Current Cardiovascular Imaging Reports (2019) 12: 8
https://doi.org/10.1007/s12410-019-9483-7

CARDIAC COMPUTED TOMOGRAPHY (B CHOW AND G SMALL, SECTION EDITORS)

Plaque Assessment on Serial Coronary CTA

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Published online: 14 February 2019

Abstract

Purpose of Review This review addresses the role of serial coronary computed tomography angiography (CTA) on the evaluation of atherosclerosis progression, risk stratification, and targeting individual pharmacotherapy.

Recent Findings The presence, extent, and severity of coronary artery disease (CAD) detected by coronary CTA are associated with an adverse prognosis. Similarly, the presence of high-risk plaque features such as positive remodeling, low-attenuation plaque, spotty calcifications, and napkin-ring sign are associated with major adverse cardiac events. More recently, examinations using serial coronary CTA have also shown that these static CTA plaque features are associated with a more rapid progression of atherosclerosis on follow-up imaging and may identify a subset of patients at increased risk for plaque rupture. While the impact of serial CTA findings on management and hard outcomes remains a topic of ongoing investigation, available data supports the ability of statin therapy to reduce CTA-identified plaque burden and modify plaque composition.

Summary Coronary CTA identifies various plaque features associated with an increased risk of plaque progression and adverse cardiac events. Available data support the use of CTA to individualize statin therapy and utilize serial CTA imaging to study the impact of pharmacotherapy on plaque burden and outcomes.

Keywords Atherosclerosis · Atherosclerotic plaque · Plaque progression · Coronary artery disease · Coronary computed tomography angiography

Introduction

Coronary artery disease (CAD) is typically caused by atherosclerosis, a slow progressive disease that remains asymptomatic for decades until it progresses to symptomatic chronic stable angina due to a flow-limiting stenosis, or sudden plaque rupture and acute coronary syndrome (ACS) [1]. Although this process usually manifests as a stepwise sequential progression [2], studies suggest that the most acute plaque rupture occurs in previously nonobstructive plaques [3•]. Conversely, recent data suggests some vulnerable plaques may progress faster and lead to plaque rupture of obstructive lesions by an accelerated increase in plaque burden [4••].

Some of the inherent limitations to understanding this pathophysiology lie in our ability to visualize atherosclerotic plaque in vivo. Until recently, in vivo studies of CAD progression were performed using invasive angiography, intravascular ultrasound, and/or optical coherence tomography [5]. These techniques are associated with higher costs and a small, yet non-negligible, risk of complications that precludes its use for serial imaging of plaque progression in lower risk individuals. More recently, coronary computed tomography

This article is part of the Topical Collection on *Cardiac Computed Tomography*

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angiography (CTA) has evolved as an established technique for the noninvasive evaluation of CAD.

Coronary CTA is now recognized as a valid imaging modality to visualize the coronary arteries [6], with high sensitivity and specificity for the detection of obstructive CAD [7]. However, its most exclusive feature is the ability to directly image many features of coronary atherosclerosis noninvasively. Due to its high spatial and contrast resolution, it allows the detection of more atherosclerosis than invasive angiography [8]. Consequently, coronary CTA is used to evaluate the presence, extent, and severity of CAD, disease progression, and plaque characteristics associated with an increased risk for major adverse cardiac events (MACE). In turn, available data supports the ability of CTA to identify patients that may benefit from more aggressive treatment strategies—including patients with extensive nonobstructive plaque that may go undetected by standard noninvasive functional testing. In this review, we address the value of assessing the severity, extent, and composition of coronary atherosclerosis by coronary CTA. Additionally, we will discuss the role of these plaque features on the evaluation of disease progression by serial coronary CTA, and the potential impact of these findings on individual therapy.

Coronary CTA for the Assessment of Atherosclerosis Severity

The severity of each individual coronary atherosclerotic lesion is one of the key features of any clinical coronary CTA report. While a minimal luminal area (MLA) reduction is preferred for stenosis assessment, owing to variation in lesions and vessel eccentricity, the vast majority of clinical studies and the current gold standard (invasive angiography) employ minimal luminal diameter (MLD) for stenosis grading. Current guidelines recommend a semiquantitative assessment of luminal diameter reduction relative to the nearest normal proximal reference, graded as minimal (< 25% stenosis), mild (25–49% stenosis), moderate (50–69% stenosis), severe (70–99% stenosis), or occluded [9]. More recent recommendations even suggest treatment strategies based on the stenosis and number of vessels involved, although clinical trials to support this "image-guided" treatment scheme are needed [10•].

