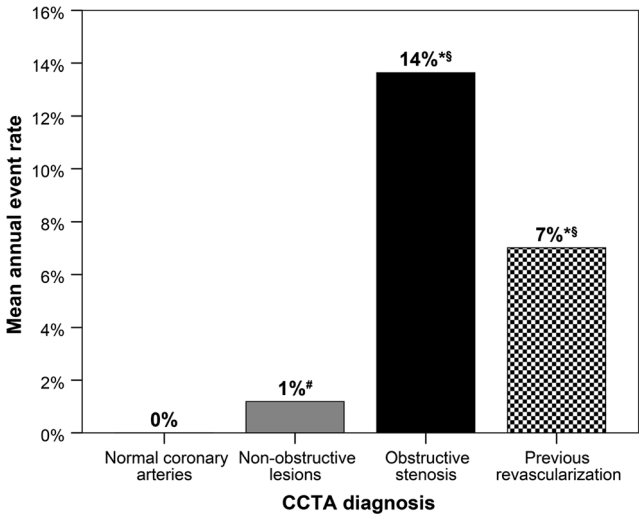


Fig. 3 Mean annual MACE rate according to CCTA diagnosis. P-values for pairwise comparisons using Mann-Whitney U-test: *$P < 0.001$ vs. normal; #$P = 0.003$ vs. normal; §$P < 0{,}001$ vs. non-obstructive. Global comparison using Kruskall-Wallis test showed $P < 0.001$. *MACE* major adverse cardiac event, *CCTA* coronary computed tomography angiography

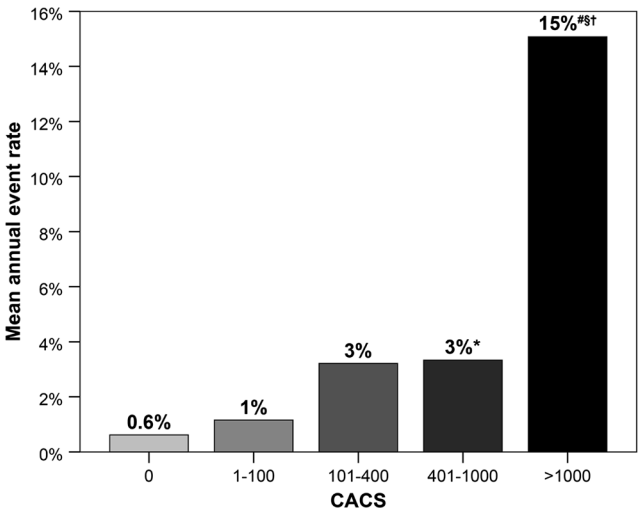


Fig. 4 Mean annual MACE rate according to CACS. P-values for pairwise comparisons using Mann-Whitney U-test: *$P < 0.05$ vs. CACS 0; #$P < 0.001$ vs. CACS 0; § $P \leq 0.001$ vs. CACS 1-100; †$P < 0.05$ vs. CACS 101-400. Global comparison using Kruskall-Wallis test and testing for increasing trend both showed $P < 0.001$. *MACE* major adverse cardiac event

Table 3 Univariate Cox regression hazard analysis for MACE (n = 371)

Variable	Hazard ratio	95% CI	P value
Clinical characteristics			
Age (per increase in years)	1.04	1.02–1.07	0.002
Male gender	2.34	1.21–4.53	0.012
BMI (per increase in kg/m^2)	1.07	1.02–1.13	0.006
Cardiovascular risk factors			
Arterial hypertension	–	–	NS
Diabetes mellitus	2.15	1.08–4.27	0.028
Dyslipidaemia	1.75	1.02–3.00	0.042
Positive family history	0.45	0.25–0.83	0.010
Smoking	–	–	NS
Symptoms			
Typical angina pectoris	2.67	1.46–4.91	0.001
Atypical angina pectoris	0.50	0.28–0.89	0.018
Dyspnoea	2.12	1.12–4.02	0.021
Asymptomatic	–	–	NS
Previous cardiac events			
Myocardial infarction	2.94	1.26–6.87	0.013
PCI	2.86	1.44–5.68	0.003
CABG	–	–	NS
CACS (per increase in Agatston units, n = 223)	1.000	1,000–1,001	<0.001
CCTA findings:			
Normal coronary arteries	0.02	0.00–0.20	0.001
Any coronary lesions	46.99	5.07–435.81	0.001
Non-obstructive lesions (vs. normal)	–	–	NS
Obstructive stenosis	11.57	5.46–24.48	<0.001
Segment involvement score (SIS, per unit)	1.38	1.27–1.50	<0.001
Segment severity score (SSS, per unit)	1.14	1.10–1.18	<0.001

