Advancements in cardiovascular imaging: serial coronary CT and myocardial CT perfusion quantification techniques

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Part 1

Role of serial coronary computed tomography angiography in the evaluation of coronary artery disease

2 Utilizing (serial) coronary computed tomography angiography (CCTA) to predict plaque progression and major adverse cardiac events (MACE): results, merits and challenges

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Abstract

Objectives: To present an overview of studies using serial coronary computed tomography angiography (CCTA) as a tool for finding both quantitative (changes) and qualitative plaque characteristics as well as epicardial adipose tissue (EAT) volume changes as predictors of plaque progression and/or major adverse cardiac events (MACE) and outline the challenges and advantages of using a serial non-invasive imaging approach for assessing cardiovascular prognosis.

Methods: A literature search was performed in PubMed, Embase, Web of Science, Cochrane Library and Emcare. All observational cohort studies were assessed for quality using the Newcastle–Ottawa Scale (NOS). The NOS score was then converted into Agency for Healthcare Research and Quality (AHRQ) standards: good, fair and poor.

Results: A total of 36 articles were analyzed for this review, 3 of which were meta-analyses and one was a technical paper. Quantitative baseline plaque features seem to be more predictive of MACE and/or plaque progression as compared to qualitative plaque features.

Conclusions: A critical review of the literature focusing on studies utilizing serial CCTA revealed that mainly quantitative baseline plaque features and quantitative plaque changes are predictive of MACE and/or plaque progression contrary to qualitative plaque features. Significant questions regarding the clinical implications of these specific quantitative and qualitative plaque features as well as the challenges of using serial CCTA have yet to be resolved in studies using this imaging technique.

Abbreviations

%DS: Percentage diameter stenosis
ACS: Acute coronary syndrome
CAD: Coronary artery disease
CCTA: Coronary computed tomography angiography
CI: Confidence interval
CX: Circumflex artery
EAT: Epicardial adipose tissue
EFV: Epicardial fat volume
HR: Hazard ratio
HRP: High-risk plaque features
HU: Hounsfield units
ICA: Invasive coronary angiography
IQR: Interquartile range
IVOCT: Intravascular Optical Coherence Tomography
IVUS: Intravascular Ultrasound
LAD: Left anterior descending artery
LAPV: Low-attenuation plaque volume
LAP: Low-attenuation plaque
LM: Left main
MACE: Major adverse cardiac events
OR: Odds ratio
PAV: Percentage atheroma volume
PR: Positive remodeling
TPV: Total plaque volume

1. Introduction.

Coronary artery disease (CAD) is still one of the leading causes of death and loss of disability-adjusted life years worldwide (1). The clinical course of CAD mainly consists of progression of atherosclerosis punctuated by merely unpredictable clinical events despite treatment (2). Plaque phenotypes are clinically relevant as vulnerable plaque is prone to rupture and may lead to major adverse cardiac events (MACE) (3). Also, it has been demonstrated that epicardial adipose tissue (EAT) shares the same embryologic origin as intra-abdominal fat, which is associated with CAD(4). This underlies the importance of accurate identification and risk stratification of patients at risk for future atherosclerosis progression and MACE. Besides invasive techniques such as intravascular ultrasound (IVUS), intravascular optical coherence tomography (IVOCT) and invasive coronary angiography (ICA), coronary computed tomography angiography (CCTA) is a non-invasive imaging approach that allows for both qualitative and quantitative assessment of coronary plaque (5). A previous meta-analysis has shown high correlations between CCTA features and measures of coronary plaque as compared to IVUS (6). As such, CCTA has rapidly emerged as a non-invasive tool for plaque assessment (7). More recent studies have demonstrated the ability of serial CCTA to assess changes in plaque burden and plaque morphology as well as changes in EAT volume (8-11). Use of serial CCTA may be beneficial for both symptomatic and asymptomatic patients as recent expert recommendations state that CCTA may be performed as the first-line test for evaluating patients with no known CAD who present with stable typical or atypical chest pain, or other symptoms which are thought to represent a possible anginal equivalent. Subsequently, CCTA may be performed in asymptomatic high-risk individuals, especially in those who have a higher likelihood of having a large amount of noncalcified plaque (12).

This review presents an overview of studies using serial CCTA as a tool for finding both quantitative (changes) and qualitative plaque characteristics as well as EAT volume changes as predictors of plaque progression and/or MACE and outlines the challenges and advantages of using a serial non-invasive imaging approach for assessing cardiovascular prognosis. Details regarding the search strategies, quality assessment and selection criteria can be found in the supplementary material.

2. Image analysis of serial CCTA.

Recent development in plaque quantification software allows for semiautomated methods to quantify plaque volume on a single CCTA, drastically increasing the speed of assessment (13). Plaque volumes can be automatically sub-classified by composition using predefined intensity cutoff values in Hounsfield units (HU). These predefined intensity cutoff values in HU currently available have been obtained by comparing CCTA with IVUS or by histological examination. However, cutoff values vary (14). Nowadays,

