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iREVIEW

STATE-OF-THE-ART REVIEW

Advances in Coronary Computed Tomographic Angiographic Imaging of Atherosclerosis for Risk Stratification and Preventive Care

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ABSTRACT

The diagnostic evaluation of coronary artery disease is undergoing a dramatic transformation with a new focus on atherosclerotic plaque. This review details the evidence needed for effective risk stratification and targeted preventive care based on recent advances in automated measurement of atherosclerosis from coronary computed tomography angiography (CTA). To date, research findings support that automated stenosis measurement is reasonably accurate, but evidence on variability by location, artery size, or image quality is unknown. The evidence for quantification of atherosclerotic plaque is unfolding, with strong concordance reported between coronary CTA and intravascular ultrasound measurement of total plaque volume ($r > 0.90$). Statistical variance is higher for smaller plaque volumes. Limited data are available on how technical or patient-specific factors result in measurement variability by compositional subgroups. Coronary artery dimensions vary by age, sex, heart size, coronary dominance, and race and ethnicity. Accordingly, quantification programs excluding smaller arteries affect accuracy for women, patients with diabetes, and other patient subsets. Evidence is unfolding that quantification of atherosclerotic plaque is useful to enhance risk prediction, yet more evidence is required to define high-risk patients across varied populations and to determine whether such information is incremental to risk factors or currently used coronary computed tomography techniques (eg, coronary artery calcium scoring or visual assessment of plaque burden or stenosis). In summary, there is promise for the utility of coronary CTA quantification of atherosclerosis, especially if it can lead to targeted and more intensive cardiovascular prevention, notably for those patients with nonobstructive coronary artery disease and high-risk plaque features. The new quantification techniques available to imagers must not only provide sufficient added value to improve patient care, but also add minimal and reasonable cost to alleviate the financial burden on our patients and the health care system.
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

IVUS = intravascular ultrasound

PAV = percent atheroma volume

TCFA = thin cap fibroatheroma

The diagnostic evaluation of coronary artery disease (CAD) is undergoing a dramatic transformation with an ever-increasing focus on the burden of atherosclerotic plaque. Coronary computed tomography angiography (CTA) has become the diagnostic technique for visualizing and quantifying key morphologic attributes and precursor features that contribute to lesion progression and future clinical events. The 3-dimensional, volumetric nature of coronary CTA is particularly well suited for not only qualitative visualization but also quantification of stenosis severity and atherosclerotic plaque within an individual coronary artery segment and summed throughout the arterial tree.[1,2] In this review, we highlight the strengths and limitations of current techniques for quantifying coronary CTA measurement of stenosis severity and atherosclerotic plaque and identify areas of clinical need, particularly highlighting the need for clinical trials for evaluating whether various preventive therapies lead to atherosclerotic plaque regression or stabilization and, ultimately, risk reduction. There are other high-quality reviews focusing on the artificial intelligence methods used for automated coronary CTA interpretation.[2-5] Our goal is to provide a review examining the state of the evidence for coronary CTA-quantified measurements as they would be applied for risk stratification and to guide preventive care. We focus our discussions on the use of newer technology and how it will facilitate a more integrative approach to enhance the clinical utility of coronary CTA quantitative measures and potential disadvantages for specific patient subsets. As a preamble to our discussion, it is noteworthy that there is a lack of comparative evidence of new quantitative software with traditional semiautomated methods. The current review must be taken within the context of this limitation whereby newer evidence may undervalue more traditional approaches and ultimately has the risk of increasing the cost of coronary CTA services.

POTENTIAL TARGETS FOR COMPARING CORONARY CTA ATHEROSCLEROSIS MEASUREMENTS

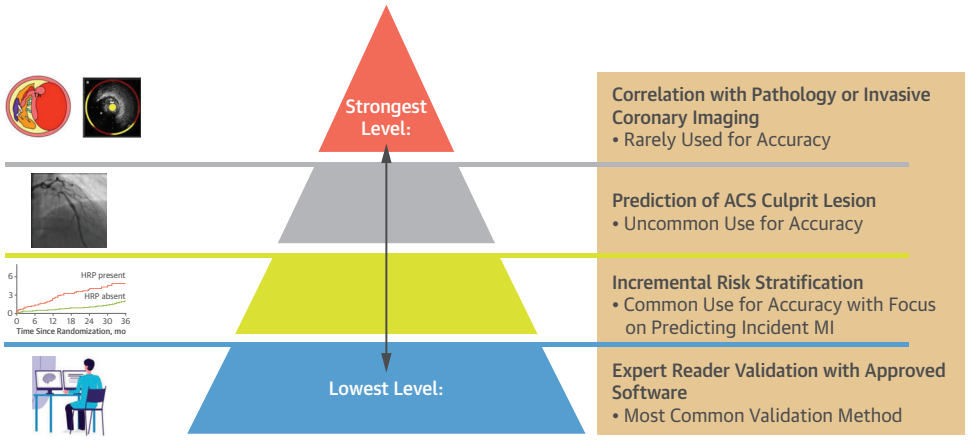
Many coronary CTA measures have substantive research correlating atherosclerotic plaque with pathologic findings in sudden cardiac death, in invasive imaging (eg, intravascular ultrasound [IVUS]) in acute coronary syndromes (ACS), or for risk stratification for major CAD events. The concept that coronary CTA can similarly measure these previously identified high-risk features—from pathology or invasive imaging or related to major CAD events—is integral to the use of coronary CTA to guide successful preventive care as a test for guiding the need and intensity of preventive care strategies. The accuracy of coronary CTA to serve as a surrogate for these previous findings is essential to understand the meaning of atherosclerosis progression and, ultimately, how preventive therapies can influence (ie, halt or regress) coronary CTA measures of atherosclerosis, as well how positive changes in coronary CTA plaque burden may relate to therapeutic risk reduction.

When reviewing the available evidence for the quantitative software programs, varied evidence is reported with regard to comparative accuracy. Direct correlation with pathology or invasive imaging is perhaps the most valid link for coronary CTA measures (**Figure 1**). Correlating coronary CTA measures as predictive of the ACS culprit lesion or other major CAD events is also essential to understand the relationship for preventive risk reduction, including previous and potential treatment trials and their varied therapeutic risk reduction. Perhaps the least reliable or more subjective is when quantitative findings are correlated with expert reads. To date, most programs have some evidence across these different measures, with few having concordance data with pathologic findings. Even though we believe that these coronary CTA measures can provide insight into the underlying atherosclerotic process, there are important limitations, including many "unknowns" about plaque instability, the dynamic nature of risk prediction, variable event timing, and the current low positive predictive value of coronary CTA findings in relation to ACS.[6]

TRADITIONAL SEMIAUTOMATED APPROACHES FOR QUANTIFICATION OF ATHEROSCLEROTIC PLAQUE

Methods for quantifying atherosclerotic plaque have been available for many years, but given the lengthy time required for manual measurement (from 20 minutes to 6 or more hours, depending on the extent of atherosclerosis), application has been limited to the research setting. On coronary CTA, atherosclerotic plaque is measured in coronary arteries and branches >1.5-2.0 mm in diameter. Moreover, atherosclerosis is defined as tissue >1 mm^2 within or adjacent to the lumen that is discriminated from surrounding pericardial tissue, fat, or lumen and identified in ≥2 planes.

