



## Invited review

# Noninvasive assessment of coronary atherosclerosis by cardiac computed tomography for risk stratifying patients with suspected coronary heart disease



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## 1. Introduction

Coronary computed tomography angiography (CCTA) allows direct, noninvasive visualization of the coronary lumen, vessel wall, and coronary atherosclerosis. With the possibility of CCTA to provide spatial resolution that approaches that by conventional angiography,<sup>1</sup> atherosclerotic plaque can be reliably identified, as confirmed by the gold standard of histopathology.<sup>2</sup> Many studies have demonstrated the prognostic value of coronary atherosclerosis assessment by CT for predicting all-cause mortality, cardiac death, myocardial infarction, or unstable angina.<sup>3–5</sup> Consistently, incremental prognostic value of atherosclerotic plaque evaluation has been observed to statistical models based on demographical, clinical, and laboratory variables.<sup>6–12</sup> The severity of coronary artery disease (CAD) can be assessed and reported in multiple ways, but the overall plaque volume from all coronary segments has shown a graded risk increase for each unit of increased plaque volume. Atherosclerotic plaque burden has been traditionally graded based on the maximal stenosis severity, number of vessels with obstructive stenosis, or number of affected segments. Most clinical trials in CAD have used a simple categorization using the number of coronary arteries with  $\geq 50\%$  stenosis with special consideration of left main or proximal left anterior descending (LAD) coronary artery involvement.<sup>13</sup> Recently, advanced atherosclerotic plaque features have been identified, including low-attenuation plaque, positive remodeling, napkin ring sign, or spotty calcification which may provide additional risk information.<sup>14–16</sup> However, the value of assessing these features for clinical practice has not been established.<sup>17</sup> This review will provide an overview and a discussion of cardiac CT's utility for risk stratifying patients based on coronary atherosclerotic plaque assessment.

## 2. Pathophysiology of ACS

Acute coronary events result from a complex interplay between coronary atherosclerosis, inflammation, and plaque destabilization, which may lead to vascular thrombosis under certain conditions.<sup>18</sup> With few exceptions (e.g., artery dissection, emboli, vasospasm) the presence of coronary atherosclerosis is required for acute coronary syndromes (ACS) to occur. Atherosclerotic plaques may trigger vascular thrombosis and ACS after they rupture (two third) or erode (one third) and in few instances are provoked by a calcific nodule.<sup>19,20</sup> Ruptured coronary plaques causing ACS typically contain a large necrotic core with an inflamed, thin ( $< 65 \mu\text{m}$ ), fibrous cap.<sup>19,20</sup> The exact mechanism leading to vascular thrombosis remains speculative but it appears that thrombotic conducive factors are required at the time of plaque disruption, with at least some of them being hereditary, some circumstantial.<sup>18</sup> Based on the common constellation of plaque features associated with rupture and acute coronary events, the term 'vulnerable' plaque has been coined. In hopes to identify "vulnerable plaques" before they may rupture and thus to prevent possible ACS, numerous investigations have been conducted using various invasive and non-invasive imaging tools. However, pathology and clinical studies revealed that atherosclerotic plaques frequently rupture without causing ACS.<sup>17</sup> Indeed, clinically silent plaque rupture is the predominant pattern and subsequent healing is an established mechanism for plaque growth.<sup>17,21</sup> Since most plaque ruptures do not lead to clinical syndromes, the significance of detecting rupture prone plaques has been questioned.<sup>17,22</sup> On the other hand, repeated plaque disruptions, such as occurring in patients with progressive and extensive atherosclerosis, increases the probability of vascular thrombosis in response to plaque disruptions over time. The total atheroma volume, its metabolic ac-

*Abbreviations:* ACS, acute coronary syndrome; CAD, coronary artery disease; CAD-RADS, the Coronary Artery Disease – Reporting and Data System; CCTA, coronary computed tomography angiography; MACE, major adverse cardiac events; IVUS, intravascular ultrasound

