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Practice guidelines

Standards for quantitative assessments by coronary computed tomography angiography (CCTA)
An expert consensus document of the society of cardiovascular computed tomography (SCCT)

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ABSTRACT

In current clinical practice, qualitative or semi-quantitative measures are primarily used to report coronary artery disease on cardiac CT. With advancements in cardiac CT technology and automated post-processing tools, quantitative measures of coronary disease severity have become more broadly available. Quantitative coronary CT angiography has great potential value for clinical management of patients, but also for research. This document aims to provide definitions and standards for the performance and reporting of quantitative measures of coronary artery disease by cardiac CT.

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Abbreviation list

CCTA	computed coronary tomography angiography
CAD	coronary artery disease
CAD-RADS	the coronary artery disease reporting and data system
CTO	chronic total occlusion
DL	deep-learning
IVUS	intravascular ultrasound
SCCT	Society of Cardiovascular Computed Tomography
TAV	total atheroma volume
TPV	total plaque volume

1. Introduction

The present document is an Expert Consensus Document on standards for quantitative assessments by coronary computed tomography angiography (CCTA). The document is intended to inform practitioners, researchers, and other interested parties of the opinion of the Society of Cardiovascular Computed Tomography (SCCT) concerning quantitative CCTA methods. Thus, the reader should view the Expert Consensus Document as the best attempt of the SCCT to inform and guide clinical/research practice in this area where rigorous evidence may not yet be available or the evidence to date is not widely accepted.

During the past decade, CCTA has become increasingly important in both clinical care and research. For the clinical management of patients semiquantitative measures of coronary artery disease (CAD) are often sufficient. Existing guidelines recommend reporting of coronary stenoses by categories of obstructive severity rather than an exact percentage stenosis measurements.[1] Coronary plaque can be visually classified as predominantly calcified, non-calcified and partially calcified. The amount of coronary calcium can be measured on non-enhanced CT scans in absolute terms such as volume or calcium hydroxyapatite mass, although semi-quantitative Agatston scores are more commonly reported. Semi-quantitative scores, for instance the Segment Involvement Score, have been developed to report the global quantity of both calcified and non-calcified atherosclerotic plaque on CCTA.[2] The Coronary Artery Disease Reporting and Data System (CAD-RADS) was introduced to "improve communication between interpreting and referring physicians, facilitate research, and offer mechanisms to contribute to peer review and quality assurance, ultimately resulting in improvements to quality of care".[3] The recently released CAD-RADS™ 2.0 includes semi-quantitative assessment of stenosis and plaque, as well as functional parameters.[4] Other disease classification scores may predict the response to revascularization, such as the CT SYNTAX score for coronary revascularization, and the CT-RECTOR score for chronic total occlusions (CTO).[5,6] These well-described semiquantitative scores and classifications, which are valuable for guidance of clinical management of patients with CAD, are primarily based on visual interpretation without the need for quantification.

The prognostic value of coronary plaque on CT, by qualitative and (semi-)quantitative techniques, has been demonstrated in numerous cohorts and has been comprehensively discussed in prior SCCT consensus documents.[7] In addition to well-known measures of global plaque burden (e.g. calcium score, segment-involvement-score), more recently the napkin-ring sign was identified as a specific CT marker of plaques with a large necrotic core associated with adverse clinical events.[8] In the SCOT-HEART cohort, Williams et al., recently showed that low-attenuation plaque burden is the strongest predictor of fatal or non-fatal myocardial infarction, irrespective of cardiovascular risk score, coronary artery calcium burden or area stenosis.[9]

With expanding availability of tools for comprehensive coronary analyses used both in research clinical care, the field currently lacks standards for the *quantitative* image interpretation of and reporting of results. The lack of standards has affected the ability of clinicians/researchers to communicate findings using a common language. Similarly, the literature has been confounded by ambiguous terminology and various alternative synonyms for similar structures and measurements. CCTA has been recognized as a promising noninvasive tool to monitor CAD progression and assess the effects of medical therapy or mechanical interventions in clinical trials. Specific and clear definitions and as well as standardization of methodology are essential for CCTA to mature as an accurate and reproducible endpoint in clinical research. Therefore, this document aims to provide a framework for standardization of nomenclature, methodology and reporting of quantitative CCTA analyses.

In accordance with SCCT policy, writing group members and reviewers are required to disclose relationships with industry; see Appendices 1 and 2 for detailed information. The document was approved by the Society of Cardiovascular Computed Tomography's Board of Directors on [date TBD].

2. Image acquisition, quality, and analysis

2.1. Image acquisition

Optimization of image acquisition is key to obtain high quality data sets that will allow for quantitative analyses. A comprehensive review of the various image acquisition parameters is beyond the scope of this document, but it is important to consider that compromises are unavoidable and that favored tradeoffs will depend on the specific study requirements. As a general statement, for quantitative coronary evaluations in research studies image quality and consistency will often be prioritized, over ease of acquisition, to assure accurate and reproducible measurements. While generic guidance for CCTA acquisition optimization is available elsewhere,[10] the following summary is specifically targeted towards the facilitation of quantitative plaque measurements.

