CrossMark

COMPUTED TOMOGRAPHY

Prognostic value of coronary atherosclerosis progression evaluated by coronary CT angiography in patients with stable angina

Hui Gu[1,2] · Yang Gao[2] · Zhihui Hou[2] · U. Joseph Schoepf[3] · Alan N. Snyder[3] · Taylor M. Duguay[3] · Ximing Wang[1] · Bin Lu[2]

Abstract

Objectives To investigate the progression of coronary atherosclerosis burden by coronary CT angiography (CCTA) and to demonstrate its association with the incidence of major adverse cardiac events (MACE).

Methods We retrospectively studied patients with stable angina who had undergone repeat CCTA due to recurrent or worsening symptoms. Lipid-rich, fibrous, calcified and total plaque burden as well as coronary diameter stenosis were quantitatively analysed. The incidence of MACE during follow-up was determined.

Results The final cohort consisted of 268 patients (mean age 52.9 ± 9.8 years, 71 % male) with a mean follow-up period of 4.6 ± 0.9 years. Patients with lipid-rich, fibrous, calcified and total plaque burden (%) progression, as well as coronary diameter stenosis (%) progression had a significantly higher incidence of MACE than those without (all $p < 0.05$). The progression of lipid-rich plaque (HR = 1.601, $p = 0.021$), total plaque burden (HR = 2.979, $p = 0.043$) and coronary diameter stenosis (HR = 4.327, $p < 0.001$) were independent predictors of MACE (all $p < 0.05$).

Conclusions Patients presenting with recurrent or worsening symptoms associated with coronary artery disease who have coronary atherosclerosis progression on CCTA are at an increased risk of future MACE.

Key Points
- *Repeat CCTA can provide information regarding the progression of coronary atherosclerosis.*
- *Coronary atherosclerosis progression at CCTA is independently associated with MACE.*
- *CCTA findings could serve as incremental predictors of MACE.*

✉ Ximing Wang
   wangximing_369@sina.com

✉ Bin Lu
   bluvip@126.com

1   Department of CT, Shandong Provincial Key Laboratory of Diagnosis and Treatment of Cardio-Cerebral Vascular Diseases, Shandong Medical Imaging Research Institute, Shandong University, #324, Jingwu Road, Jinan, Shandong 250021, China

2   Department of Radiology, Fuwai Hospital, State Key Laboratory of Cardiovascular Disease, National Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, #167 Bei-Li-Shi Street, Xi-Cheng District, Beijing 100037, China

3   Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, 25 Courtenay Drive, Charleston, SC 29403, USA

Abbreviations

CABG	Coronary artery bypass grafting
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCTA	Coronary CT angiography
CI	Confidence interval
HR	Hazard ratio
IVUS	Intravascular ultrasound
ICC	Intra-class correlation coefficients
MACE	Major adverse cardiac events
OR	Odds ratio
PCI	Percutaneous coronary intervention

Springer

Introduction

The insidious process of atherosclerosis can result in stenosis formation or plaque rupture within the coronary arteries, causing myocardial damage and major adverse cardiac events (MACE) [1]. Serial assessment of coronary plaque burden has contributed to our understanding of the natural history and pathophysiology of coronary artery disease (CAD). Previous studies using repeat coronary artery calcium (CAC) scans found CAC and its progression to be predictive of MACE [2]; however, calcified plaque is only one of many components involved in coronary atherosclerosis.

Non-invasive contrast-enhanced coronary computed tomography angiography (CCTA) is capable of visualising plaque composition, morphology and distribution, as well as assessing lumen stenosis severity. Its ability to quantify coronary plaque burden has rendered it a valuable modality to evaluate overall coronary atherosclerosis and its progression in low to intermediate risk patients [3, 4]. Schuhbaeck et al. [5] report that there is high reproducibility of coronary atherosclerotic plaque volume measurements using this technology. Therefore, they concluded that serial studies to determine progression of coronary atherosclerotic plaque were feasible. Recently, the SCOT-HEART trial demonstrated that, in patients with suspected CAD, CCTA could clarify the diagnosis, enable targeting of intervention and reduce the future risk of myocardial infarction [6].

With the growing application of CCTA it is not uncommon for patients to undergo more than one CCTA study, especially with recurrent or worsening symptoms. Interestingly, few studies have focused on the quantitative evaluation of coronary atherosclerosis progression, which is the evidence required to evaluate the potential role of this imaging biomarker and its effect on cardiovascular outcomes. One previous study demonstrated that plaque progression detected by serial CCTA is an independent predictor of acute coronary syndrome [7]. However, coronary atherosclerosis progression in patients with stable angina and its association with MACE is insufficiently studied. We hypothesised that coronary atherosclerosis progression at repeat CCTA is associated with a higher incidence of MACE. Therefore, we quantitatively analysed patients with stable angina who underwent repeat CCTA with recurrent or worsening symptoms to investigate coronary atherosclerosis progression and its association with MACE.

Methods

Study population

Institutional Review Board approval was obtained and a waiver of informed consent was granted. We retrospectively analysed data of 371 patients with stable angina who had undergone repeat CCTA from 2009 to 2015. Exclusion criteria included the following: (1) patients with previous coronary revascularisation (percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]) between serial CCTA examinations (n = 51); (2) patients with incomplete serum biochemical tests at baseline (n = 17); (3) patients with unevaluable CT images in either scan (n = 9); (4) patients with a time interval < 30 days between baseline and follow-up CCTA (n = 0) [7]. A total of 294 patients were enrolled and 26 (8.8 %) were lost to follow-up. Consequently, the final study consisted of 268 patients (see study flow chart in Fig. 1). Cardiovascular risk factors, symptoms, baseline serum biochemical results and medications were collected using electronic medical records. Incomplete serum biochemical tests were defined as a lack of any of the following markers: triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein and blood glucose. To improve the validity of the study, two experienced radiologists independently evaluated the image quality of each coronary segment according to Zhang et al. [8]. All patients with an image quality rating of 1 in either of the two scans were excluded. In cases of disagreement, a joint reading session was performed to reach a consensus decision.