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tivity, and risk factors predisposing to thrombosis, therefore, are most strongly associated with acute coronary event risk.<sup>17</sup> The value of detecting *individual* plaque characteristics remains unclear. The PROSP-ECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial evaluated the association of non-culprit lesion characteristics with risk of major adverse cardiac events (MACE) in patients with recent ACS.<sup>23</sup> In 673 patients, intravascular ultrasound (IVUS) identified 3160 lesions in the proximal to middle parts of the three main coronary arteries; of which 596 (in 313 patients) were classified as thin-cap fibroatheroma by virtual histology. Individual plaque burden > 70% (hazard ratio [HR] 5.0), minimal lumen area  $\leq$  4.0 mm (HR 3.2) and IVUS defined TCFA (HR 3.4) were associated with adverse outcome but events almost entirely consisted of repeat hospitalization for chest pain—not myocardial infarction or death. Only 6 myocardial infarctions occurred, demonstrating limited positive predictive value of TCFA. Similar findings were reported in the smaller VIVA (virtual histology – IVUS) study.<sup>24</sup> Temporal changes of vulnerable plaques, which may see increased calcium content, smaller necrotic core, leading to stabilization over time, may contribute to the limited prognostic value of vulnerable plaques.<sup>25</sup>

### 3. CCTA for coronary artery disease risk stratification

CCTA is capable of detecting atherosclerotic plaque before it causes luminal narrowing or subsequent myocardial ischemia.<sup>2,26,27</sup> Given the presence of coronary atherosclerosis is a requisite for the vast majority of acute coronary events, reliable exclusion of atherosclerotic disease is associated with exceedingly low probability of coronary events in the near future. The Western Denmark Heart Registry included 16,949 individuals with new-onset symptoms suggestive of CAD who underwent CCTA. Approximately 50% of patients had no coronary atherosclerosis which was associated with only 1.5% rate of death, myocardial infarction or coronary revascularization at 3.5 years of follow-up.<sup>28</sup> These low event rates in patients with suspected CAD but without evidence of coronary atherosclerosis have been replicated in multiple reports from the multicenter CONFIRM registry in a large variety of subpopulations.<sup>4,5,9,29</sup> Absence of CT detected atherosclerosis confers long-term low risk for future cardiac events, even in the presence of cardiovascular risk factors.<sup>5,28</sup> On the other hand, when coronary plaque is present, a gradual increase in MACE risk is observed with increasing CAD severity.

The burden of CT detected atherosclerosis can be reported in multiple ways (see Table 1). The traditional grading is that of normal, non-obstructive, and obstructive disease with the latter being variably defined as  $\geq$ 50 or  $\geq$ 70% stenosis. Obstructive stenosis is further

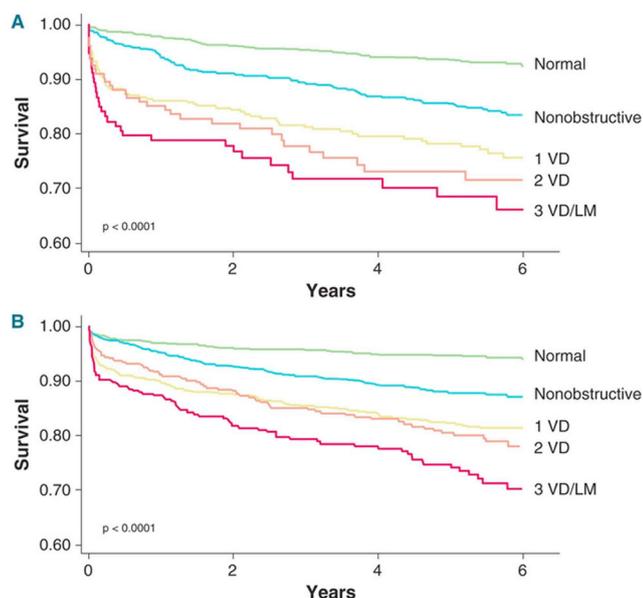
differentiated into 1, 2, or 3-vessel disease and/or left main CAD. This classification arose from the cardiac catheterization laboratory and has been used in many clinical trials establishing treatment options for patients with CAD.<sup>30,31</sup> More recently, the Coronary Artery Disease – Reporting and Data System (CAD-RADS) proposed a classification based on the highest stenosis severity and additional “high-risk” characteristics but this system has not been shown to hold an advantage over simple traditional reporting.<sup>32,33</sup> Furthermore, CAD-RADS has been criticized for its complex structure and omission of critical components, e.g., consideration of proximal LAD disease, or the extent of non-obstructive atherosclerosis.<sup>34</sup> Non-obstructive CAD has recently emerged as an important factor for risk assessment. Bittencourt et al. followed 3242 patients undergoing CCTA for a median of 3.6 years and showed that patients with extensive non-obstructive plaque – defined as involvement of more than 4 coronary segments - had similar heightened risk for myocardial infarction or cardiovascular death as patients with obstructive plaque but with  $\leq$  4 diseased coronary segments.<sup>35</sup> Although the relative risk of MACE in patients with non-obstructive CAD is lower than those with obstructive disease, the larger prevalence of non-obstructive CAD leads to more coronary events occurring in these patients.<sup>14,36</sup> In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study, 74/137 (54.0%) of patients experiencing a composite of all-cause death, myocardial infarction, or unstable angina, had non-obstructive (< 70%) stenosis at baseline.<sup>3</sup> In the ICONIC (Incident Coronary Syndromes Identified by Computed Tomography) study, 153/234 (65.4%) of patients experiencing ACS had < 50% stenosis and 97/129 (75.1%) of the culprit precursor lesions were < 50% at baseline by CCTA.<sup>14</sup> In SCOT-HEART (Scottish Computed Tomography of the Heart), 17/42 (40.5%) of patients experiencing myocardial infarction or coronary death had 1–70% stenosis by baseline CT.<sup>36</sup>