The strategy to quantify lesions based on the maximal luminal reduction is based on studies demonstrating that obstructive lesions, defined as a MLA reduction greater that 50%, led to significant flow reduction during states of increased demand, whereas lesions with a MLA reduction greater that 70% led to flow reduction even in resting states [11]. Although this association between the degree of stenosis and the presence of ischemia may cause and effect patient symptoms, this correlation is not fixed, and several studies have demonstrated considerable disagreement between flow and reductions in luminal area. Nonetheless, the extent of luminal reduction and myocardial ischemia are known to correlate with the risk of myocardial infarction and death. This association between the burden of CAD and cardiovascular events has also been demonstrated in patients undergoing coronary CTA, as CTA-identified stenosis severity [12•] and plaque burden are associated with adverse cardiac events [13].

Coronary CTA for the Assessment of Atherosclerosis Extent

Initial studies using invasive angiography have demonstrated that the number of vessels with obstructive CAD is an important predictor of survival [14]. This evolved to the concept that the more extensive the CAD, the higher the risk of plaque rupture. More recently, the prognostic value of the extent of nonobstructive CAD has also been demonstrated both for invasive angiography and coronary CTA (Fig. 1) [3•, 15]. To quantify the extent of CAD, the segment involvement score (SIS) [13] was developed based on the segment model proposed by the Society of Cardiovascular Computed Tomography (SCCT). By this model, each segment with atherosclerotic plaque scores a point, and a higher SIS score correlates with high event rates [16].

By comparison, the segment severity score (SSS) encompasses both the extent and severity of coronary atherosclerosis [13]. The SSS uses the same segment model as the SIS, but the score for each segment goes from zero to three depending on the degree of stenosis in each segment. While the SSS has also been demonstrated to be associated with events [17], it remains unclear if the additional information provided by the SSS results in incremental prognostic value beyond the SIS. Several other scores combining the presence, extent, and severity of CAD on coronary CTA have also been reported, although the clinical use of these scores remains limited in routine practice.

Coronary CTA for the Assessment of Plaque Morphology

Histological studies have demonstrated that plaque characteristics defined as vulnerable plaques are predictive of acute plaque rupture [18]. Since then, various imaging modalities have attempted to identify specific features associated with plaque vulnerability (Fig. 2) [19] Due to the ability of coronary CTA to noninvasively evaluate plaque composition, it has become one of the most MACE.

Plaque Composition

Plaque composition by coronary CTA can be defined according to its density as calcified, noncalcified, or partially calcified. Various studies have evaluated the impact of plaque composition on the incidence of cardiovascular events.