2.1.1. Scanner technology

A great variety of scanners are currently in use, ranging from earlier generation 64-detector row scanners to wide-array platforms, dual-source systems and most recently photon-counting detector CT. Higher spatial resolution, temporal resolution and longitudinal coverage improve image quality and consistency. In addition, vendors use different variations of iterative reconstruction algorithms and techniques to reduce image noise and motion artifacts, which also affect image quality and appearance. Uniformity of the CT platform within a specific research study is ideal, but it is often difficult to achieve in practice between multiple sites and over a longer period. In that case, standardizing scan and reconstruction parameters should be pursued but is generally incompletely achieved due to fundamental differences between scanners.

2.1.2. Spatial resolution

Plaque quantification requires visualization of structures at the limit of the current spatial resolution of CT. The fundamental spatial resolution of the scanner is largely defined by the hardware (focal spot size, tube-detector distance, detector size, sampling rate, rotation speed). The thinnest detector collimation should be selected for image acquisition. To take full advantage of the fundamental spatial resolution, thin image slices ($<$1 mm) should be reconstructed using a large matrix size (at least 512×512) and a small field of view (20 cm or less). Sharp reconstruction kernels enhance structural detail, but combined with thin slices, there will be a tradeoff with increasing image noise, or a higher radiation exposure to compensate for increased noise. Iterative reconstruction techniques may help to enhance image quality but should be used uniformly for consistency between studies.

2.1.3. Temporal resolution

In clinical practice, the tolerable degree of motion artifacts depends on CAD severity. For quantitative studies motion-free images are critical. The fastest available rotation time should be selected. Heart rate

reduction and rhythm control (e.g. with beta-blockers) are recommended, independent of the scanner platform. A wider data acquisition window will allow reconstruction of multiple cardiac phases and selection of dataset least affected by residual cardiac motion.

2.1.4. Image contrast and noise

Contrast resolution and image noise are dependent on the applied tube voltage and tube current. Tube voltage, as well as tube current, are often lowered to minimize radiation exposure, but this may adversely affect the ability to delineate plaque on the images. Adequate administration of intravenous contrast medium and nitroglycerin improve assessment of the vessel lumen including smaller branches. On the other hand, strong coronary enhancement by a high concentration of contrast medium or the use of a low tube voltage setting (e.g. 80 kVp) also increase attenuation values in the adjacent plaque. Coronary calcifications will be more discretely visualized with less blooming using a high (e.g. 120 kVp) rather than a low tube voltage. The key parameter for accurate evaluation remains image quality and therefore reducing image noise is usually the guiding principle. As noted above, efforts should be made to use the scanner specific techniques available to reduce noise, understanding that this may reduce contrast resolution. Emerging techniques such as multi-energy CT and photon counting CT will play a larger role in the future.[11,12]

2.2. Artifacts and image degradation

Good image quality is central to quantitative plaque assessment, and artifacts that affect visual assessment also affect quantitative evaluation. These may lead to challenges in identification of edges of the lumen, wall, plaque or epicardial fat, and cause under or overestimation of plaque volumes or stenosis severity, and misclassification of plaque subtypes. Therefore, steps to reduce CCTA artifacts (Supplement Table 1) will also improve the accuracy of quantitative plaque assessment.

Motion artifacts can lead to challenges regarding the detection boundaries of the coronary lumen or plaque.[13] The associated high or low attenuation streaks can be mis-interpreted as calcified or non-calcified plaque. Misalignment artifacts ("stairstep" artifacts) can cause under or overestimation of plaque since parts of the coronary artery may be missed or included twice within the data set. This can cause challenges for coronary segmentation and automated vessel tracking. It can also increase the time required for manual editing or increase the amount of manual editing if semi-automated segmentation is performed.

High density material can cause partial volume averaging ("blooming effect"), beam hardening (photon starvation and change in photon beam effective energy) and streaking artifacts. For coronary artery calcification this can challenge edge identification, leading to overestimation of calcium volume or stenosis severity. Artifactual low attenuation artifacts from beam hardening may cause overestimation of low attenuation plaque subtypes. Appropriate windowing can help mitigate the effect of these phenomenon and improve image interpretation.

Image noise may cause challenges in detecting boundaries of the coronary lumen or plaque. For clinical imaging we would not recommend tube current/voltage to be increased just to allow quantitative assessment. However, in research studies focused on changes in quantitative assessment it is important to standardize imaging parameters based on body habitus, and increased tube current may provide more robust assessment. Poor contrast enhancement can also lead to challenges in identifying the presence of plaque and detecting boundaries.