To combine the complex information of plaque location, extent, severity, and composition, multiple scores have been developed optimizing prognostic information from CCTA assessment.<sup>4,6,37–39</sup> Most of these scores require plaque and stenosis information from all coronary artery segments, typically performed for 15–19 segments of the coronary tree. The CONFIRM score was developed and validated in 17,793 patients and demonstrated incremental value for predicting mortality compared to clinical risk assessment alone when adding the number or proximal, mixed or calcified plaques, and number of stenosis  $\geq$  50%.<sup>6</sup> The Leiden CTA score, which incorporates plaque composition and stenosis from each coronary segment, showed improvement of discrimination and reclassification of events compared with assessment of maximal per-patient stenosis severity only (C-statistic 0.768 vs 0.742,  $P = 0.001$ ).<sup>7</sup> The burden of atherosclerosis has been proven to

**Table 1**  
Overview of atherosclerotic CT risk scores.

Score name	Score includes	Outcomes
CONFIRM score <sup>8</sup>	NCEP ATP III added with number of proximal segments with calcified or mixed plaques and number of proximal segments with $\geq$ 50% stenosis	C-statistic for prediction of death among 15219 patients increased was 0.696 for CONFIRM score vs 0.675, $P < 0.001$ for NCEP ATP III score
Modified Duke CAD index <sup>4</sup>	Based on the severity of stenosis, proximal location of the stenosis and the number of involved coronary arteries	Significantly worsening survival for increasing Duke categories among 1127 patients
CT Leaman score <sup>39</sup>	Based on location, severity, composition, and extent of stenoses	Good risk stratification performance for non-fatal myocardial infarction and death among 1196 patients
Leiden CTA score <sup>7</sup>	Based on location, severity, composition, and extent of stenoses	Superior discrimination of myocardial infarction and death compared with maximal stenosis severity per patient (C-statistic 0.768 vs 0.742, $P = 0.001$ )
Segment stenosis score (SSS) <sup>4</sup>	Each single coronary artery segment is scored for stenosis severity (0–3) and summed to per-patient	Significantly worsening survival for increasing SSS among 1127 patients
Traditional CAD classification <sup>33</sup>	Normal, non-obstructive, 1-, 2-, or 3-vessel/left main obstructive CAD	C-index of 0.710 for prediction of myocardial infarction or death among 5039 patients
CAD-RADS (without high-risk plaque assessment) <sup>33</sup>	According to the CAD-RADS document, but without assessment of high-risk plaque	C-index of 0.705 for prediction of myocardial infarction or death among 5039 patients

CAD, coronary artery disease; CAD-RADS, The Coronary Artery Disease-Reporting and Data System; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.