Coronary CT angiography protocol

All examinations were performed with a dual-source CT scanner (SOMATOM Definition or SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). An oral beta-blocker (metoprolol; Betaloc, AstraZeneca, Cambridge, England) was administered to all patients with a resting heart rate > 90 beats/min. After an initial non-contrast-enhanced calcium scoring CT scan, patients underwent contrast-enhanced CCTA using prospective ECG-triggering. The
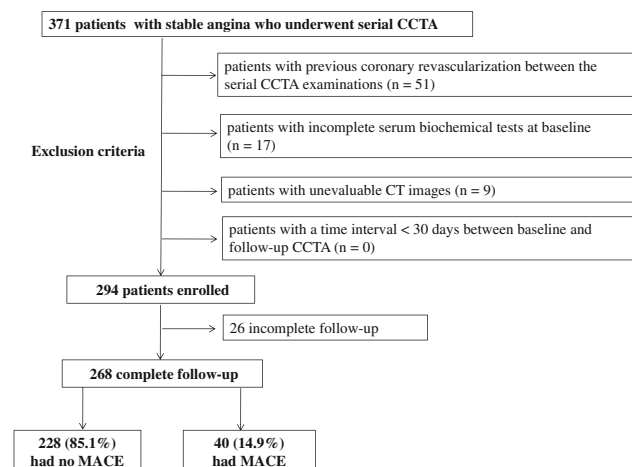

Fig. 1 Flow diagram of patient recruitment. *CCTA* coronary computed tomography angiography, *CT* computed tomography, *MACE* major adverse cardiac events

following parameters were used: collimation $2 \times 64 \times 0.6$ mm by using z-flying focal spot; gantry rotation 0.28 s; tube voltage 120 kV or 100 kV; tube current 400–500 mAs; field of view (FOV) 200–250 mm. Contrast medium (iohexol (Omnipaque 350 mgI/ml, GE Healthcare, Little Chalfont, UK) or iopromide (Ultravist 370 mgI/ml, Bayer, Berlin, Germany)) was injected at a rate of 4–5 ml/s. A triple-phase contrast material injection protocol was used. CCTA images were reconstructed with a section thickness of 0.625 mm.

Quantitative analysis by coronary CT angiography

Plaque analysis was performed using an off-line three-dimensional semi-automated image analysis workstation (Vitrea Version 6.6, Vital images, Minnetonka, MN, USA) by two observers who were blinded to clinical parameters. The coronary tree was automatically extracted. Each of the major epicardial vessels (the left anterior descending, the left circumflex and the right coronary artery) were individually analysed from the ostium to the point at which the internal vessel calibre decreased to less than 2 mm. Automated longitudinal contouring of the inner lumen and outer wall was performed, and results were manually adjusted when deviations were noted [9]. We measured the same vessel with the same origins and lengths for each of the patient's two scans. Previous studies have demonstrated the accuracy of CCTA to characterise and quantify coronary plaque and support the feasibility of using CCTA to assess atherosclerotic plaque burden [10–12]. As reported in Inoue's previous study [13], the software colour codes coronary plaques and lumen based on varying HU profiles as follows: lipid-rich plaque (-100–30 HU), fibrous plaque (30–150 HU), calcified plaque (350–1,000 HU) and lumen (150–350 HU). A previous study using intravascular ultrasound (IVUS) demonstrated that an attenuation threshold of 30 HU provides a sensitivity of 91 % and specificity of 100 % for the detection of lipid-rich plaque [14]. In addition, other authors [15, 16] have established the intensity-threshold of calcified plaque to be 130 HU on non-contrast-enhanced CT examination and of 350 HU in CCTA studies. Total plaque volume included lipid-rich, fibrous and calcified plaque components of the aforementioned three major vessels. The vessel volume of each patient was defined as the combined lumen volume of the three main vessels plus the total measured plaque volume. Coronary diameter stenosis (%) was an adjunct calculation provided by the plaque burden analysis.

Plaque burden (X) was defined as plaque volume divided by the vessel volume on a per-patient level, where X stands for lipid-rich, fibrous, calcified or total plaque burden. Change in plaque burden (X) was defined as plaque burden at the second CCTA study (X) minus initial plaque burden (X).

$$(X)Plaque{\cdot}Burden\ \% = \left[(X)Plaque.Volume\Big/Vessel.Volume\right] \times 100$$

The rate of plaque burden (X) change was defined as plaque burden at the second CCTA study minus the initial plaque burden divided by the plaque burden at the initial scan.

$$Rate\ of\ (X)\ plaque\ burden\ change\ \% = \frac{(X)Plaque\ Volume_2\Big/Vessel\ Volume_2 - (X)Plaque\ Volume_1\Big/Vessel\ Volume_1}{(X)Plaque\ Volume_1\Big/Vessel\ Volume_1} \times 100$$

Significant progression was defined as a rate of change > 0.05 %. The plaque burden and the change in plaque burden were both expressed as percentages. Change of coronary diameter stenosis was defined as diameter stenosis at the second CCTA study minus diameter stenosis at the initial study and its change was also expressed by percentage.

Follow-up

Follow-up information was collected through clinical visits or telephone contact. We verified all reported events by reviewing hospital records or initiating direct contact with the respective attending physicians. Study endpoints were defined as any occurrence of cardiac events defined as cardiac death (including any death without definitive non-cardiac cause), non-fatal myocardial infarction, unstable angina pectoris requiring hospitalisation or coronary revascularisation. The definition of non-fatal myocardial infarction was based on the criteria of typical acute chest pain and persistent ST-segment elevation or positive cardiac enzymes. Unstable angina pectoris was defined as typical acute chest pain with negative cardiac enzymes if CAD could not be excluded as the cause of symptoms according to guidelines [17].

Statistical analysis

All statistical analyses were performed using SPSS software package (version 17.0, SPSS, Chicago, IL, USA). The Kolmogorov Smirnov test was used for assessing normality of data distribution. For descriptive statistics continuous variables were expressed as mean ± standard deviation or median (interquartile range (IQR)), and categorical variables were

expressed as frequency (percentages). The differences between the groups were tested by the χ2 statistic and the unpaired Student's t-test or Mann-Whitney U test. Intra-class correlation coefficients (ICCs) were used to calculate the reliability of intra-observer and inter-observer analysis. For cumulative event rates of MACE Kaplan-Meier plots were generated and log-rank test was performed. The association between clinical characteristics, CT measures and MACE were estimated by using Cox proportional hazard model. Multivariate logistic regression analysis was used to identify predictors for the clinical characteristics and CT findings. A p value <0.05 was considered statistically significant.