It may not be possible to remedy some artifacts, and this may necessitate the exclusion of that segment, vessel, or scan from the quantitative analysis. Combinations of artifacts may be particularly problematic, such as the presence of both calcium blooming and motion artifacts. Image quality can be classified using a Likert scale (ranging from non-interpretable to excellent). A combination of image quality and vessel size will determine whether a segment can be analyzed. Segments with severe artifacts should be excluded from analysis. Segments with moderate artifacts may be possible to analyze if they are in larger proximal segments. Segments with mild artifacts may not be possible to analyze if they are in small distal vessels. For plaque analyses stented segments are typically excluded.

2.3. Vessel and lumen segmentation

Quantitative assessment of plaque can be fully manual or semi-automated using plaque analysis software (including algorithms based on machine-learning). It is important to consider using a software with documented accuracy and reproducibility.

Due to limitations of CT spatial resolution, it is recommended that quantitative plaque analyses are limited to vessels with a normal diameter of 2.0 mm or more. This is in contrast to clinical CCTA readings that do have a formal diameter limit (1.5mm) for qualitative evaluations. For non-calcified coronary plaque and epicardial fat, which immediately surround the coronary arteries, the specific challenges are the relatively small differences in CT attenuation values between these two tissues. Non-calcified plaque attenuation has also been shown to vary substantially with the degree of contrast enhancement in the coronary lumen (i.e. iodine concentration), tube potential and reconstruction kernels.[14–17]

Manual plaque analysis: In manual analysis, atherosclerotic plaques are first identified visually. The expert reader visually identifies the lumen, the plaque components (non-calcified and calcified) as well as the epicardial adipose tissue surrounding the coronary arteries. Plaque can then be measured manually by the expert reader by tracing lumen and vessel boundaries in contiguous cross-sections of the coronary arteries. It has been reported that CCTA underestimates non-calcified plaque volumes when compared to intravascular ultrasound (IVUS); this has primarily been attributed to the lower spatial resolution of CCTA compared to IVUS (i.e. small plaque with thickness below 500 μm are usually not detected by CCTA).[18]

Window-level display settings: The use of a "vessel-wall" display setting normalized for the lumen attenuation in the proximal coronary branches is helpful to differentiate plaque from surrounding epicardial adipose tissue in CCTA.[19] An example of display settings derived and used in prior studies are a window width at 155% and window center at 65% of the mean luminal attenuation values, which has been reported to provide optimal concordance between CCTA and IVUS for plaque measurements.[19–22]

Semi-automated plaque analysis: For semi-automated plaque analysis, segmentation of vessel, lumen and surrounding epicardial fat are delivered by computer algorithms. Plaque is classified as the atherosclerotic tissue between the outer contour of the segmented vessel and the lumen contour; non-calcified and calcified plaque are defined as plaque components distinct from the lumen within the vessel wall. These tools are "semi-automated," because they require a human reader to check and correct the contours, as well as indicate the region of interest where the algorithm must execute the task.

Several studies using 64-detector row CT and beyond, have shown that coronary plaque volume and remodeling quantified from CCTA correlates strongly with IVUS.[18,20,22–25] A meta-analysis of 42 studies with 1360 patients noted no significant differences, versus IVUS, in plaque volumes or area, or area stenosis and high sensitivity (93%) and specificity (92%) to detect any plaque.[26]

An analysis from the PARADIGM registry showed that when fixed plaque attenuation thresholds are used for non-calcified plaque components, low tube voltage affected plaque measurements, mainly through an increase in luminal contrast attenuation[27]; therefore consistent luminal attenuation is recommended for serial quantitative CT plaque studies.

Inter-observer and inter-scan variability of manual and semi-automated plaque measurements have been reported in several studies; these are summarized in Supplement Table 2.[28,29] Based on

reproducibility and practical concerns (i.e. labor intensiveness), the use of semi-automated lumen and vessel segmentation is preferable.

2.4. Deep learning based vessel segmentation

Application of deep learning (DL) models in cardiac CT are diverse, ranging from identification of different plaque types, quantification of calcium score, or performance of lumen segmentation.[30–35] Fully automated machine-learning algorithms, and especially deep learning segmentation methods, promise to provide a faster method for plaque analysis.[36] In the future fully user-free segmentation of medical images may be possible, but the application of DL for CCTA has many obstacles that still must be surmounted.

The availability of representative image data is critical for the development of effective AI models for image segmentation.[37] Typically, large amounts of curated image data, for instance contours of the vessel boundaries by experts using semi-automatic methods, are required for the training stage of the algorithm development. These image annotations require the use of automatic methods and careful manual confirmation/validation of results by the expert. As the data annotation is a central point of any DL model development, the criteria to perform manual annotation should follow the same guidelines and recommendations presented in Section IIC. Moreover, as with any other diagnostic approach in its stages prior to integration, DL-based models must be subjected to (i) careful validation using the corresponding gold-standards, such as invasive coronary angiography for stenosis evaluation or IVUS for plaque quantification; and to (ii) external validation in a fully independent cohort. Generalization capacity refers to the performance of the DL models when processing data with features that were not seen in the training phase. The use of new scanners, reconstruction algorithms, or artifacts that are not present in the training dataset may lead to inaccurate results (see Section IIB). In this regard, transfer learning is a strategy to retrain existing DL models and adapt their predictive capabilities to new data at a low cost.[37] DL models are not different from other kinds of mathematical algorithms and the user must be prepared to overrule wrong segmentations or predictions.