an algorithm which uses adaptive attenuation thresholds based on the principle that plaque attenuation values are influenced by luminal contrast densities may be used. These contrast densities in turn are affected by a variety of factors including cardiac output and patient body size. Furthermore, luminal contrast densities decrease along the length of vessels and are lower in vessel segments with a severe stenosis. Adaptive HU cut-off values may overcome these problems by depending on regional attenuation contrast in the lumen (14, 15). In a recent study by de Knegt et al., fixed HU cutoff values were compared to adaptive HU cutoff values. Fixed HU thresholds underestimated fibrous and fibrofatty plaque volumes and overestimated necrotic core and dense plaque volumes compared to adaptive HU thresholds. Also, volumes of dense calcium plaque differed with increasing tertiles of luminal contrast density when using fixed HU thresholds instead of using adaptive HU thresholds. This highlights the importance of using an adaptive HU threshold algorithm when evaluating plaque composition (16). An imaging example demonstrating the superiority of adaptive HU thresholds over fixed HU values is depicted in Fig. 1. When assessing serial CCTA, analysis of the same coronary segments in baseline and follow-up scans is crucial for serial plaque comparison. Several studies utilizing serial CCTA facilitate co-registration of coronary segments and lesions by using anatomical landmarks like branching vessels and distance from the ostium which is done manually by visual analysis (17-19). Figure 2 depicts an example of serial CCTA.

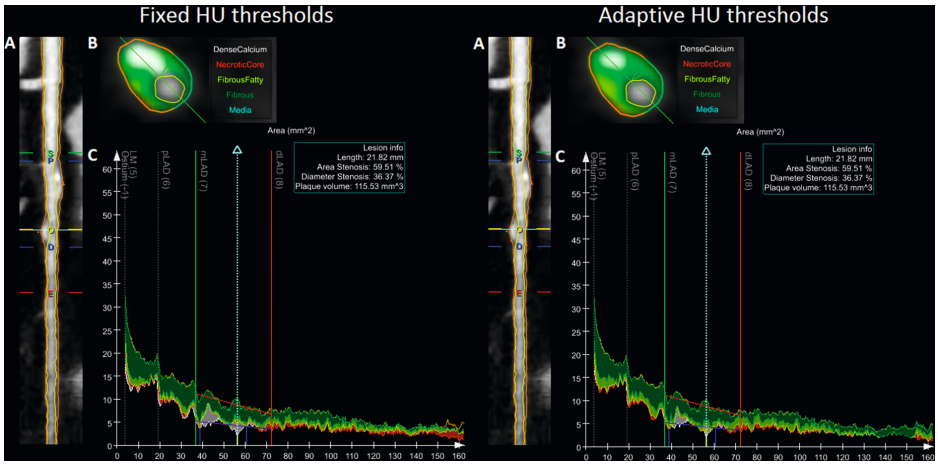

Fig 1. Example of quantitative analysis of the left anterior descending coronary artery (LAD) using fixed and adaptive HU thresholds. Panel A represents the straightened multiplanar reconstruction where S and E are the start and the end of the segment respectively; P and D are the proximal and distal borders of the lesion respectively. O represents the point of maximal obstruction. Consequently, panel B represent the transverse view of the vessel at this point. The color overlay in both the graph (Panel C) and the transverse view represents the different plaque tissue types. It must be noted that from visual assessment of the color overlay it can be seen that the fixed HU method characterized this plaque as having more dense calcium and less fibrofatty tissue compared to the adaptive method (16).

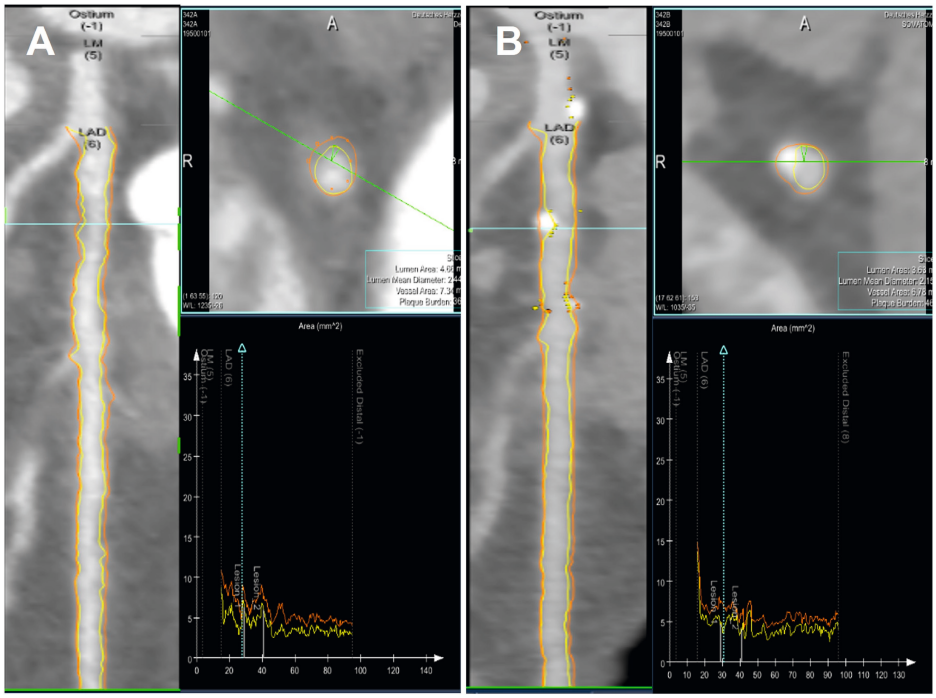

Fig 2. Example of a patient with an interscan period of six years between the baseline (shown on the left side, panel A) and follow-up scan (shown on the rights side, panel B). The investigated vessel is the left main (LM) and left anterior descending artery (LAD) demonstrating a total of three newly formed calcified plaques; one in the LM and two in the proximal segment of the LAD. In this case branching of the circumflex artery (CX) can be used as an anatomical landmark for co-registration by visual analysis. The orange line marks the outer vessel wall and the yellow line the lumen of the coronary artery (8).