Results

Population characteristics

Of the 294 patients who had repeat CCTA, 268 could be contacted for follow-up, resulting in a follow-up rate of 91.2 %. There were no significant differences found in the baseline characteristics between the follow-up group and the group lost to follow-up. 193 patients of the follow-up group (71 %) were male with a mean age of 52.9 ± 9.8 years. Repeat CCTAs were performed after a mean interval time of 668 ± 323 days after the initial CCTA examination. The median effective radiation dose of each CCTA was 3.9 mSv. Baseline clinical characteristics of patients with and without MACE are presented in Table 1. In patients with MACE, diabetes mellitus, dyslipidemia, history of smoking and family history of CAD were significantly more prevalent than in those without MACE. Patients with MACE also had a significantly higher level of low-density lipoprotein cholesterol (LDL-C) at baseline (3.3 ± 1.0 vs. 3.0 ± 1.1, $p = 0.046$) and a lower proportion of statin therapy (27.5 % vs. 47.4 %, $p = 0.047$).

Cardiac events

During a mean follow-up time of 4.6 ± 0.9 years, 40 patients (14.9 %) experienced a MACE. Of the 40 patients with MACE, 32 underwent coronary revascularisation (PCI n = 27; CABG n = 5) and eight required hospitalisation due to

Table 1 Baseline characteristics

Characteristics	Full cohort (n = 268)	No MACE (n = 228)	MACE (n = 40)	p value
Male	193 (71.0)	164 (71.9)	29 (72.5)	0.941
Age (years)*	52.9 ± 9.8	52.4 ± 9.7	55.7 ± 10	0.056
BMI (kg/m^2)*	25.9 ± 3.1	25.7 ± 3.0	27.1 ± 3.5	0.120
Diabetes mellitus	54 (20.1)	39 (17.1)	15 (37.5)	0.001
Dyslipidemia	108 (40.3)	86 (37.7)	22 (55.0)	0.030
Hypertension	69 (25.7)	58 (25.4)	11 (30.0)	0.149
History of smoking	38 (14.1)	24 (10.5)	14 (35.0)	0.005
Family history of CAD	52 (19.4)	36 (15.8)	16 (40.0)	0.011
Treatment regimen				
Statin	112 (41.8)	101 (47.4)	11 (27.5)	0.047
Aspirin	116 (43.3)	102 (44.7)	14 (35.0)	0.253
Beta-blocker	77 (28.7)	70 (30.7)	7 (17.5)	0.089
Calcium channel blocker	25 (9.3)	21 (9.2)	4 (10.0)	0.874
Antidiabetic drugs	49 (18.3)	43 (18.9)	6 (15.0)	0.421
TG (mmol/ L)§	1.6 (1.2-2.4)	1.6 (1.2-2.4)	1.7 (1.2-2.6)	0.876
TC (mmol/ L)*	4.8 ± 1.1	4.8 ± 1.1	4.9 ± 1.2	0.589
LDL-C (mmol/L)*	3.0 ± 0.9	3.0 ± 1.0	3.3 ± 1.1	0.046
HDL-C (mmol/ L)§	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (1.0-1.4)	0.894
Hs-CRP (mg/L)§	1.3 (0.7-2.3)	1.4 (0.8-2.3)	1.0 (0.4-2.4)	0.081
Blood glucose (mmol/L)§	5.6 (5.1- 6.1)	5.6 (5.1-6.1)	5.6 (5.1-6.4)	0.756
Intervals time between CCTA (days)*	668 ± 323	667 ± 324	668 ± 322	0.959

Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

*Data are means ± standard deviations

§ data are median (interquartile range)

MACE major adverse cardiac events, *CAD* coronary artery disease, *TG* triglycerides, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Hs-CRP* high-sensitivity C-reactive protein, *CCTA* coronary CT angiography

unstable angina; however, none of the patients suffered cardiac death or non-fatal myocardial infarction. The remaining 228 (85.1 %) patients did not experience MACE during a mean follow-up of 4.7± 1.3 years.

Atherosclerosis progression and major adverse cardiac events (MACE)

Atherosclerotic plaque characteristics and progression are given in Table 2. At baseline, the burden (%) of lipid-rich, fibrous, calcified and total plaque were 17.4 ± 2.6, 27.8 ± 5.2, 4.6 (2.4–7.4) and 50.9 ± 8.2, respectively. Coronary diameter stenosis (%) was 60.5 (53.0–83.0). There were no significant differences in these quantitative parameters between patients with and without MACE ($p > 0.05$ for all). At follow-up, quantitative parameters of total plaque burden and coronary diameter stenosis were all significantly higher in patients with MACE than those without MACE.

After combining serial CCTA data, the plaque progression (%) of lipid-rich, fibrous, calcified and total plaque were 0.3 (-9.4–9.1), -1.8 (-9.5–7.1), 7.7 (-30.7–75.3) and 0.24 (-7.9–8.01), respectively. Coronary diameter stenosis progression was 10.7 (0–28.5) %. There was significant progression of lipid-rich plaque burden (%), fibrous plaque burden (%), calcified plaque burden (%), and total plaque burden (%) in patients with MACE compared with those without MACE (6.5 (-3.9–11.6) vs. -0.9 (-10.1–8.3), $p = 0.023$; 3.9 (-4.8–13.0) vs. -2.6 (-10.0–6.9), $p = 0.009$; 34.4 (-4.8–97.7) vs. 3.3 (-33.6–

66.0), $p = 0.005$; and 6.6 (2.5–12.6) vs. -0.8 (-8.8–6.9), $p < 0.001$; respectively). Coronary diameter stenosis (%) progression was 17.5 (1.8–29.8) in patients with MACE and 7.1 (0–15.7) in patients without MACE ($p = 0.021$).

Cox proportional hazard models

Table 3 gives risk-adjusted predictors of clinical factors and CCTA findings for predicting MACE. The prevalence of diabetes mellitus (hazard ratio [HR] = 1.698, $p = 0.043$), history of smoking (HR = 2.033, $p = 0.002$), family history of CAD (HR = 1.206, $p = 0.026$), progression of lipid-rich plaque burden (HR = 1.601, $p = 0.021$), progression of total plaque burden (HR = 2.979, $p = 0.043$), and progression of coronary diameter stenosis (HR = 4.327, $p < 0.001$) were associated with MACE. Figure 2 depicts the Kaplan-Meier curves of MACE according to change of total plaque burden (A), lipid-rich plaque burden (B) and coronary diameter stenosis (C). Patients with a progression in their lipid-rich plaque burden, total plaque burden and coronary diameter stenosis all exhibited a higher event rate (all $p < 0.05$, log-rank test) than patients with non-progression of atherosclerotic plaque.

