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Invited review

## How accurate is atherosclerosis imaging by coronary computed tomography angiography?

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## ABSTRACT

Invasive coronary plaque imaging such as intravascular ultrasound and optical coherence tomography has been widely used to observe culprit or non-culprit coronary atherosclerosis, as well as optimize stent sizing, apposition and deployment. Coronary computed tomographic angiography (CTA) is non-invasively available to assess coronary artery disease (CAD) and has become an appropriate strategy to evaluate patients with suspected CAD. Given recent technologies, semi-automated plaque software is available to identify coronary plaque stenosis, volume and characteristics and potentially allows to be used for the assessment of more details of plaque information, progression and future risk as a surrogate tool of the invasive imaging modalities. This review article aims to focus on various evidence in coronary plaque imaging by coronary CTA and describes how accurate coronary CTA can classify coronary atherosclerosis.

## 1. Introduction

Coronary artery disease (CAD) is the major cause of death in adults in most countries. Despite “near normal” findings of coronary arteries by invasive coronary angiography (ICA), numerous patients were later found to experience myocardial infarction (MI) or cardiac death, implying that the pathogenetic mechanisms underlying atherosclerosis could be involved.<sup>1</sup>

Invasive modalities such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) have been used to identify the presence, extent, volume, and characteristics of coronary atherosclerosis and have long contributed to help understand the mechanisms of MI.<sup>2,3</sup> “Vulnerable plaque” or “high risk plaque” has been recognized as a key contributor to the incidence of MI or cardiac death, and commonly found by IVUS or OCT.<sup>2,3</sup> The role of cardiac imaging in the early diagnosis of coronary atherosclerosis has grown significantly in the current era. Given its high diagnostic yield, coronary computed tomography angiography (CTA) has been widely adopted and coronary CTA has become an initial strategy for the diagnosis among patients with stable chest pain.<sup>4</sup>

The pathogenesis of the underlying atherosclerosis is incompletely

understood; therefore, numerous studies have investigated the pathophysiology of atherosclerosis in order to prevent future cardiovascular events. In this review article, we summarized the current studies investigating the current state of the art atherosclerosis imaging by coronary CTA and how it compares to more invasive imaging modalities.

## 2. Validation of CT measurements

## 2.1. Qualitative assessment of coronary atherosclerosis by coronary CTA

Numerous studies have assessed coronary plaque using coronary CTA and compared these measures to IVUS, OCT and histology<sup>5–12</sup> (Table 1). Previously, the studies have mainly focused on the detection of stenosis severity and plaque volume by coronary CTA, but later studies have been designed to focus on the detection of high-risk plaque (HRP). In ex vivo data with 284 cross-sections, average plaque burden correlated well between IVUS and coronary CTA ( $r = 0.45–0.52$ ,  $p < 0.001$ ).<sup>13</sup> From the ATLANTA study in 60 patients undergoing both of IVUS with radiofrequency backscatter analysis (IVUS/VH) and coronary CTA, Voros et al. reported modest to good correlations between IVUS/VH and coronary CTA ( $r = 0.41–0.84$ ).<sup>12</sup> Voros et al. have

Abbreviations: CTA, Computed tomography angiography; IVUS, Intravascular ultrasound; OCT, Optical coherence tomography

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**Table 1**  
Qualitative assessment of coronary atherosclerosis by coronary CTA.