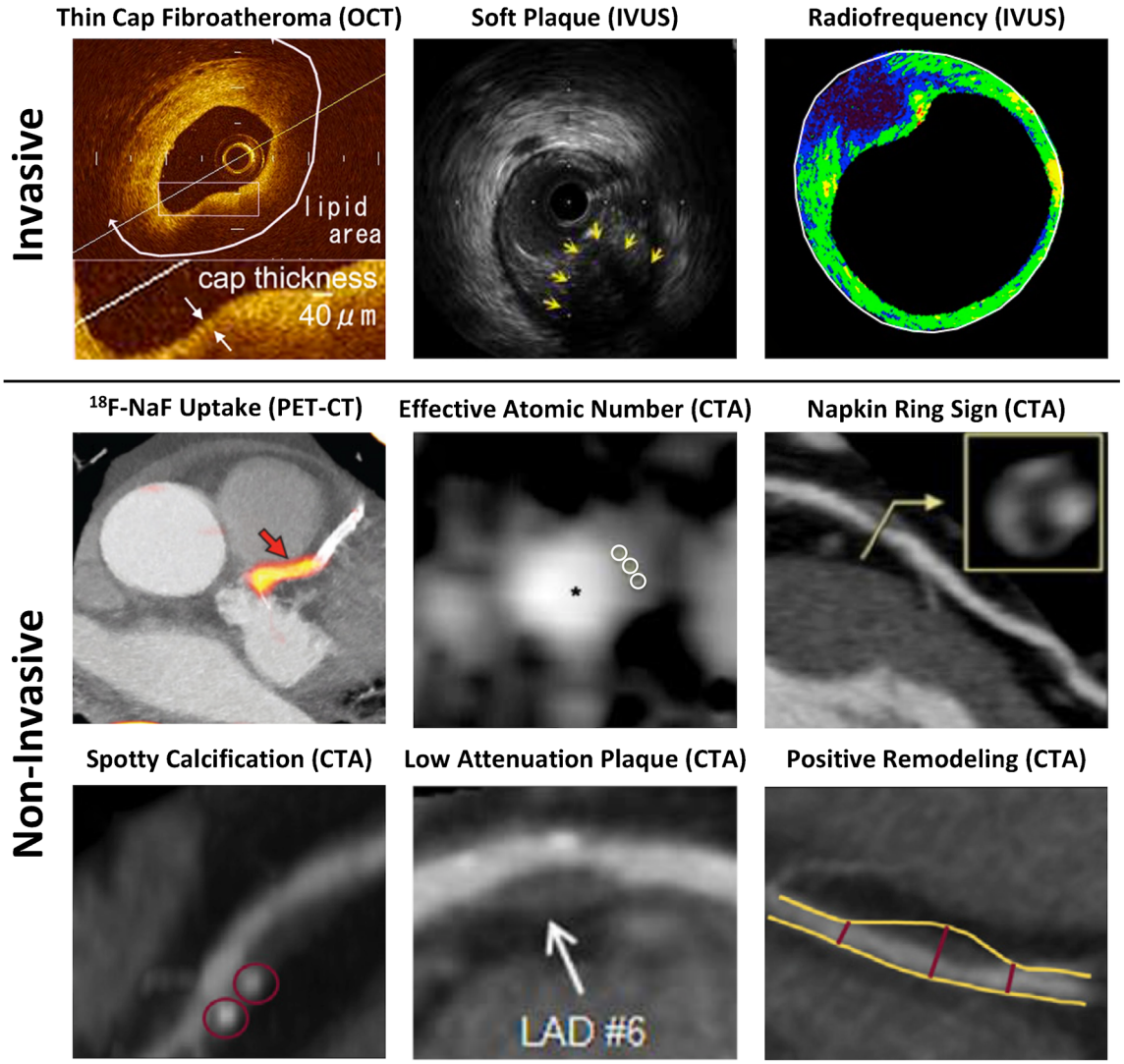

Fig. 1 Examples of plaque measures identified by invasive and noninvasive imaging: **a** optical coherence tomography (OCT) demonstrating thin-cap fibroatheroma; **b** intravascular ultrasound (IVUS) identified soft plaque (yellow arrows); **c** color-coded integrated backscatter IVUS images of coronary artery plaque and overlying fibrous cap (fibrous [green], dense fibrosis [yellow], lipid pool [blue and purple], calcification [red]); **d** positron emission tomography computed tomogram (PET-CT) identified 18F-sodium fluoride (NaF) uptake at the site of a culprit plaque (red arrow); **e** coronary computed tomography angiography (CTA) identified effective atomic number (EAN); **f** CTA-identified "napkin-ring sign"; **g** CTA-identified spotty calcification; **h** CTA-identified low-attenuation plaque; **i** CTA-identified positive remodeling. (Reproduced with permission from Shah NR et al. [19], with permission from Elsevier)

Noncalcified plaques tend to be more metabolically active and are associated with an increased risk of plaque rupture [20]. However, other plaque features, such as spotty calcification, positive remodeling, plaque density, and presence of the napkin-ring sign may offer additional prognosis.