FIGURE 1 Potential Targets and Level of Evidence to Define Accuracy and Correlation of Outcomes for Automated Coronary CTA Measurements



ACS = acute coronary syndrome; CTA = computed tomography angiography; MI = myocardial infarction.

Typically, these older semiautomated programs automatically detect the boundary between the coronary lumen and the vessel wall, as well as the boundary between the outer vessel wall and epicardial fat, and thus reduce interobserver variability when compared with manual segmentation. Once detected, boundaries often require manual adjustments, which may be extensive, depending on the burden of atherosclerosis and image quality. The volume between the lumen and outer wall boundaries constitutes the "plaque volume" by subtraction. Quantitative stenosis severity is evaluated by area or diameter as compared with automatically chosen normal reference segments.

Measures of total plaque volume reflect the sum of all plaque from all coronary segments. Commonly, the percentage of the overall vessel volume occupied by plaque is presented as the percent atheroma volume (PAV), which is total plaque volume divided by the coronary volume. Alternatively, the same ratio is also termed *plaque burden* or *percent aggregate plaque volume*.[7] The PAV is also frequently used and measured when plaque volume is normalized to vessel length.

The composition of atherosclerotic plaque is grouped according to its density as measured in Hounsfield units (HU). The values range from lower to higher values that purportedly relate to necrotic core, fibrofatty, fibrous, and calcified plaque by IVUS and/or pathology.[8] The HU categories are as follows: low density (−30 to 30); fibrofatty (30-130); fibrous (130-350); and calcified plaque (>350).[9,10] An alternate HU range for low-density plaque has also been proposed from −30 to 75 HU with improved correlative findings with virtual histology IVUS.[10,11] Newer reports also categorize calcified plaque as follows: low (351-699 HU); medium (700-999 HU); and 1 k (≥1,000 HU).[12] Thresholds can be normalized to scan (eg, luminal contrast density) parameters and then measurements summed on the basis of voxel-based quantitation. The compositional range in atherosclerotic plaque and potential overlapping HU ranges are detailed in **Figure 2**. Of note, the HU range for intravenous contrast (100-500 HU) is broad and overlaps with atherosclerotic plaque compositional subgroups. These fixed thresholds fail to consider individual variation in luminal attenuation[13,14] An alternative approach, adaptive thresholding uses scan-specific classification atherosclerotic plaque composition, as automatically derived from luminal attenuation of "normal blood pool" as measured in the aorta.[15] To date, comparative analysis has not defined the superiority of 1 approach over the other, but adapting to specific scan details does overcome issues with the use of fixed thresholds.

VISUAL MARKERS OF HIGH-RISK ATHEROSCLEROTIC PLAQUE ASSOCIATED WITH ACS

Additional visually identified markers have been correlated with ACS, either at the time of the event or as precursor features. These high-risk ACS features are generally assessed visually but have played a

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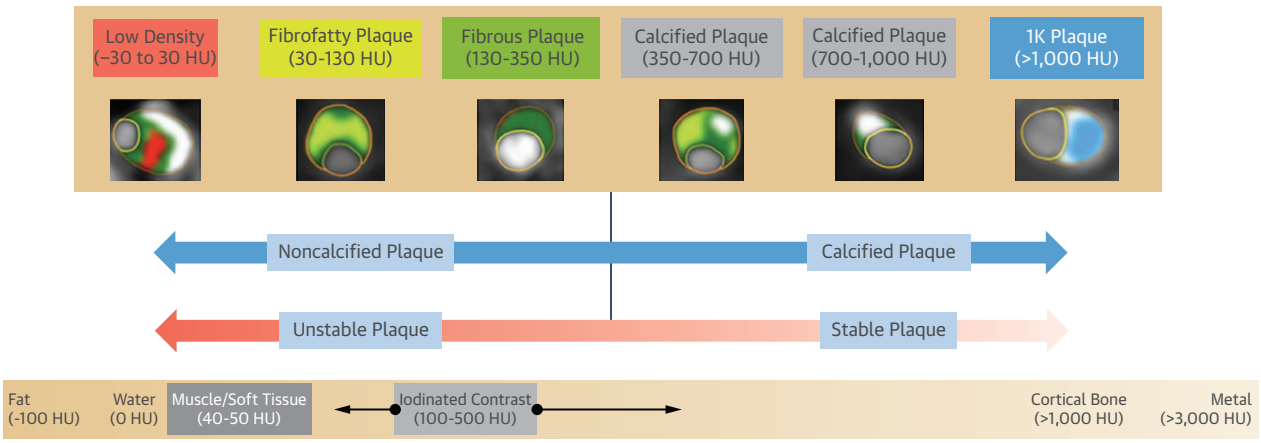
FIGURE 2 Atherosclerotic Plaque Composition Defined by Computed Tomography Radiodensity (in HU)*



Potential overlapping HU densities. These overlapping densities may affect accurate classification of specific plaque subgroups, especially for noncalcified plaque.
*Midpoint range or average HU values.

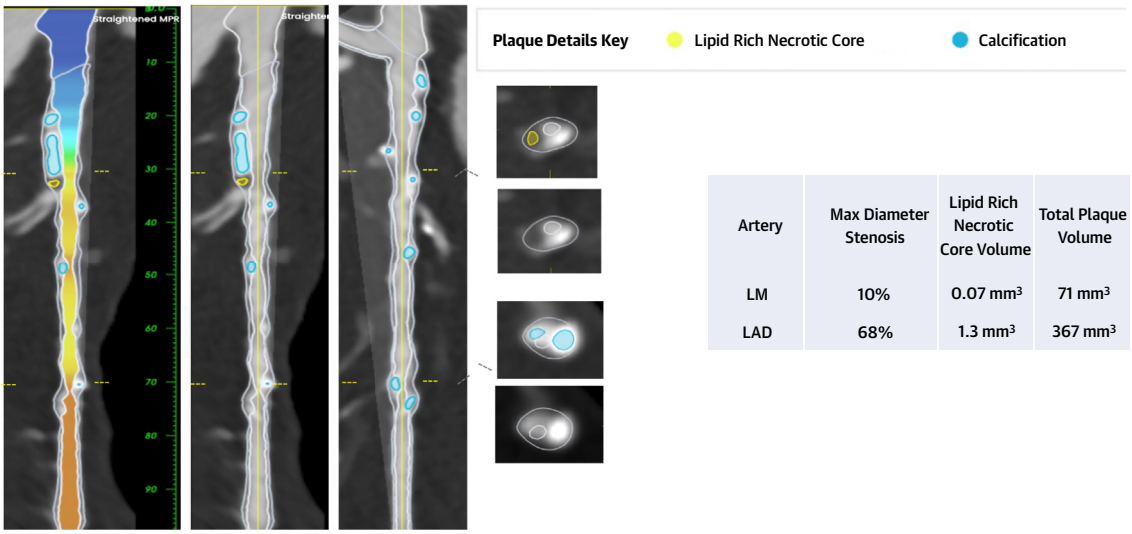
prominent role in the evidence base for the utility of coronary CTA in assessing atherosclerotic plaque.[16-20] In general, the evidence to define features of ACS on coronary CTA is largely descriptive, noting a higher burden of noncalcified plaque that also identifies those at a higher temporal risk (ie, near-term risk).[21,22] In 1 of the first series from the ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II) trial in patients presenting with acute chest pain and negative electrocardiograms and troponin levels, the presence of specific high-risk plaque features (ie, positive remodeling, low-density plaque, napkin ring sign, or spotty calcification) increased the likelihood of ACS (OR: 8.9; $P = 0.006$), even after adjustment for ≥50% stenosis and clinical risk factors (age, sex, number of risk factors).[23] Moreover, from the ICONIC (Incident COronary Syndromes Identified by Computed Tomography) case-control study, patients experiencing ACS following coronary CTA more often had a large volume of fibrofatty ($P = 0.009$) and low density ($P = 0.026$) plaque as well as high-risk plaque features, such as positive remodeling.[9] Consistent with the invasive literature, the ACS culprit lesion was more often a nonobstructive stenosis on the prior coronary CTA.[9]