3. Nomenclature and definitions

CCTA images depict the enhanced lumen as well as atherosclerotic plaque in the wall of the coronary artery. Compared to invasive angiography it displays more completely the extent of CAD, even if the disease does not impact the lumen dimensions substantially. Separation of individual "lesions", traditionally defined by invasive angiography as lumen narrowing where atherosclerosis is present, may not be as straightforward on CT images if diffuse CAD is present. Given the fact that atherosclerotic plaque expands outward and many plaques go undetected by invasive angiography, "lesion" by traditional definition has become a misnomer. Nowadays, and particularly in CCTA studies, the term atherosclerotic lesion often includes both stenotic and non-stenotic atherosclerotic plaques. To avoid confusion, in this document we will avoid the term *lesion* entirely. In the intravascular imaging literature, atherosclerotic disease is typically termed atheroma, while in CCTA publications the term plaque is more widely used. Therefore, total atheroma volume (TAV) as introduced by IVUS, is termed total plaque volume (TPV) in this document.

In Tables 1 and 2 are outlined the definitions of key variables to quantify lumen, vessel and plaque dimensions, typically by diameter, area or volume. Cross-sectional variables are reported as a unique value (either a diameter or an area) at a given point in the vessel (Fig. 1, panels A and B). These variables are also used for the calculation of internally normalized variables such as the area stenosis. In general, 2-dimensional (i.e., area) and 3-dimensional (i.e., volume) parameters are preferred over 1-dimensional parameters (i.e., diameters or perimeters) because of higher overall reproducibility.

4. Coronary plaque assessment

The traditional definition of *plaque* on CCTA is the presence of tissue structures $\geq$1 mm^2 within or adjacent to the coronary artery lumen, identified in at least two independent planes, that can be distinguished from the surrounding tissues (epicardial fat) and the lumen.[38] This definition, which was developed before (automated) segmentation tools became available, is still valid for qualitative plaque characterization and semiquantitative plaque burden scores. For analyses using (semi-)automated segmentation and quantification tools, plaque is defined as the space between the inner lumen and outer vessel boundaries, occupied by atherosclerotic tissue.

4.1. Semi-quantitative CCTA plaque analysis

Using conventional post-processing tools, plaques can be qualitatively classified as *predominantly calcified*, i.e. containing mostly high-density

Table 1
Relative performance of quantitative coronary CT parameters.

	Ease of scan performance	Diagnostic accuracy	Acquisition reproducibility	Analysis reproducibility	Clinical relevance	Target for intervention
Lumen parameters						
Minimal lumen area (mm^2)	+++	+++	++++	+++	+++*	++
Diameter stenosis (%)	+++	+++	++++	++	+++++	++
Area stenosis (%)	+++	+++	++++	+++	++++	++
Plaque parameters						
Calcium score (Agatston score)	+++++	++	+++	+++++	+++	+
Total plaque volume (mm^3)	++	++	+++	+++	++	+++
Percent plaque volume (%)	++	++	++**	+++	++	+++
Normalized proximal plaque size (mm^3)	++	+++	+++	++++	+++	+++
Total non-calcified plaque volume (mm^3)	++	++	++	++	+++	++++
Total low-attenuation plaque volume (mm^3)	+	+	+	++	++++	++++

Ease of scan performance: ranging from dedicated scan protocols on state-of-the-art equipment by a highly skilled team (+) to routine protocols that can be performed on most cardiac CT systems by less experienced teams (+++++). **Diagnostic accuracy**: degree of technical validation of the CT parameter against reference standards (histology, intra-coronary imaging). **Acquisition reproducibility**: degree of variation in outcome between scans and different scanners. **Analysis reproducibility**: degree of variation in outcome between analysis ranging from poorly reproducible or only by identical analysis software and same reader (+), to highly reproducible between software packages and readers (+++++). **Clinical relevance**: degree the CT parameter is important for clinical outcome and patient management. **Target for intervention**: degree the CT parameter can serve as a surrogate endpoint and is amenable to pharmaceutical or mechanical interventions. Percent plaque volume: total plaque volume divided by the total vessel volume. Normalized proximal plaque size: total plaque in a proximal coronary segment normalized for the length of the vessel segment. This table is based on working group consensus and reflects the current state of the field, which may change with the introduction of higher-resolution CT technology (photon-counting CT) or further-advanced, validated analysis software (including AI-based techniques). *Relevant for left main disease. **The %PV is affected by changes in vessel size and the use of nitroglycerine.

Table 2
Quantitative plaque variables.

