

EDITORIAL COMMENT

Will Plaque Quantification on Coronary CTA End Our Infatuation With Lumen Stenosis?*



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What did the angiogram show? This question is asked thousands of times daily around the world after invasive or noninvasive coronary angiography and is invariably answered as units that are universally understood: *percent diameter stenosis*. Since the days of Dr. Mason Sones and Dr. Charles Dotter, pioneers in invasive coronary angiography approximately 6 decades ago, percent diameter stenosis of the coronary lumen has served as the universally accepted measure to define the severity and guide the treatment of coronary artery disease (CAD). Indeed, stenosis and the location of coronary lesions on invasive coronary angiography or coronary computed tomography angiography (CTA) are among the strongest predictors of adverse cardiovascular outcomes in individuals and populations. Elegantly simple and concise, percent stenosis is frequently remembered by patients, demanded by surgeons, and beloved by cardiologists, despite knowledge that stenosis only modestly predicts functional significance defined by invasive fractional flow reserve.

Unlike traditional coronary angiography (lumengraphy), 3-dimensional coronary CTA can detect, characterize, and quantify coronary atherosclerosis across nearly the entirety of the epicardial coronary

arterial tree (1). Research over the past decade has consistently shown that adverse plaque features, such as positive remodeling, spotty calcification, low attenuation, and the napkin ring sign (central lower attenuation with peripheral plaque enhancement), identify plaques more likely to represent thin-cap fibroatheromas that result in acute coronary syndromes (2). Moreover, the presence of these plaque vulnerability features improves risk prediction beyond stenosis alone (3,4). More recently, advanced plaque quantification software and machine learning techniques have been used to more fully assess and quantify plaque on coronary CTA, providing measures of total plaque volume as well as the volume of plaque subtypes, such as noncalcified, calcified, partially calcified, fibrous, fibrofatty, and low attenuation (5,6). Demonstrating the potential of plaque quantification, in a post hoc analysis of the prospective randomized controlled SCOT-HEART (Scottish Computed Tomography of the Heart) trial, low-attenuation (<30 HU) plaque volume on coronary CTA measured using semiautomated research software (AutoPlaq, Cedars-Sinai Medical Center, Los Angeles, California) was the strongest predictor of future myocardial infarction, irrespective of coronary artery calcium score, clinical risk factors, or stenosis severity (7).

Despite advances in plaque quantification technology, coronary CTA currently is interpreted and reported clinically in much the same way as conventional invasive coronary angiography. For example, the Society of Cardiovascular Computed Tomography's Coronary Artery Disease Reporting and Data System (CAD-RADS) classifies disease severity (0 to 5) according to the worst percent lumen stenosis. High-risk (vulnerable) plaque features are described as present when ≥ 2 features are visualized within a plaque, but they are reported in a binary fashion (present or absent in the entire scan) and not

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FIGURE 1 Milestones for Clinical Adoption of Plaque Quantification on Coronary Computed Tomography Angiography

Whole-Heart Plaque Quantification Milestones to Widespread Clinical Adoption				
Optimization of Image Quality	Measurement Validation	Establishing Spectrum of Disease	Standardized Reporting	Imaging-Guided Intervention
Attain high image quality, while minimizing exposure to radiation and contrast	Evaluate measurement accuracy across the range of <ul style="list-style-type: none"> - Tube potentials - Noise levels - Vendors 	Define optimal mild/moderate/severe plaque volume thresholds <ul style="list-style-type: none"> - According to patient, lumen size - Normalized for age, gender, ethnicity 	Enrich reporting nomenclature to encapsulate <ul style="list-style-type: none"> - Plaque features and extent - Stenosis and plaque volumes - Pericoronary milieu 	Clinical trials of imaging-guided: <ul style="list-style-type: none"> - Lifestyle regimens - Medical therapies - Revascularization

quantified or further characterized with regard to the number of high-risk plaques or their location (8). The number of segments with plaque, the segment involvement score (SIS), and other semiquantitative scores of CAD extent and severity shown to add prognostic value beyond stenosis also are not a part of CAD-RADS and are not typically reported. A few of the limitations to the clinical use of volumetric coronary plaque quantification include a lack of standardization in measurement and reporting techniques, terminology, and disease severity thresholds (mild, moderate, severe) for plaque volumes according to age and gender.