**Fig. 1. Prognostic value of plaque burden for myocardial infarction and death**

Increased severity of coronary artery disease was associated with greater risk for myocardial infarction and death in (A) women and (B) men. Patients without coronary artery disease are at the lowest risk for events. Derived from Schulman-Marcus et al.<sup>5</sup>

meaningfully adjust the risk for future events as compared with clinical patient evaluation based on demographics and laboratory variables only.<sup>5,40</sup> Fig. 1 illustrates the graded increase of events with increasing atherosclerotic burden. Absence of CAD in high-risk populations such as diabetics,<sup>40</sup> or heterozygous familial hypercholesterolemia,<sup>41</sup> patients with cardiac symptoms,<sup>42</sup> also portends long-term low risk of MACE. Of 206 heterozygous familial hypercholesterolemia patients with sub-optimal LDL levels on treatment ( $150 \pm 56$  mg/dl), absence of calcium in 101 patients was associated with no MACE during a median of 3.7 years follow-up.<sup>41</sup>

#### 4. Comparison with functional imaging

Functional cardiac testing has been the traditional way of evaluating patients with suspected CAD, using the presence and extent of myocardial ischemia for diagnostic and prognostic information. A large body of evidence supports low event risk in patients with normal stress testing findings (43). However, prognostic data are strongly dependent on the population risk which is demonstrated by the risk differences for myocardial infarction and cardiac death among patients with normal exercise vs. normal pharmacologic nuclear stress testing (0.65 vs. 1.78% per year).<sup>43</sup> These data reveal that patients may be at close to high risk for events despite normal nuclear stress testing results if patients with greater co-morbidity (and greater underlying atherosclerosis burden) are tested. In comparison, rates of myocardial infarction or cardiac death are exceedingly low: less than 0.03% among 41,960 patients tested with CCTA.<sup>44</sup>

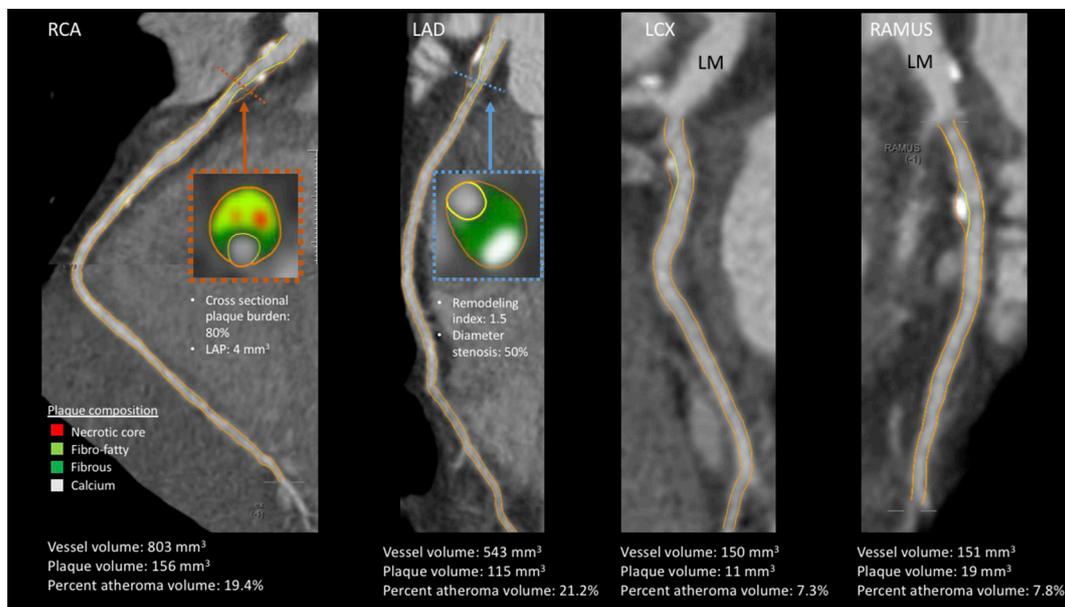
Over the past decades, lower risk patients have undergone coronary heart disease testing and the use of preventive medical therapy has increased, both of which have contributed to lower rates of myocardial ischemia and lower adverse events in clinical studies.<sup>45,46</sup> Older nuclear myocardial perfusion data demonstrated an approximately 5–10 fold higher relative risk for severely abnormal tests compared with normal results.<sup>47,48</sup>

