

# Advances in Cardiovascular Imaging

## Noninvasive Imaging of Atherosclerotic Plaque Progression Status of Coronary Computed Tomography Angiography

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**Abstract**—The process of coronary artery disease progression is infrequently visualized. Intravascular ultrasound has been used to gain important insights but is invasive and therefore limited to high-risk patients. For low-to-moderate risk patients, noninvasive methods may be useful to quantitatively monitor plaque progression or regression and to understand and personalize atherosclerosis therapy. This review discusses the potential for coronary computed tomography angiography to evaluate the extent and subtypes of coronary plaque. Computed tomographic technology is evolving and image quality of the method approaches the level required for plaque progression monitoring. Methods to quantify plaque on computed tomography angiography are reviewed as well as a discussion of their use in clinical trials. Limitations of coronary computed tomography angiography compared with competing modalities include limited evaluation of plaque subcomponents and incomplete knowledge of the value of the method especially in patients with low-to-moderate cardiovascular risk. (*Circ Cardiovasc Imaging*. 2015;8:e003316. DOI: 10.1161/CIRCIMAGING.115.003316.)

**Key Words:** atherosclerosis ■ coronary artery disease ■ inflammation ■ myocardial infarction ■ plaque, atherosclerotic

Ischemic heart disease is the most common cause of death and disability worldwide.<sup>1</sup> The underlying process of atherosclerosis in the coronary vessel wall may progress to stenosis or plaque rupture<sup>2,3</sup> often leading to myocardial damage. The evolution of early changes in the vessel wall leading to pathological lesions is conceptualized as a sequential progression from minimal to severe plaque<sup>4</sup> (Figure 1). However the temporal evolution of processes that contribute to plaque formation (eg, inflammation, lipid accumulation, calcification or plaque rupture, healing) have rarely been serially monitored in humans. Direct visualization of the disease process in the vessels may help guide patient management and understand the effects of therapy.

A current limitation in the understanding of coronary atherosclerotic disease in vivo is our ability to noninvasively track and monitor the disease process over time. On a population level, HMG-CoA reductase (statin) medications are effective in reducing cardiovascular disease event rates presumably through the stabilization and perhaps regression of atherosclerotic plaque. At present, individualized assessment of plaque response to therapy is inferred by cholesterol monitoring. However, cholesterol targets are derived based on a population<sup>5</sup>; their relationship to a single individual's disease status is often less clear. In other disciplines such as cancer therapy or infection, imaging of treatment response is critical to assess the success of medical treatments. For atherosclerosis, noninvasive imaging methods that can accurately assess change in coronary plaque burden over time hold the

promise to personalize medical therapy as well as accelerate drug development. At present, the response of atherosclerosis to medical therapy has been demonstrated conclusively only using invasive techniques including catheter coronary angiography<sup>6,7</sup> and intravascular ultrasound (IVUS). IVUS in particular has been shown to be useful for this purpose.<sup>8–11</sup>

The purpose of this review is to provide an overview of recent developments in coronary computed tomography angiography (CCTA) with respect to other imaging methods for defining the extent and subtypes of coronary atherosclerosis. A prior limiting factor of serial CCTA examination has been the relatively high radiation dose. Dramatic developments in CCTA techniques have reduced radiation exposure from CCTA from 15 to 20 mSv to below 1 mSv in selected patients.<sup>12</sup> For plaque characterization and quantification, high image quality is necessary, so that higher radiation doses are likely needed than ultralow doses used for detection of coronary stenosis. The limitations and potential areas of development of CCTA technologies are emphasized in the discussion below.

### Background

#### Pathology: Dynamics of Coronary Artery Disease

The initial course of atherosclerotic disease is thought to begin in early adulthood. In young adults lesions in the arterial vessel wall have been observed surprisingly frequently<sup>13</sup> but the prognostic relevance of early, adaptive, or reversible changes

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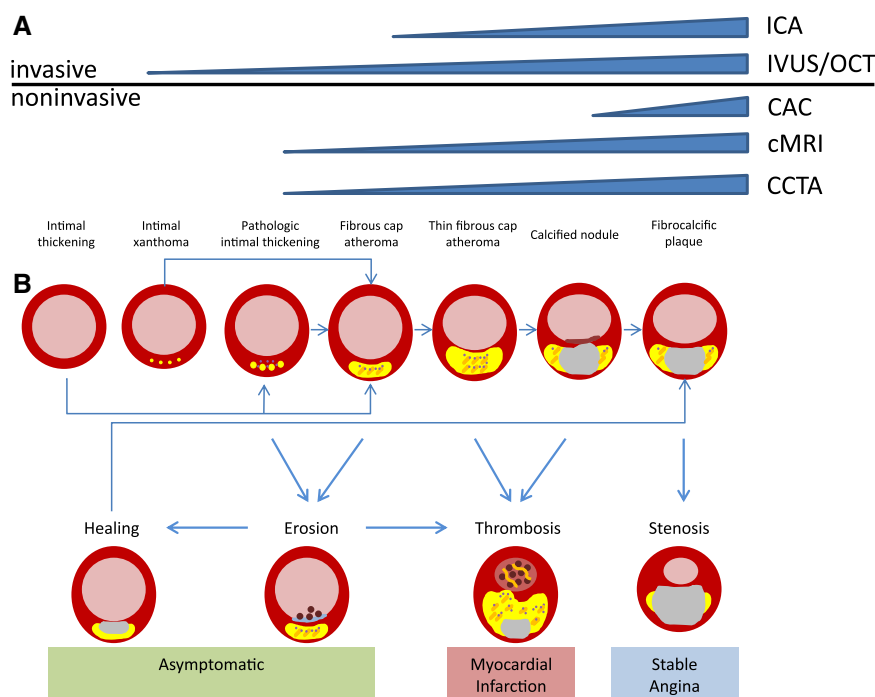
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**Figure 1.** Imaging assessment of atheroma in response to therapy. Development of the atherosclerotic lesion and methods for detection. **A**, The capabilities of various imaging techniques to delineate each pathological correlate of CAD are shown. Optical coherence tomography (OCT) is able to detect earliest phases of plaque formation such as the intimal xanthoma or pathological intimal thickening. In contrast, computed tomographic (CT) calcium score (non-contrast calcium score [CAC]) detects a later stage plaque with calcification. Coronary CT angiography (CCTA) can detect earlier lesions such as fibrous cap atheroma without calcification. **B**, Progression is a nonlinear process. Transitions that have been described in the literature are depicted by arrows. In the earlier stages of atherosclerosis erosions can occur, leading to either asymptomatic healing or possibly to lumen thrombosis and myocardial infarction. Repeated cycles of rupture and healing might lead to the more stable lesion fibrocalcific plaque. A thin cap atheroma can rupture and directly lead to lesion thrombosis and infarction. Less commonly dense calcified nodules can penetrate the fibrous cap and cause thrombosis. Fibrocalcific plaques might represent an end stage of the atherosclerosis process and can contain extensive calcifications. Because of a stable fibrous cap and lower lipid content, these lesions rarely cause thrombosis but can cause chronic ischemic symptoms because of lumen narrowing.<sup>3,4</sup> CCTA indicates coronary CT angiography; cMRI, coronary MRI; ICA, invasive coronary angiography; and IVUS, intravascular ultrasound.