Spotty Calcifications

Microcalcifications inside the coronary plaque seem to destabilize its structure and increase the risk of rupture [21••]. While microcalcifications or small (<1 mm) spotty calcifications are below the spatial resolution of coronary CTA, intermediate (1–3 mm) and large (≥ 3 mm) spotty calcifications may be visualized on high-resolution CTA datasets. These CTA-identified spotty calcifications correlate with high-risk plaque features on IVUS radiofrequency (IVUS-VH) and a higher likelihood of plaque rupture [22, 23].

Positive Remodeling

While increasing plaque burden ultimately leads to luminal area reduction and flow limitation by stenosis, the initial remodeling process occurs with plaque growth outwards and resulting in no luminal reduction [24]. This phenomenon, referred to as positive remodeling (PR), is associated with an increased lipid core and risk of plaque rupture [22]. PR can be

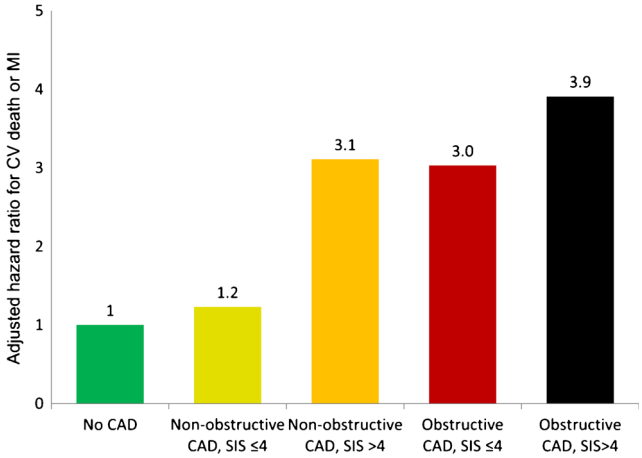

Fig. 2 Hazard ratio for the occurrence of cardiovascular (CV) death or myocardial infarction (MI) according to the presence, severity, and extent of coronary artery disease (CAD). The hazard ratios are significantly different ($p < 0.05$) for all pairwise comparisons except no CAD vs nonobstructive CAD, segment involvement score (SIS) ≤ 4; and nonobstructive CAD, SIS > 4 vs obstructive CAD, SIS ≤ 4. (From Bittencourt MS et al. [3•])

calculated by coronary CTA using the short axis image of the vessel, and it is considered positive when the overall vessel area is greater than 1.1, or 10% larger than the reference area without stenosis.

Low-Attenuation Plaque and Napkin-Ring Sign

Beyond broad classification of plaque as noncalcified versus calcified, specific measurements of composition based on plaque density may add prognostic information. Initial studies demonstrated that culprit plaques in acute coronary syndrome typically have a lower density than plaques in stable CAD [25••]. This yielded a cutoff of < 30 HU as one threshold for "low attenuation" plaque. Additionally, a specific pattern of plaque composition described as the napkin-ring sign (NRS) can be seen in cases with a low-attenuation central area surrounded by a high-attenuation ring [26]. Although the prevalence of these findings is relatively low among CTA exams, the presence of low-attenuation plaque and/or NRS are associated with an increased risk of MACE independent of other cardiovascular risk factors [22, 27••, 28].

Association of Multiple High-Risk Features

Despite their significant association with events, the presence of any of the previously described high-risk plaque features (PR, low-attenuation plaque, spotty calcification, and NRS) is relatively uncommon, and their individual positive predictive value is relatively low. Thus, most studies have evaluated the performance of a combination of those markers to identify individuals at an increased risk of plaque rupture. In a study by Motoyama et al., the presence of at least two high-risk features was associated with an increased risk of acute coronary syndrome [22]. Similarly, in a subanalysis of the PROMISE study, the presence of at least two high-risk plaque features was associated with an increased risk of MACE (6.4% vs 2.4%; hazard ratio, 2.73; 95% CI, 1.89–3.93). Notably, their findings remained significant even after adjustment for stenosis severity (adjusted hazard ratio [aHR], 1.72; 95% CI, 1.13–2.62). In support of these findings, a recent SCCT expert consensus recommends including the presence of high-risk plaque features among standard reports, when present [10•].