Importantly, the 2 core features of ACS consistently reported are a positively remodeled lesion with a large burden of low-density plaque.[19,23-25] One feature that is easily quantified is positive remodeling, defined as the ratio of outer vessel diameter at the site of plaque divided by the average outer diameter of the proximal and distal vessel >1.1. To date, however, automated measurement of coronary CTA high-risk features (eg, positive remodeling) for ACS prediction have not been reported. Such quantitative measures would enable predictive models to incorporate continuous values, as opposed to our common reliance on binary measures. Quantitative approaches may also better enable the identification of features such as the napkin ring sign, a qualitative marker with widely varying prevalence rates likely reflecting underestimation of its occurrence and thereby prognostic significance.[16]

NEWER ARTIFICIAL INTELLIGENCE METHODS FOR CORONARY CTA QUANTIFICATION OF ATHEROSCLEROSIS

In this section, we focus our discussion on newer evidence on automated segmentation of coronary arteries to improve overall diagnostic efficiency (ie, time to diagnosis) and accurate measurement of obstructive and nonobstructive atherosclerosis. There are older reports on this subject, but in this review, we focus on the clinical approaches to automated coronary CTA measurement. Recent advances in automated software solutions for coronary CTA have received Food and Drug Administration clearance and are available for clinical use, and they could be integral to devising coronary CTA-guided preventive strategies. However, important considerations should be noted. There are automated programs developed by individuals for site use as well as

FIGURE 3 **Atherosclerotic Plaque Quantification in the LM and LAD Coronary Arteries**



Artery	Max Diameter Stenosis	Lipid Rich Necrotic Core Volume	Total Plaque Volume
LM	10%	0.07 mm^3	71 mm^3
LAD	68%	1.3 mm^3	367 mm^3

Images courtesy of Todd Villines, MD, of ELUCID Bioimaging. LAD = left anterior descending; LM = left main.

commercial programs. We have no way of determining whether any 1 method is superior or whether these newer approaches are superior to traditional semiquantitative methods. As we highlight the newer deep learning algorithms that form the basis for automated coronary segmentation, the reader should take caution regarding whether these advances result in significant progress in image interpretation because evidence is currently lacking. Moreover, several programs require subscription services and are performed only off-site, which is a major hurdle to efficient patient care.

These newer quantitative programs are largely cloud-based for performance of coronary segmentation, lumen and vessel wall labeling, and quantification of atherosclerotic plaque (including by composition) and stenosis severity. These services apply computationally intensive image processing methods including iterative prediction models and convolutional neural networks. They do *reduce* the need for manual correction of each of the steps performed in semiautomated programs, including centerline extraction, luminal and vessel segmentation, lesion boundary identification for stenosis severity, and plaque composition identification. However, even when using newer artificial intelligence-based quantitative programs, automated centerlines can diverge off course into side branches or into the left ventricular wall. Thus, manual correction is still needed and, depending on the program, may be performed only by the commercial service and not by the imager interpreting the coronary CTA scan.

Algorithms are trained against a ground truth, largely an imaging expert annotation, and they lack additional validation for prognostication or with pathologic findings (**Figure 1**). The accuracy of segmentation algorithms has been assessed against ground truth in a test set with metrics such as the Dice coefficient or Jaccard Index. To date, automated techniques remain under development but do result in a reduction in time spent on manual adjustment. Thus, the newer software programs applying artificial intelligence-based methodologies do facilitate efficient image interpretation and likely reduce interobserver variability. However, a key limitation of these quantitative approaches is that, as with all prediction models, performance will deteriorate when applied to images that differ from the training set, such as different disease prevalence, artifacts, and changes to the luminal or vessel wall with varied scanners or image reconstructions. In the following sections, we review the accuracy data for automated coronary CTA interpretation as guiding clinical care. One example of atherosclerotic plaque quantification is detailed in **Figure 3**.

ACCURACY OF QUANTIFYING CORONARY STENOSIS WITH CORONARY CTA

Accurate measurement of stenosis severity is critical to making interventional decisions, including whether percutaneous or surgical decisions can be guided by coronary CTA measurements. Comparisons among quantitative measurements of stenosis severity have been reported, with several approaches using a machine learning algorithm that is based on the geometry and shape of the coronary lumen.[26] This approach yielded a high degree of concordance, on a per lesion level, with an area under the curve of 0.94, when compared with an expert reader.[26] Area measurements may be preferable over diameter measures given variation in the lumen's noncircular shape.[27] Related reports also achieved high levels of accuracy for automated stenosis severity measurement, with 1 report applying deep learning measurements yielding a correlation of 0.96 when compared with manual annotation of coronary stenosis by an expert imager ($P < 0.001$).[26,28] In the CLARIFY (CT EvaLuation by ARtificial Intelligence For Atherosclerosis, Stenosis and Vascular MorphologY) study, the accuracy of automated measurement for a stenosis ≥50% was 80% and 97% for diagnostic sensitivity and specificity, respectively, using 3 expert readers as the gold standard.[29] In a subanalysis from the CREDENCE (Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia) trial, as compared with invasive quantitative coronary angiography, the automated stenosis measurement had a *per patient* sensitivity and specificity of 94% and 68%, respectively.[30] Overall, there are limited data exploring the contributing factors leading to decreased specificity, such as errors related to image quality, stenosis location, and vessel size.