such as fatty streak or intimal thickening remains a matter of debate. Pathology studies seek to integrate autopsy findings from various stages of atherosclerosis to provide a putative sequence of events.<sup>4</sup> In brief, intimal thickening is observed early in the disease process. The early atherosclerotic lesion is composed of smooth muscle cells and is affected by increased macrophage and lipid influx. If this process continues, a necrotic core is formed and the lesion progresses to a fibrous cap atheroma. The necrotic core contains lipids and apoptotic macrophages. A stable fibrous cap may prevent rupture of the lesion. If the fibrous cap loses matrix proteins and smooth muscle cells, a thin cap atheroma can result. Intraplaque hemorrhage is also seen frequently in this entity, leading to further enlargement of the lipid core. The risk of plaque rupture is increased as the fibrous cap thins and the lipid core enlarges.<sup>14</sup> The fibrocalcific plaque is considered to be more stable, although the processes involved in calcification are not fully understood.

### Subclinical Coronary Disease

It is generally conceived that therapeutic intervention for atherosclerosis is most effective when started at an early stage of the progressive disease process.<sup>15</sup> Imaging tools have provided a substantial database of knowledge on disease burden. Imaging of the larger surface vessels (carotid

or femoral arteries) has been extensively used to detect early systemic vascular pathology.<sup>16</sup> Calcium detection using non-contrast CT provides a direct approach to assessing coronary atherosclerosis burden. The coronary artery calcium score has strong predictive power for cardiovascular events in asymptomatic subjects.<sup>17</sup> However, calcium deposition is felt to be a late event in the formation of atherosclerotic plaque. The relevance of noncalcified plaque is emphasized by prospective IVUS studies that show coronary fibroatheroma without significant calcification confers an elevated risk for myocardial infarction.<sup>18</sup> Noncalcified plaque is more common than calcified plaque in asymptomatic individuals aged <45 years. The ability to noninvasively image noncalcified plaque or wall thickening of the coronary arteries using MRI or CT enables the detection of earlier stages of atherosclerotic disease.<sup>19,20</sup>

## Imaging of Atherosclerotic Plaque Burden and Progression

### Invasive Coronary Imaging

#### Intravascular Ultrasound

Invasive coronary angiography delineates the vessel lumen with high quality, but the amount and composition of atherosclerotic plaque are not shown. The additional

step of IVUS<sup>21</sup> constitutes the current gold standard for plaque quantification. Multiple studies using IVUS and other techniques have revealed a robust relation between statin therapy and plaque regression<sup>11,22–35</sup> (Table 1). In the ASTEROID trial coronary atheroma volume regressed by 6.8% during 24 months of high-intensity lipid therapy.<sup>23</sup> A meta-analysis of IVUS trials including 7864 patients showed an association between plaque regression and decreased cardiovascular events.<sup>36</sup>

### Optical Coherence Tomography

Optical coherence tomography provides an order of magnitude higher resolution when compared with IVUS but lacks delineation of the outer vessel boundary because of weaker penetration. Optical coherence tomography has the unique ability to directly visualize thin cap fibroatheroma (cap diameter <65  $\mu\text{m}$ ; resolution of optical coherence tomography, 10  $\mu\text{m}$ ).<sup>37</sup> Using serial optical coherence tomography imaging, Habara et al<sup>24</sup> recently showed that the fibrous cap thickness of lipid-rich plaque increased after 9 months of lipid treatment.

### Near Infrared Spectroscopy

Near infrared spectroscopy is able to image the lipid content of plaques. A short-term follow-up study showed a significant reduction in plaque lipid content as early as 7 weeks after starting intensive statin treatment.<sup>25</sup>

## Magnetic Resonance Imaging

### Coronary MRI

MRI demonstrates the coronary vessel lumen and characterizes the coronary vessel wall.<sup>38–40</sup> Using black blood imaging in the Multi-Ethnic Study of Atherosclerosis (MESA) study, coronary MRI demonstrated greater coronary artery wall thickness in individuals with a greater number of cardiovascular risk factors.<sup>39</sup> Similar methods demonstrated that HIV patients had an increased right coronary artery wall thickness when compared with control patients.<sup>20</sup> Positive remodeling may also be visualized using MRI.<sup>40</sup> No studies have examined coronary plaque regression using MRI. Routine clinical use of coronary MRI has been limited to niche applications mainly because the high technical requirements to achieve consistent quality.