Multivariate regression of plaque progression

Progression of lipid-rich plaque burden, total plaque burden, coronary diameter stenosis and their association with baseline clinical and laboratory characteristics are shown

Table 2 Quantitative measurements on CCTA parameters and their changes for predicting MACE

Characteristics	Full cohort (n = 268)	No MACE (n = 228)	MACE (n = 40)	p value
Baseline				
Lipid plaque burden (%)*	17.4 ± 2.6	17.5 ± 2.6	16.8 ± 2.8	0.122
Fibrous plaque burden (%)*	27.8 ± 5.2	28.0 ± 5.5	26.7 ± 4.5	0.177
Calcified plaque burden (%)	4.6 (2.4-7.4)	4.5 (2.5-7.2)	4.7 (2.2-8.4)	0.955
Total plaque burden (%)*	50.9 ± 8.2	50.8 ± 8.0	49.4 ± 9.0	0.260
Coronary diameter stenosis (%)	60.5 (53.0-83.0)	60.0 (52.0-83.0)	65.5 (59.0-81.8)	0.560
Follow-up				
Lipid plaque burden (%)	17.6 (10.4-25.4)	16.8 (10.4-26.5)	20.0 (13.0-23.3)	0.845
Fibrous plaque burden (%)	26.4 (22.2-32.6)	26.2 (22.0-33.3)	27.2 (22.9-31.5)	0.904
Calcified plaque burden (%)	10.1 (-10.9-57.5)	8.6 (-15.3-69.6)	12.1 (4.6-22.5)	0.541
Total plaque burden (%)	50.1 (45.8-57.1)	49.8 (44.5-56.3)	55.4 (48.9-60.4)	0.004
Coronary diameter stenosis (%)*	68.1 ± 18.0	66.4 ± 18.2	77.3± 13.1	< 0.001
Atherosclerosis progression				
Lipid plaque burden (%)	0.3 (-9.4-9.1)	-0.9 (-10.1-8.3)	6.5 (-3.9-11.6)	0.023
Fibrous plaque burden (%)	-1.8 (-9.5-7.1)	-2.6 (-10.0-6.9)	3.9 (-4.8-13.0)	0.009
Calcified plaque burden (%)	7.7 (-30.7-75.3)	3.3 (-33.6-66.0)	34.4 (-4.8-97.7)	0.005
Total plaque burden (%)	0.24 (-7.9-8.01)	-0.8 (-8.8-6.9)	6.6 (2.5-12.6)	< 0.001
Coronary diameter stenosis (%)	10.7 (0-28.5)	7.1 (0-15.7)	17.5 (1.8-29.8)	0.021

Unless otherwise specified, data are median (interquartile range)

*Data are means ± standard deviations.

Table 3 Multivariate predictors of MACE in this cohort

| Parameters	Univariable		Multivariable	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Male	1.108 (0.550–2.231)	0.774	1.042 (0.601–1.936)	0.891
Age (years)	1.021 (0.983–1.039)	0.453	1.007 (0.973–1.084)	0.793
BMI (kg/m^2)	1.145 (1.043–1.269)	0.009	1.017 (0.814–1.031)	0.597
Diabetes mellitus	4.364 (2.299–8.284)	< 0.001	1.698 (1.117–2.582)	0.043
Dyslipidemia	2.058 (1.093–3.877)	0.025	1.008 (0.619–1.240)	0.276
Hypertension	1.177 (0.624–2.221)	0.616		
History of smoking	5.254 (2.778–9.937)	< 0.001	2.033 (1.306–3.163)	0.002
Family history of CAD	3.899 (1.653–6.584)	< 0.001	1.206 (1.096–1.429)	0.026
Treatment regimen				
Beta-blocker	0.568 (0.261–1.123)	0.153		
Aspirin	0.793 (0.412–1.524)	0.486		
Statin	0.684 (0.352–1.327)	0.261		
Calcium channel blocker	1.338 (0.474–3.781)	0.583		
Antidiabetic drugs	0.632 (0.265–1.508)	0.301		
Blood biochemistry baseline				
TG (mmol/L)	1.018 (0.891–1.165)	0.790		
TC (mmol/L)	0.962 (0.722–1.283)	0.793		
LDL-C (mmol/L)	0.926 (0.652–1.316)	0.668		
HDL-C (mmol/L)	0.928 (0.474–1.851)	0.832		
Hs-CRP (mg/L)	1.941 (1.303–2.123)	0.448		
Blood glucose (mmol/L)	0.936 (0.743–1.180)	0.577		
Baseline CCTA				
Lipid plaque burden	1.080 (1.041–1.121)	<0.001	1.003 (0.872–1.100)	0.542
Fibrous burden	1.057 (0.997–1.120)	0.031	1.026 (0.973–1.084)	0.328
Calcified burden	1.376 (1.042–2.911)	<0.001	1.094 (0.728–1.642)	0.367
Total burden	1.032 (0.999–1.065)	0.054		
Coronary diameter stenosis	1.583 (0.896–2.796)	0.114		
Atherosclerosis progression				
Lipid plaque burden	3.802 (1.368–5.738)	<0.001	1.601 (1.116–2.697)	0.021
Fibrous plaque burden	2.818 (1.467–5.414)	0.002	1.007 (0.973–1.084)	0.793
Calcified plaque burden	4.405 (2.026–9.580)	<0.001	1.583 (0.896–2.796)	0.114
Total plaque burden	5.558 (2.551–12.112)	<0.001	2.979 (1.347–4.200)	0.043
Coronary diameter stenosis	7.421 (3.261–13.246)	<0.001	4.327 (1.453–8.471)	<0.001

CI confidence interval, *CAD* coronary artery disease, *TG* triglycerides *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Hs-CRP* high-sensitivity C-reactive protein, *CCTA* coronary CT angiography

in Table 4. The progression of lipid-rich plaque burden was associated with baseline dyslipidemia (odds ratio [OR] = 3.131, *p* < 0.001), statin therapy (OR = 0.348, *p* = 0.001) and baseline LDL-C (OR = 2.522, *p* = 0.015). Progression of total plaque burden was associated with dyslipidemia (OR = 1.847, *p* = 0.028) and statin therapy (OR = 0.596, *p* = 0.022). Progression of coronary diameter stenosis was associated with the occurrence of diabetes mellitus (OR = 1.489, *p* = 0.043), dyslipidemia (OR = 1.277, *p* = 0.026), history of smoking (OR = 1.437, *p* = 0.044) and statin therapy (OR = 0.544, *p* < 0.001). Figures 3 and 4 are

examples of plaque burden regression and progression during repeat CCTA, respectively.