Authors	Number	Modality	Main findings	Reference
Leber AW J Am Coll Cardiol. 2006	36 vessels in 19 patients	IVUS	1. Plaque volume; $r^2 = 0.69$ , $p < 0.001$ 2. Plaque volume between coronary CTA and IVUS 1. Non-calcified; $59.8 \pm 76.6 \text{ mm}^3$ vs. $67.7 \pm 67.9 \text{ mm}^3$ 2. Mixed; $47.7 \pm 87.5 \text{ mm}^3$ vs. $57.5 \pm 99.4 \text{ mm}^3$ 3. Calcified; $65.8 \pm 110.0 \text{ mm}^3$ vs. $53.2 \pm 90.3 \text{ mm}^3$	5
Achenbach S. Circulation. 2004	83 coronary segments in 22 patients	IVUS	1. Sensitivity and specificity for the detection of plaque 1. Any; 85% and 88% 2. Calcified; 94% and 94% 3. Noncalcified; 78% and 87% 2. Plaque volume between coronary CTA and IVUS $24 \pm 35 \text{ mm}^3$ vs. $43 \pm 60 \text{ mm}^3$ , $p < 0.001$	6
Leber AW J Am Coll Cardiol. 2004	68 vessels in 37 patients	IVUS	1. Hypoechoic, hyperechoic, calcified plaques $49 \pm 22\text{HU}$ vs. $91 \pm 22\text{HU}$ vs. $391 \pm 156\text{HU}$	7
Voros S JACC Cardiovasc Interv. 2011	50 lesions in 50 patients	IVUS	1. Plaque volume 1. Noncalcified; $r = 0.84$ , $p < 0.001$ 2. Percentage of noncalcified volume; $r = 0.41$ , $p = 0.003$ 3. Calcified; $r = 0.65$ , $p < 0.001$ 4. Percentage of calcified volume; $r = 0.41$ , $p = 0.003$ 2. Percentage of atheroma volume; $r = 0.51$ , $p < 0.001$ 3. Minimal lumen diameter; $r = 0.55$ , $p < 0.001$ 4. Percentage of diameter stenosis; $r = 0.44$ , $p = 0.001$ 5. Minimal lumen area; $r = 0.65$ , $p < 0.001$ 6. Percentage of area stenosis; $r = 0.44$ , $p = 0.001$	12
Stolzmann P Eur Radiol. 2012	284 images in donor hearts	IVUS	1. Plaque burden 1. Filter back projection; $r = 0.45$ , $p < 0.001$ 2. Adaptive statistical iterative reconstruction; $r = 0.52$ , $p < 0.001$ 3. Model-based iterative reconstruction; $r = 0.49$ , $p < 0.001$	13

Abbreviations; CTA- Computed tomographic angiography; IVUS – Intravascular ultrasound; HU- Hounsfield Unit.

subsequently reported a meta-analysis of coronary atherosclerosis imaging by coronary CTA compared to IVUS-VH from several studies.<sup>14</sup> In their analysis, they noted that, while overestimation of luminal area by coronary CTA was observed, plaque area and volume were comparable between coronary CTA and IVUS. These earlier studies included relatively small numbers of patients ranging from 12 to 50 patients, and in which some were performed by 16-slice coronary CTAs.<sup>14</sup> Although these studies are important to demonstrate the ability of coronary CTA to assess coronary atherosclerosis, more detailed assessment of plaque by advanced coronary CTA techniques remains needed.

## 2.2. Qualitative assessment of high-risk plaque by coronary CTA

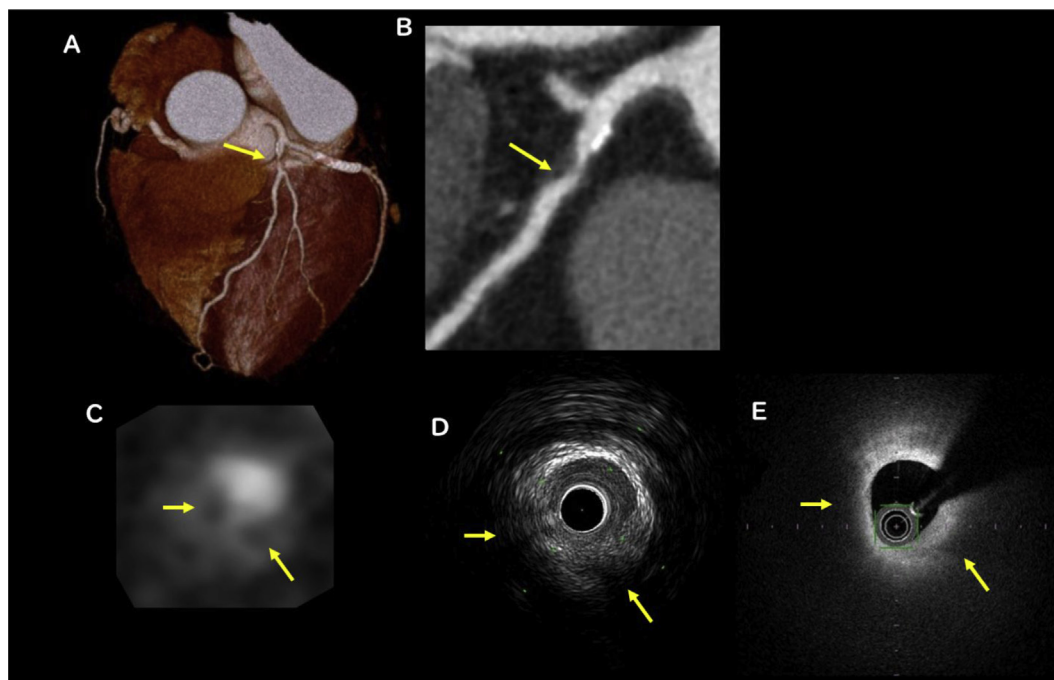
Qualitative measures of HRP by CTA include low attenuation plaque (LAP), positive remodeling (PR), spotty calcification and napkin ring sign (NRS) (see Fig. 1). Prior studies have shown that coronary CTA can confidently identify these features and have demonstrated good concordance with HRP by the invasive imaging modalities and histology (Table 2). The IVUS or OCT-based definitions of HRP are commonly applied to coronary CTA and optimal thresholds of HRP features have been similarly used for coronary CTA-based definitions. Achenbach and colleagues have observed that coronary CTA based coronary PR showed high correlation when compared to IVUS ( $r = 0.82$ ).<sup>15</sup> In other study by Kroner et al., coronary CTA-based PR was also associated with increased volume in necrotic lipid rich cores and thin-cap fibroatheroma (TCFA) by IVUS.<sup>16</sup>