### Carotid MRI

The relatively large size and superficial position of the carotid arteries make these vessels amenable to assessment by MRI. Because of excellent soft tissue resolution of MRI, imaging of plaque subcomponents can be accomplished<sup>16</sup> in addition to plaque burden quantification. MRI has been used in longitudinal studies that have elucidated predictors of progression including intraplaque hemorrhage,<sup>41</sup> treatment effects such as lipid depletion<sup>42</sup> or plaque regression.<sup>26,27</sup>

Nevertheless, cardiac events outnumber cerebrovascular events. In an analysis of the MESA data, calcium score was a

**Table 1. Examples of Longitudinal Atherosclerosis Imaging Trials**

Authors	Modality	Design	Main Imaging Finding	n
Lichtlen et al <sup>22</sup>	Invasive angiography	Prospective, randomized	Severity and number of stenoses increases over time	230
Nissen et al <sup>11</sup>	Coronary IVUS	Prospective	Change in percent atheroma volume 1.6 (atorvastatin) vs 0.3 (pravastatin)	502
Nissen et al <sup>23</sup>	Coronary IVUS	Prospective	6.8% plaque volume regression using statin	349
Habara et al <sup>24</sup>	Coronary OCT	Prospective	Fibrous-cap thickness increased after 9 mo statin/ezetimibe	63
Kini et al <sup>25</sup>	Coronary NIRS	Prospective	Short-term reduction of plaque lipid content with high-intensity lipid therapy	87
Corti et al <sup>26</sup>	Carotid MRI	Prospective	18% wall volume regression in statin therapy	29
Sibley et al <sup>27</sup>	Carotid MRI	Prospective, randomized	10% wall volume regression in statin therapy	145
Arad et al <sup>28</sup>	Coronary calcium score	Prospective, randomized	No effect of statin treatment on CAC progression	2005
Hoffmann et al <sup>29</sup>	CCTA, volume (CP, NCP, mixed plaque)	Retrospective observational	Noncalcified plaque increased from 21 to 29 mm <sup>3</sup> (38%)	63
Tardif et al <sup>30</sup>	CCTA, volume (NCP), number of plaques, plaque CT numbers	Prospective, randomized	Volume of noncalcified plaque Placebo: 6% increase VIA-2291: –4.9% decrease	28
Burgstahler et al <sup>31</sup>	CCTA, volume (NCP, CP)	Prospective, atorvastatin	Noncalcified plaque decreased by 24%	20
Papadopoulos et al <sup>32</sup>	CCTA, lumen diameter and area, total plaque volume, remodeling index (...)	Prospective, observational	Normalized atheroma volume increased by 47 mm <sup>3</sup> (6.7%)	32
Zeb et al <sup>33</sup>	CCTA, volume (NCP, CP, low attenuation plaque), remodeling index	Retrospective	28% decrease in noncalcified plaque volume	60
Lehman et al <sup>35</sup>	CCTA, number of slices with plaque (NCP, CP)	Prospective	12.7% increase in number of slices with plaque.	69
Lo et al <sup>34</sup>	CCTA, lumen stenosis, volume (NCP, total), high risk plaque features	Prospective, randomized, atorvastatin	Plaque volume Placebo: +18.2%, Atorvastatin: –4.7%	37

The lower part of the table shows a selection of CCTA plaque progression trials. Design, sample size, patient population, follow-up time, and CT scanner technology are heterogeneous among these examples. CAC indicates non-contrast calcium score; CCTA, coronary CT angiography; CP, calcified plaque; CT, computed tomography; IVUS, intravascular ultrasound; MP, mixed (partially calcified) plaque; NCP, noncalcified plaque; NIRS, near infrared spectroscopy; and OCT, optical coherence tomography.

better predictor of subsequent CVD events than carotid IMT.<sup>43</sup> Thus, direct imaging of the coronary vessels promises better predictive power for cardiovascular events when compared with carotid imaging.

## Computed Tomography

### Non-Contrast CT Calcium Score

Non-contrast CT calcium score scoring is extensively used for risk stratification in clinical practice. The most common method to quantify calcium is the Agatston calcium score. The method exclusively focuses on the calcified plaque component and is unable to quantify vascular stenosis. Nevertheless, there exists a tremendous amount of data indicating a strong and robust predictive power of this test.<sup>44</sup> Data from the MESA show an incremental predictive value for cardiovascular events of the calcium score when added to traditional risk factors.<sup>17</sup>

Despite the extensive research support for non-contrast CT calcium score as a tool for risk stratification, data on the ability of the calcium score to reflect treatment effects are inconclusive. Several nonrandomized studies showed evidence of a slower progression of coronary calcifications in patients treated with statins when compared with untreated patients<sup>45–47</sup> as reviewed by Priester et al.<sup>48</sup> However, in the prospective randomized St. Francis heart study,<sup>28</sup> the baseline calcium score was the only significant predictor for cardiovascular events; change of coronary calcium after 2 and 4 years was not affected by treatment with atorvastatin or placebo. Change of calcium score did not predict cardiovascular events after adjusting for baseline calcium score. The prospective randomized Beyond Endorsed Lipid Lowering With EBT

Scanning (BELLES) trial reported by Raggi et al<sup>49</sup> compared atorvastatin 80 mg with pravastatin 40 mg and found no significant difference in progression of coronary calcium volume after 1 year (15.1% and 14.3%, respectively). IVUS studies have shown that calcified lesions are less likely to be influenced by medical therapies.<sup>50</sup> Thus, calcium score does not seem to be useful for assessing plaque regression for either clinical purposes or research studies.

### Contrast-Enhanced CT Coronary Angiography

In clinical practice, CCTA is mainly used in symptomatic subjects at moderate risk according to the Appropriate Use Criteria.<sup>51</sup> CCTA can characterize not only lumen stenosis but also plaque subcomponents (calcified, noncalcified) and arterial remodeling. The degree and characteristics of atherosclerosis are highly relevant to the concept of overall coronary plaque burden. The importance of overall plaque burden was emphasized by a study showing that patients with widespread nonobstructive CAD had similar event rates when compared with patients with localized obstructive disease<sup>52</sup> using qualitative assessment. Moreover, quantitative analysis of overall coronary plaque volume is now available. Studies showing increased noncalcified plaque volumes in acute coronary syndrome (ACS) patients<sup>53</sup> or in obese diabetics<sup>54</sup> as well as response to statin therapy<sup>34</sup> suggest that overall coronary plaque burden may have clinical relevance.