Importantly, functional testing is only able to detect severely obstructive atherosclerotic disease (which is associated with inducible ischemia) while it is insensitive to non-obstructive disease.<sup>49,50</sup> With

only approximately 20–25% of nuclear testing being abnormal among a typical population of patients presenting with stable chest pain, such as in PROMISE, an important subgroup of patients with coronary atherosclerosis without inducible ischemia remains undetected.<sup>46</sup> An analysis of PROMISE by Hoffmann et al. in 4500 patients randomly assigned to CCTA and 4602 patients to functional testing, test results were normal in 78% of patients in the functional arm while CCTA was normal in only 33%.<sup>3</sup> Importantly, rates of death, myocardial infarction or unstable angina hospitalization were 2.1% with a normal functional test vs 0.9% with a normal CCTA during approximately 2 years of follow-up.<sup>3</sup> Patients with a mildly abnormal functional test experienced as many events as those with a normal functional test (2.1% vs 2.1%), while patients with mildly abnormal CCTA findings had more than 3-fold increased risk (3.0% vs 0.9%). Event rates for severely abnormal CCTA and functional tests were similar (10.5% vs 9.6%). These results illustrate the stronger negative predictive value of a normal CCTA vs. functional testing due to its ability to exclude non-obstructive atherosclerosis not causing ischemia. Furthermore, the relative risk for events of severely abnormal CCTA results vs. normal CCTA is much higher (factor 10) than with functional testing (factor 4) resulting in better risk stratification.<sup>3</sup> The 5-year-results of SCOT-HEART revealed a 41% lower risk of myocardial infarction and CAD related death in patients assigned to the CCTA strategy compared to those in the traditional testing group.<sup>36</sup> These data impressively demonstrate the significance of revealing (non-obstructive) atherosclerotic disease which is not detected by stress testing and, importantly, the associated risk amelioration with standard prevention. Therefore, direct comparison of CCTA with functional testing has demonstrated the superiority of CCTA for risk stratification and management of patients with suspected CAD.<sup>3</sup>

#### 5. Quantitative evaluation of coronary atherosclerotic plaque burden

Current semi-quantitative CCTA atherosclerosis evaluation can be extended by the use of automated, reproducible, quantification of coronary plaque volume. Several software tools allow detailed and objective evaluation of coronary atherosclerosis. Visually, coronary segments are considered normal or abnormal based on the presence of atherosclerotic plaque. A basic differentiation of plaque composition classifies into predominantly calcified, mixed, or non-calcified tissue. In addition, stenosis assessment may be derived using previously mentioned classifications. Quantitative evaluation of plaque nevertheless is time-consuming due to often required manual editing of vessel wall and lumen border annotations, but it allows for accurate whole artery plaque quantification with excellent intra- and inter-observer reproducibility by core-laboratory assessment.<sup>25</sup> It offers unique 18-segment coronary arterial evaluation which is not achievable by other non-invasive imaging but only by costly 3-vessel invasive intravascular imaging. In addition to total atheroma volume, quantitative plaque evaluation facilitates the assessment of maximum cross-sectional plaque burden, low-attenuation plaque volume, and remodeling index.<sup>14,51,52</sup> The ICONIC study specifically addressed whether a comprehensive quantitative evaluation of coronary atherosclerotic plaque enhances risk stratification beyond visual plaque assessment or stenosis grading. From the CONFIRM registry, 234 patients with ACS were matched with 234 patients without ACS after baseline CCTA.<sup>14</sup> As a result of the matching, overall volume of quantitatively evaluated plaque was similar between cases and controls; but cases had a higher burden of non-calcified plaque, higher maximal cross-sectional plaque burden, more diffuse CAD, and high-risk plaque features. Similarly, a greater proportion of non-calcified plaque was associated with unstable angina presentation.<sup>51</sup> Another study investigated the incremental prognostic utility of per-patient volume of low-attenuation plaque over clinical and visual plaque burden scores among 1577 patients with 5.5 years of follow-up for death and ACS. Low-attenuation plaque burden increased the C-statistic when added to 3 separate models: (1) the



**Fig. 2.** Whole heart quantitative plaque evaluation by CCTA

LAD, left anterior descending artery; LAP, low-attenuation plaque; LCX, left circumflex; LM, left main; RCA, right coronary artery.