3. Quantitative and qualitative plaque features.

Assessment of CCTA images can be performed on a quantitative or qualitative basis. Quantitative analysis focusses on volumetric plaque measurements such as total plaque volume (TPV), calcified or noncalcified plaque volume, low-attenuation plaque volume (LAPV) and percentage atheroma volume (PAV). The latter is calculated as a percentage by dividing the plaque volume by the vessel volume (20). Quantitative analysis on CCTA is an adequate predictor of cardiac death and the occurrence of acute coronary syndrome (ACS) (21). Qualitative analysis focusses on plaque composition based on the plaque density (attenuation). Hence, CCTA can identify different plaque components. These qualitative features include plaque composition (noncalcified or calcified) and high-risk plaque features (HRP) (22). HRP features identified by CCTA include positive remodelling (PR), low-attenuation plaque (LAP), napkin-ring sign and spotty calcification (21, 23-28). PR describes the increase in vessel diameter at the lesion site compared to a reference segment (24), often defined as a remodelling index of ≥ 1.1 (5, 9, 10, 24, 27, 29). LAP is a

noncalcified plaque with an attenuation of < 30 HU (9, 11, 25, 27, 28). The napkin-ring sign is defined as a combination of a low-attenuation core surrounded by a rim-like area of higher attenuation (9, 11, 23, 25). Lastly, spotty calcification is an intra-lesion calcific plaque < 3 mm in diameter (9, 10, 24, 27-29). A meta-analysis by Nerlekar et al. assessing the relationship between HRP features on prognosis has clearly demonstrated that all HRP features were strongly associated with MACE, including napkin-ring sign (HR, 5.06; 95% CI, 3.23–7.94; $P < 0.001$), low-attenuation plaque (HR, 2.95; 95% CI, 2.03–4.29; $P < 0.001$), positive remodelling (HR, 2.58; 95% CI, 1.84–3.61; $P < 0.001$), and spotty calcification (HR, 2.25; 95% CI, 1.26–4.04; $P = 0.006$). The presence of ≥2 HRP features had highest risk of MACE (HR, 9.17; 95% CI, 4.10–20.50; $P < 0.001$) (30). Imaging examples of HRP progression are depicted in Figs. 3 and 4.

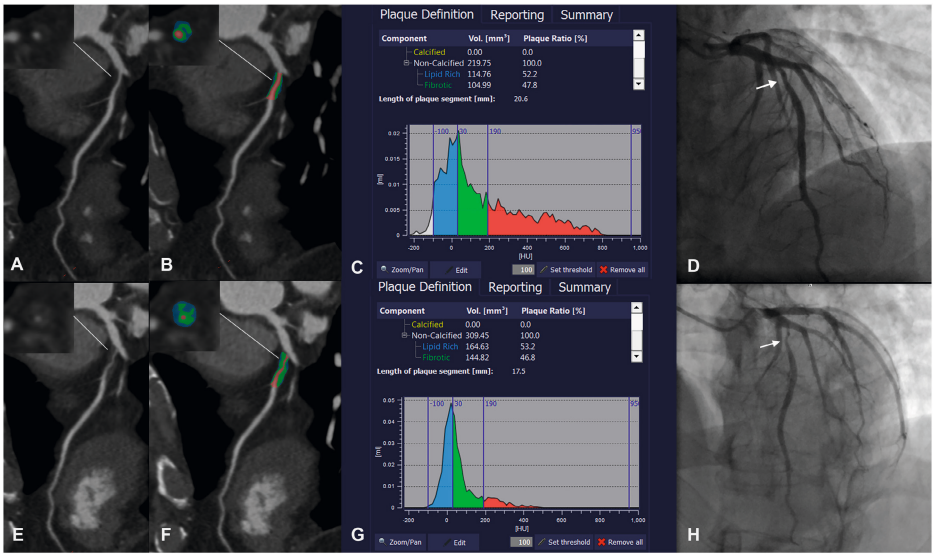

Fig 3. Example of a patient with LAP progression, a HRP feature. Panel A demonstrates a non-calcified plaque at baseline CCTA in the proximal LAD with moderate stenosis which is also visualized by baseline ICA in panel D. The colour coded image in panel B demonstrates the presence of LAP components labelled in blue. Further visualization of plaque components can be done using a histogram depicted in panel C. LAP component volume was 114.76 mm^3. At 12 month follow-up significant lesion progression with severe stenosis is observed (panel F - H). Note the increase of the LAP component volume to 164.63 mm^3 (9).