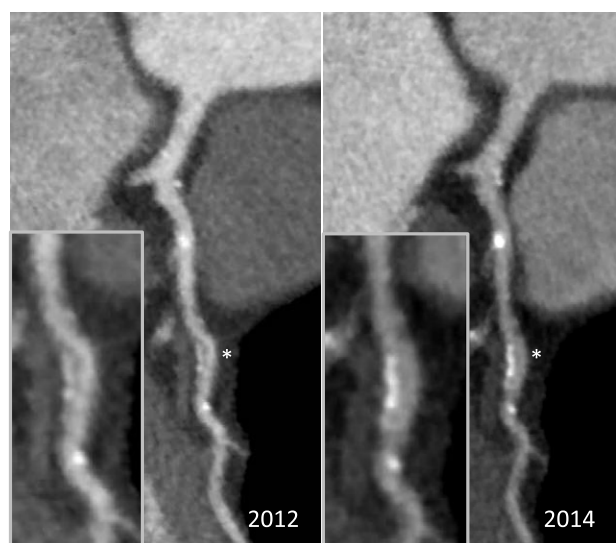
CCTA has been extensively compared with IVUS<sup>55–65</sup> (reviewed in 66 and 67; overview in Table 2). A meta-analysis concluded that overall plaque volumes measured using CCTA and IVUS do not differ significantly on a study sample basis.<sup>67</sup> A recent study showed an excellent correlation of individual plaque measurements ( $r=0.94$  for expert-assisted

**Table 2. Overview of Selected Studies Comparing CCTA With Intravascular Ultrasound**

Authors	Number	CT Technology	Method	Mean Difference, mm <sup>3</sup>
Brodoefel et al <sup>55</sup>	14	64 slice 120 kVp	Automatic (Vitrea SurePlaque, Toshiba)	+7.7
Dey et al <sup>56</sup>	20	64 slice 120 kVp	Automatic (Autoplaq, Cedars-Sinai Medical Center) and manual	10.7 (automatic NCP) –5.1 (manual NCP)
Harada et al <sup>57</sup>	17	64 slice 120/135 kVp	Automatic	+58 (total) –16 (fibrous)
Bruining et al <sup>58</sup>	48	16 slice 120 kVp	Semiautomatic (CURAD)	+32.75 (total)
Akutagawa et al <sup>59</sup>	21	64 slice	Automatic (Vitrea SurePlaque, Toshiba)	–46.7 (total)
Pedrazzini et al <sup>60</sup>	57	64 slice 100/120 kVp	Automatic (CardIQ Xpress Pro, GE)	+1.9 (total)
Park et al <sup>61</sup>	151	64 slice 100/120 kVp	Automatic and semiautomatic (QAngio CT, Medis, NL)	Total: –22.28 (automatic) +12 (expert) NCP: –27 (automatic) –3.6 (expert)
de Graaf et al <sup>62</sup>	57	64 slice (16) 320 slice (41) 120 kVp	Automatic (QAngio CT, Medis, NL)	+36.5
Nakazato et al <sup>63</sup>	27	64 slice 100/120 kVp	Manual	–4.4 (total)
Schepis et al <sup>64</sup>	70	64 slice 120 kVp	Manual	–1 (total)
Otsuka et al <sup>65</sup>	47	64 slice 120 kVp	Manual	–2 (total) –9 (NCP) –4 (CP)

CCTA indicates coronary computed tomography angiography; CP, calcified plaque; NCP, noncalcified plaque, and positive mean difference, overestimation of volume by CCTA.





**Figure 2.** Example of plaque change in the LAD for 2 years. The lesion (\*) plaque volume (2012) was 151 mm<sup>3</sup> and (2014) an increased amount of calcification is seen but the lesion plaque volume decreased to 135 mm<sup>3</sup> (change, −11%). The patient was on atorvastatin 20 mg.

semiautomated method).<sup>61</sup> An ex vivo study highlights the limitations of CCTA, especially in detecting small noncalcified plaques (<1 mm) and potential misclassification of plaque subcomponents.<sup>68</sup>

A limitation of CT is the relatively poor soft tissue contrast particularly compared with excellent soft tissue contrast available with MRI. A critical issue for measurement of noncalcified plaque is the outer vessel border which is the demarcation between adventitia or plaque and surrounding fat tissue.<sup>69</sup> Identification of the outer vessel border is feasible, but is optimally performed at low noise (ie, higher radiation) levels. In addition, CT technology performs poorly when compared with MRI for the identification of plaque subcomponents. Although radiation for CCTA has been markedly reduced and can approach 1 mSv, in our experience, quantification of plaque is not readily performed at this ultralow radiation dose. Technical developments in CCTA including spectral (multienergy) CT and improved detector systems may eventually provide increased capability in this regard.

### Coronary CT Angiography Assessment of Plaque Burden and Progression

CCTA has matured to a routine clinical tool with excellent sensitivity (≥80%) and specificity (99%) for coronary artery stenosis.<sup>70,71</sup> Besides the assessment of stenosis, CCTA can measure overall plaque burden. A key issue that remains to be determined is the capability of CCTA to track changes in plaque burden over time (Figure 2). This section addresses the current state of the art of CCTA for quantitative measurement of plaque burden with respect to image acquisition and processing.

### CT Acquisition

Based on IVUS data, the change in extent of coronary plaque seems to be small for a timeframe of 1 or 2 years. Thus,

serial imaging of the coronary arteries by CCTA requires consistent and high-quality CT acquisitions using the same CCTA instrument for many years. An example of technical change of CCTA is reflected by radiation dose data: a median dose of 12.5 mSv for CTA was reported in a multicenter analysis 2009<sup>72</sup> but third generation CCTA scanners achieve comparable image quality with a dose of <1 mSv<sup>12,73</sup> (Figure 3). Faster acquisition speeds have been achieved by faster rotation, larger detectors, and dual source systems. This also results in reduced artifacts which may provide increased reproducibility and improved plaque quantification and characterization.<sup>74</sup>

Recently, complex image reconstruction (iterative reconstruction) has been introduced in commercial CT systems, which improves image quality with regard to noise, resolution, artifacts, and most importantly diagnostic accuracy.<sup>75</sup>

### Quantification of Plaque by CCTA

For the assessment of plaque progression, the quantification and characterization of plaque are key issues. For semiquantitative methods, the location of coronary segments is determined by the American Heart Association nomenclature adapted for CCTA.<sup>76</sup> Methods for scoring the degree of plaque in coronary segments are described below.