Example of whole-heart atheroma quantification of the coronary tree consisting of, in this case, RCA, LAD, LCX and RAMUS (side branches are quantified but not shown). Lumen (yellow border annotations) and vessel wall (orange border annotations) are semi-automatically annotated with manual adjustments where needed. Tissue between vessel wall and lumen is defined as plaque and summated to per-vessel level. Cross-sectional analysis of a lesion in the proximal RCA (orange dotted line) demonstrates very high plaque burden (80%) with a necrotic core (red code plaque tissue) of 4 mm<sup>4</sup>. Similarly, a cross section is of a proximal LAD lesion is demonstrated depicting high plaque burden, mild stenosis (50%), and positive remodeling (remodeling index 1.5). Percent atheroma volume is defined as plaque volume/vessel volume \* 100%. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Morise clinical score + the presence of obstructive CAD (0.767 vs 0.701,  $P < 0.01$ ), (2) the Morise score + the coronary artery calcium score (0.771 vs 0.722,  $P < 0.01$ ), or (3) the Morise + the segment involvement score (0.771 vs 0.735,  $P < 0.01$ ).<sup>52</sup> These results<sup>14,51,52</sup> highlight the incremental value of quantifying whole coronary artery plaque burden (non-calcified plaque burden based on attenuation thresholds, extent of arterial remodeling compared with proximal location, plaque burden as a function of vessel volume) above visual, dichotomized evaluation of high risk plaque and stenosis severity (which is indirectly related to overall plaque burden).

Quantification of plaque on CCTA is a novel field for which there is little guidance for standardizing measurements and reporting. Broadly accepted methodologies, as developed for IVUS,<sup>53</sup> need to be established. Multiple approaches of plaque quantification have been applied: lesion based,<sup>54</sup> only proximal segments,<sup>51</sup> or whole coronary tree quantification (Fig. 2).<sup>14</sup> Similarly, atherosclerotic burden has been reported as a summation of plaque from all the present coronary lesions or from all evaluable segments,<sup>55,56</sup> (referred to as total ‘plaque volume’) plaque volume normalized to vessel length,<sup>57</sup> or normalized to vessel volume (percent atheroma volume).<sup>57</sup> Differences in number of evaluated segments, length of the vessels, small diameter segments (vessels with < 2 mm lumen diameter are usually not quantified), or adjustments for vessel size (e.g., for sex or patients body size) will result in differences between these 3 metrics. Normalization for reduced vessel length, e.g. in case of unevaluable segments, likely better reflects plaque burden as opposed to simply summing the volume of plaque, which may lead to underestimation. Total vessel volume depends on patient body surface area, and therefore, may be more relevant in a vessel with small vs. large total volume size. Normalization for vessel volume (as done with percent atheroma volume) may be most appropriate to account for inter-individual differences.<sup>58</sup>

### 5.1. Assessment of individual “high-risk” plaque features

Despite the outlined conceptual limitations of detecting so called “vulnerable plaques”, there are a number of clinical studies suggesting that certain plaque features assessed by CCTA may provide independent prognostic value. The following plaque characteristics by CT have been linked to increased risk of coronary events: External (positive) vascular remodeling, low-attenuation plaque (typically defined as less than 30 Hounsfield units [HU]), “napkin ring” sign, and “spotty” calcification (Table 2). Motoyama et al. found low density plaque and external vascular remodeling associated with ACS risk in a retrospective analysis of patients undergoing CCTA at baseline and follow-up.<sup>59</sup> Ferencik et al. reported similar findings in an analysis of the PROMISE trial.<sup>16</sup> Most recently, Williams et al. found plaques with external remodeling or low-attenuation associated with adverse outcomes in the SCOT-HEART trial.<sup>15</sup> Surprisingly, however, studies have not considered traditional CAD grading for comparison or adjustment.<sup>60</sup> Patients with “high-risk” plaque features will naturally confer greater risk compared to those without plaque because such “high-risk” plaque is associated with the presence, burden, and severity of atherosclerotic disease. Indeed, the frequency of “high-risk” plaque features correlates with the extent and severity of CAD.<sup>16</sup> To conclude incremental value of “high-risk” plaque, analyses must adjust for the burden of atherosclerosis. Of note, the associations of “high-risk” plaque reported by Williams et al. lost statistical significance after adjustment for calcium score (a crude surrogate for plaque burden).<sup>15</sup> Lee et al. provided a comprehensive analysis from the PARADIGM (Progression of AtheRosclerotic PLAque Determined by Computed TomoGraphic Angiography Imaging) study which included data on both coronary atheroma burden and “high-risk” plaque features yielding an area under the curve of 0.753 and 0.756 for predicting adverse events, respectively.<sup>61</sup> Not only is such small