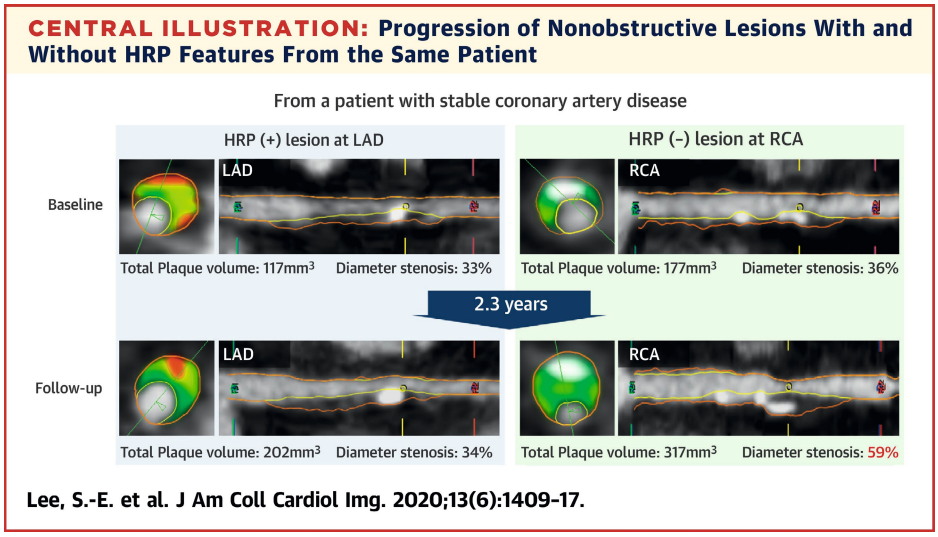

Fig 4. Example of a patient with plaque progression in a plaque with and without HRP features. A plaque in the right coronary artery (RCA) without HRP features progressed to an obstructive lesion at follow-up. Contrary, a plaque with HRP features in the LAD from the same patient remained nonobstructive at follow-up (10).

4. CCTA derived plaque features for predicting plaque progression.

Several studies have assessed the relationship between CCTA-derived quantitative and qualitative plaque features as predictors for plaque progression. (8-10, 29). In the past, serial IVUS has demonstrated the prognostic importance of plaque progression by showing an association with clinical outcomes (31). Table 1 lists details of studies utilizing serial CCTA to assess the relationship between CCTA-derived quantitative and qualitative plaque features as predictors for plaque progression and/or MACE.

In a large study by Han et al., predictors of rapid plaque progression were assessed. Rapid plaque progression was defined as an increase of baseline PAV of more than 1% per year on follow-up CCTA. A machine learning framework was used to assess several qualitative and quantitative CCTA-based plaque features. Quantitative features were the most important to predict plaque progression followed by qualitative features and last clinical/laboratory features. Specifically, the PAV at baseline was the most important predictor (information gain value: 0.193, regression coefficient (β): 0.529; $p < 0.01$). (29). Lee et al. assessed the progression from non-obstructive lesions to obstructive lesions compared to the presence of high-risk plaque features. Both total PAV and percentage diameter stenosis (%DS) at baseline were significant risk factors for the development of obstructive lesions (HR, 1.04 [95%CI, 1.02-1.07], and HR, 1.07 [95%CI, 1.04-1.10], respectively; all p <

0.05). Interestingly, the presence of high-risk plaque features was not a significant risk factor (p = 0.433). In lesions without HRP features, baseline total PAV (HR, 1.035 [95%CI, 1.002-1.067]; p = 0.031) and baseline %DS (HR, 1.081 [95%CI, 1.049-1.115]; p < 0.001) were independent predictors for development of obstructive lesions. However, in lesions with HRP features, only baseline total PAV independently predicted progression to obstructive lesions (HR: 1.102 [95%CI: 1.035-1.174]; p = 0.003) (10). Weber et al. also demonstrated the importance of quantitative plaque features as a significant correlation between baseline TPV and TPV progression (spearman's rho = 0.33; p < 0.01). The progression in TPV was mainly determined by a progression of calcified plaque volume (7.6 mm^3 [interquartile ranges 0.2 and 33.6] vs. 16.6 mm^3 [interquartile ranges 1.8 and 62.1]; p < 0.01). Also, patients with obstructive CAD at follow-up had a significantly higher TPV at baseline (384.9 mm^3 [interquartile ranges 182.8 and 538.1] vs. 45.1 mm^3 [interquartile ranges 10.3 and 102.9]; p < 0.01) (8). Yu et al. reported predictors for plaque progression assessed at serial CCTA in patients with solely non-culprit intermediate stenoses. LAP at baseline was an independent predictor of lesion volume progression at follow-up (OR, 16.74 [95%CI, 5.02-55.84]; p < 0.001) (9). Lee et al. demonstrated that adding HRP features to a per-lesion predictive model for developing obstructive lesions containing plaque volume and clinical risk factors increased the C-statistic from 0.830 [95% CI: 0.828-0.833] to 0.895 [95% CI: 0.893-0.897]; p = 0.003. Also, the per lesion HRP feature model was significantly better than the per-patient HRP feature model (C-statistic: 0.825 [95% CI, 0.823-0.827] vs. 0.895 [95% CI, 0.893-0.897], p < 0.001) (32).