#### Segment Involvement Score

A simple and highly reproducible semiquantitative measurement is the segment involvement score which describes the number of segments affected by any plaque as seen on CCTA<sup>77,78</sup> (Figure 4). A score >5 has been shown to have additional prognostic value for overall survival independent of clinical risk factors.<sup>78</sup> Because the individual lesion severity is not taken into account, the use of a categorical score for monitoring small changes in plaque progression seems limited.

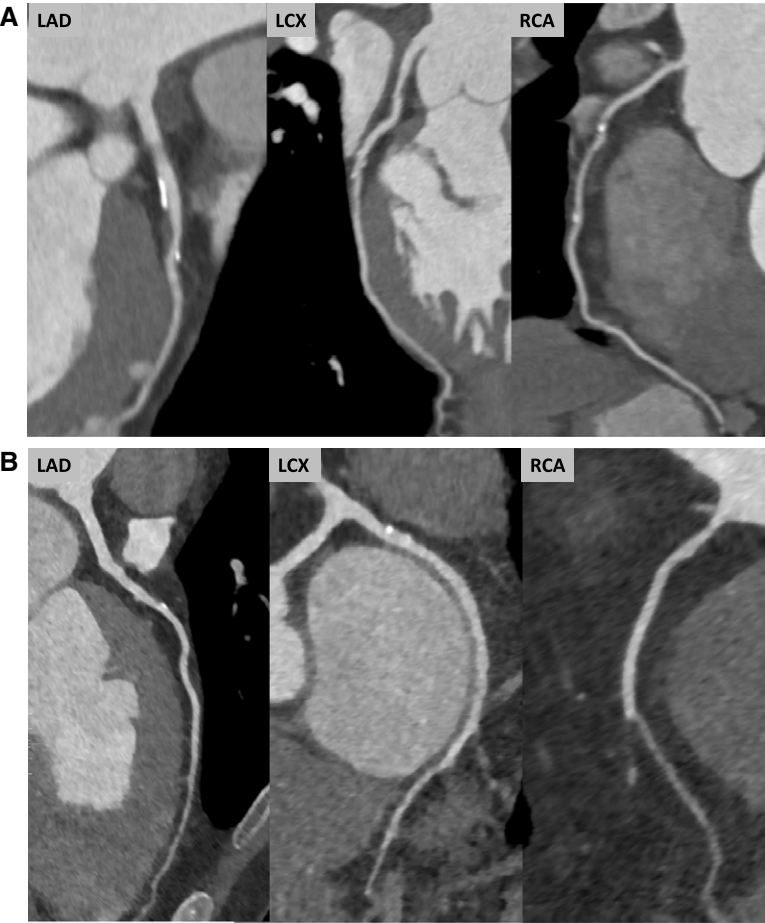
#### Segment Stenosis Score

The segment stenosis score (SSS) assigns a number from 0 to 3 to each segment based on maximum diameter stenosis in each segment (0 for <30%, 1 for 30%–49%, 2 for 50%–69%; and 3 for ≥70%). Segments are then added to yield the SSS. Incremental prognostic value of the SSS method has been shown.<sup>78</sup> The progression of stenosis may potentially be followed over time on a semiquantitative level using the SSS.

#### Segmental Plaque Score

The amount of plaque present and severity of stenosis are not necessarily correlated. An approach to account for both severity of stenosis and degree of plaque is the segmental plaque score. For this score, the amount of plaque (both calcified or noncalcified) in each segment is graded visually into the categories none or trace=0, mild=1, moderate=2, and severe=3.<sup>79</sup> As with the prior scores, a total score is derived as the sum of the individual segment scores.

The segment scores described above may be readily applied but all rely on angiographic naming conventions of coronary artery segments. In a segment-free approach, Lehman et al<sup>35</sup> first identified the centerline of each coronary artery. The number of cross-sections along the centerline showing any plaque was then counted. In the same manner calcified and noncalcified plaque was assessed.



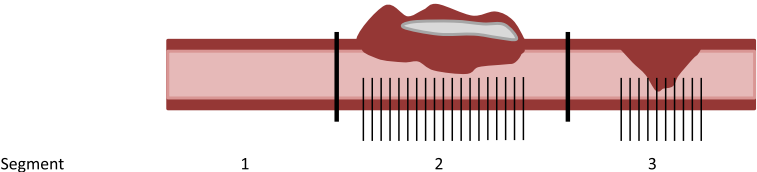
**Figure 3.** Examples for high-quality computed tomography angiography imaging at relatively low doses (**A**: 1 mSv, 90 kV; **B**: 0.5 mSv, 80 kV). These are high-pitch prospectively ECG-triggered acquisition reconstructed with model-based iterative reconstruction.