Parameter	Definition and formula
Lumen	The space within the intimal boundary that is filled by (contrast-enhanced) blood, excluding thrombus or other protruding tissue (Fig. 1).
Reported as diameter (mm), area (mm^2) & volume (mm^3)	
Vessel	The space within the outer vessel boundary, generally defined by the interface with the low-attenuation epicardial fat (Fig. 1).
Reported as diameter (mm), area (mm^2) & volume (mm^3)	
Plaque	The space between the outer vessel boundary and the lumen that is occupied by atherosclerotic tissue.
Reported as thickness (mm), area (mm^2) & volume (mm^3)	Plaque = vessel– lumen
Length (mm)	This is applicable to the analysis of a coronary segment/vessel rather than the characterization of an individual and isolated plaque Distance parallel to the longitudinal axis of the vessel, often based on the coronary center-lumen line. Examples are plaque, coronary segment or stent length.
Short-axis cross-sectional variables and internally normalized variables	
Minimum lumen diameter (mm) and area (MLA -mm^2)	Smallest lumen diameter and area within the diseased vessel section. These variables are used to calculate the diameter and area stenosis (Fig. 1).
Maximum lumen diameter (mm) and area (mm^2)	Largest lumen diameter and area within a lesion, segment or vessel, including in abnormally dilated arteries.
Maximum vessel diameter and area (mm^2)	The largest vessel diameter and area within a vessel or section, used for instance in abnormally dilated arteries.
Reference lumen/vessel dimensions	Cross-sectional dimensions as previously described, obtained at a normal part of the vessel as close to the vessel section of interest to perform relative measurements, i.e. stenosis, outward remodeling. Deciding on the proximal or distal reference site is subjective and often a compromise between proximity and normalcy, and the balance will be affected by the specific study objectives. In case of both a proximal and a distal reference dimension, the reference vessel dimension will be an average of both. Reference sites beyond large side branches should be avoided. A practical approach to classify a side branch as non-significant is a relative diameter cut-off of <50%, which would correspond to a lumen area size of <25%. Interpolated reference vessel dimensions take into account the distance of the reference samples to the narrowest section, and potentially other features along the vessel, to improve estimation of the nominal dimensions at the site of interest. Average RLA = (Proximal RLA + Distal RLA)/2
Reference lumen diameter (RLD, mm), area (RLA, mm^2)	
Reference vessel diameter (RVD, mm), area (RVA, mm^2)	
Area stenosis (%AS)	Stenosis severity at the narrowest section (MLA) relative to the (averaged/interpolated) reference lumen area. %AS = [(RLA– MLA)/RLA] x 100%
Diameter stenosis (%DS)	Stenosis severity at the narrowest section (MLD) relative to the (average/interpolated) reference lumen diameter. %DS = [(RLD – MLD)/RLD] x 100%
Plaque burden (PB, %)	Plaque burden indicates the amount of plaque as a proportion of overall vessel size Cross-sectional plaque burden = [plaque area/vessel area]*100% Volumetric plaque burden = [plaque volume/vessel volume]*100%
Remodeling index (RI)	Enlargement of vessel dimensions to accommodate plaque development compared to normal vessel sections. Remodeling index (RI) = (maximum vessel area/reference vessel area) Positive or outward remodeling: RI $\geq$ 1.10. Negative or constrictive remodeling: RI < 0.90.
Volumetric and derived variables	
Lumen, vessel and plaque volume (mm^3)	Volumetric dimensions are typically calculated by integrating 2D segmentations on serial cross-sections that are equally spaced along the center-lumen line. Automated software may derive these parameters directly through volumetric segmentation of the lumen or vessel boundaries. Typically, volumetric dimensions are limited to specific vessel segments. To compare between individuals/cohorts or temporal changes of volumetric parameters it is important to account for the length and location of the interrogated vessel section (Fig. 1).
Total plaque volume (TPV, mm^3)	The difference between vessel and lumen volume for the studied region TPV per vessel = total vessel volume – total lumen volume
Averaged cross-sectional dimensions	From an equidistant range of cross-sections along the center-lumen line, or a volumetrically segmented vessel section, average cross-sectional dimensions can be calculated.
Mean lumen, vessel and plaque area (mm^2)	Mean vessel area = vessel volume/segment length Mean vessel area = VA_1,VA_2 + VA_3 … + VA_n)/n
Percent plaque volume (%PV)	Total plaque volume divided by the total vessel volume encompassing each coronary artery in the coronary artery tree (>2mm diameter). %PV per vessel = [TPV per vessel/total vessel volume] x 100
Subclassified plaque volume (mm^3) and percentage (%)	Volume of calcified, non-calcified or low-attenuation plaque, typically based on attenuation values, as an absolute measure (mm^3) or as a proportion of the total plaque (%). Normalization as described previously. Percent calcified plaque = calcified volume/plaque volume x 100% Percent noncalcified plaque = noncalcified volume/plaque volume x 100%