The CT-based low attenuation plaque is a HRP feature and thought to reflect “lipid-rich plaque”. In the study of 105 patients including acute coronary syndrome (ACS) and stable angina, CT values in the OCT-derived TCFA group was significantly lower compared to that in the no OCT-derived TCFA group ( $35.1 \pm 32.3 \text{ HU}$  vs.  $62.0 \pm 33.6 \text{ HU}$ ,  $p < 0.001$ ).<sup>17</sup> In addition, OCT-derived TCFA was more associated with higher incidence of coronary CTA-based PR ( $> 1.05$ ) compared to no OCT-derived TCFA (52% vs. 23%,  $p = 0.01$ ).<sup>17</sup> The differentiation between the compositions of plaque features using coronary CTA are principally led by CT values defined as a Hounsfield unit (HU). In order to differentiate LAP with other non-calcified plaque components

including fibrous or fibro-fatty plaque, CT values range from 30 to 75 HU,<sup>11,18–22</sup> and therefore, the optimal thresholds of HU are not standardized to date. This is probably because CT values in coronary plaque, especially non-calcified plaque, are affected by several factors such as concentration of contrast,<sup>18,23,24</sup> acquisition parameters such as tube potential and convolution kernels used.<sup>25,26</sup> In this regard, it remains controversial to define a single cut-off of HUs for the qualitative identification of LAP. Similar to the cut-off of LAP, the proportion of LAP volume and PR values may also be more accurate in predicting plaque vulnerability. Tomizawa et al. have investigated the association between TCFA by OCT and various HRP features by coronary CTA.<sup>21</sup> They found that continuous variables of low attenuation volume ( $< 60\text{HU}$ ) and PR index by coronary CTA showed better diagnostic performance to identify OCT-TCFA compared to categorical thresholds of PR ( $> 1.1$ ) and the presence of low attenuation plaque ( $< 30\text{HU}$ ).<sup>21</sup>

With respect to spotty calcification (SC), the length of calcified plaque with  $< 3 \text{ mm}$  has been commonly applied for the definition of SP by coronary CTA.<sup>27,28</sup> Several studies, however, have failed to show the prognostic value of coronary CTA derived SC to predict MACE or ischemia.<sup>29,30</sup> This is due probably to limited special resolution of coronary CTA to identify IVUS or OCT derived SC,<sup>5</sup> and it is thought that coronary CTA-based SC is more similar to macro-calcification detected by IVUS or OCT. Therefore, a smaller SC by coronary CTA may more reflect an increased prevalence of necrotic core by IVUS.<sup>31</sup>

Other HRP features such as ruptured plaque and thrombus that are commonly present in culprit lesions may also be detectable by coronary CTA. A recent paper has revealed that coronary CTA has a high specificity (91%) but low sensitivity (33%) to identify ruptured plaque by IVUS.<sup>32</sup> In another study, Takaoka et al. have retrospectively explored 31 patients who underwent 64-slice CTA and were diagnosed as unstable angina pectoris ( $n = 19$ ) or non-ST elevation acute myocardial infarction ( $n = 12$ ). They have found that HUs were similar between soft plaques and thrombi detected by IVUS ( $32.9 \pm 8.7$  vs.  $43.2 \pm 10.7 \text{ HU}$ ,  $p = 0.268$ ), whereas their HUs were significantly lower compared to those of fibrotic plaques ( $82.5 \pm 22.6 \text{ HU}$ ).<sup>33</sup> Lower HU in a plaque are therefore suggested as being a high risk because of LAP or thrombus, however, there is no method to separately distinguish