Table 1. Studies utilizing serial CCTA to assess the relationship between CCTA derived quantitative and qualitative plaque features as predictors for plaque progression and/or MACE

Study	Year	Number of patients analyzed	Design	CT technique	Image analysis	Interscan interval	Population	Endpoint(s)	Most important predictor(s)
Han et al. (29)	2020	1,083	Prospective	≥64 slice	Semiautomated	Median: 3.3 years (IQR: 2.6-4.8)	Patients with 2 CCTA scans with ≥ 2-year interval.	Rapid plaque progression	PAV at baseline (information gain value: 0.193, regression coefficient (β): 0.529; p<0.01)
Weber et al. (8)	2020	350	Retrospective	16-slice CT, 64-slice single source & 64-slice dual source	Semiautomated & automated	Median: 42 months (IQR: 23-69)	Patients with suspected obstructive CAD based on clinical presentation.	TPV progression	TPV at baseline (spearman's rho = 0.33; p<0.01) Calcified plaque volume (baseline: 7.6 mm^3 [IQR: 0.2 and 33.6] vs. follow-up: 16.6 mm^3 [IQR: 1.8 and 62.1]; p<0.01)
								Obstructive CAD	TPV at baseline (384.9 mm3 [IQR: 182.8 and 538.1] vs. 45.1 mm3 [IQR: 10.3 and 102.9]; p<0.01
Yu et al. (9)	2018	140	Prospective	128-slice single source multi-detector CT	Manual, semiautomated & automated	Mean: 14.6 ± 2.2 months	Patients with stable angina or atypical chest pain with one unrevascularized intermediate coronary stenosis considered a non-culprit lesion.	Lesion volume progression	LAP at baseline (multivariate analysis: OR 16.74 (5.02-55.84); p<0.001)
								MACE	Higher prevalence of baseline LAP (40.00% vs. 12.80%; p = 0.015). Lesion volume progression (Kaplan-Meier curve: 56.25% vs. 4.84%; log-rank p<0.001
Lee et al. (10)	2020	1,297	Prospective	≥64 slice	Semiautomated	Mean: 3.8 ± 1.6 years	Patients with 2 CCTA scans with ≥ 2-year interval.	Plaque progression	PAV and %DS at baseline (HR (95% CI): 1.04 (1.02 - 1.07), and HR (95% CI): 1.07 (1.04 - 1.10), respectively; all p < 0.05) Lesions without HRP at baseline; total PAV (HR (95%CI): 1.035 (1.002-1.067); p=0.031) and baseline %DS (HR (95%CI): 1.081 (1.049-1.115); p<0.001) Lesions with HRP features; baseline total PAV (HR (95%CI) 1.102 (1.035-1.174); p=0.003)

Study	Year	Number of patients analyzed	Design	CT technique	Image analysis	Interscan interval	Population	Endpoint(s)	Most important predictor(s)
Psaltis et al. (4)	2016	64	Retrospective	320-row multidetector CT	Manual & semiautomated	Median: 25.2 months	Patients with chest pain, dyspnea in stable setting and no ACS.	Plaque progression or development	Higher baseline EFV (β co-efficient 0.014, 95% CI: 0.003–0.026; p = 0.014)
You et al. (33)	2016	87	Retrospective	64-slice CT & 128-slice dual-source CT	Manual & semiautomated	Mean: 25.5 ± 15.7 months	Patients with at least one baseline CCTA artery plaque.	Increase of lipid-rich plaque volume	Baseline indexed EFV (multivariate analysis: OR: 1.029 [95% CI: 1.005–1.053]; p = 0.016)
Nakanishi et al. (11)	2014	517	Prospective	64-slice CT	Manual & automated	Mean: 12 ± 5 months.	Non-obese patients undergoing serial multidetector CCTA for the evaluation of CAD.	Increased prevalence of obstructive plaques and plaques with PR and LAP	Increase in EAT volume (p<0.001, p<0.001, p=0.001, respectively)
Motoyama et al. (34)	2015	423	Retrospective	320-slice CT, 64-slice CT & 16-slice CT	Manual	Median: 1 year	Patients undergoing consecutive CCTA for suspected or known CAD.	MACE	Plaque progression (Kaplan-Meier curve: 14.3% vs. 0.3%, log-rank p<0.0001) Both HRP features at baseline and plaque progression at follow-up (Kaplan-Meier curve: 27%, log-rank p<0.0001) Non-HRP lesions developing in HRP lesions with a significant stenosis at follow-up (3 out of a total of 9 ACS events (15.4%))
Rosendaelet al. (35)	2020	1166	Prospective	≥64 slice	Semiautomated	At least 2 years	Patients with 2 CCTA scans with ≥ 2-year interval.	MACE	>1.0% ΔPAV increase per year: 27.2% vs. <1.0% ΔPAV increase per year: 9.5% at 10 years (Kaplan-Meier curve, log-rank p<0.001) <1.0% ΔPAV increase per year + low baseline PAV: 6.5% vs. >1.0% ΔPAV increase per year + high baseline PAV: 30.2% (Kaplan-Meier curve, log-rank p<0.001)

Study	Year	Number of patients analyzed	Design	CT technique	Image analysis	Interscan interval	Population	Endpoint(s)	Most important predictor(s)
Lee et al. (32)	2020	1297	Prospective	≥64 slice	Semiautomated	Mean: 3.8 ± 1.6 years	Patients with 2 CCTA scans with ≥ 2-year interval.	Obstructive CAD	Per lesion analysis: Adding HRP features to a predictive model containing plaque volume and clinical risk factors increased the C-statistic to 0.895 [95% CI: 0.893-0.897]; p=0.003
Gu et al. (36)	2020	757	Retrospective	64-slice dual-source CT	Manual	Mean: 2.0 years	Patients with non-obstructive CAD, who underwent a 2nd CCTA requested by the treating physician or had new/worsening symptoms.	MACE	Three vessel plaque progression (HR: 2.37, p=0.026) Severe proximal plaque progression (HR: 3.65, p=0.003)

Table 1. TPV: Total plaque volume. LAP: Low attenuation plaque. PAV: Percent atheroma volume. %DS: Percentage diameter stenosis. EFV: Epicardial fat volume. MACE: Major adverse cardiac events. CAD: Coronary artery disease. HRP: High risk plaque. CT: Computed tomography. CCTA: Coronary computed tomography angiography. PR: Positive remodelling. EAT: Epicardial adipose tissue. IQR: Interquartile range. ACS: Acute coronary syndrome. OR: Odds ratio. HR: Hazard ratio. CI: Confidence interval.