Patients with previous revascularisation (n = 34) were not included in this analysis

MACE major adverse cardiac events, *CI* confidence interval, *BMI* body mass index, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *CCTA* coronary computed tomography angiography, *CACS* coronary artery calcium score

CCTA and CACS for MACE prediction using ROC analysis in this subpopulation of patients who underwent both CCTA and CACS revealed a slightly larger AUC for CCTA findings than for CACS, particularly for SSS, but the differences fell short of statistical significance (Fig. 5).

Reclassification after CCTA

In the subgroup of patients with appropriate data for cardiovascular risk stratification using the ESC SCORE (n = 142), reclassification analysis showed that 50% of the patients were reclassified after CCTA, particularly those at moderate risk (72%, see Table 6). Comparison of ROC curves regarding MACE prediction demonstrated a significantly higher AUC for CCTA diagnosis versus ESC SCORE (0.82 [0.75–0.88] vs. 0.65 [0.57–0.73]; P = 0.005).

Discussion

Our results highlight the excellent long-term prognostic performance of low-dose CCTA with prospective ECG triggering

Table 4 Multivariate Cox regression hazard analysis for MACE (n = 371)

Variable	Hazard ratio	95% CI	P value
CCTA findings:			
Normal coronary arteries	0.02	0.00–0.20	0.001
Any coronary lesions	46.99	5.07–435.81	0.001
Non-obstructive lesions (vs. normal, n = 240)	–	–	NS
Obstructive stenosis	11.41	5.39–24.17	<0.001
Segment involvement score (SIS, per unit)	1.35	1.24–1.48	<0.001
Segment severity score (SSS, per unit)	1.13	1.09–1.17	<0.001

Patients with previous revascularisation (n = 34) were not included in this analysis

Model adjusted for age, gender, body mass index, cardiovascular risk factors and symptoms

MACE major adverse cardiac events, *CI* confidence interval, *CCTA* coronary computed tomography angiography

Table 5 Multivariate Cox regression hazard analysis of CCTA findings with CACS in the regression model, for MACE (n = 223)

Variable	Hazard ratio	95% CI	P value
CACS (per increase in Agatston units)	1.001	1.000–1.001	<0.001
CCTA findings:			
Normal coronary arteries	–	–	NS
Any coronary lesions	–	–	NS
Non-obstructive lesions (vs. normal, n = 124)	–	–	NS
Obstructive stenosis	6.73	2.22–20.38	0.001
Segment involvement score (SIS)	1.20	1.05–1.38	0.008
Segment severity score (SSS)	1.07	1.01–1.14	0.014

Model adjusted for age, gender, body mass index, cardiovascular risk factors, symptoms and CACS

CACS coronary artery calcium score, *CCTA* coronary computed tomography angiography, *MACE* major adverse cardiac events, *CI* confidence interval

regarding cardiac events. All patients with normal coronary arteries in CCTA had a completely event-free survival during the median follow-up of 6.1 years. Patients with non-obstructive coronary lesions had a low risk with an annual event rate of 1% during the same period. By contrast, patients with obstructive stenosis were at much higher risk with an annual event rate of 14%. Similarly, CACS allowed risk stratification with a progressive increase of annual event rates up to 15% for patients with CACS >1,000. Multivariate Cox regression analysis revealed that CCTA findings as well as CACS were strong independent predictors of MACE.