It is perhaps the patient with nonobstructive CAD who could most benefit from comprehensive prevention as a high proportion of patients are at risk for ACS.[9,31] Thus, automated stenosis measurement may prove advantageous for evaluation of an intermediate stenosis, to reduce variability in measurement, and to serve as a second reader for the coronary CTA imager. This is particularly important when the stenosis appears close to the 50% stenosis threshold where more intensive care may ensue. A prompt analysis time can increase reliance on automated stenosis measurement in daily clinical practice. However, computational timing for the stenosis measurement has been reported to be as long as 9.7 minutes per case.[26,28,29]

Additionally, utility of these automated measures in guiding clinical decisions has yet to be reported. This is an issue as automated stenosis measurement will need to be integrated with fractional flow reserve measures by CT, per the recent chest pain guidelines.[32,33]

CORRELATING CORONARY CTA QUANTIFICATION OF ATHEROSCLEROTIC PLAQUE WITH INVASIVE CORONARY IMAGING

There is a robust body of evidence from both invasive and pathologic techniques of the role of specific coronary atherosclerotic plaque features as precursors to ACS.[33-38] The optimal scenario would be that patients with specific coronary CTA features strongly predictive of near-term risk of ACS undergo intervention, thus averting this future incident ACS event. To date, evidence is limited on the correlation between pathologic findings and coronary CTA, with 1 report correlating carotid artery findings.[2,39,40] For our discussion, we highlight the correlative evidence using invasive imaging of atherosclerotic plaque.

Thin cap fibroatheroma (TCFA) is considered causative of plaque rupture and has been described in the culprit ACS lesion. TCFA is characterized by a thin fibrous cap <65 μm in thickness overlying a large lipid pool with necrotic core adjacent to the lumen. The spatial resolution of coronary CTA, in both the x-y and z-directions, is generally limited to ~0.5 mm in each direction. Thus, coronary CTA equipment cannot visualize the microdetails of the fibrous cap.[41] However, the appearance of a napkin ring sign on a cross-sectional slice in a lesion (ie, a positively remodeled plaque with a low attenuation plaque surrounded by a rim of hyperenhancement) may represent TCFA.[23,42-44]

Although optical coherence tomography has a 10-fold higher spatial resolution as compared with IVUS, it is limited in terms of depth and penetration of image findings to ~1 to 2 mm.[45] Thus, for our discussion on quantitation of volumetric atherosclerotic plaque, we focus on the correlations with volumetric findings between IVUS and coronary CTA. There are reports comparing IVUS and coronary CTA measurement of plaque volume, with most reporting high correlation statistics ($r = 0.94$ for measurement of total plaque volume; $P < 0.0001$).[14,46-52] An important limitation to the evidence is that many reports include small sample sizes (eg, n = 11-38). One report noted that coronary CTA slightly overestimated total plaque volume on IVUS (by ~4-11.9 mm^3; $P < 0.001$).[46] The accuracy of coronary CTA for detecting IVUS coronary atherosclerotic

TABLE 1 Summarized View of Available Data on Concordance Between Coronary CTA and Varied Gold Standards, Such as an Expert Reader or Invasive Measures

Automated Measurement	Concordance Measure With Invasive Measures	Overestimation/ Underestimation Reported	Diverse Patient Validation Including Across Anatomical Subgroups	Computing Time vs Imager
Stenosis severity	Moderate	Yes	No	More
Plaque volume				
Total	High	Yes[a]	No	Less
Noncalcified	Moderate[b]	NR	No	Less
Calcified	Moderate	NR	No	More vs CAC scoring

Data from references.[41-51] [a]Potentially affecting smaller more than larger plaque volumes. [b]Reduced for low-density plaque.
CAC = coronary artery calcium; CTA = computed tomography angiography; NR = not reported.

plaque had reported sensitivity and specificity of 90% and 92%, respectively.[53] In another report of 142 patients, there were strong correlations for the percent plaque burden ($r = 0.91$; $P < 0.001$) and volume ($r = 0.94$; $P < 0.001$).[54] From a meta-analysis, there were no significant differences between total plaque volume measured by coronary CTA and IVUS ($P = 0.88$).[55] The largest series published to date (training and test data sets in 921 patients, external validation cohort with IVUS measurements in 175 patients, and prognostic validation in 1,611 patients) noted strong correlation between deep learning convolutional neural network volumetric quantification when compared with an expert reader ($r = 0.96$), with a slightly lower agreement for percent diameter stenosis ($r = 0.88$).[52] Data on reliability across the range of plaque volumes, including patients with varying arterial sizes, are not available.

Further, evidence is limited with regard to volumetric measurement by specific compositional subgroups. Zreik et al[56] used a convolutional neural network to classify noncalcified and calcified plaque and reported an accuracy of 80% when compared with expert readers. From another study, the intraclass correlation coefficient between coronary CTA and IVUS was 0.94 for total noncalcified plaque volume, but was 0.81 for low-density plaque.[52] The lower correlation for low-density plaque is likely related to the size of this subcomponent, which has averaged 0.3% of the PAV.[57]

Only 1 report examined how coronary CTA features predicted TCFA on IVUS (n = 65 patients with coronary CTA performed ≤1 month).[58] These results reveal that low-density plaque was highly predictive of a TCFA lesion ($P < 0.001$). In fact, when the low-density plaque volume was >8 mm^3, the diagnostic sensitivity was 85% and specificity was 97% for detection of a TCFA lesion. Total analysis time was 5.7 minutes for the deep learning analysis, as compared with 25.7 minutes for the expert reader.

An overview of concordance data between coronary CTA and varied gold standard measures, including expert readers or invasive measurements, is detailed in Table 1.[41-51]

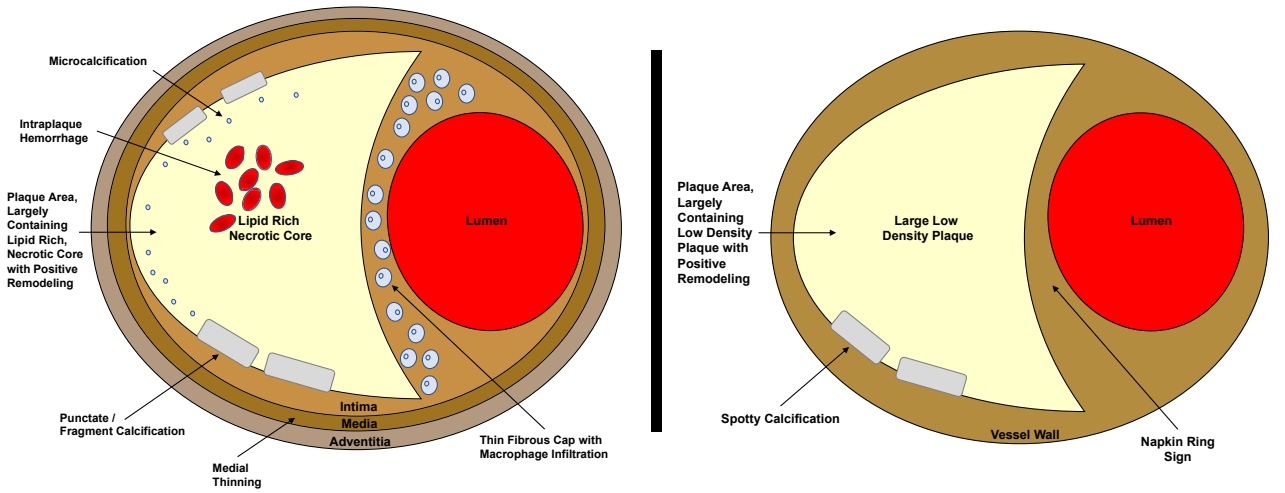
ACCURACY OF CORONARY CTA QUANTIFICATION FOR PREDICTION OF FUTURE ACS

To offset the untoward consequences of progressive atherosclerosis and ACS risk, coronary CTA measures must also be uniquely additive to prognostication,[59-63] including characteristics of coronary atherosclerotic plaque that cause future ACS. There are differences between the pathologic correlates of ACS and what can be measured by coronary CTA. A comparison of pathologic and invasive measures of ACS vs coronary CTA is shown in Figure 4.