**Fig. 1. Sample of non-calcified plaque imaging by coronary CTA, IVUS and OCT/OFDI.**

Obstructive coronary stenosis in LAD can be seen on volume rendering image (A). In the proximal segment of the LAD, non-calcified plaque with low attenuation plaque with  $\leq 30$ HU was shown by curved multiplanar reconstruction (B). Panel C provides the cross-sectional image of the plaque. Echolucent plaque (yellow arrows) with acoustic signal is seen on IVUS (SD). Necrotic core (yellow arrows) is seen as a signal-poor region with poorly defined borders and fast signal drop-off OCT/OFDI.

**Abbreviations;** CTA- Computed tomographic angiography, IVUS- Intravascular ultrasound, OCT- Optical coherence tomography, OFDI- Optical frequency domain imaging, LAD-Left anterior ascending artery. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the two high-risk features from each other.

### 2.3. Semi-quantitative plaque assessment: comparison of available programs for atherosclerosis evaluation

Given the recent technology improvements, numerous coronary CTA automated quantitative software (QCT) have been released for the evaluation of plaque volume and composition. Several studies demonstrate good agreement of plaque volume and composition when compared to histology or IVUS.<sup>8–10,34</sup> Assessment of plaque volume by semi-automated plaque software has been shown to be comparable to qualitative measures of coronary plaque. Due to its semi-automated nature and time-saving method, the clinical use in routine clinical practice to identify patients who would benefit from primary or secondary prevention could be expected in the near future.

Several QCT vendors can automatically identify lumen boundaries of the inner and outer vessels, resulting in time-saving for readers, while manual adjustments are sometimes required based on the image quality. Plaque volume and characteristics are then calculated by automated algorithm methods. Several studies regarding the accuracy of measures of plaque volume/area, especially non-calcified plaque, by QCT have been reported to date (Table 3). In the study of 70 consecutive patients with suspected CAD who underwent both of coronary CTA and IVUS, by using QCT (AUTOPLAQ (APQ), Cedars-Sinai Medical Center, Los Angeles, CA), Dey et al. has demonstrated that the agreement between the two modalities to identify non-calcified plaque volume was excellent with  $r = 0.92–0.94$  ( $p < 0.001$ ).<sup>9</sup> In another study, Boogers et al. have performed a head-to-head comparison between QCT (QAngio, Medis medical imaging systems bv, Leiden, The Netherlands) and IVUS to evaluate the minimal lumen area (MLA), percentage lumen area stenosis, plaque burden, and degree of PR.<sup>8</sup> In the study of 51 patients, the correlation for these plaque features were good ( $r = 0.75$

for MLA, 0.79 for lumen area stenosis, 0.70 for plaque burden, 0.64 for mean plaque burden, and 0.56 for PR index, respectively). In a sub-analysis for calcified and non-calcified plaque between QCT and IVUS, the diagnostic performance showed good ( $r = 0.70–0.77$ ) correlation and similar between calcified and non-calcified plaques. There was slight overestimation of luminal area stenosis by QCT was noted.<sup>8</sup> By utilizing the same software to evaluate minimal lumen area (MLA), maximal lumen area stenosis percentage (%AS), mean plaque burden percentage (%PB), and plaque volume, Park et al. have studied the comparative diagnostic performance between expert reader, non-expert reader and full-manual automatic quantitative analyses, and compared them to IVUS among 142 patients.<sup>35</sup> These measures by expert readers demonstrated excellent correlation to the measures by IVUS ( $r = 0.84–0.94$ ,  $p < 0.001$  for all). Of note, the results were slightly attenuated but still reasonable when the measurements were performed by non-expert reader or full-manual automated quantitative analyses compared to IVUS, demonstrating the acceptable measurements by use of full-manual automated analyses.<sup>35</sup>