*IVUS-like Methodology Applied to CCTA*

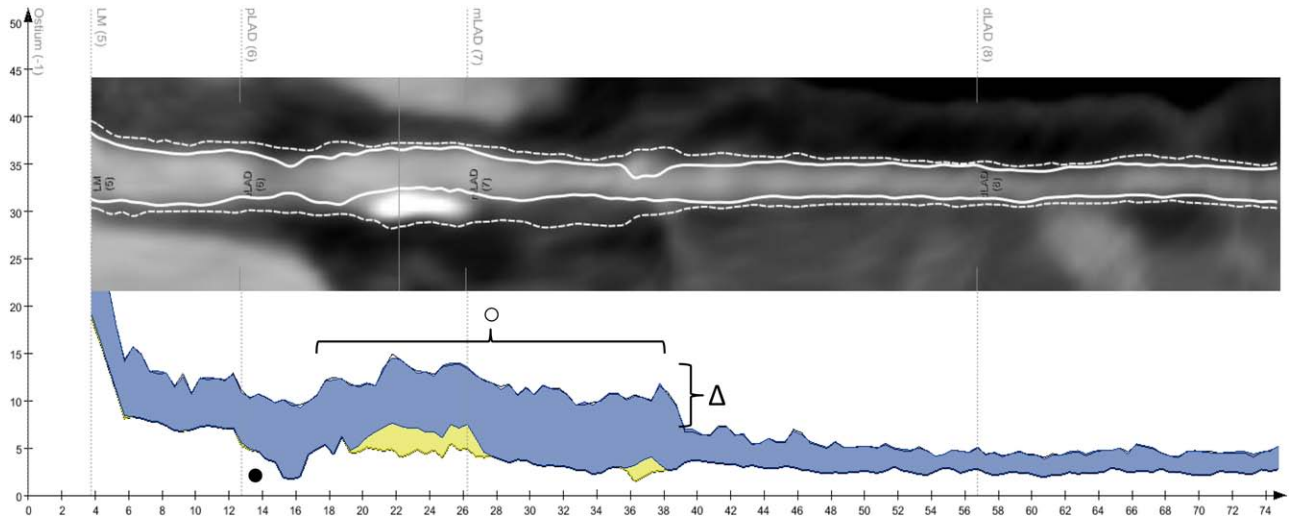
Using IVUS, plaque volumes are calculated as the difference between the external elastic membrane area and the lumen area for successive cross-sections of a coronary artery. Change in plaque volume has been successfully used to monitor plaque progression in IVUS studies. The spatial resolution of CCTA is insufficient to depict the

external elastic membrane as a separate structure, but the outer border of the vessel wall is often defined by epicardial fat. In addition, the inner border of the arterial wall is defined by iodine contrast material in the vascular lumen<sup>80</sup> (Figure 5). The difference between outer vessel volume and lumen volume constitutes the CCTA defined total plaque/media volume. From these volumes, further parameters

				Total score
Segment involvement (SIS):	0	1	1	2
Plaque burden (SPS):	0	3 (severe)	1 (mild)	4
Segment stenosis (SSS):	0	1 (30-49%)	3 (>70%)	4
Cross-section method:				
Any Plaque:	0	19	10	29
Calcified Plaque:	0	13	0	13
Noncalcified Plaque:	0	6	10	16



**Figure 4.** Semiquantitative plaque scores by coronary computed tomography angiography. Three coronary segments are shown to demonstrate the scoring system. For the segment involvement score (SIS) each coronary segment is assigned the number 1 for having any plaque or 0 for having no plaque. For the segmental plaque score (SPS) a number is assigned to each segment based on a semiquantitative plaque burden assessment (0, none or trivial; 1, mild; 2, moderate; and 3, severe). For the segment stenosis score the maximum stenosis in each segment is graded into 3 levels (0: <30%, 1: 30%–49%, 2: 50%–69%, and 3: ≥70%). For each of these methods the sum of all segments constitutes the respective score. For the method proposed by Lehman et al<sup>35</sup> (cross-section method) vessel cross-sections spaced at 1 mm intervals along the vessel centerline are evaluated for the presence of plaque. The number of affected cross-sections represents the measurement of the total plaque burden. This can be repeated for calcified plaque and noncalcified plaque.



**Figure 5.** View of a LAD partially calcified plaque with a large noncalcified component. The inner lumen boundary and the outer vessel boundary are defined. Based on computed tomographic density (Hounsfield unit), calcified and noncalcified plaque subcomponents are classified. The graph shows the plaque quantification of this vessel (blue, noncalcified; yellow, calcified). The large mixed plaque (○) with positive remodeling (Δ) and preserved lumen as well as an intermediate stenosis without calcification (●) can be identified on the graph. (QAngioCT, Medis, NL).

such as percent atheroma volume or normalized atheroma volume can be derived.<sup>81</sup>

Defining the lumen and outer vessel boundaries is time consuming and observer dependent when performed manually. Multiple software packages offer automatic and semiautomatic modes. Overall studies using manual measurements or automatic methods showed similar results<sup>67</sup> (Table 2). Automatic segmentation can be technically difficult because of variations in lumen attenuation, overlap in CT numbers of iodine and calcified plaque, and inherently low tissue contrast of CT. For segmentation the centerline of the vessel is defined first to generate a curved multiplanar reconstruction. An edge finding algorithm traces the lumen border taking into account the current lumen attenuation and an optional manual correction of the contours is offered. In the next step the outer contours are generated. Traditionally, fixed HU cutoffs have been used to differentiate plaque subtypes but lumen attenuation can affect plaque attenuation. This can be addressed using adaptive thresholds that account for partial volume averaging because of lumen attenuation values.<sup>62</sup> Accurate, reproducible, and fully automatic measurements would be ideal for plaque progression studies but in our experience user interaction is often necessary for optimal contours. A study directly comparing different plaque measurement methods with IVUS

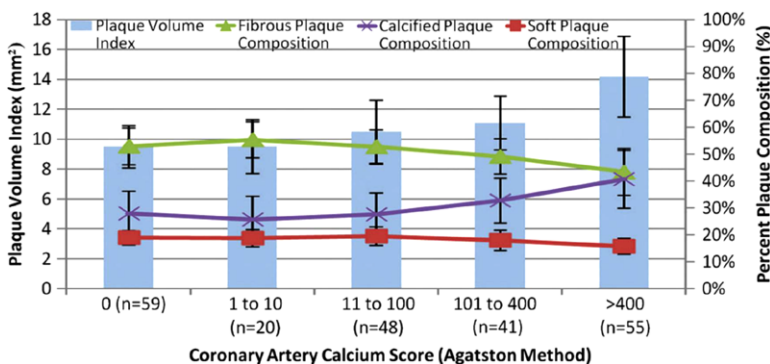
showed the best results for semiautomatic expert-guided measurements.<sup>61</sup>

Semiautomated quantification of plaque volume was of incremental predictive value in a study of patients with stable angina pectoris.<sup>82</sup> In patients with ACS plaque volume predicted recurrent ACS in univariate analysis.<sup>83</sup>