Coronary CTA for the Assessment of Plaque Progression

The vast majority of evidence regarding the prognostic value of coronary CTA is derived from single "static" evaluations of the coronary arteries by coronary CTA. However, atherosclerosis is a dynamic process and the by definition, atherogenesis is a process that changes over time. To this end, serial CAD imaging using coronary CTA may be a useful adjunct to visualize plaque progression, the impact of various therapies on plaque, and identify individuals who may benefit from treatment. Additionally, serial imaging may allow the identification of patterns of plaque progression that might be associated with a higher incidence of cardiovascular events and serve as a prognostic tool to risk stratify patients. Due to those facts, there is considerable interest in the noninvasive evaluation of coronary atherosclerotic plaque progression in the literature.

Early studies were performed looking at coronary artery calcium progression in selected individuals such as individuals on hemodialysis, using alendronate, with high homocysteine and others. Those studies are limited as they have only evaluated coronary artery calcification, not atherosclerotic plaque progression, and they are not included in the present review. Additionally, several early small studies of selected individuals have been performed using electron bean computed tomography [29]. Since those studies had a small sample size, a limited duration of follow-up, and an inclusion of only very selected populations and were limited by a high-interscan variability related to the poor spatial resolution of this technology, those studies will not be included in the present analysis. Finally, several mechanistic studies designed to evaluate the impact of various drugs on plaque progression have been proposed but are not yet completed. Those studies include evaluation of the effects of rosiglitazone [30], dalcetrapib [31], icosapent ethyl [32], and anticoagulants [33]. There is also a recent publication of the study design of the evaluation of the effects of HIV on plaque progression [34]. Those studies have not yet been published and its results are not yet available.

Still, several studies have been performed to evaluate plaque progression with repeated coronary CTAs. Those studies can be divided into three groups. First, studies of convenience sample

which included individuals who underwent repeated coronary CTAs for clinical indications. Most of those have evaluated clinical and imaging predictors associated with plaque progression. Second, several studies were designed to evaluate the impact of treatment on plaque progression. While some of those studies were convenience samples where individuals exposed and nonexposed were compared, others were prospective randomized studies. Finally, some recent studies evaluated the role of plaque progression in the incidence of cardiovascular events after the repeated coronary CTA.

Clinical and Imaging Features Associated with Plaque Progression

Most studies evaluating predictors of plaque progression were small studies with convenience samples of individuals who underwent repeated scans for clinical reasons. This group includes studies of stable suspected CAD, post-acute chest pain presentation and evaluation of non-culprit lesions post-PCI. The key features of those studies are summarized in Table 1. Those studies have a variable duration of follow-up from 12 to more than 36 months, and even within studies, the duration of follow-up is highly variable, with at least one study including follow-up from 7 to 60 months [35]. The comparison between studies is also limited as there is no standard definition of plaque progression. While some studies performed quantitative assessment of plaque area or volume, other studies performed semiquantitative or subjective visual evaluation of plaque burden, and at least one study reported direct pairwise comparison of images.

The individual predictors associated with plaque progression are also highly variable, but in general, the clinical predictors associated with faster plaque progression are related to the classic risk factors for atherosclerotic disease, such as LDL-cholesterol levels, diabetes, smoking, and history of dyslipidemia. Additionally, some studies also report that visceral and epicardial fat are directly associated with plaque progression, and two studies suggest that the presence and extent of baseline plaque, particularly noncalcified plaque, are associated with increased likelihood of progression. The clinical implications of those findings, however, is limited, as those predictors are already part of the known risk factors and their treatment is currently based on the clinical risk stratification of this population.

Pharmacological Impact in Plaque Progression

Based on this concordance between plaque progression and cardiovascular events as described by other imaging methods, changes in atherosclerotic plaque composition and burden might be good surrogate therapeutic targets for interventions. The key studies of effects of drug treatment on plaque progression are summarized in Table 2. Most of those studies included

Table 1 Details of studies evaluating predictors of plaque progression measured by coronary CTA