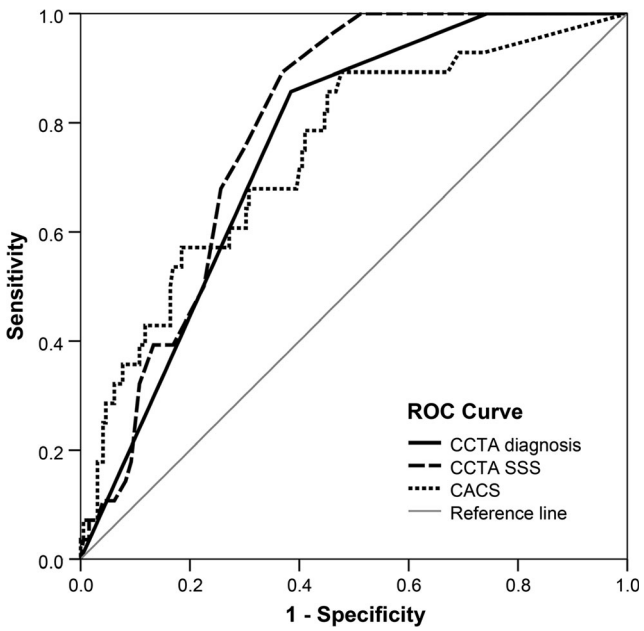


Fig. 5 ROC curves for MACE prediction in patients with CCTA and CACS (n = 223). CCTA diagnosis: AUC 0.755 (0.678–0.831) CCTA SSS: AUC 0.791 (0.727–0.855) CACS: AUC 0.745 (0.647–0.842) All pairwise comparisons of ROC curves showed non-significant P-values. Each curve vs. reference line: P < 0.001. *ROC*: receiver operating characteristic. *MACE* major adverse cardiac event, *CCTA* coronary computed tomography angiography, *CACS* coronary artery calcium score, *SSS* summed severity score, *AUC* area under the curve (with 95% confidence interval)

Contrary to a normal CCTA scan, however, a CACS of 0 could not predict freedom from MACE during the follow-up. This confirms that non-calcified coronary lesions are associated with a cardiovascular risk not assessed by CACS. Moreover, CCTA findings of obstructive stenosis and lesion scores remained independent MACE predictors even after adjustment for CACS. This underlines the additional predictive value of stenosis assessment using CCTA over CACS measurement. In direct comparison, CCTA yielded a slightly better prognostic performance than CACS. The difference, however, did not reach statistical significance. Finally, reclassification analysis showed the ability of CCTA to reclassify 50% of the patients compared with ESC SCORE, particularly in patients at moderate risk, with a significant improvement of MACE prediction.

Our findings are in line with previous results on the short-term prognostic value after low-dose CCTA with prospective ECG triggering, already suggesting an accurate stratification of patients into risk categories based on stenosis severity [22]. Similarly, several meta-analyses [4–6] and the large CONFIRM registry [7] concluded that the absence of coronary lesion on CCTA was associated with a very low risk of events, whereas obstructive stenosis predicted a much poorer prognosis after follow-up periods of 2–3 years. However, these studies did not assess the prognostic performance of CCTA on the long term. To our knowledge, only few studies have assessed a longer follow-up after CCTA than in the present study. Among them, Ostrom et al. showed that the presence of atherosclerosis and an increasing number of coronary lesions were associated with an increase in all-cause mortality in 2,538 symptomatic patients with a mean follow-up of 6.5 years after electron-beam CT [9]. In multivariate analysis, obstructive stenosis and three-vessel non-obstructive lesions remained the only independent predictors of mortality. In this cohort, however, most cases of death occurred in patients without obstructive CAD and the cause of death was unknown, rendering the results difficult to interpret. In a recent study, Dougoud et al. confirmed the excellent incremental prognostic value of CCTA

Table 6 Reclassification analysis after CCTA in patients with ESC SCORE, without previous revascularisation (n = 142)

ESC SCORE*	CCTA diagnosis by risk level	Reclassification after CCTA	Overall reclassification
Low risk:	Normal: 29 (71%)	Higher class: 12 (29%)	Lower class: 34 (24%)
41 patients (29%)	Non-obs.: 3 (7%)		Higher class: 37 (26%)
	Obstructive: 9 (22%)		Total: 71 (50%)
Moderate risk:	Normal: 11 (22%)	Lower class: 11 (22%)	
50 patients (35%)	Non-obs.: 14 (28%)	Higher class: 25 (50%)	
	Obstructive: 25 (50%)	Total: 36 (72%)	
High or very high risk:	Normal: 9 (18%)	Lower class: 23 (45%)	
51 patients (36%)	Non-obs.: 14 (27%)		
	Obstructive: 28 (55%)		

* Risk categories were defined according to the 10-year risk of fatal cardiovascular disease with the ESC SCORE: <1% (low); 1–4% (moderate); ≥5% (high or very high). All diabetic patients were considered at high or very high risk according to ESC SCORE

CCTA coronary computed tomography angiography, *ESC* European Society of Cardiology

diagnosis using retrospective ECG gating in 218 patients with a median follow-up of 6.9 years [13]. The present study extends previous knowledge by demonstrating the excellent prognostic long-term performance of CCTA with state-of-the-art low-dose prospective ECG triggering technique, resulting in a mean radiation dose exposure of 1.7 mSv. The latter highlights an improved risk-to-benefit ratio, and, thus, further corroborates the clinical value of low-dose CCTA with prospective ECG triggering.