tissue; *predominantly non-calcified*, i.e. no discernible calcification; or *partially calcified plaque*, i.e. both calcified and non-calcified tissue is present. The adjective "predominantly" is added because histopathological studies have shown that exclusively calcified plaques are rare, while non-calcified plaques may contain very small calcifications beyond the resolution of CT. Calcified tissue is typically defined by attenuation values higher than the lumen (brighter). Tissue with attenuation values distinctively higher than non-calcified tissue, but lower than the contrast-enhanced lumen, may still be classified as calcium if it is embedded in non-calcified plaque. It is recommended to avoid plaque classifications that inappropriately suggest mechanical or histological characteristics that cannot be reliably assessed by CCTA, including *soft*, *hard*, *mixed*, *vulnerable*, *lipid-rich* and *fibrous* plaque.

Among the many semi-quantitative plaque characteristics that have been investigated, a few features with demonstrated prognostic value are referred to as high-risk plaque features. These include positive vessel remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign.[39–45] Positive or outward vessel remodeling is defined as an outer vessel area that is >10% larger than a representative reference site. Spotty calcifications are small scattered calcified lesions. A definition

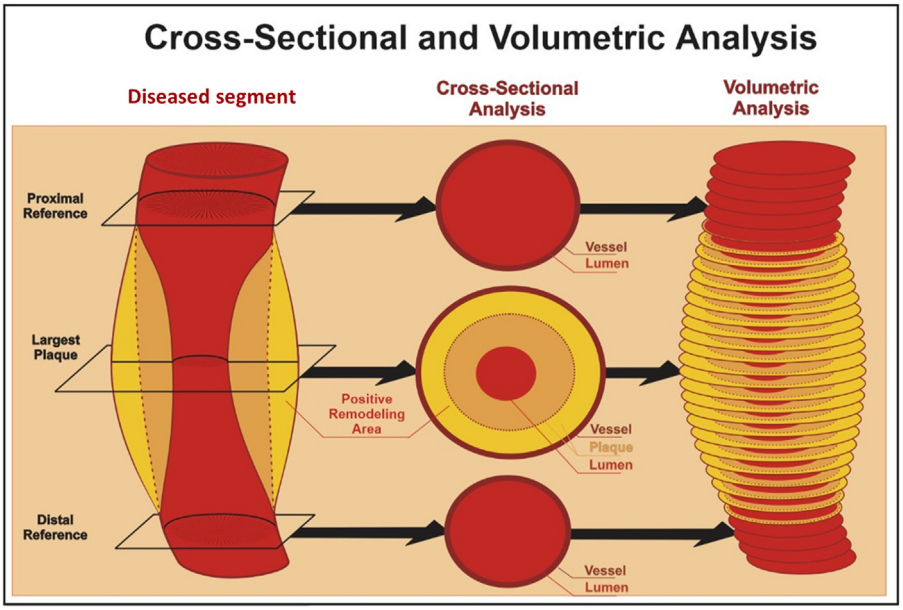

Fig. 1. Graphic representation of commonly reported variables by computed tomography angiography.

based on a maximum diameter of 3 mm in any direction has been proposed, although measured dimensions highly depend on acquisition and reconstruction parameters, as well as window display settings.

Low attenuation plaque components are considered as the surrogate for the lipid-rich parts of atherosclerotic plaques and thin-cap fibroatheromas.[46] For manual sampling of plaque attenuation values, it is recommended to obtain the average attenuation values from a sufficiently large region-of-interest. Small or single-voxel samples should be avoided because these can produce non-representative attenuation measurements due to the inherent presence of image noise.[16] Table 3. Indeed, measured attenuation values in non-calcified plaque vary across a wide range and are affected by the contrast enhancement of the coronary lumen and reconstruction kernels.[16] Although a range of thresholds have been reported, an upper threshold of 30 HU has typically been used for low attenuation plaque, based on prognostic studies that examined both low attenuation plaque as a visually assessed plaque feature and quantitative volume or burden. This threshold has also been verified against lipid-rich plaque identified by IVUS.[8,9,19,24,42]

The napkin-ring sign is a qualitative plaque feature, defined as a non-calcified plaque with two features when viewed in short-axis cross-section: a central area of lower CT attenuation that is apparently in contact with the lumen; and a ring-like higher attenuation plaque tissue surrounding this central area.[47,48] Important to note that no attenuation measurements are needed to describe the napkin-ring sign. Histopathological studies have shown that the napkin-ring sign is a specific CT marker of plaques with a large necrotic core, and outcome studies have demonstrated this feature is associated with future adverse clinical events.[49]

The CAD- RADS™ 2.0 reporting system recommends noting plaques that clearly demonstrate two or more high-risk features.[4] It is important to note that the prevalence of these plaque features on CCTA is relatively high and thus their positive predictive value to identify plaques that will cause future events is modest.