Study	Sample size	Population	Duration of follow-up (months)	How progression was measured	Predictors of progression
Lehman et al. 2009 [43]	69	Convenience repeated scans with acute chest pain, no ACS	24	Number of cross-sections with plaque	• Baseline plaque • Smoking
Imai et al. 2012 [44]	553	Convenience repeated scans with nonobstructive CAD	38	Subjective increase in plaque area or increase in CAC	• Visceral fat
Ayad et al. 2015 [45]	200	Convenience repeated scans	25 ± 20	Various area and volumetric-based parameters	• Diabetes • Dyslipidemia • Noncalcified plaque • Visceral fat • Hypercholesterolemia
Psaltis et al. 2016 [35]	64	Convenience repeated scans	25 (7 to 60 range)	Direct visual comparison, automated plaque quantification	• LDL concentration
Sakellarios et al. 2017 [46]	32	Convenience repeated scans, post-PCI non-culprit lesion	36	Quantitative change in plaque volume	
Nakanishi et al. 2016 [47]	142	Convenience with repeated scans	41 ± 22	Semi-automated quantitative	• Diabetes
Tan et al. 2017 [48]	131	Prospective post-PCI	12	Visual assessment	• Epicardial fat

a relatively small sample size with a limited follow-up between 6 and 38 months and evaluated statins compared to controls.

In a small retrospective study, the use of statins was associated with a significant change in plaque composition, with a reduction in the noncalcified plaque component, including low-attenuation plaques, and an increase in the calcified plaque component [36]. This was accompanied by a small, yet significant, reduction in plaque volume. Another larger observational study has demonstrated that a more aggressive LDL-cholesterol level, below 70 mg/dL was associated with a significantly lower progression in plaque burden compared to individuals with higher LDL-cholesterols (13 mm^3 vs 44 mm^3, $p = 0.01$) [37]. Similarly, in a study of an HIV population, the use of statins was associated with a reduction in noncalcified plaque, a prevalence of plaques with high-risk features [38].

More recently, one large registry, the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) study, also evaluated the differences in plaque progression according to the use of statin therapy. Its use was associated with a slower progression of plaque volume (− 21% reduction/year in percent atheroma volume), phenotypic plaque transformation towards more calcified plaque, and a 35% reduction in high-risk plaque development [39, 40]. At least two other studies have used repeated coronary CTAs to evaluate the effect of candesartan, and angiotensin receptor blocker, and VIA-2291, a leukotriene inhibitor, on plaque progression. Both studies demonstrated that the drug of interest results in slower plaque progression when compared to placebo.

Nevertheless, these studies of drug effects on plaque progression have several important limitations. First, the definition of plaque progression is highly variable, and some studies have multiple definitions of questionable clinical value. Furthermore, the use of multiple outcomes increases the risk of false positive findings, and no studies report adequate post hoc adjustment. As described for the study of predictors of plaque progression, the follow-up is variable. Finally, most studies are convenience non-randomized samples with limited adjustment for confounding, which limit the interpretation of their results.

Plaque Progression and Prediction of Clinical Events

Although studies using other imaging modalities have demonstrated that plaque progression is associated with worse outcomes, until recently, no data on the prognostic value of coronary CTA which detected plaque progression was available. The main studies evaluating the prognostic value of plaque progression detected by coronary CTA are summarized in Table 3.

Three smaller studies were published in 2017, two including samples of individuals with suspected CAD and one with individuals post-PCI. The latter evaluated plaque progression by visual assessment whereas the other two performed

Table 2 Details of studies evaluating the effects of drug therapies on plaque progression measured by coronary CTA

Study	Sample size	Population	Duration of follow-up (months)	Intervention	Control group	How progression was measured	Conclusion
Suzuki et al. 2011 [49]	36	Prospective inclusion	24	Candesartan plus statin	Statin	Proximal vessel area	Candesartan protected from progression
Zeb et al. 2013 [36]	100	Convenience repeated scans with or without statin treatment	13	Statin	No statin	Volumetric plaque measurement	Statin slowed progression
Li et al. 2016 [50]	206	Convenience with repeated scans and mild noncalcified plaque	18 (6 to 35 range)	Low- and high-dose statin	No statin	Quantification of plaque components	Statin slowed plaque progression, particularly noncalcified plaque
Shin et al. 2017 [37]	147	Convenience with repeated scans and plaque at baseline	38 (28 to 58 interquartile range)	Statin	No statin	Quantitative plaque measurement	Lower LDL-cholesterol associated with slower plaque progression
Matsumoto et al. 2017 [51]	54	Prospective ACS	6	VIA-2291	Placebo	Quantitative plaque composition	VIA-2291 slowed plaque progression
Lo et al. 2015 [38]	40	Prospective study of HIV individuals with subclinical atherosclerosis	12	Statin	Placebo	Semiquantitative analysis	Statin was associated with a reduction in noncalcified plaque and high-risk features
Lee et al. 2018 [40]	1255	Prospective registry	> 24	Statin	No statin	Quantitative analysis	Statin was associated with slower plaque progression