4.1. Epicardial adipose tissue.

Numerous studies investigated the relationship between EAT and coronary artery plaque progression (4, 11, 33). EAT is a metabolically active organ that shares the same embryologic origin as intra-abdominal fat, which is associated with CAD. Under pathological circumstances, EAT has been shown to be a rich source of inflammatory adipokines. Given that inflammation is a fundamental component of the atherosclerotic process, it is postulated that EAT may influence the development and progression of coronary artery disease by contributing to the local inflammatory burden within and around atherosclerotic plaque (4). Psaltis et al. assessed the relationship between epicardial fat volume (EFV) and coronary artery plaque progression; higher baseline EFV was associated with the progression or development of coronary artery plaque (β coefficient 0.014 [95%CI, 0.003–0.026]; p = 0.014). Interestingly, change in EFV over time was not (p = 0.860) (4). You et al. also found that baseline indexed epicardial fat volume was an independent predictor of rapid increase in lipid-rich plaque volume (OR, 1.029 [95% CI, 1.005–1.053]; p = 0.016). Nevertheless, annual changes in indexed epicardial fat volume were not associated with parallel changes in lipid-rich, fibrous or calcified coronary plaque volume (p = 0.286, p = 0.500, p = 0.096; respectively) (33). However, both studies contained patients that were overweight at baseline (BMI (kg/m^2) ± SD: 29.3 ± 5.8 for Psaltis et al and 25.1 ± 3.3 for You et al). On the contrary, Nakanishi et al. solely focused on non-obese patients and demonstrated that increase of EAT volume (>10 mL) during follow-up was associated with an increased prevalence of obstructive plaques (p < 0.001) and plaques with high-risk features, such as PR (p < 0.001) and LAP (p = 0.001), in non-obese patients with CAD (11). Figure 5 depicts an example of EAT analysis.

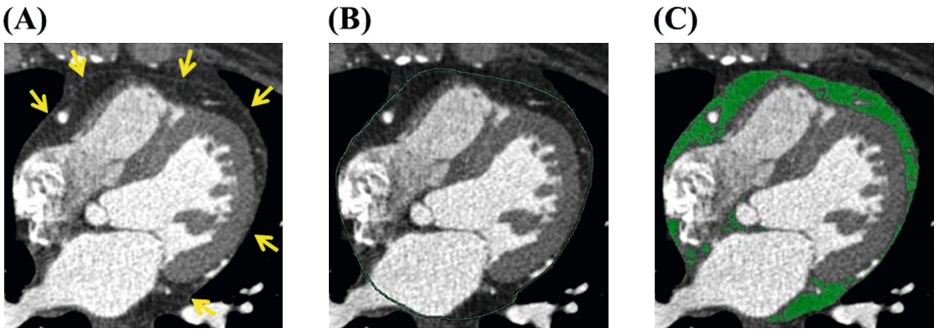

Fig 5. An example representing the measurement of EAT volume. The yellow arrows in panel A represent the pericardium in a cross-sectional slice. Segmentation of the EAT is achieved by tracing the pericardium in the axial view represented by the green line (Panel B). Subsequently, the adipose tissue can be identified by using threshold attenuation values of 30 to 250 HU which is represented by the green area in panel C (11).