Of note, we found that low-dose CCTA with prospective ECG-triggering has the potential to identify patients at very low cardiac risk, namely those with normal coronary arteries who did not suffer from any MACE during the 6.1-year follow-up period. The 'warranty period' of a normal CCTA, thus, seems to be very long, rendering repeat testing within this period unnecessary. Other non-invasive imaging tests based on myocardial perfusion are limited to detecting only flow-limiting lesions, i.e. obstructive stenosis. Thus, patients with normal perfusion tests may have several non-obstructive lesions that go undetected and are therefore at higher risk than patients with normal coronary arteries in CCTA. This may explain to some extent the shorter 'warranty periods' of about 2–4 years reported after stress echocardiography [37], SPECT [38], PET [39] and magnetic resonance imaging [40], depending on baseline patient risk.

Regarding the comparison between CCTA and CACS, both tests were previously shown to offer a robust prognostic performance. An additional value of CCTA over CACS is a matter of debate in the literature. The predictive value of CACS is supported by strong data [24]. However, short-term [26, 27] and long-term studies [11, 13] reported a possible superior predictive value of CCTA over CACS for cardiac events. In line with these data, our results suggest a tendency towards a higher predictive value from CCTA over CACS, but without significant difference in direct comparison. Of note, our low-risk patient sample was not primarily powered for this analysis. Nevertheless, the fact that patients with a CACS of 0 may experience MACE highlights the ability of CCTA to detect non-calcified lesions, which are associated with a non-negligible cardiac risk [25]. Moreover, although CACS is strongly associated with cardiac events at the cohort level, it does not provide a clear decisional cut-off on an individual basis. By contrast, CCTA does provide a practical cut-off value of ≥50% stenosis to support the decision towards further diagnostic and therapeutic work-up for the individual patient in everyday clinical practice.

It may be perceived as a potential limitation of this study that elective coronary revascularizations were included in our composite end-point. This, however, ensures comparability with similar previous studies also including these events [10–13]. Moreover, we used cardiac death in our end-point instead of all-cause death, as previously reported [10, 11], because we were able to retrieve information on the cause of death and did not expect CCTA to accurately predict non-cardiac death. Furthermore, our decision to exclude early revascularizations from the analyses, but not the patients undergoing them, may be considered as a further limitation of our study. Since many patients with obstructive stenosis diagnosed by CCTA underwent early revascularisation, excluding all these patients would have substantially reduced our sample of high-risk patients and thus hampered our ability to demonstrate the accurate risk stratification by CCTA and CACS, as reported in recent studies [12, 13]. Besides, CACS was only performed in a subgroup of patients, limiting the power of our analyses involving this parameter. However, our CACS sample remains larger than in recent similar reports [13]. Finally, the MACE rate of 25% reported in our study may appear high. This may be due to the long follow-up and to the inclusion of elective revascularisations, of patients with known CAD, and of patients with intermediate to high risk. In line with the

results of the present study, Dougoud et al. found a MACE rate of 21% during a follow-up of 6.9 years after CCTA [13]. Our study also has some mentionable strengths, such as the long follow-up of 6.1 years and the extensive data collected, allowing multivariate modelling and detailed analysis of outcome predictors. Moreover, the use of prospective ECG triggering led to an important reduction of radiation dose compared to previous methods [14], but not as low as the latest technical refinements [41–43]. Finally, our study design closely reflecting the everyday practice of CCTA ensured a high generalisability of our results.

Conclusion

Low-dose CCTA with prospective ECG triggering has an excellent prognostic performance with a warranty period of at least 6 years for patients with normal coronary arteries.

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Compliance with ethical standards:

Guarantor The scientific guarantor of this publication is Ronny R. Buechel.

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Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained. Study subjects or cohorts overlap:

The study population was shared with a previous report on short-term outcome after CCTA (Buechel et al., Heart 2011; 97 (17):1385-90).

Methodology

- retrospective
- prognostic study, observational
- performed at one institution

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