semiquantitative analysis. All three studies concluded that plaque progression, particularly lipid-rich, noncalcified plaques, are independent predictors of event.

Recently, one large study performed serial coronary CTA exams in 1345 individuals from seven countries with a mean interval of 3.8 years between the two scans. In this study, the population was divided into two groups: rapid and non-rapid progressors according to the rate of atherogenesis [41]. As expected, rapid progression of plaque was more likely to occur in older patients, males, and patients with cardiovascular risk factors. Interestingly, a family history of CAD was not associated with disease progression in this cohort. While there was no significant association between total cholesterol or LDL-cholesterol and plaque progression, individuals with rapid progression had lower HDL-cholesterol levels. In another study, however, a high LDL-cholesterol during follow-up was associated with plaque progression irrespective of the baseline LDL-cholesterol levels [42].

One particularly interesting aspect of this study was the fact that two coronary CTA-derived parameters from the baseline coronary CTA were strongly associated with rapid progression: baseline plaque burden and presence of high-risk features. While the total plaque volume in non-rapid progressors was approximately 8 mm^3, rapid progressors had plaques with 96 mm^3. Additionally, low-attenuation plaques and PR were twice as likely in the rapid progressors as in non-rapid progressors, while spotty calcification was three times more common.

Collectively, those results suggest that the main predictors of plaque progression are the same predictors we have previously identified as predictors of adverse events. Importantly, even after accounting for clinical risk factors, baseline plaque burden, and high-risk features, the discrimination of rapid progressors was limited, with an area under the ROC curve of 0.689 (95% CI, 0.688–0.689), suggesting there are probably several other unmeasured aspects that might influence plaque progression in stable patients. However, the strong similarities between the predictors of rapid plaque progression and predictors of incident events suggest that plaque progression might be an adequate surrogate marker for incident events in individuals with stable CAD.

This study also provided data on the prognostic implications of serial coronary CTA imaging. As expected, baseline plaque burden and presence of high-risk features were associated with incident events. The addition of annual change in plaque burden provided additional improvement in discrimination beyond those parameters ($p < 0.001$), and this was particularly true for individuals with a high baseline plaque burden with rapid plaque progression (Fig. 3).

Limitations for the Use of Plaque Progression

Despite the extensive progression in the use of coronary CTA for the evaluation of atherosclerotic plaque progression, several important limitations of the present study still preclude the clinical use of plaque progression for the definition of therapeutic intervention and prognostic evaluation of individual patients. First, most studies included individuals in whom coronary CTA was repeated for clinical reasons. This results in selection bias, and the disease progression of other individuals who did not require repeated testing is unknown. This results in a bias towards faster disease progression that is unlikely to be present if the test is systematically repeated.

Second, the duration of follow-up is highly variable across studies. Thus, it is not yet known what the expected atherosclerotic progression rate should be. The variable duration of follow-up also has implications on the evaluation of plaque components and its progression. Since most studies have a limited duration of follow-up, the progression of calcified plaque is likely to be small and to have limited prognostic value. Thus, it is not surprising that in studies with limited follow-up, the progression of noncalcified plaque is the main driver of plaque features associated with events. However, if such studies were continued for longer-term follow-up, one could expect that the calcified component might play a major role for prognosis.