Although these data suggested that CT verified plaque volume was associated with that by IVUS, the non-calcified plaque area was likely to be overestimated when compared to histology.<sup>36</sup> Schlett et al. have compared non-calcified plaque volume by QCT to those using histology as a reference standard in five ex vivo hearts. They have shown that, when the area between the inner and outer lumen boundaries were considered as a “plaque”, the area of LAP demonstrated a 120% higher overvalue compared to when non-calcified area between the inner and outer boundaries were not considered as a plaque.<sup>36</sup> Despite good spatial resolution of coronary CTA, it cannot distinguish the vessel wall and non-calcified plaque by histology. Indeed, the confirmation of “no plaque” by coronary CTA and fibrous-plaque by optical frequency domain imaging was associated with mild lesions by histology in three donor hearts.<sup>37</sup> In this regard, “no visible plaque” on coronary CTA can

**Table 2**  
Qualitative assessment of high-risk plaque by coronary CTA.

Authors	Number	Modality	Main findings	Reference
Achenbach S. J Am Coll Cardiol. 2004	26 sites in 13 patients	IVUS	1. Vessel area; $20 \pm 7 \text{ mm}^2$ vs. $18 \pm 8 \text{ mm}^2$ The mean absolute difference; $3 \pm 3 \text{ mm}^2$ 2. PR index (CTA vs. IVUS) $1.1 \pm 0.3$ vs. $1.1 \pm 0.4$ , $R^2 = 0.82$ , $p = 0.001$	15
Kröner ES Am J Cardiol. 2011	99 plaques in 45 patients	VH-IVUS	1. Percent necrotic core in lesions with and without PR by coronary CTA $15.7 \pm 7.8\%$ vs. $10.2 \pm 7.2\%$ , $p < 0.001$ 2. TCFA lesions in lesions with and without PR by coronary CTA $43.2\%$ vs. $4.8\%$ , $p < 0.001$	16
Han D. Atherosclerosis 2018	8 post-mortem sudden coronary death hearts	Histology	Accuracy, sensitivity and negative predict value of different CT values for predicting lipid rich plaque 1. $< 30\text{HU}$ ; 64%, 14% and 66% 2. $< 45\text{HU}$ ; 65%, 19% and 67% 3. $< 60\text{HU}$ ; 64%, 35% and 69% 4. $< 75\text{HU}$ ; 68%, 57% and 76% 5. $< 90\text{HU}$ ; 67%, 57% and 75%	11
Kashiwagi M. JACC Cardiovasc Imaging 2009	105 lesions in 105 patients	OCT	1. CT values in the TCFA and non-TCFA lesions $35.1 \pm 32.3\text{HU}$ vs. $62.0 \pm 33.6\text{HU}$ , $p < 0.001$	17
Motoyama S Circ J. 2007	98 plaques in 37 patients	IVUS	1 Soft, fibrous, calcified plaques $11 \pm 12\text{HU}$ vs. $78 \pm 21\text{HU}$ vs. $516 \pm 198\text{HU}$ 2 Soft; $< 30\text{HU}$ , Fibrous; $31\text{--}150\text{HU}$ , Calcified; $151\text{--}380\text{HU}$	19
Marwan M. Atherosclerosis. 2011	55 plaques in 40 patients	IVUS	1. CT values in the fibrous and lipid-rich plaques $96 \pm 40\text{HU}$ vs. $67 \pm 31\text{HU}$ , $p = 0.006$ 2. The mean percentage of pixels $< 30\text{HU}$ in the fibrous and lipid-rich plaques $6 \pm 10\%$ vs. $16 \pm 10\%$ , $p < 0.001$ 3. 5.5% pixels with $< 30\text{HU}$ to identify lipid-rich plaques Sensitivity, specificity, the negative and positive predictive value 95%, 80%, 86% and 93%	20
Tomizawa J Cardiovasc Comput Tomogr. 2017	129 plaques in 106 patients	OCT	1. To predict TCFA by OCT 1. $\text{RI} > 1.1$ , minimum CT number $< 30\text{HU}$ and NRS; AUC 0.74 2. $\text{RI} > 1.1$ , minimum CT number $< 30\text{HU}$ and NRS; AUC 0.72 3. Regression model by RI, proportion of low attenuation volume $< 60\text{HU}$ and NRS	21
Yang DH. Eur Radiol. 2008	31 lesions in 28 symptomatic patients	OCT	1. Lumen area; $R = 0.859$ Limits of agreement; $-0.5 \pm 3.7\text{mm}^2$ 2. Coronary CTA characteristics in TCFA vs. no-TCFA by OCT 1. Coronary CTA detected LAP ( $< 30\text{HU}$ ); 58.0% vs. 18.5% 2. Coronary CTA detected NRS; 31.9% vs. 8.8% 3. Coronary CTA detected PR; 68.1% vs. 48.0%	22
Van Velzen JE J Nucl Cardiol. 2011	300 plaques in 108 patients	VH-IVUS	Non-calcified vs. small ( $< 1 \text{ mm}$ ) vs. intermediate ( $1\text{--}3 \text{ mm}$ ) vs. large spotty ( $> 3 \text{ mm}$ ) vs. dense calcifications 1. Prevalence of %necrotic core 13% vs. 20% vs. 14% vs. 17% vs. 14%, $p = 0.003$ 1. Prevalence of %TCFA 22% vs. 31% vs. 17% vs. 9% vs. 6%, ( $p < 0.05$ for small vs. large spotty)	31
Obaid DR J Cardiovasc Comput Tomogr 2017	71 plaques in 63 patients	VH-IVUS	1 To predict ruptured plaque by coronary CTA features (ulceration or intra-plaque dye penetration) Sensitivity and specificity; 33% and 91% 2. Prevalence of coronary CTA plaque features in ruptured vs. intact plaque 1. Coronary CTA detected NRP; 56% vs. 31%, $p = 0.03$ 2. Coronary CTA detected spotty calcification; 54% vs. 47%, $p = 0.57$ 3. Coronary CTA detected LAP; 56% vs. 77%, $p = 0.21$ 4. Coronary CTA detected RI; 44% vs. 59%, $p = 0.21$	32
Takaoka H Int J Cardiol. 2012	31 lesions in 31 ACS patients	IVUS	1. CT values in soft plaque, thrombi and fibrotic plaque $32.9 \pm 8.7\text{HU}$ vs. $43.2 \pm 10.7\text{HU}$ vs. $82.5 \pm 22.6\text{HU}$	33