### Characterization of Plaque by CCTA

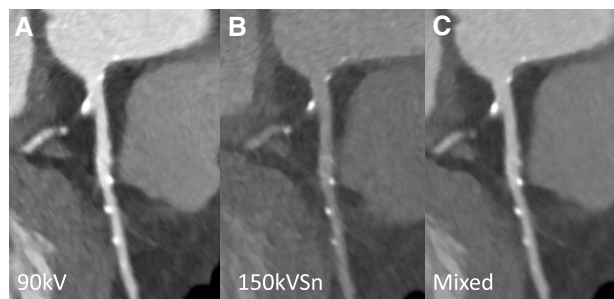
Calcified and noncalcified plaque have different pathophysiology and prognostic implications and thus their separate components of plaque have been emphasized in CCTA analysis. Noncalcified plaque was seen more frequently in acute chest pain when compared with stable angina patients.<sup>84</sup> The amount of noncalcified plaque was an independent predictor of adverse events in a population with stable angina.<sup>82</sup>

Using CCTA, calcified versus noncalcified plaque can be quantified based on CT density cutoff values. Using this approach, Kwan et al<sup>54</sup> showed that the percentage of calcified plaque was greater in diabetic patients with high calcium scores and larger CCTA total plaque volumes (Figure 6). An ex vivo comparison to histology showed the ability of CCTA to differentiate noncalcified, mixed, and calcified plaques.<sup>85</sup> Further subclassification of noncalcified plaque into fibrous or fatty components using CT attenuation<sup>85,86</sup> values is less



**Figure 6.** The relationship between calcium score and plaque subtypes by coronary computed tomography angiography in diabetic patients. Patients with greater calcium scores had lower percentage of noncalcified plaque components. Reprinted from Kwan et al<sup>54</sup> with permission of the publisher. Copyright ©2014, the Radiological Society of North America.





**Figure 7.** Example of a dual-energy coronary computed tomographic acquisition on a dual-source scanner. **A**, A 90-kV tube voltage, **(B)** 150-kV tube voltage and tin filter applied, **(C)** overlay of both images. Overall, the 90-kV image has higher image contrast. The attenuation of iodine is higher at lower kV (**A**) when compared with high kV (**B**). This may be useful for algorithmic plaque segmentation. The lumen border is also better visualized at 90 kV which is helpful for the assessment of noncalcified plaque. Calcium blooming artifacts are more seen at 150 kV when compared with those seen at 90 kV. The overlay image **C** seems to be useful for clinical assessment.

reliable. A key difficulty is that voxel sizes of CCTA are relatively large when compared with the pathology being measured with resulting uncertainty in plaque density measurements. As indicated above, CCTA also has relatively low soft tissue contrast resolution, so that attenuation differences between varying plaque components are small.

There are several solutions for further improvement in plaque characterization. Improved spatial resolution of the technique will reduce partial volume effects and improve classification of atheroma density. Dual-energy CT can reduce blooming effects that occur close to calcium and iodine and in theory lead to more valid density measurements of plaques<sup>87,88</sup> (Figure 7). Boll et al<sup>89</sup> showed that dual-energy CT resulted in higher accuracy for calcified plaque measurements. Another possible application is better separation of iodine and calcium and thereby improving plaque segmentation.<sup>90</sup> Dual-energy CT technology is rapidly improving because of better energy separation combined with improved spatial and temporal resolution of the latest generation of CT devices (Figure 8). Future

developments have the potential to provide high-speed multi-energy acquisitions using low radiation doses.<sup>91</sup> Applications of dual energy in CCTA have recently been reviewed.<sup>92</sup>

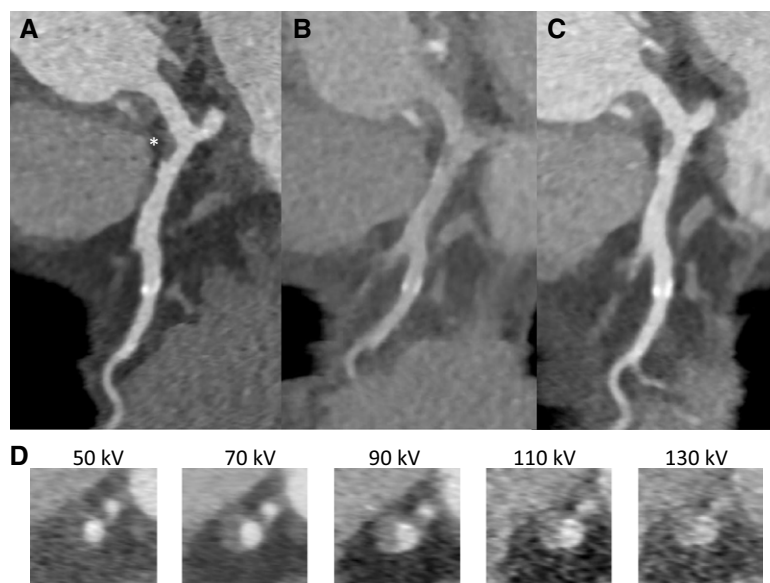
Apart from tissue classification, CCTA can also visualize morphological plaque features that have been shown to provide additional diagnostic and prognostic information (reviewed in 93). Spotty calcification, small (<3 mm) calcification surrounded by noncalcified plaque, has been associated with accelerated plaque progression using IVUS data<sup>94</sup> and was seen more frequently in culprit lesions when compared with stable lesions.<sup>84</sup> The napkin sign (a ring of high attenuation around a coronary plaque), positive remodeling, low Hounsfield unit plaque, and spotty calcium were associated with ACS independently of stenosis in an analysis of the ROMICAT II trial.<sup>95</sup>

Morphological high-risk CT plaque features may also be an indicator of a higher level of vascular inflammation as indicated by a positron emission tomography/CT study of the carotid arteries<sup>96</sup> and a positron emission tomography/CCTA coronary study in HIV patients.<sup>97</sup> This might be useful for research in populations with increased levels of inflammation, for example, caused by obesity, smoking, or increased inflammatory states because of specific diseases (autoimmune or chronic infectious).