Reproducibility

A subsequent re-analysis of 30 randomly selected patients demonstrated validation of this software in analysing atherosclerosis plaque on a patient level. The R-R interval range was 71–75 % and the mean difference of the rate of plaque burden change was < 0.05 % (total plaque burden: 0.01 ± 0.02 %; lipid-rich plaque burden: 0.01 ± 0.01 %; fibrous plaque burden: 0.01 ± 0.02 %;
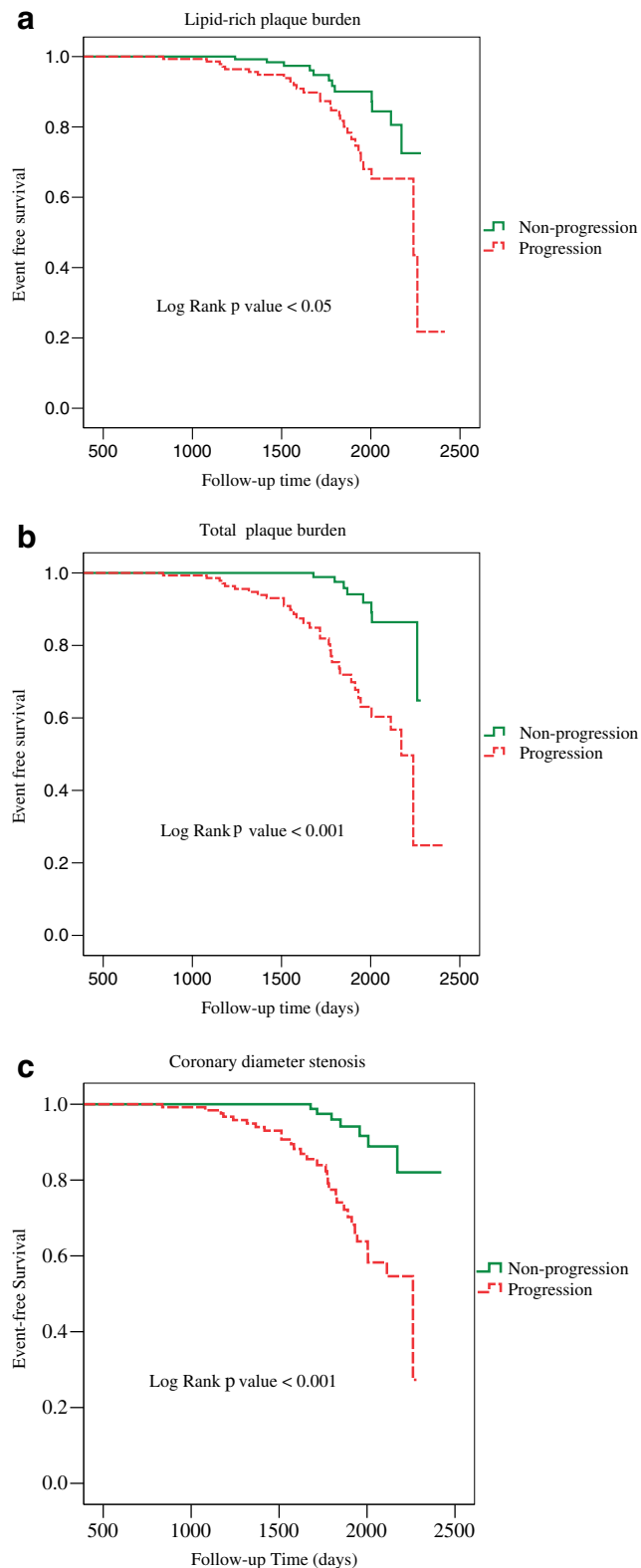
Fig. 2 Kaplan-Meier survival curves of patients without plaque progression (green line) and patients with plaque progression (red line) of (**a**) lipid-rich plaque burden, (**b**) total plaque burden and (**c**) coronary diameter stenosis; log rank $p < 0.05$. Patient follow-up was performed after a mean period of 4.6 ± 0.9 years. MACE included coronary revascularisation (PCI and CABG), cardiac death and hospitalisation due to unstable angina. We observed significantly more MACE in the cohort of patients with progression of lipid plaque burden (HR = 1.601, p = 0.021), total plaque burden (HR = 2.929, p = 0.043) and coronary diameter stenosis (HR = 4.327, p <0.001) when compared to patients who did not have any plaque progression. *MACE* major adverse cardiac events, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *HR* hazard ratio

CCTA (ICC = 0.92, 95 % CI: 0.90–0.95) and the second CCTA (ICC = 0.93, 95 % CI: 0.91–0.96).

Discussion

This study demonstrated that repeat CCTA examinations are an effective tool to evaluate coronary atherosclerosis progression and monitor changes in coronary stenoses, both of which were also shown to be associated with MACE. The ability to assess the progression of luminal stenosis and atherosclerotic plaque burden is a major benefit of repeat CCTA analysis in patients presenting with recurrent symptoms related to CAD. CCTA's reproducibility as a reliable method to assess coronary atherosclerosis progression has already been established [10–12]. Previous studies have highlighted the feasibility of repeat CCTA examinations to monitor the progression of CAD, including the association of plaque progression with future episodes of accurate coronary syndrome [7, 13]. In addition, plaque characteristics derived from CCTA datasets have been shown to be in good accordance with IVUS [18].