**Abbreviations;** CTA- Computed tomographic angiography; VH-IVUS – Virtual histology intravascular ultrasound; PR- Positive remodeling; HU- Hounsfield Unit; TCFA- Thin-cap fibroma; OCT- Optical coherence tomography; RI- Remodeling index; LAP- Low attenuation plaque; NRS- Napkin ring sign; ACS- Acute coronary syndrome.

be accounted for “vessel wall” by histology and should not be considered as a non-calcified plaque.

“Non-calcified plaque” on coronary CTA contains various compositions such as fibrous, fibro-fatty and LAP. These plaque compositions are of importance to validate between high-risk and stable plaques for stratifying future risk. These software vendors can assess not only plaque area and volume, but can also evaluate numerous non-calcified plaque features, such as fibrous, fibro-fatty and LAP, similar to virtual histology-IVUS (VH-IVUS). Fujimoto et al. have studied whether QCT using a labeling method was better than traditional CT-number based method to identify plaque volume and characteristic when compared to VH-IVUS.<sup>10</sup> In the study of 33 consecutive patients, the labeling method correlated better to VH-IVUS compared to the CT-number based method in order to identify necrotic core ( $r = 0.75$  vs.  $0.42$ ) and fibrous areas ( $r = 0.80$  vs.  $0.59$ ). Non-calcified plaque, especially LAP is prone to be affected by several factors such as contrast media, calcium and image noise, resulting in overestimation of the presence and volume of

LAP. Indeed, in the same study by Fujimoto et al., necrotic core area by CT-number based method was significantly larger compared to that by IVUS ( $3.8 \pm 3.1$  vs.  $2.0 \pm 1.6 \text{ mm}^2$ ,  $p = 0.02$ ), while the area between the labeling methods ( $2.3 \pm 1.7 \text{ mm}^2$ ) and VH-IVUS did not differ ( $p = 0.35$ ).<sup>10</sup> The new algorithm of plaque imaging by automated CT software (i.e. labeling method) can better differentiate LAP from image noise, demonstrating more accurate detection of LAP.