Considerable knowledge gaps exist relating lower-risk patients undergoing coronary CTA to the dynamic and unpredictable nature of risk spurned by systemic inflammatory and other factors promoting the event. Moreover, there are marked methodologic issues, including a short duration of follow-up with few observed ACS events. In lower-risk cohorts, longer follow-up times are required to capture disease progression and longer-term ACS risk. Moreover, there is often a limited depth of detail with regard to the acute event that is being predicted, such as myocardial infarction type, culprit lesion, intercurrent treatment, and details of angiographic findings (ie, nonculprit disease) at the time of ACS. All these details can enhance our knowledge and improve coronary CTA prediction of ACS.

Several reports have examined the use of quantitative measures for predicting incident myocardial infarction.[31,64] In a post hoc analysis from the SCOT-HEART (Scottish COmputed Tomography of the HEART) trial of 1,769 patients with stable chest pain, revealed that incident myocardial infarction occurred

FIGURE 4 Precursor Features of Acute Coronary Syndrome



(Left) Features based on pathology and invasive imaging. **(Right)** Features based on coronary computed tomography angiography correlates. Many features associated with acute coronary syndrome are too small to be imaged with coronary computed tomography angiography, such as microcalcification and intraplaque hemorrhage. Larger-sized spotty calcification can be imaged with coronary computed tomography angiography.

more often among those patients with a greater burden of atherosclerotic plaque data consistent with invasive imaging.[64] In particular, low-density plaque conferred the greatest risk of future myocardial infarction, independent of a cardiovascular risk score, coronary artery calcium score, and stenosis severity. These investigators noted a significant risk threshold for a low-density plaque burden of >4%, with a relative hazard of 4.7 ($P < 0.001$).[31] Interestingly, the relative hazard for myocardial infarction was significantly higher among patients with nonobstructive CAD. For patients with nonobstructive CAD, the hazard for incident myocardial infarction was 6.6 for those with low-density plaque burden >4% ($P = 0.003$), whereas no increased risk was noted for those with a plaque burden <4% ($P = 0.80$).[31]

In an additional SCOT-HEART report, a deep learning measurement of total plaque volume was used to predict incident myocardial infarction (n = 41).[52] A threshold of ≥238.5 mm^3 was associated with a relative hazard of 5.4 ($P = 0.0042$), even when controlling for deep learning measurement of stenosis severity and clinical risk factors.[52] Previous reports used lower risk-based thresholds,[16] including 1 report identifying a cutoff of >179 mm^3, thereby supporting optimizing risk detection may be best when using risk-based thresholds,[65] and that these thresholds may vary across specific patient groups. These latter findings suggest that we have much more evidence that is required to define high-risk patient subgroups, across varied populations at varied risk of major CAD events.

LIMITATIONS TO AUTOMATED CORONARY CTA INTERPRETATION

Of foremost concern with regard to quantification of coronary CTA findings is that image quality must be in the good to excellent range. From the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, nearly 30% of scans were of suboptimal quality (ie, with image artifact, stents, or excessive calcification).[66,67] Additionally, each quantitative software program has been applied in varied (and often highly selected) patient groups and with limited or inadequate validation. Readers should ponder carefully how the presented evidence is inadequate to understand accuracy among patients with a wide-ranging disease burden, from no burden to extensive atherosclerosis. To date, standards for presentation of data do not exist and can include per lesion, per vessel, or per patient cumulative results. It is important to understand how measurement variability in a lesion or vessel contributes to incomplete assessment of the total quantitative plaque burden. Moreover, often average measurement differences are presented between a given software program and the gold standard (eg, expert reader). These frequently appear as minimal differences (eg, differences in coronary CTA

vs IVUS volume measures), yet a review of the Bland-Altman plots can often reveal greater variability (eg, using a mean difference in total plaque volume of 25 mm^3 with 95% limits of agreement from −63 to 113 mm^3) This wide variability would differentially impact plaques of varying sizes. That is, a 25 mm^3 difference in total plaque volume between coronary CTA and IVUS is less concerning in a patient with quantitative measurement of 400 mm^3 but is excessive for a patient with 38 mm^3 of atherosclerotic plaque. These differences between the gold standard for atherosclerotic plaque and coronary CTA are critical to establish a therapeutic benefit, so that differences may validly reflect alterations in the disease burden.

We have some evidence that accuracy is reduced in low-density plaque and in other cases where the concordance is reduced in the setting of smaller plaques.[68] In general, there is an inverse relationship between measurement variation and the volume of plaque, with smaller volumes having greater variation. These results are consistent with the reported high interobserver variability reported across various volumetric measures, with variance statistics ranging from 17% to 37%.[42,68] Discordance in coronary CTA plaque measurement is also influenced by image quality, vessel size, and the extent of coronary calcification.[42] Thus, we can expect that targeting a benefit for treatment will require a higher burden of atherosclerosis.