One meta-analysis demonstrated that the sensitivity and specificity of CCTA to detect coronary plaque compared with IVUS were 93 % and 92 %, respectively, with an area under the receiver-operating curve of 0.97 [19]. Our study evaluated plaque burden progression using serial CCTA datasets that were acquired in the same cardiac phase. Plaque parameters were analysed on a per-patient level (total plaque burden) rather than a per-plaque level because it would have been unreasonable to evaluate changes in plaque burden of individual plaques. Furthermore, considering that total plaque burden is a composite of lipid-rich, fibrous and calcified plaque, total plaque burden provides a more robust analysis to demonstrate its predictive value of MACE. The PROSPECT study found that IVUS interrogated lesions with a plaque burden > 70 % at baseline had a strong association with future clinical events [20]. However, the association between the change of atherosclerosis burden and clinical events is currently unknown. Our study included patients with stable angina who underwent repeat CCTA examinations due to recurrent or worsening symptoms, and demonstrated that patients with plaque and

calcified plaque burden: 0.01 ± 0.03 %). Intra-observer and interobserver reliability for vessel volume, any plaque volume detection and coronary diameter stenosis were excellent for the first

Table 4 Multivariate association between clinical factors and atherosclerosis progression

Parameters	Lipid plaque burden			Total plaque burden			Coronary diameter stenosis		
	OR	95.0 % CI	p value	OR	95.0 % CI	p value	OR	95.0 % CI	p value
Male	0.498	(0.262–0.945)	0.053	0.910	(0.397–2.086)	0.823	1.014	(0.969–1.062)	0.549
Age (years)	0.988	(0.961–1.017)	0.418	0.994	(0.956–1.034)	0.773	1.239	(0.822–1.757)	0.131
BMI (kg/m^2)	1.067	(0.972–1.172)	0.174	1.045	(0.927–1.177)	0.476	2.459	(0.723–9.472)	0.172
Diabetes mellitus	0.751	(0.319–1.772)	0.514	1.557	(0.556–4.359)	0.399	1.489	(1.014–2.158)	0.043
Dyslipidemia	3.131	(1.717–5.710)	< 0.001	1.847	(1.067–3.199)	0.028	1.277	(1.089–2.835)	0.026
Hypertension	0.626	(0.325–1.206)	0.161	1.328	(0.671–2.628)	0.415	1.294	(0.908–1.845)	0.154
History of smoking	1.682	(0.348–2.312)	0.216	1.328	(0.671–2.628)	0.415	1.437	(1.001–2.768)	0.044
Family history of CAD	1.971	(0.773–2.431)	0.173	1.246	(0.553–2.808)	0.597	1.265	(0.816–1.963)	0.293
Interval time between CCTA	1.000	(0.999–1.000)	0.277	1.006	(0.820–1.233)	0.957	1.043	(0.892–1.403)	0.557
Treatment regimen									
Statin	0.348	(0.185–0.653)	0.001	0.596	(0.217–0.935)	0.022	0.544	(0.392–0.756)	<0.001
Aspirin	1.023	(0.539–1.939)	0.945	1.047	(0.435–2.520)	0.919	1.342	(0.918–1.962)	0.129
Beta-blocker	1.502	(0.780–2.894)	0.224	0.955	(0.405–2.254)	0.916	1.029	(0.730–1.451)	0.870
Calcium channel blocker	1.343	(0.449–4.020)	0.598	0.257	(0.257–0.054)	0.088	1.099	(0.724–1.669)	0.657
Antidiabetic drugs	0.776	(0.175–3.432)	0.738	2.268	(0.323–5.922)	0.410	1.082	(0.672–1.742)	0.754
Blood biochemistry baseline									
TG (mmol/ L)	1.238	(0.952–1.611)	0.111	1.006	(0.754–1.051)	0.171	1.040	(0.962–1.123)	0.325
TC (mmol/ L)	0.629	(0.309–1.283)	0.203	1.012	(0.684–1.497)	0.953	1.103	(0.969–1.257)	0.139
LDL-C (mmol/L)	2.522	(1.197–5.314)	0.015	0.872	(0.566–1.342)	0.533	1.050	(0.896–1.230)	0.545
HDL-C (mmol/ L)	2.264	(0.923–5.551)	0.074	1.159	(0.657–2.046)	0.610	0.851	(0.556–1.304)	0.460
Hs-CRP (mg/L)	0.971	(0.872–1.081)	0.593	1.006	(0.909–1.112)	0.913	1.001	(0.948–1.057)	0.969
Blood glucose (mmol/ L)	1.150	(0.978–1.351)	0.090	1.115	(0.940–1.323)	0.210	1.078	(0.966–1.204)	0.180