4.2. CCTA derived plaque features for predicting MACE.

High-risk features of plaque such as PR, LAP and spotty calcification are found to be linked to plaque rupture and MACE (34). Multiple studies have investigated the relationship between CCTA-derived features of plaque and MACE on serial CCTA (9, 11, 34). Yu et al. (9) found that patients with MACE showed a statistically significant higher prevalence of LAP at baseline compared to patients in the MACE-absent subgroup (40.0% vs. 12.8%; p = 0.015). Prevalence of spotty calcification, napkin-ring sign and PR was not statistically different between the MACE and MACE-absent subgroups (13.33% vs. 6.40%, p = 0.291; 46.67% vs. 28.00%, p = 0.147; 73.33% vs. 60.00%, p = 0.406; respectively). Interestingly, also no significant difference existed between the two groups with regard to quantitative plaque features such as TPV, lesion length and diameter stenosis (44.6 mm^3 vs. 46.3 mm^3, p = 0.479; 10.5 mm vs. 13.0 mm, p = 0.166; 55.0% vs. 62.0%, p = 0.077, respectively for the MACE and MACE-absent subgroups). Yet, the lesion volume progression subgroup showed a higher incidence of MACE compared to the non-lesion progression subgroup (56.25% vs. 4.84%; log-rank p < 0.001). Notably, the MACE subgroup was small (15/140) (9). Motoyama et al. described that patients with plaque progression had a significantly higher incidence of MACE (14.3% vs. 0.3%, log-rank p<0.0001). Also, when classified in groups according to the presence of HRP features, the patients with both HRP at baseline CCTA and plaque progression at follow-up showed the highest frequency of MACE (27%, log-rank p < 0.0001). Conversely, in patients with HRP lesions at baseline which did not progress during follow-up, MACE did not occur. Interestingly, non-HRP lesions also led to MACE and the ones that progressed over time on a volumetric basis and evolved from non-HRP to HRP were more likely to result in MACE (3 out of a total of 9 events (15.4%)) (34). Rosendael et al. demonstrated that at 10 years, patients with an increase of >1.0% PAV/year had a higher risk of MACE compared to patients with an increase of <1.0% PAV/year (27.2% vs. 9.5%; log-rank p < 0.001). Patients were further stratified by the median baseline PAV. Patients with an increase <1.0% PAV/year and low baseline PAV experienced the lowest rates of MACE at 10 years, whilst those above the median baseline PAV and >1.0% increase in PAV/year experienced the most events (6.5% vs. 30.2%, p < 0.001) (35). Gu et al. identified patients with non-obstructive CAD who underwent a second CCTA. Those who developed any plaques coexisting in the left anterior descending, the left circumflex, and the right coronary artery (three-vessel plaque progression) between the two scans had an increased chance of MACE (HR, 2.37, p = 0.026). Furthermore, patients having a nonobstructive proximal lesion in the left anterior descending, left circumflex, or the right coronary artery, which developed in a ≥70% stenosis (severe proximal plaque progression) between the two scans, also had an increased chance of MACE (HR, 3.65, p = 0.003) (36)

5. Therapeutic measures to decrease plaque progression.

Several studies utilized serial CCTA to assess the effect of different medical therapies -mostly statins- on plaque progression (17, 19, 37, 38). Zeb et al. demonstrated that statin use causes a significant decrease of both LAP and noncalcified plaque volumes (–12.2 ± 19.2 vs. 5.9 mm^3 ± 23.1, $p < 0.0001$ and –47.7 ± 71.9 vs. 13.8 mm^3 ± 76.6, $p < 0.001$, respectively, for statin and non-statin users) and a non-statistically significant increase in the amount of calcified plaque volume in statin users compared to non-statin users (37). Smit et al. also demonstrated that statin use was associated with a significant reduction of noncalcified plaque progression (1.0±16.0 vs. 6.4±13.9 mm^3; P=0.049) compared to non-statin users. Statin users in turn showed an increase in calcified plaque progression (9.0±12.2 vs. 3.3±8.6 mm^3; P = 0.001) (19). A study by Lee et al. utilizing the large PARADIGM registry also demonstrated that over time statin therapy increased plaque calcification and reduced HRP features as lesions in statin-taking patients experienced higher annualized progression of calcified PAV (1.27 ± 1.54 mm^3 per year vs. 0.98 ± 1.27 mm^3 per year, respectively; $p < 0.001$) but slower progression of noncalcified PAV than lesions in statin-naive patients (0.49 ± 2.39 mm^3 per year vs. 1.06 ± 2.42 mm^3 per year, respectively; $p < 0.001$) (17). At baseline CCTA, statin-taking patients exhibited a higher prevalence of HRP, PR and spotty calcification (13.7% vs. 10.0%; 56.0% vs. 47.6%; and 10.2% vs. 6.8%, respectively; all $p < 0.05$), with no differences in LAP (8.5% vs. 8.4%, respectively; $p = 0.95$). The annualized incidence of HRP, PR, spotty calcification and LAP were lower (0.9% per year vs. 1.6% per year; 5.2% per year vs. 7.2% per year; 0.2% per year vs. 0.5% per year; and 0.8% per year vs. 1.0% per year, respectively; $p < 0.001$ for all) for statin- versus non-statin-taking patients respectively (17). It must be noted that differences in baseline characteristics between the statin- and non-statin-taking groups may have impacted results.

Li et al. demonstrated that not solely statin use but also statin dosage plays a key role in aiding plaque regression as patients receiving intensive statin therapy demonstrated significantly higher annualized regression of LAP volume, TPV and % plaque volume compared to patients receiving moderate statin therapy. Interestingly, a higher baseline LAP volume was also associated with higher TPV regression (P<0.001). Thus, patients with greater baseline LAP volume were more likely to benefit from statin therapy (38). Figure 6 depicts an imaging example of assessment of therapy efficacy on plaque presence using serial CCTA.

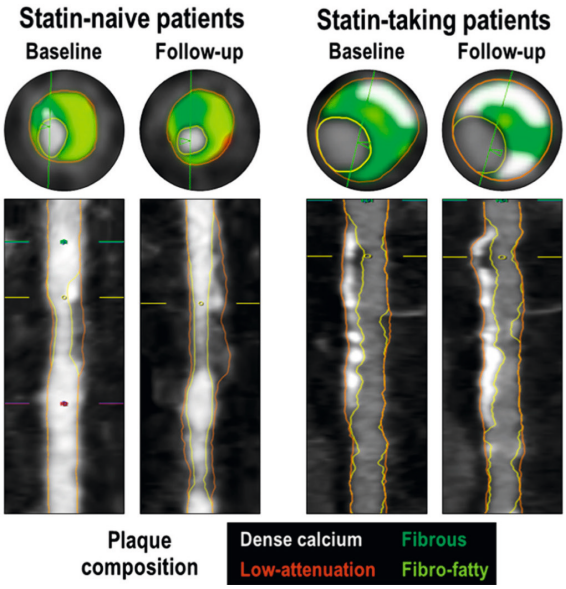

Fig 6. CCTA images of lesions at baseline and follow-up among statin-naïve patients and statin-taking patients. Statin taking patients expressed slower progression of noncalcified PAV compared to statin-naïve patients. Noncalcified PAV is the summation of fibrous, fibro-fatty and low attenuation PAV (17).