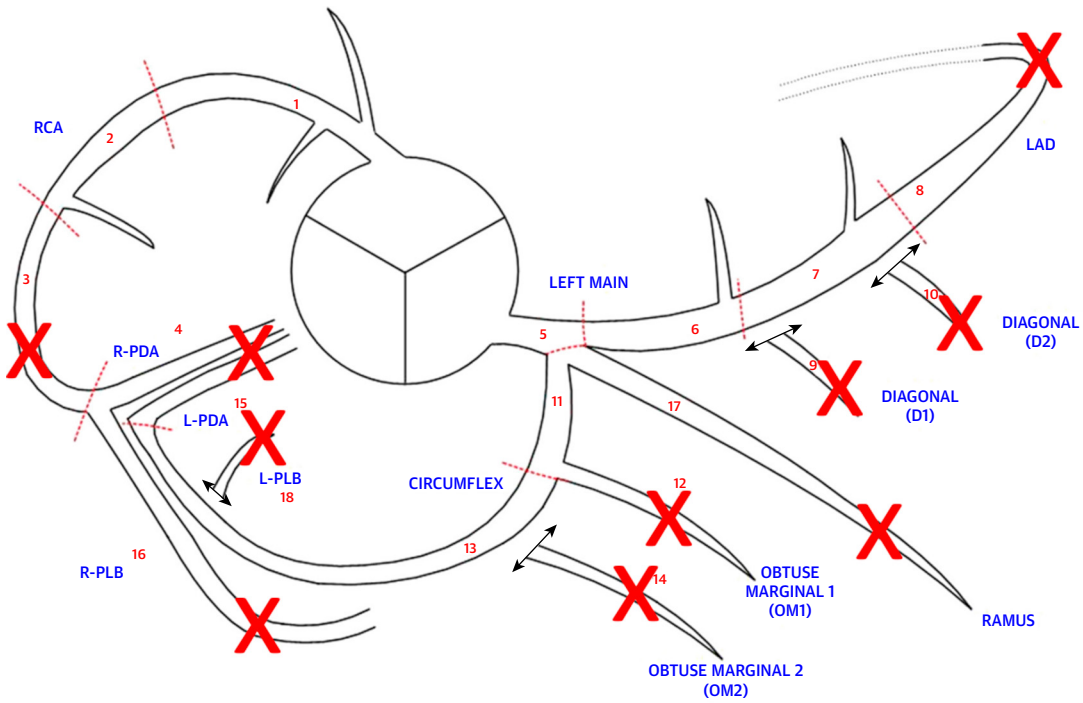
There are also patient subsets with small (<1.5 mm) or tortuous vessels and issues with image quality (eg, noise, stents or other metal, and excess calcification) where automated measurements are affected. When summed across the arterial tree, comprehensive volume measures will be incomplete in those patients with smaller arteries where only a portion of their arterial bed contributes to total plaque measurement.

Few reports have detailed average coronary artery dimensions,[69-72] with sizes varying substantially by age, sex, body weight, heart size, and coronary dominance and across diverse racial and ethnic subgroups. These data support that the size of most distal segments and the obtuse marginal, diagonal, and the proximal descending coronary arteries are often <2 mm and will likely not be included in a quantitative measurement (**Figure 5**). For women, smaller coronary arteries further affect measurement and may exclude both middle and distal coronary artery segments. One may argue that the loss of distal measurements in total plaque volume is not important because the proximal segments are the most important for ACS risk. However, women often have diffuse nonobstructive atherosclerosis, and to that extent, their volumetric burden will be incompletely measured.[73,74] These findings would be further exacerbated if nitrates are not used.[69] Importantly, data are not available on how many segments are missed and the proportion of patients affected by smaller arterial dimensions.

Furthermore, various coronary CTA-specific technical considerations also affect image quality and therefore plaque measurements. Plaque attenuation is affected by adjacent components and partial volume effect and shadowing, with greater influence exerted by dense components.[75,76] Increased density of adjacent calcified plaque may raise the density of contiguous low-density plaque, by partial volume effect, leading to erroneous misclassification as fibrous plaque. Adjacent contrast density will regularly change from study to study for several reasons, including change in patient weight, contrast volume, and rate of administration, and it will artifactually affect plaque densities. Standardizing plaque thresholds to account for contrast attenuation in adjacent vessels improves the accuracy of quantification of compositional subgroups.[77,78]

It is well known that the accuracy for distinguishing varied plaque composition subgroups is affected by calcium blooming artifact. In addition, there are overlapping Hounsfield unit densities for plaque composition (especially for low-density [−30 to +30 HU] and fibrofatty [30-130 HU] plaque) and the density of intraluminal contrast medium, the vessel outer wall, and pericoronary fat.[79] Thus, precise delineation of noncalcified plaque volumes may vary across readers and coronary CTA software. Different workstations may also yield different plaque volumes, as demonstrated by Oberoi et al,[80] who evaluated the reproducibility of noncalcified plaque burden quantification from coronary CTA across different commercial analysis platforms and showed poor interplatform reproducibility. Although newer platforms may yield closer results, head-to-head comparisons of the latest technologies have not been performed. Moreover, there is an inverse relationship between tube potential and plaque density. From a report of 1,236 patients, higher-tube voltage scanning (from 80 to 120 kV) was associated with a decrease in luminal attenuation (on average 689 to 391 HU; $P < 0.0001$).[81] This resulted in a compositional shift toward a greater proportion of noncalcified plaque, largely due to alterations in blood pool and luminal attenuation; these differential findings are generally ignored in multicenter studies. These findings may profoundly affect the utility of coronary CTA findings to guide preventive care, thereby resulting in underuse or overuse of disease-modifying therapies, such as statins.

FIGURE 5 Small Coronary Artery Segments and Automated Quantitation Software



Coronary artery segments marked with a **red X** often have diameters <2 mm and may not be measured with automated quantitation software. Thus, total volumetric measurements would potentially underestimate atherosclerotic plaque burden. L-PDA = left posterior descending artery; L=PLB = left posterolateral branch; R-PDA = right posterior descending artery; R-PLB = right posterolateral branch; RCA = right coronary artery; other abbreviation as in Figure 3.

Moreover, the IVUS technique for calcified plaque quantitation is problematic as a result of shadowing precluding measurement of calcium thickness, and other plaque components adjacent to the calcium may also be obscured.[2] IVUS measurements rely on an assessment of the arc of calcium with limited comparison with coronary CTA volumetric measures.[82]

There has been a lack of standardized definitions for atherosclerotic plaque, and in the last decade, coronary CTA equipment has been constantly changing. In our review, we highlight evidence from the last 10 years, but this includes varied ranges for plaque composition and older equipment with differing and often suboptimal spatial and temporal resolution. The extent to which accuracy can be maintained across coronary CTA equipment is unknown. Importantly, standardized reporting of coronary CTA findings is now recommended by the Society of Cardiovascular CT CAD-Reporting and Data System (CAD-RADS) 2.0.[83] These new quantitative measures will require simplification and integration into future CAD-RADS statements to foster assimilation into standardized image interpretation.

Photon-counting CT is a new technology being introduced into clinical use. This technique, using photon-counting detectors, varies considerably from the current energy-integrating detectors; several reviews provide a more in-depth understanding of the technology.[84-86] The application of photon-counting CT will result in a higher contrast-to-noise ratio, high spatial resolution, and a reduction in calcium blooming artifact.[84,86] However, this ability to obtain multienergy information may require different slice thickness, reconstruction kernels, and other material classification techniques, and different monoenergetic images.[86,87] Further research will be required for determining whether the improved image quality from photon-counting CT will translate into enhanced atherosclerotic plaque quantification techniques.