**Table 2**  
Predictive value of high-risk plaque features.

High risk plaque (HRP) feature	Study	Population	Findings
HRP defined as LAP and PR	Motoyama et al. <sup>75</sup>	1059 patients who experienced 15 ACS events during 2 years of follow-up	45 patients with HRP experienced 10 (2.2%) of the 15 ACS events; PR and/or predicted ACS (HR 22.8, 95% CI 7–75)
HRP defined as LAP and PR	Motoyama et al. <sup>59</sup>	3158 patients who experienced 88 ACS events during 4 years of follow-up	294 patients with HRP experienced 48 (16.3%) of the 88 ACS events. 2864 patients without HRP experienced 40 events. C-statistic of a clinical model with the presence of > 70% stenosis increased with the addition of HRP (0.818 vs 0.874 P < 0.001)
HRP defined as either LAP, PR, and Napkin ring sign	Otsuka et al. <sup>76</sup>	543 patients with normal SPECT, experienced 25 ACS events during 3.4 years of follow-up	Patients with HRP had a 9.4 (2.66–33.4) times increased risk in multivariable analysis
HRP defined as LAP and PR	Yamamoto et al. <sup>77</sup>	511 patients experienced 15 cardiac death or ACS during 3.3 years of follow-up	Patients with lesions with HRP were at 11.2 (3.71–36.7) times increased risk, adjusted for > 50% stenosis
HRP defined as either LAP or PR	Williams et al. <sup>15</sup>	1769 patients experienced 41 coronary death or myocardial infarction during 5 years of follow-up	Patients with HRP were at 3 (1.6–5.6) times increased risk. The association was not significant after adjusting for calcium score (HR 1.2, 95% CI 0.55–2.52)
HRP defined as ≥2 out of LAP, PR, and SC	Chang et al. <sup>14</sup>	234 who developed ACS matched with 234 controls on overall plaque burden, age, sex, and cardiovascular risk factors	The presence of HRP increased ACS risk by 1.6 (95% CI 1.2–2.1)
HRP defined as at least one of LAP, PR, or NRS	Ferencik et al. <sup>16</sup>	4415 experienced 131 events (death, myocardial infarction, unstable angina) during 25 months of follow-up	The presence of HRP was associated with MACE after adjustment for stenosis (≥70%, or ≥50% in left main) and ASCVD score: HR 1.72 [95% CI 1.13–2.62]

HRP, high risk plaque; LAP, low-attenuation plaque; NRS, napkin ring sign; PR, positive remodeling; SC, spotty calcification.

difference unlikely clinically significant, most events consisted of coronary artery revascularization while only few acute coronary events were recorded. At this time, therefore, there is no conclusive evidence that identifying individual “high-risk” plaque features is associated with incremental value to traditional CAD assessment for predicting acute coronary events nor is there evidence of clinical utility of such assessment. It is conceivable that the presence of *multiple* risk features and plaques may provide additional risk information to our current CAD classification.<sup>61</sup> In the ICONIC study, where patients with future ACS were matched to controls without future ACS based on qualitative plaque extent and cardiovascular risk factors, adverse plaque features were defined in a continuous (as apposed to binary) way, which is more likely to provide incremental risk assessment.<sup>14</sup> For instance, low-attenuation plaque was measured as volume in the entire coronary tree and patients with future ACS possessed a higher proportion. The exact role of “high-risk” plaque in addition to plaque burden will need further exploration.