In this issue of *JACC*, Andreini et al. (9) performed a multicenter prospective cohort study of 544 consecutive individuals who underwent coronary CTA for suspected but not known CAD. Only patients with low (0 to 1 traditional risk factors, nondiabetic) or high (≥ 3 risk factors) clinical risk were included. Interestingly, patients with CAD present but involving <5 segments (SIS 1 to 4) were excluded. Experts in cardiac computed tomography (CT) performed qualitative and quantitative assessments of coronary atherosclerosis using commercially available vendor software (PlaqID, GE Healthcare, Milwaukee, Wisconsin). Coronary stenosis and high-risk plaque features were assessed in standard fashion. Total coronary plaque volume (mm^3) was reported on a per-patient level, not indexed to coronary artery length or patient size, and plaque was quantified and categorized as noncalcified (<150 HU), fibrofatty (30 to 150 HU), or low attenuation (<30 HU). A strength of the study was the measurement of several circulating biomarkers to include high-sensitivity troponin, in addition to risk factors and several validated CT risk scores (SIS, CT-Leaman).

Andreini et al. (9) conclude that quantitative measurement of plaque volume was superior to traditional risk factors, biomarkers, lumen stenosis (to include multivessel disease), high-risk plaques,

and several validated CT and/or clinical risk scores for predicting the combined endpoint of acute coronary syndrome, cardiac death, or elective late revascularizations (>6 months after CTA) over 5 years. Specifically, higher volumes of noncalcified and low-attenuation plaque were the strongest predictors of the combined endpoint on multivariable and reclassification analyses. In patients with severe lumen stenosis, those with high noncalcified plaque volume demonstrated the highest risk for adverse events.

Andreini et al. (9) are to be commended for this important addition to the growing body of published data suggesting that it is the volume of coronary atherosclerosis, especially low-attenuation and noncalcified plaque, that most powerfully predicts risk when assessed by coronary CTA. So, are the days of percent stenosis as the primary standard bearer for describing and reporting CAD severity over? Not just yet. Several important limitations to the current study should prompt readers to view these results as hypothesis generating. First, the study population was relatively small and highly selected based on their risk factor profile, CTA findings, and image quality. Most patients ($n = 342$) had no CAD on CTA, a population known to be at exceedingly low risk. Furthermore, 42 patients who underwent coronary revascularization within 6 months after CTA were censored from the outcomes analysis. Ultimately, there was a very small number of hard cardiovascular outcomes (8 myocardial infarctions, 1 cardiovascular death), with elective late revascularizations, a soft outcome prone to selection bias, composing the majority (13 of 22) of “events.” Lastly, it should be noted that coronary plaque volume was measured semiquantitatively with manual lumen and plaque boundary corrections by experts in the field and using studies screened for adequate image quality.

Despite these limitations, these data are exciting when viewed in the broader context of the growing

body of published data evaluating whole-heart plaque quantification using coronary CTA. However, much work remains to be done before its routine clinical use (Figure 1). First, high image quality CTA studies are a pre-requisite for accurate, reproducible, automated plaque measurements. Performing plaque quantification and characterization on overly noisy images or those with significant artifacts will undoubtedly lead to inaccurate results. Providers should strive for high image quality while always attempting to limit patient contrast and radiation exposure. As such, studies using plaque quantification must be validated across a range of tube potential (kVp) and noise levels. Similarly, studies exploring the accuracy of plaque quantification using monoenergetic (keV) spectral reconstructions are needed. Fortunately, advances in CT detector technology, iterative reconstruction, and spectral imaging technologies will likely continue to improve the ability to detect and quantify coronary atherosclerosis using CTA in an automated fashion. With multiple vendors developing competing software and the increasing use of various machine learning methods, studies are needed to assess for meaningful differences in accuracy and reproduc-

ibility across platforms. Furthermore, the optimal HU thresholds to define plaque types and the technique for reporting plaque findings will hopefully become standardized. For example, in addition to total coronary plaque volume, percent atheroma volume (the proportion of total vessel wall volume occupied by atherosclerotic plaque) and/or plaque volume indexed to coronary or patient size have been reported by many. Moreover, age- and sex-based volume thresholds for mild, moderate, and severe abnormalities remain to be defined. Finally, the impact of these features to guide interventions, whether nutritional, medical, or mechanical, begs further investigation.

With these refinements, we look forward to fulfilling the 6-decade-long journey that was started by Drs. Dotter and Sones, moving beyond the negative space of lumen stenosis to integrating the totality of features in coronary atherosclerosis.

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