Table 3 Details of studies evaluating the role of plaque progression on the prediction of incident cardiovascular events

Study	Sample size	Population	Duration of follow-up (months)	How progression was measured	Predictors of events
Tan et al. 2017 [52]	103	Prospective post-PCI	12	Visual assessment	Noncalcified plaque progression associated with events
Gu et al. 2017 [53]	953	Convenience sample of repeated scans	Unclear	Semiquantitative	Plaque progression associated with events
Gu et al. 2018 [54]	268	Convenience sample of repeated scans	24 ± 12	Semiquantitative	Lipid-rich plaque progression, t otal plaque progression associated with events
Lee et al. 2018 [41]	1345	Convenience sample	≥ 24	Quantitative	Baseline plaque burden, high-risk plaque, annualized change in plaque burden

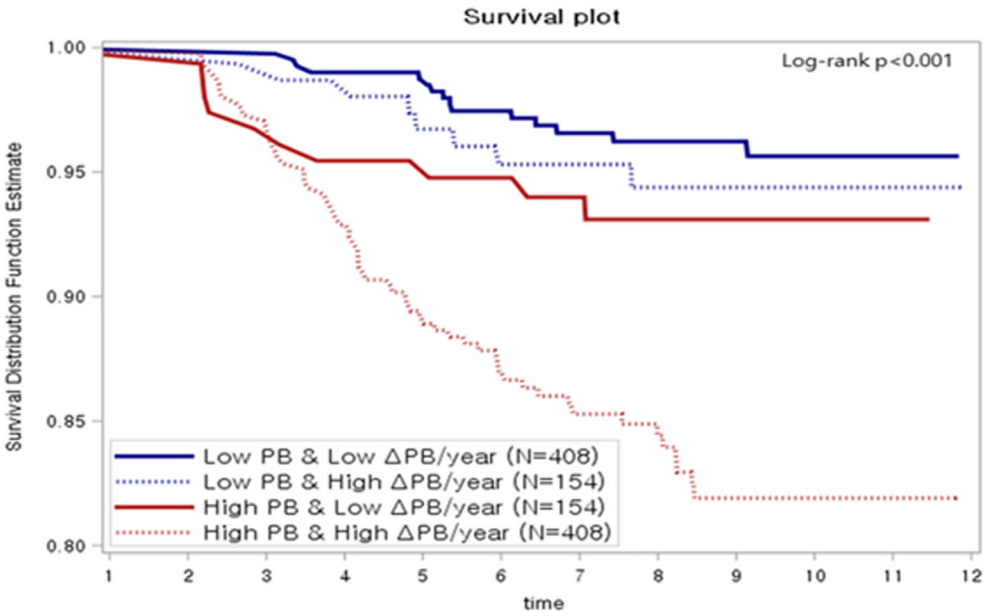

Fig. 3 Event-free survival of patients with different combinations of cross-sectional and longitudinal quantitative indices. When patients were stratified into 4 groups based on baseline plaque burden (PB) and annual progression rate of PB, patients who had both high PB and rapid progression rate experienced the worst clinical outcomes. ΔPB/year, annual progression of plaque burden. (Reproduced with permission from Lee SE et al. [41])

Third, studies have used variable acquisition protocols, and technology for imaging acquisition has evolved over the years. Although most changes in protocol should not have a large impact on the overall amount of plaque, improvements in image quality are likely to impact the total plaque volume. Additionally, changes in contrast injection protocol and kV used in the acquisition can affect the plaque density on coronary CTA. Since plaque density is the feature used to differentiate the plaque components in quantitative analysis, changes in those parameters may impact comparison of studies performed with different techniques.

Fourth, the actual definition of plaque progression and fast progression is not yet standardized. While some studies report changes in overall plaque volume, other studies report changes in individual plaque components, and yet other studies report changes in luminal area or semiquantitative or visual plaque assessment. Without a clear definition of what constitutes coronary atherosclerotic plaque, this entity cannot be adequately reported for clinical purposes.

Conclusions

Several characteristics of CAD detected by coronary CTA have meaningful prognostic implications. The use of serial coronary CTA for the evaluation of disease progression not only is feasible but also provides incremental prognostic information. This value of serial coronary CTA has led to the use of atherosclerosis progression by coronary CTA as a surrogate target for therapy. However, further data is needed on how to adequately implement the information of plaque progression in the routine clinical care.

Compliance with Ethical Standards

Conflict of Interest Guilherme Monteiro, Roberto C. Cury, and Marcio S. Bittencourt declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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