#### 2.4. Intra-/inter-reader variability of plaque imaging by coronary CTA

Assessment of plaque volume can be affected by different reconstruction algorithms<sup>38</sup> or readers experience.<sup>35</sup> CT images can be reconstructed by several post-processing image algorithms, such as filter back projection and iterative reconstruction, to improve diagnostic accuracy of coronary CTA. Since the FBP is likely to lead to increased image noise, streak artifacts and poor low-contrast detectability, the iterative reconstruction algorithms are widely used and

**Table 3**  
Comparison of available semi-quantitative plaque programs for atherosclerosis evaluation.

Authors	Number	Modality	Software	Main findings	Reference
Boogers MJ. Eur Heart J. 2012	146 lesions in 51 patients	IVUS	QAngio	1. Minimal lumen area; $r = 0.75$ , $p < 0.001$ 2. Lumen area stenosis; $r = 0.79$ , $p < 0.001$ 3. Plaque burden; $r = 0.70$ , $p < 0.001$ 4. Mean plaque burden; $r = 0.64$ , $p < 0.001$ 5. Remodeling index; $r = 0.56$ , $p < 0.001$	8
Dey D. Radiology. 2010	22 noncalcified plaques in 20 patients	IVUS	AUTOPLAQ	1. Plaque volume; $r = 0.94$ , $p < 0.001$ 2. Mean plaque volume; $r = 0.92$ , $p < 0.001$ $105.9 \pm 83.5\text{mm}^3$ vs. $116.6 \pm 80.1\text{mm}^3$	9
Fujimoto S. Int J Cardiovasc Imaging. 2014	37 plaques in 33 patients	IVUS	SurePlaque	1. Necrotic core area; $R = 0.75$ , $p < 0.0001$ 2. Fibrous area; $R = 0.80$ , $p < 0.0001$	10
De Graaf MA Int J Cardiovasc Imaging. 2013	108 lesions in 57 patients	VH-IVUS	QAngio	1. Plaque volume; $r = 0.928$ , $p < 0.001$ 2. Fibro-fatty tissue volume; $r = 0.714$ , $p < 0.001$ 3. Fibrotic tissue volume; $r = 0.695$ , $p < 0.001$ 4. Necrotic core volume; $r = 0.523$ , $p < 0.001$ 5. Dense calcium volume; $r = 0.736$ , $p < 0.001$	34
Park HB Eur Radiol. 2015	150 segments in 142 patients	IVUS	QAngio	1. Minimal lumen area; $r = 0.80$ , $p < 0.001$ 2. Maximal lumen area stenosis; $r = 0.82$ , $p < 0.001$ 3. Plaque volume; $r = 0.84$ , $p < 0.001$ 4. Mean plaque burden; $r = 0.84$ , $p < 0.001$	35

Abbreviations as in Table 2.

provided by different vendors. The iterative reconstruction techniques can provide better image quality while maintaining low radiation dose, by more accurately and comprehensively modeling various resolutions with source-detector position, numerous x-ray photon distributions and 3D scatter images.<sup>39</sup> Stolzmann et al. demonstrated that reproducibility of plaque burden by coronary CTA and IVUS was excellent with no significant difference between CT reconstruction algorithms.<sup>13</sup> These recent new algorithms for reconstructing the images provide better image quality with less noise, resulting in more accurate correlation with IVUS compared to traditional reconstruction algorithms.<sup>38</sup> Dual energy CT (DECT) may have a potential to distinguish between vulnerable and stable plaques.<sup>40</sup> In the study of 32 ex-vivo coronary arteries scanned by DECT, the energy dispersive X-ray spectroscopy (EDS) provided high accuracy and area under the curve to differentiate vulnerable plaque from stable plaque, with 87% and 0.85, respectively.<sup>40</sup>

Recent studies demonstrated good agreement for the reproducibility and reliability of quantitative assessment of coronary atherosclerosis volume by QCT when using different radiation energy.<sup>41</sup> From the analysis of 95 patients who underwent serial coronary CTAs with same kilovoltage (kVp) within 90 days, length and volume of coronary plaque didn't statically differ between the two scans in per-segment analysis. The trend was similar to the per-lesion analysis. Notably, in both per-segment and per-lesion analyses among 24 patients with different KVp, the results didn't show significant differences of plaque length and volume.<sup>41</sup> The findings of the study have indicated that the evaluation of clinical risk or implications for medical interventions targeting coronary atherosclerosis can be allowed by assessing serial semi-quantitative CT measures. Indeed, such studies have been explored in these recent years.<sup>42-49</sup>