CI confidence interval, *CAD* coronary artery disease, *TG* triglycerides, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Hs-CRP* high-sensitivity C-reactive protein, *CCTA* coronary CT angiography
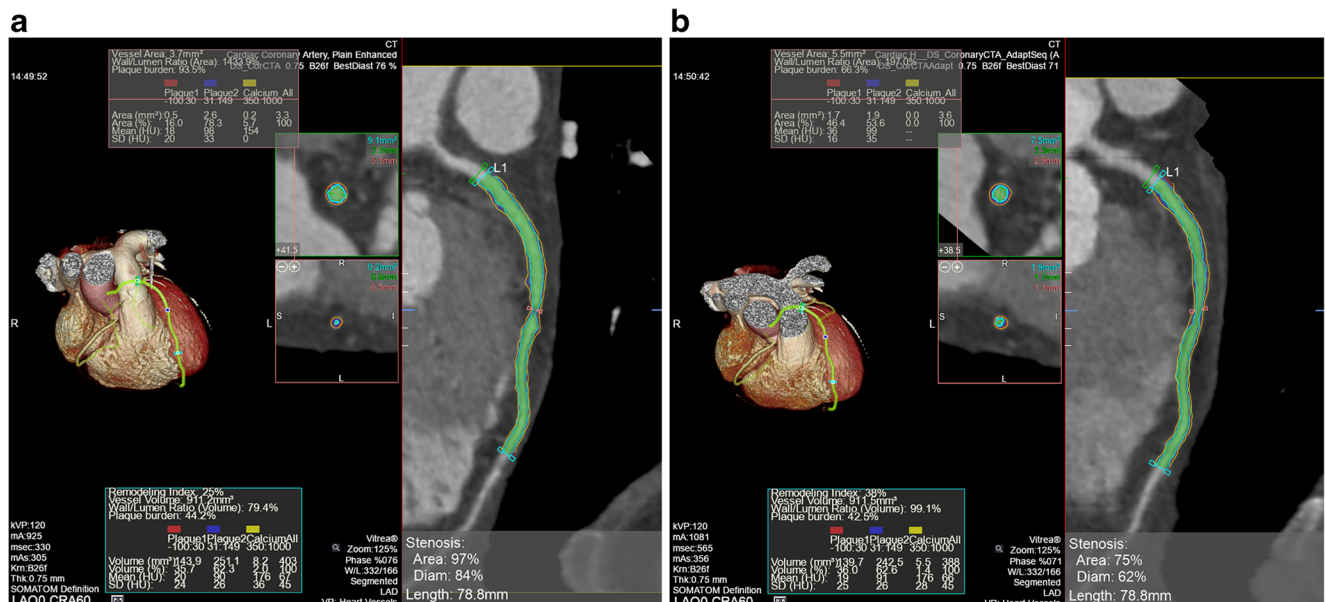
Fig. 3 Automated plaque detection in CCTA study of a 50-year-old man without MACE reveals stability or slight regression of total plaque burden. Red represents lipid-rich plaque, blue represents fibrous plaque, yellow represents calcified plaque, and green represents vessel lumen. Initial CCTA (**a**) was performed in 2012 with a total plaque burden within the LAD of 44.2 %. The same patient underwent a second CCTA study (**b**) in 2014 where the total plaque burden within the LAD had decreased to 42.5 %. *PCI* percutaneous coronary intervention, *CCTA* coronary computed tomography angiography, *LAD* left-anterior descending artery
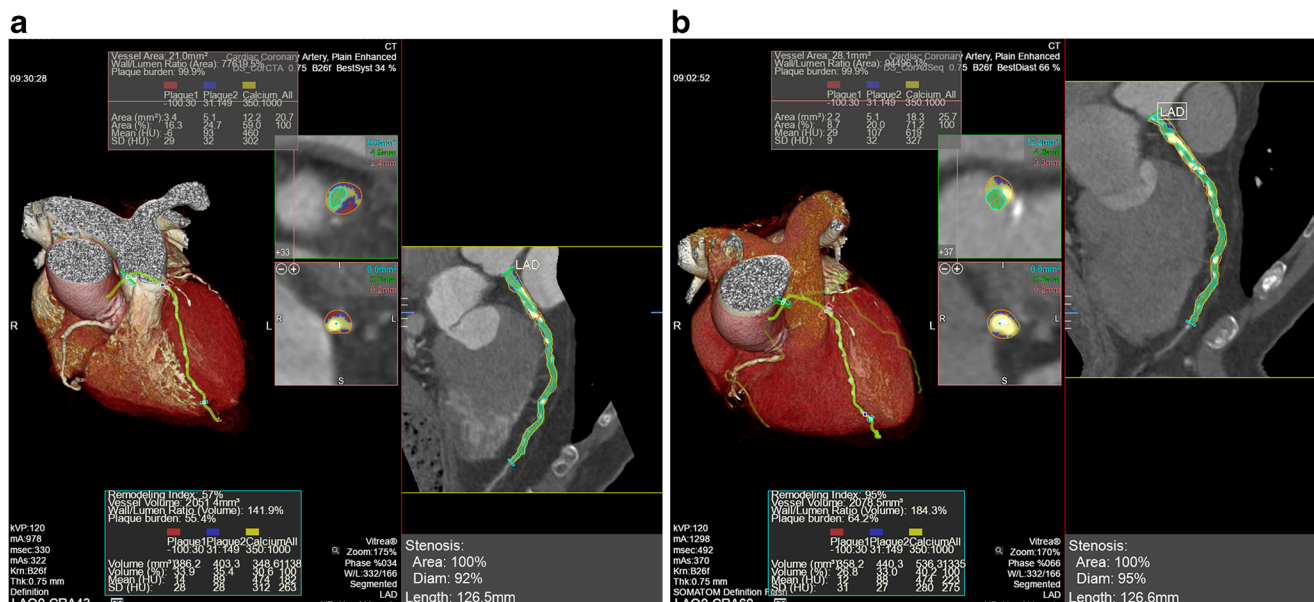
Fig. 4 Automated plaque detection in CCTA study of a 64-year-old man who eventually underwent PCI demonstrates progression of total plaque burden. Red represents lipid plaque, blue represents fibrous plaque, yellow represents calcified plaque, and green represents vessel lumen. Initial CCTA (**a**) was performed in 2010 with a total plaque burden within the LAD of 55.4 %. The same patient underwent a second CCTA study (**b**) in 2013 where the total plaque burden within the LAD had increased to 64.2 %. *PCI* percutaneous coronary intervention, *CCTA* coronary computed tomography angiography, *LAD* left-anterior descending artery

stenosis progression had a higher incidence of MACE than those without plaque or stenosis progression. The interval time between CCTA scans ranged between 256 and 1,551 days. Our study excluded patients with < 30 days between CCTA examinations in accordance with Motoyama et al. [7]. Although 80 % of patients had approximately 2–3 years between CCTA examinations, a prospective cohort study with a greater patient population may be needed to identify the most appropriate interval time for symptomatic patients to undergo a repeat CCTA.

Several studies investigating the effect of statin treatment on the plaque progression using repeat CCTA examinations have been published [13, 21]. These studies demonstrated that statin therapy prevented plaque progression by reducing the volume of low-density plaque. Likewise, others have focused on risk factors related to the progression of coronary atherosclerosis and showed that a history of diabetes mellitus and dyslipidemia are correlated with the plaque progression [22]. However, these studies did not include details of medical treatment and follow-up after repeat CCTA. Becker et al. [23] and the MESA study [24] showed that MACE were associated with the presence of CAC, but these studies did not relate these findings to lipid-rich plaque, fibrous plaque or total plaque burden. Our study used calcified plaque burden instead of CAC score. CAC is not included in our study because the calcified plaque burden parameter provides similar information to that of CAC. Additionally, the specificity of CAC to diagnose obstructive CAD is low due to a high false-positive rate [25].

We found that the progression of plaque burden and the progression of coronary stenosis on repeat CCTA are associated with MACE. It is worth mentioning that there were no cardiac-related deaths in either of the study cohorts. This could be attributed to the fact that our patient population had CCTA twice. Repeated visits with their treating physician could indicate that this population has an active interest in their health. A larger population with more follow-up should be considered for future investigations. Baseline plaque burden was not associated with MACE, which is most likely due to the lack of statistical significance between the number of patients with MACE and without MACE at baseline.

The guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) state that the treatment of high cholesterol can reduce the risk of atherosclerosis in patients with cardiovascular diseases [26]. The 2014 recommendations of the National Lipid Association (NLA) for the patient-centred management of dyslipidemia also concluded that the LDL-C is the root cause of atherosclerosis [27]. Statin therapy is recommended for patients experiencing dyslipidemia in order to prevent the progression of coronary atherosclerosis [28]. In our investigation, statin therapy was associated with reduced lipid-rich plaque progression and that elevated LDL-C and dyslipidemia were associated with lipid-rich plaque progression. Diabetes mellitus has previously been associated with higher coronary plaque burden [29]. Bamberg et al. reported that cardiovascular risk factors have been linked to the presence of coronary atherosclerotic plaque in a cross-sectional study [30]. Other studies have reinforced that

changes in cardiac risk factors, such as diabetes mellitus or tobacco use, affects the outcome of patients with CAD [31, 32]. Our study was in agreement with these conclusions, demonstrating that diabetes mellitus and smoking were associated with MACE and correlated with coronary plaque burden. However, almost all pharmacological treatments including statins, aspirin, beta-blockers and antidiabetic drugs were prescribed less in the population that experienced MACE. We should emphasise that medications were recorded as what was prescribed to patients at the time of the initial CCTA examination.

Limitations

This study included a relatively small cohort and was not free from selection bias due to the retrospective design. Our results should be confirmed in larger, prospective, multicentre investigations. We only considered baseline cardiovascular risk factors and medical therapies – changes in cardiac risk and in medical therapies were not taken into consideration.

In conclusion, repeat CCTA examinations are an effective way to monitor the progression of coronary atherosclerotic plaque burden. In light of the fact that patients with progressive atherosclerosis plaque have a greater risk of experiencing future MACE, repeat CCTA examinations could be indicated in patients presenting with recurrent or worsening symptoms related to CAD.

References

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 20:1262–1275
2. Budoff MJ, Hokanson JE, Nasir K et al (2010) Progression of coronary artery calcium predicts all-cause mortality. JACC Cardiovasc Imaging 3:1229–1236
3. Rodriguez K, Kwan AC, Lai S et al (2015) Coronary plaque burden at coronary CT angiography in asymptomatic men and women. Radiology 277:73–80
4. Lehman SJ, Schlett CL, Bamberg F et al (2009) Assessment of coronary plaque progression in coronary computed tomography angiography using a semiquantitative score. JACC Cardiovasc Imaging 2:1262–1270
5. Schuhbaeck A, Dey D, Otaki Y et al (2014) Interscan reproducibility of quantitative coronary plaque volume and composition from CT coronary angiography using an automated method. Eur Radiol 24:2300–2308
6. The SCOT-HEART investigators (2015) CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet 385:2383–2391
7. Motoyama S, Ito H, Sarai M et al (2015) Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 66:337–346
8. Zhang LJ, Qi L, Wang J et al (2014) Feasibility of prospectively ECG-triggered high-pitch coronary CT angiography with 30 mL iodinated contrast agent at 70 kVp: initial experience. Eur Radiol 24:1537–1546
9. Kwan AC, May HT, Cater G et al (2014) Coronary artery plaque volume and obesity in patients with diabetes: the factor-64 study. Radiology 272:690–699
10. Voros S, Rinehart S, Qian Z et al (2011) Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (Assessment of Tissue Characteristics, Lesion Morphology, and Hemodynamics by Angiography With Fractional Flow Reserve, Intravascular Ultrasound and Virtual Histology, and Noninvasive Computed Tomography in Atherosclerotic Plaques) I study. J Am Coll Cardiol Intv 4:198–208
11. Papadopoulou SL, Neefjes LA, Schaap M et al (2011) Detection and quantification of coronary atherosclerotic plaque by 64-slice multidetector CT: a systematic head-to-head comparison with intravascular ultrasound. Atherosclerosis 219:163–170
12. Hoffmann U, Moselewski F, Nieman K et al (2006) Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol 47:1655–1662
13. Inoue K, Motoyama S, Sarai M et al (2010) Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. JACC Cardiovasc Imaging 3:691–698
14. Motoyama S, Kondo T, Anno H et al (2007) Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. Circ J 71:363–366
15. Hong C, Becker CR, Schoepf UJ, Ohnesorge B, Bruening R, Reiser MF (2002) Coronary artery calcium: absolute quantification in nonenhanced and contrastenhanced multi-detector row CT studies. Radiology 223:474–480

16. Kruk M, Noll D, Achenbach S et al (2014) Impact of coronary artery calcium characteristics on accuracy of CT angiography. JACC: Cardiovascular Imaging 7:49–58

17. Anderson JL, Adams CD, Antman EM et al (2011) 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 123:e426–e579

18. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM et al (2012) Natural history of coronary atherosclerosis by multislice computed tomography. JACC Cardiovasc Imaging 5:S28–S37

19. Fischer C, Hulten E, Belur P et al (2013) Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. J Cardiovasc Comput Tomogr 7:256–266

20. Stone GW, Maehara A, Lansky AJ et al (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364:226–235

21. Hoffmann H, Frieler K, Schlattmann P et al (2010) Influence of statin treatment on coronary atherosclerosis visualised using multi-detector computed tomography. Eur Radiol 20:2824–2833

22. Ayad SW, ElSharkawy EM, ElTahan SM, Sobhy MA, Laymouna RH (2015) The role of 64/128-slice multidetector computed tomography to assess the progression of coronary atherosclerosis. Clin Med Insights Cardiol 9:47–52

23. Becker CR (2005) Estimation of cardiac event risk by MDCT. Eur Radiol 15:B17–B22

24. Joshi PH, Patel B, Blaha MJ et al (2016) Coronary artery calcium predicts cardiovascular events in participants with a low lifetime risk of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 246:367–373

25. Greenland P, Bonow RO, Brundage BH et al (2007) ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 49:378–402

26. Stone NJ, Robinson JG, Lichtenstein AH et al (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 63:2889–2934

27. Adhyaru BB, Jacobson TA (2016) New cholesterol guidelines for the management of atherosclerotic cardiovascular disease risk: a comparison of the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines with the 2014 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia. Endocrinol Metab Clin North Am 45:17–37

28. Puri R, Nissen SE, Ballantyne CM et al (2013) Factors underlying regression of coronary atheroma with potent statin therapy. Eur Heart J 34:1818–1825

29. Maffei E, Seitun S, Nieman K et al (2011) Assessment of coronary artery disease and calcified coronary plaque burden by computed tomography in patients with and without diabetes mellitus. Eur Radiol 21:944–953

30. Bamberg F, Dannemann N, Shapiro MD et al (2008) Association between cardiovascular risk profiles and the presence and extent of different types of coronary atherosclerotic plaque as detected by multidetector computed tomography. Arterioscler Thromb Vasc Biol 28:568–574

31. UKPDS Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352:837–853

32. Wilson K, Gibson N, Willan A, Cook D (2000) Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 160:939–944