4.2. *Quantitative CCTA plaque analysis*

Applications with (semi-)automated segmentation of the inner and outer vessel wall can produce numerous measures of lumen narrowing and plaque burden (Fig. 2). It is recommended to measure the length of the plaque from the proximal to the distal normal edge. Within the segmented plaque, tissue types can be subclassified based on attenuation values. The default thresholds and terminology for the tissue subclassifications vary between software applications (Fig. 3). Most software define the threshold for (dense) calcification as >350HU. Calcified plaque with a very high CT density of >1000 HU (so-called 1K plaques), associated with lower risk of acute coronary syndrome, may be classified

Table 3
Effect of selected CT parameter modifications on quantitative plaque assessment.

CT parameter modification	Effect on image quality	Effect on plaque quantification
↓ Tube voltage	↑ Lumen attenuation	↑ Calcified plaque volume
	↑ Attenuation values for all plaque components	↓ Low-attenuation plaque volume
↑ Tube current	↓ Image noise	↑ Homogeneity of plaque attenuation values
	↑ Overall image quality	↑ Reproducibility
↑ Intra-coronary iodine concentration	↑ Lumen attenuation	↑ Calcified plaque volume
	↑ Attenuation values for all plaque components	↓ Low-attenuation plaque volume
↑ Reconstruction kernel sharpness	↑ Lumen contour sharpness	↓ Homogeneity of plaque attenuation values
	↑ Image noise	
↑ Iterative reconstruction strength	↓ Image noise	Small effects on attenuation values and plaque size in some studies

Effect of isolated modifications and assumption of fixed HU-thresholds for segmentation of inner and outer vessel boundaries and plaque components.