### 3. The potential utility of coronary CTA for predicting coronary artery plaque progression and ischemia

Monitoring plaque progression, regression and stabilization is a key to prevent cardiovascular events. Although IVUS has been historically used as a golden-standard to observe the natural history of plaque development, this technique is not ideal for multiple assessments of atherosclerosis due to an invasive procedure. Our group has recently studied the association between local plaque progression by IVUS and overall atherosclerosis progression by coronary CTA. While the numbers were small ( $n = 11$ ), we have shown the good correlation between local plaque progression by IVUS and overall plaque progressions by

coronary CTA ( $r = 0.82$ ;  $P = 0.002$ ).<sup>50</sup> The findings suggested that coronary CTA can be substituted with IVUS for monitoring plaque progression or regression in a non-invasive fashion and potentially used for both of primary and secondary prevention. Indeed, multiple studies have recently revealed that coronary CTA is a good modality to assess plaque regression by improvement of cholesterol level,<sup>46,47</sup> statin<sup>42,51</sup> and dietary supplements.<sup>43,44</sup>

Another potential utility of coronary CTA is to predict ischemia by assessing plaque stenosis, morphology and/or volume.<sup>52-56</sup> Park et al. have revealed that increased prevalence of high-risk plaque features was associated with ischemia, especially when positive remodeling and low attenuation plaque were present.<sup>52</sup> Diaz-Zamudio et al. has investigated if plaque characteristics assessed by quantitative CT software can predict ischemia and found that total, non-calcified and low attenuation plaque burden were associated with ischemia.<sup>55</sup> Conversely, there are only few reports on the prediction of ischemia by IVUS or OCT.<sup>57-59</sup> Coronary CTA may be a potential approach because the entire coronary vessel can be evaluated for atherosclerosis, allowing for detailed information to identify ischemia (as compared to only segmental plaque information by IVUS or OCT). However, there have been no such studies on head to head comparison of these invasive and non-invasive imaging modalities for predicting ischemia.

### 4. Current limitations of coronary CTA ability for plaque imaging

It is still challenging that coronary CTA cannot display some key elements for high risk plaque, i.e. macrophage activity, thin-cap fibroatheroma (TCFA), neovascularization, plaque rupture or plaque erosion, which can be visualized by OCT. This limitation could be problematic to more accurately identify patients who are at high risk for future cardiovascular events, and further who would benefit from revascularization or aggressive medical therapy. Several studies on the early revascularization by bioabsorbable vascular scaffolding for vulnerable plaque detected by IVUS (The PROSPECT-ABSORB [Multicentre Prospective Natural History Study Using Multimodality Imaging in Patients With Acute Coronary Syndromes Combined With a Randomized, Controlled, Intervention Study], NCT02171065), OCT (The PECTUS [Pre-Emptive, OCT Guided Angioplasty of Vulnerable, Intermediate Coronary Lesions: A Randomized Trial], NTR5590) or NIRS-IVUS (The PREVENT study [The Preventive Implantation of Bioresorbable Vascular Scaffold on Functionally Insignificant Stenosis With Vulnerable Plaque Characteristics], NCT02316886) have being

ongoing in recent years, while such studies using coronary CTA have not been designed to date.

New technologies such as radiomics or machine learning, however, may more accurately characterize high risk plaque features visualized by these modalities.<sup>60</sup> In the recent study of 25 patients who underwent coronary CTA, invasive coronary angiography with both of IVUS and OCT, as well as sodium-fluoride positron emission tomography (NaF18-PET), compared to conventional CT parameters, coronary CTA radiomics demonstrated higher diagnostic performance to identify attenuated plaque by IVUS (area under the curve (AUC): 0.59 vs. 0.72,  $p < 0.001$ ), OCT derived TCFA (0.66 vs. 0.80,  $p < 0.001$ ) and NaF18-positivity (0.65 vs. 0.87,  $p < 0.001$ ).<sup>60</sup> Another study by Masuda et al. has revealed that the Gini index by machine learning showed a higher AUC to identify fatty or fibro-fatty plaque compared to the conventional method using the CT number (0.92 vs. 0.83,  $p = 0.001$ ).<sup>61</sup> These techniques allow use of more detailed information from the images compared to the visualized information that we have currently used and may potentially result in more accurate assessment using coronary CTA images. More studies using these novel techniques are required in the upcoming years.

## 5. Conclusions

Advances in the current technology of coronary CTA allow accurate identification of plaque volume and plaque characteristics when compared to invasive imaging modalities or histology. Evolving evidence from recent studies indicate that coronary atherosclerosis by coronary CTA can play an essential role in primary/secondary prevention.

## Disclosures

Dr. Leipsic has a research agreement with GE Healthcare, and is a consultant to and holds stock options in Circle Cardiovascular Imaging and Heartflow. Dr. Budoff receives grant support from GE and National Institutes of Health. The other authors have no conflict of interest.

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