6. Benefits and challenges of serial CCTA.

A critical challenge in serial CCTA is the wide range of commercially available CT scanners and the rapid technological developments. Several studies used different scanner types with different specifications and performance at baseline and at follow-up (8, 10, 29, 33, 34). Symons et al. performed a systemic comparison of scanner variability in serial CCTA, in which plaque volume was measured with the same or a different CCTA scanner within 30 days. Plaque volume variability was ±18.4% (coefficient of variation) when the same scanner was used at baseline and follow-up, whilst the plaque volume variability was ±29.9% when different scanners were used (39). This highlights the importance of standardized CCTA protocols in future prospective studies.

No professional society guidelines dictate the methods for the routine usage of serial CCTA for evaluating progression of CAD. Therefore, it remains unclear which choice of endpoint measurement is the most appropriate (40). The usage of different endpoints could impede study comparison. Furthermore, the ideal inter-scan interval remains unclear. However, one may conclude that a relatively short inter-scan interval may inhibit the detection of newly formed plaques. On the contrary, a relatively long inter-scan interval may contribute to different CCTA protocols being used. As is observed from numerous studies cited in this review, one may propose that an inter-scan interval of at least 1-2 years would seem reasonable.

Development and implementation of radiation dose reduction tools for coronary CCTA have rapidly been expanded as high radiation exposure is known to increase the risk of cancer. As noted in the SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT, several scanner settings such as tube current and tube potential should be kept to a minimum to limit radiation exposure whilst also maintaining adequate image quality (41).

Currently, all studies utilizing serial CCTA for plaque progression are using visual analysis of anatomical landmarks and vessel branches for alignment between baseline and follow-up CCTA. Hence, automatic co-registration would be feasible to match corresponding points on the coronary tree in the baseline and follow-up scan. This has recently been demonstrated by Cao et al. but remains to be tested in a clinical setting (42).

Despite its challenges, serial CCTA has emerged as an important non-invasive imaging technique to track the effectiveness of medication on coronary plaque progression. In a review by Taron et al., the authors showed that serial CCTA could successfully demonstrate the efficacy of anti-atherosclerotic treatments (40) and Dahal et al. have demonstrated the importance of serial CCTA in tracking coronary atheroma progression in studies using new pharmacotherapies (43). Furthermore, when combining therapies and cardiovascular outcomes, serial CCTA can give an insight in the mechanistic correlations of coronary atherogenesis (44). Current benefits and challenges of serial CCTA are reported in Table 2.

Table 2. Benefits and challenges of serial CCTA

Benefits	**Challenges**
Assessment of changes in plaque burden and plaque morphology.	Establishing low radiation protocols to prevent unnecessary exposure during successive CCTA's.
Predicting (rapid) plaque progression and/or MACE.	Currently no consensus on endpoint measurements.
Semiautomated measurements allows objective sequential measurements.	Usage of different CT-scanners at baseline and follow-up.
Measuring the effect of different medical therapies on plaque progression.	The ideal interscan interval remains unclear.
Giving an insight in mechanistic correlations of coronary atherogenesis	Automatic co-registration to match corresponding points on the coronary tree in the baseline and follow-up scan instead of using visual analysis of anatomical landmarks.
	Implementation of machine learning for plaque analysis.

Table 2. MACE: Major adverse cardiac events. CCTA: Coronary computed tomography angiography. CT: Computed tomography.

7. Conclusions.

Serial CCTA has rapidly emerged as the non-invasive modality to track atherosclerotic plaque changes and to assess the impact of different treatment strategies on CAD. Multiple studies utilizing serial CCTA have demonstrated that baseline quantitative plaque features as well as quantitative plaque changes -contrary to qualitative plaque features- are the most important in predicting plaque progression and MACE over time. However, it must be noted that although statistically quantitative plaque features remain the most important predictors of cardiovascular prognosis, qualitative features also have a substantial contribution. Furthermore, use of serial CCTA has been proven to be useful in the assessment of (statin) therapy efficacy on plaque progression and has revealed that statins slowed the overall progression of coronary atherosclerosis volume with increased plaque calcification and reduction of HRP features.

For optimal interpretation of serial CCTA, the following suggestions can be taken into consideration. First, the use of standardized acquisition protocols for both baseline and follow-up CT scans seems preferable, as well as adaptive HU threshold algorithms for the evaluation of plaque composition. Second, to date, no expert consensus has been available on the ideal inter-scan interval between baseline and follow-up CT scan. However, based on current studies, this interval could potentially be set at 1-2 years. Third, it seems favourable to quantify plaque as automated as possible. It should, however, be stressed that for now serial CCTA solely remains an important research tool for identifying surrogate endpoints predictive of MACE and is unlikely to feature as part of the clinical workup of patients. Ultimately, serial CCTA is a promising technique for the evaluation of cardiovascular prognosis yet technical details remain to be refined.

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