### Clinical Trials for CCTA Plaque Regression

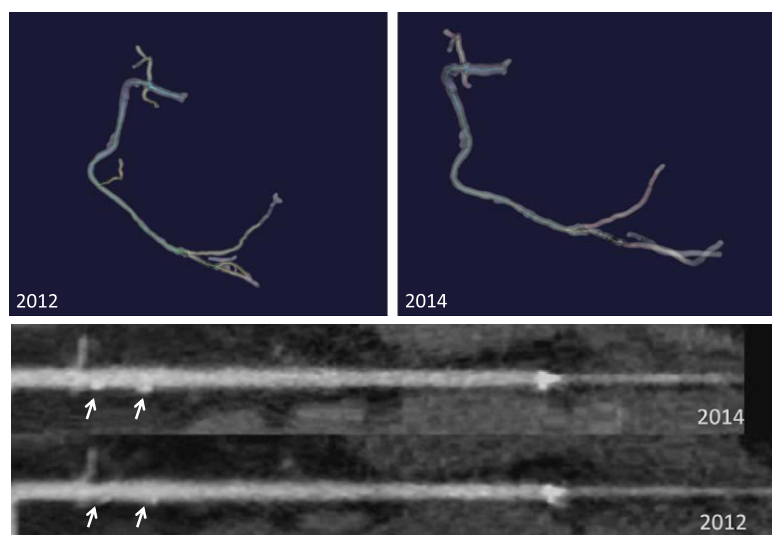
To date, most studies assessing plaque regression by CCTA have evaluated patients with ACS or have been retrospective clinical reviews (Table 1, lower part). Zeb et al<sup>33</sup> retrospectively studied patients who underwent 2 CCTA examinations for clinical indications and used semiautomatic quantification software to compare plaque volumes. In 60 patients treated with statins, the noncalcified plaque volume was reduced after ≈1 year, whereas calcified plaque volume was unchanged.

For ACS patients, Lehman et al<sup>35</sup> recruited 69 patients from the prospective ROMICAT trial. A second CT was performed after 2 years and a semiquantitative score was used for quantification. The study showed an increase in plaque burden



**Figure 8.** Dual-energy plaque imaging example. A dual-energy acquisition with 90 kV (**A**) and 150 kV tin filtered (**B**) is shown (mixed, **C**). A cross-section of a plaque (\*) is shown in **D** at simulated monochromatic photon energies (Siemens Force, Software: SyngoVia). At a low simulated energy (**D**, 50 kV) the contrast is mainly driven by iodine and the outer vessel border is ill defined. At 70 and 90 kV, the differentiation of plaque and surrounding fat tissue is improved. In this acquisition higher simulated voltages do not show further improved image quality.





**Figure 9.** Image comparison: 2 computed tomography (CT) angiographies of the same patient performed 2 years apart. Similar centerlines of the RCA are selected (**upper**) and corresponding curved multiplanar reconstructions were generated (**lower**) using VMTK (vmtk.org). This form of visualization could facilitate comparison of 2 CT data sets. Slight progression of atherosclerosis is seen in the proximal RCA (arrows).

of 13% driven by an increase of noncalcified plaque with no significant increase of calcified plaque.<sup>35</sup> Papadopoulou et al<sup>32</sup> prospectively recruited patients with ACS in the PROSPECT trial to undergo a second CT after 3 years. A semiautomatic quantification software was used and results showed an increase in plaque volume of 5.8% accompanied by compensatory positive remodeling.

Recently, Lo et al<sup>34</sup> reported the results of a prospective randomized double-blinded lipid therapy trial in HIV patients. This study underscores the remarkable changes in plaque size that can be observed using CCTA (change +12% in placebo group versus −4.7% in atorvastatin group for lesion total plaque volume for 1 year). Notably, the noncalcified plaque regressed by 19.4% in the atorvastatin group. In addition, the high risk plaque features low attenuation and positive remodeling were reduced.

Taken together, these initial studies are comparable in showing change in noncalcified plaque volume rather than calcified plaque.

### Limitations and Challenges of CCTA

There are several issues that have to be clarified for future CCTA plaque follow-up imaging trials. A key issue is high reproducibility (test–retest) which needs to be firmly established. A study conducted in 30 patients on different CT scanners showed reasonable interscan reproducibility (repeatability coefficient 109 mm<sup>2</sup> for plaque volume measurement and below 10% for plaque composition) using a semiautomatic quantitative software.<sup>98</sup>

Excellent reproducibility of CCTA images is necessary to reduce sample size in clinical trials and to allow serial assessment of CCTA studies. Image quality is of high importance. For example, in a randomized trial with CT evaluation as a secondary end point in a subgroup 28 of 88 patients had to be excluded because of insufficient image quality in one of the examinations.<sup>30</sup> The reproducibility study by Schuhbaeck et al<sup>98</sup> noted suboptimal image quality as the most important reason for diverging measurements. Finally, image analysis methods need further optimization. Analytic methods for plaque assessment with CCTA are not standardized. For

example, guidelines developed for IVUS discourage measurement of individual plaque volumes because the beginning and end of a plaque is poorly defined<sup>99</sup> and instead advocate using anatomic landmarks. Similar approaches have not been adapted to CCTA image analysis. Future image analysis tools enabling a side by side visualization could facilitate image comparison and improve the assessment of plaque progression (Figure 9).

### Summary

The current use of coronary CT angiography has focused on depiction of coronary stenosis. Rapid advances in image reconstruction have allowed substantially lower radiation doses for CCTA. Multienergy technology and improved detector technology have also resulted in improved image quality. Recent research efforts have demonstrated the potential of CCTA for quantification of calcified and noncalcified plaque. Research to date for CCTA plaque quantification has mostly focused on high-risk populations or has been retrospective; additional prospective studies of low to moderate risk subjects are needed to determine the reliability of the CCTA method and to clarify the role of CCTA to detect plaque progression or regression.

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### Disclosures

None.

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