The metabolic activity of coronary atherosclerotic disease, on the other hand, carries promise for an important marker of increased risk. Motoyama et al. showed in their analysis that plaque progression was the strongest predictor of ACS at follow up.<sup>59</sup> Recently, Oikonomou et al. provided compelling data on perivascular fat attenuation assessment by CT as a marker of inflammation for risk of mortality beyond that predicted by CAD severity.<sup>62</sup> Fluorine-18 sodium fluoride (NaF) positron emission tomography (PET) imaging identifies lesions that develop microcalcifications may indicate active plaque biology and vulnerability.<sup>63</sup> It is conceivable that the combination of coronary atheroma volume and metrics of vascular inflammation will provide the strongest predictors of outcome in patients with CAD.

## 6. Clinical implications

Diagnostic assessment should be tailored to management options. At this time, patients with suspected CAD may receive risk factor modification only, various intensities of medical management, and coronary artery revascularization. For patients with stable symptoms and normal left ventricular systolic function, improved survival with revascularization vs. medical therapy alone has only been shown for patients with high-risk coronary anatomy, i.e., left main disease, three-vessel CAD, or two-vessel CAD including the proximal LAD.<sup>64–66</sup> Therefore, assessment of high-risk coronary anatomy is most critical in patients with stable symptoms and CTA has shown high sensitivity for identifying such

patients.<sup>50</sup> In patients with obstructive CAD but without high-risk anatomy or impaired left ventricular systolic function, a symptom-guided approach appears most reasonable.<sup>67</sup> Assessment of plaque characteristics by CT, on the other hand, has not shown to impact patient management and must be considered investigational at this time.

Arguably the largest potential impact of atherosclerosis assessment by CT relates to its ability to assess for non-obstructive plaque. Analysis of the PROMISE trial revealed that almost 2/3 of all myocardial infarctions and cardiovascular deaths occurred in patients with non-obstructive CAD.<sup>3</sup> This analysis also showed that a strategy of using stress testing for evaluating patients with suspected CAD reports normal test results in 67% of patients who suffer myocardial infarction or cardiovascular death at follow-up (vs. 12% by CCTA). Given approximately 10,000,000 stress tests currently performed in the US every year, identifying patients with non-obstructive CAD by CCTA provides the opportunity to identify many symptomatic patients with coronary atherosclerosis in whom implementation of directed prevention has been shown to reduce the risk of myocardial infarction.<sup>68,69</sup> Clinical practice guidelines in the UK have accommodated this recent evidence and support CCTA as first-line test in patients with stable chest pain. A similar change may be imminent in the US.<sup>70</sup>

## 7. Summary and future directions

Noninvasive detection, quantification, and characterization of CAD may be regarded as one of the most significant advances in cardiovascular imaging of the past decades. A substantial body of evidence has accumulated supporting the ability of CCTA for reliably identifying patients with coronary atherosclerosis and for providing risk stratification that is superior to clinical predictors and stress testing. Three features of CCTA have shown to be particularly powerful for risk assessment in patients with suspected CAD: 1. The exclusion of coronary atherosclerotic disease—which is associated with exceedingly low risk (lower than a normal stress test) of myocardial infarction or death at follow up of at least 5-years; 2. The detection of non-obstructive CAD—which is not detectable by stress testing and accounts for the majority of patients suffering myocardial infarction or cardiovascular death at follow up; and 3. The detection of obstructive CAD—which allows consideration of intensive prevention and possibly, coronary artery revascularization. The upcoming years will see greater efforts to investigate the utility of specific imaging information for guiding patient management. Novel research fields looking for clinical

implementation are plaque biology imaging with fluorine-18 sodium fluoride (NaF) PET or deep learning for automated image analysis and plaque quantification. NaF uptake has been proposed as marker of plaque inflammation and interesting correlations have been observed with “high-risk” plaques or low-attenuation plaques.<sup>63,71,72</sup> Studies need to confirm the added value in risk stratification. Deep learning or radiomics allow for automated extraction of data/variables from images of coronary arteries that can not be visually perceived.<sup>54,73</sup> Machine learning models have shown to improve integration of clinical variables and plaque information by more accurate risk stratification.<sup>37,74</sup> Further, deep learning algorithms that allow for fully automated coronary artery segmentation will aide in plaque quantification of large datasets and help exporation of the added prognostic or clinical role. Foremost, CCTA is posed to be the central imaging tool for triaging patients with suspected CAD.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcct.2019.08.009>.

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