TABLE 2 Trials and Registries With Atherosclerotic Plaque Outcomes by Invasive or Coronary CTA Imaging

Trial or Registry	Imaging Modality	Intervention	Imaging Endpoints	Concordance With Larger Cardiovascular Outcomes Trial
TTrials[79]	Coronary CTA	Testosterone gel	↑ Total plaque volume ↑ Noncalcified plaque	–
PARADIGM Registry[80]	Coronary CTA	Statins (observational use)	↓ **PAV progression** ↓ **HRP** ↑ Calcified plaque, especially 1k plaque	+++
GLAGOV Trial[81]	IVUS	Evolucumab	↑ **PAV regression**	+++
PACMAN-AMI Trial[82]	IVUS, OCT, NIRS	Alirocumab	↑ **Regression** ↑ **Fibrous cap thickness**	+++
EVAPORATE Trial[83]	Coronary CTA	Icosapent ethyl	↓ **Total plaque volume** ↓ **Low-density, fibrous, and fibrofatty plaque**	+++
HUYGENS Trial[84]	OCT	Evolucumab and statins	↑ **Fibrous cap thickness** ↓ **Maximum lipid arc and macrophage index** ↑ **Regression of PAV**	+++

Findings reported in **bold** are positive with regard to halted or regressed atherosclerotic plaque measurements. The TTrial noted adverse increases in total and noncalcified plaque following treatment with testosterone gel. The remaining trials revealed evidence concordant with the larger cardiovascular outcome trials eliciting relative risk reduction with treatment

– to +++ = strength of concordance from negative to strong; CTA = computed tomography angiography; GLAGOV = GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound; HRP = high-risk plaque; HUYGENS = High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study; IVUS = intravascular ultrasound; NIRS = near-infrared spectroscopy; OCT = optical coherence tomography; PACMAN-AMI = Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction; PARADIGM = Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging; PAV = percent atheroma volume; TTrials = testosterone trials.

EVIDENCE NEEDED TO DEVISE CORONARY CTA-GUIDED PREVENTIVE CARE STRATEGIES

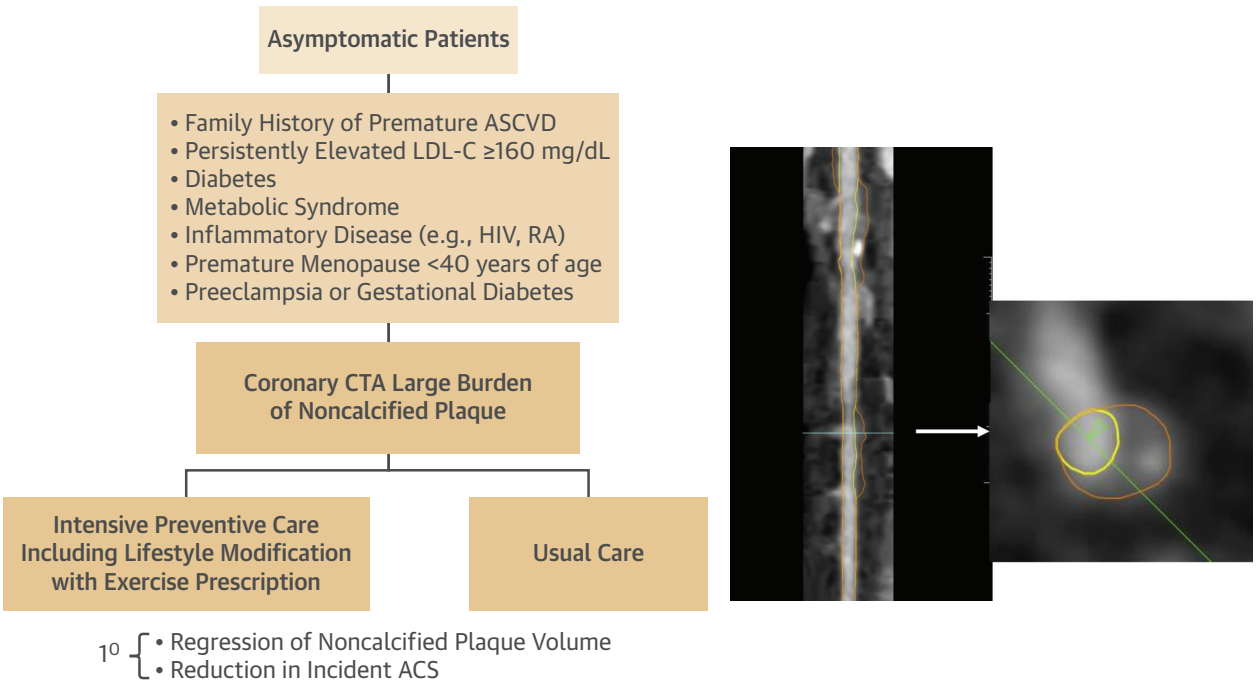
Current evidence is insufficient to provide specific image-guided therapeutic strategies. However, by allowing better identification of higher-risk patients, it is likely that imaging features could play a larger role in selection of patients for various therapeutic agents. Future research for quantitative plaque analysis may assess the efficacy of various therapeutic agents. Evidence to date supports that plaque regression by coronary CTA or IVUS is an important surrogate outcome (Table 2).[87-92] There are several relevant examples, such as the observational PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study (N = 1,255 patients underwent serial coronary CTA at a ≥2-year interval, 781 with statin therapy), which reported that statin use was associated with slower progression of overall plaque and with more rapid progression of calcified plaque.[88] Reducing low-density lipoprotein cholesterol was also associated with a reduction in noncalcified plaque components.[88] Moreover, complementing the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) trial, the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy) trial investigated the use of icosapent ethyl (an omega-3 polyunsaturated fatty acid) in a randomized double-blind placebo-controlled coronary CTA-based trial.[93] Eighty patients were randomized 1:1 to receive icosapent ethyl or placebo and were followed up with coronary CTA at 9 and 18 months. At 9 months, there was no difference in low-density plaque progression between the randomized groups, but a reduction in progression of other plaque types was noted.[91,93] At 18 months, there was a 9% reduction in total plaque volume and 17% reduction in low-density plaque volume in the icosapent ethyl group, compared with increases in the control group (11%; $P = 0.0019$; and 109%; $P = 0.0061$).[91,93] Serial coronary CTA comparisons are challenging and require matching of scan parameters (eg, kV), as recently detailed in a statement by the Society of Cardiovascular Computed Tomography.[16]

FUTURE APPLICATION OF CT PLAQUE ANALYSIS

Future research will need to target younger individuals where the focus is on early detection and intervention of at-risk atherosclerotic plaque with enrollment from diverse populations including a large proportion of women and patients of diverse race and ethnicity. We envision that plaque analysis could be used in the following types of trials:

1. *Prognostic studies:* Assessment of the association of plaque burden/plaque type with incident CAD events. Adequate image quality is essential for serial comparisons along with detailed data on incident CAD events and more lengthy follow-up time.
2. *Mechanistic trials:* Use of serial coronary CTA studies to assess whether various lifestyle or

FIGURE 6 Potential Atherosclerosis Prevention Randomized Trial and Possible Imaging Findings



(Left) Flow chart of a potential randomized trial examining the impact of preventive management on coronary atherosclerosis. **(Right)** One example of a potential eligible case with 2 nonobstructive lesions, in the proximal and middle segments of the left anterior descending coronary artery. The total volume of noncalcified plaque is 374 mm^3, with 8% of the total plaque burden being low-density plaque. In both lesions, positive remodeling is ≥1.1. The **arrow** points to the cross section **(inset).** ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CTA = computed tomography angiography; LDL-C = low-density lipoprotein cholesterol; RA = rheumatoid arthritis.

pharmacologic interventions lead to plaque stabilization or regression. These trials would use endpoints most likely to be modified by a specific intervention. Selecting the appropriate plaque quantification endpoints requires careful consideration of numerous factors, including the study group, image quality, and the reproducibility and performance of different quantitative tools. Serial coronary CTA studies could be used to provide preliminary data (ie, before planning a large outcome based trial) or could be used to assess the efficacy of various therapies in populations where a large trial is not feasible. For example, if one designs a trial to assess the efficacy of a preventive therapy in younger patients, a large trial may not be possible because it may require a very large cohort with lengthy follow-up.

3. *Outcomes trials using imaging to define or enrich patient selection:* Quantitative assessment of plaque burden could be used to define a threshold of plaque that is associated with a sufficient level of risk for entry into a larger trial (Figure 6). Such trials may be especially useful for trying to evaluate the efficacy of traditional "secondary prevention" agents across higher-risk "primary prevention" cohorts who have underlying atherosclerosis but who have not yet experienced a CAD event. It would also be interesting to examine whether an intensified prevention program, such as cardiac rehabilitation, could benefit patients with nonobstructive CAD. Moreover, it would be helpful to identify a threshold of plaque whereby treatment would be effective at halting or regressing atherosclerotic plaque, notably high-risk, noncalcified plaque. Although the specific thresholds for treatment are incompletely defined, we present some potential therapeutic targets for preventive care that are based on the newer automated coronary CTA interpretation programs shown in Table 3.[9,16,31,58,94]

IMPORTANT CONSIDERATIONS FOR THE CORONARY CTA IMAGER

When considering these newer applications for atherosclerotic imaging, the core questions to the

TABLE 3 Potential Therapeutic Targets[a] for Preventive Care Including Thresholds of Atherosclerotic Plaque Suggestive of Increased ACS Risk

	At-Risk Strata	Cutoff for Intensifying Preventive Care	Association With Near-Term Temporal Risk
Nonobstructive CAD stenosis	High	≥20%-25%	Majority of ACS culprit lesions having previous nonobstructive stenosis[21,86]
Low-density plaque burden	Highest	>4%-8% or higher	Larger plaque burden increasing near-term ACS risk[28,54]
Positive remodeling	High	≥1.1 or higher	High-risk precursor of ACS[13,21]
Noncalcified plaque volume	Moderate	≥100 mm^3 or higher	Predictor of major CAD events[13]

[a]Measures are slightly adapted (eg, rounded) from cited references and expert opinion.
ACS = acute coronary syndrome; CAD = coronary artery disease.

imager are whether the added expense would enhance the care of patients referred to them and whether their referring physicians are eager to integrate these data into preventive care. Coronary CTA is a relatively inexpensive procedure, and many of these quantitative programs will add considerable cost beyond that of the index test. Thus, at the heart of decisions to use quantitative software programs is the added value of these programs. For example, do the new quantitative programs add value over coronary artery calcium scoring, which is inexpensive and easily measured? Or does your practice thrive without adding this expensive option to standard coronary CTA image interpretation?

CONCLUDING STATEMENTS

A summary of evidence on newer approaches for automated coronary CTA interpretation reveals that the data are "under development." The strengths and limitations of quantitative measurements with coronary CTA are highlighted in the **Central Illustration**. Certainly, many issues are related to limited available data and to unknowns about how reliable these novel techniques are as an aid to the coronary CTA reader. Considerable evidence is required for these quantitative techniques to become an essential component of coronary CTA image interpretation. Current research supports that automated stenosis measurement is reasonably accurate,

CENTRAL ILLUSTRATION Strengths and Limitations for Quantification of Coronary Computed Tomography Findings

Strengths	Limitations
• Automation and time efficiency for measuring coronary stenosis and total plaque volume • Automated interpretation, which may guide reader and improve reliability (ie, serving as a second reader) • Greater attention to preventive care and slowing the progression of atherosclerotic plaque by intensified statin and other disease-modifying therapies	• Requires at least *good* image quality whereby quantitative measures from a scan with reduced image quality (eg, morbid obesity, tachycardia, motion) would be unreliable • In the presence of extensive and dense coronary calcifications, problematic plaque analysis measurement because of blooming artifacts and volume averaging • Unknown accuracy in measuring coronary arteries by location, including side branches, across varied image quality, and tortuous vessels • Limitations to the measurement of total atherosclerotic plaque volume in women and others with small coronary arteries • Questionable added value over simple semiquantitative scores, such as Duke CAD Prognostic Index or a quantitative CAC score

Bienstock S, et al. J Am Coll Cardiol Img. 2023;16(8):1099–1115.

CAC = coronary artery calcium; CAD = coronary artery disease.

HIGHLIGHTS

- Significant advances in coronary CTA now allow for detailed measurement of atherosclerosis and could be very helpful to guide preventive care, including automated quantification of stenosis severity and atherosclerotic plaque and its compositional subgroups.
- Coronary artery dimensions vary by age, sex, heart size, coronary dominance, and race and ethnicity. Accordingly, quantification programs excluding smaller arteries affect accuracy for women, patients with diabetes, and other patient subsets.
- Limited prognostic evidence is available to report on the thresholds for high-risk status on the basis of newer automated measurements of atherosclerotic plaque.
- The promise of automation with coronary CTA enhances the feasibility of imaging of atherosclerosis and the possibility of coronary CTA-guided preventive care.

but evidence on variability by location, artery size, or by image quality is unknown. Evidence is unfolding that quantification of atherosclerotic plaque is useful to enhance risk prediction, yet more evidence is required to define high-risk patients across varied populations and to determine whether such information is incremental to risk factors or currently used cardiac CT techniques (eg, coronary artery calcium scoring or visual assessment of stenosis). Thus, there is promise for the utility of coronary CTA quantification of atherosclerosis, especially if it can lead to targeted and intensive cardiovascular prevention, notably for those patients with nonobstructive CAD and high-risk plaque features. For today, imagers must take care to avoid pitfalls when using automated software.

Of the patients undergoing coronary CTA, quantification may mostly benefit the patient with substantive atherosclerosis and an elevated risk of ACS. These patients have the potential to benefit from intensified preventive care and avert a downstream CAD event. As such, clinical practices that are wholly engaged in cardiovascular prevention may value quantitation of atherosclerotic plaque more than a coronary CTA laboratory that serves as a gatekeeper to invasive angiographic procedures. If coronary CTA-detected atherosclerosis is linked to more intensive cardiovascular prevention, then this could be the "biggest win" for the imaging and cardiology communities and their patients. However, current chest pain or prevention guidelines do not include any indications for atherosclerotic plaque quantification,[32] and thus we envision limited initial use until there is definitive evidence of its clinical benefit in terms of improving patient care. In summary, as with most new techniques available for imagers, care must be taken to see whether there is sufficient added value to enhance patient care but also that the cost is reasonable for our patients and the health care system.

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