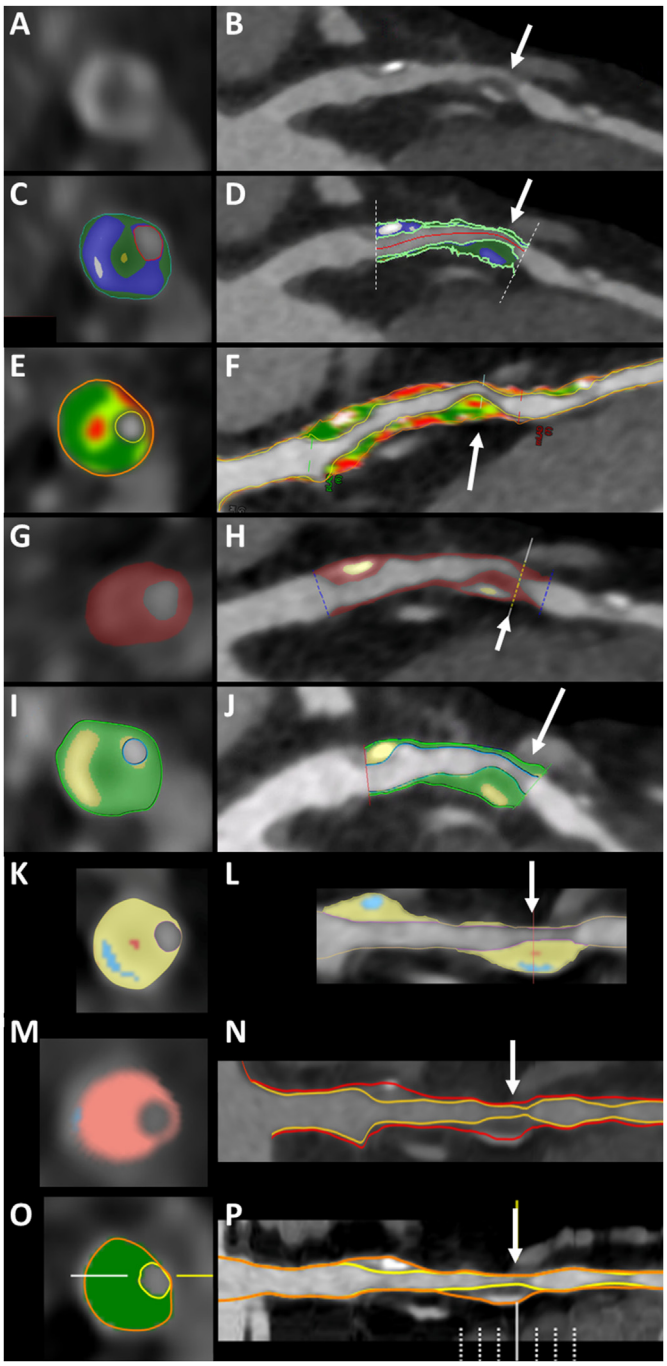

Fig. 2. Semi-automated plaque segmentation by commercially available software.
Extensive atherosclerosis in the left anterior descending coronary artery (LAD, panels A and B), analyzed using (semi-)automated, quantitative software by 7 different vendors: Aquarius Intuition by TeraRecon (Durham, NC; panels C and D), Qangio CT by Medis (Leiden, The Netherlands; panels E and F) Autoplaque V3.0 from Cedars-Sinai Medical Center (Los Angeles, CA; panels G and H), SyngoVia/Frontier CT Coronary Plaque Analysis by Siemens Healthineers (Forchheim, Germany; I and J). Cleerly LABS version 2.0 (Cleerly Healthcare, Denver CO; panels K and L) and HeartFlow Plaque Analysis (Mountain View, CA; panels M and N), CtaPlus by Shanghai Pulse Medial Technology, Inc. (Shanghai, China; panels O and P). The inner and outer vessel wall boundaries are segmented and the plaque in between is categorized and color-coded based on software-specific Hounsfield-unit thresholds. The location of the cross-section (left side) is indicated by an arrow on the curved (D, F, H, O) or straightened (J, L, N) longitudinal cross-section (right side).
The measured minimal lumen area ranged between 1.2 mm^2 and 2.3 mm^2 and the area stenosis between 65% and 88%. The total plaque volume ranged between 76 mm^3 and 486 mm^3, in part reflecting differences in interrogated vessel length, as the plaque burden (total plaque/total vessel volume) had a much a narrower range between 58% and 70%, and a single outlier at 88%. The percentage non-calcified plaque volume ranged from 75% to 99%. The proportion of plaque within the lowest attenuation category varied substantially: 0.3%–35% of the total plaque volume. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

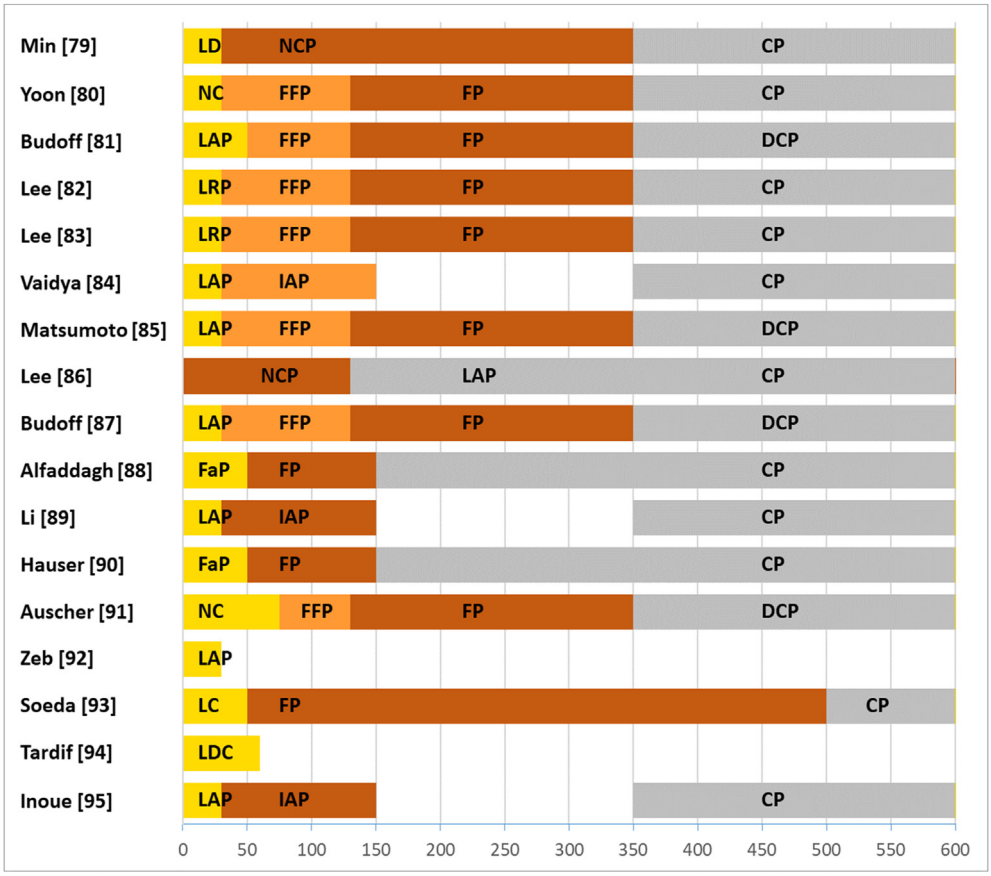

Fig. 3. Classification of plaque components on CCTA based on Hounsfield Units
Summary of Hounsfield-unit thresholds for classification of plaque components on CCTA from selected studies. Low-density plaque (LD), non-calcified plaque (NCP), calcified plaque (CP), necrotic core (NC), fibro-fatty plaque (FFP), fibrous plaque (FP), low-attenuation plaque (LAP), dense calcification plaque (DCP), lipid-rich plaque (LRP), fatty plaque (FaP), intermediate-attenuation plaque (IAP), low-density plaque (LDP), as defined by the original publications.
Evaluation of calcific plaques.[79–81,84–95]

separately.[50] For plaque within the lowest attenuation category the upper threshold varies between 30 and 75HU. As mentioned, the intensity of contrast enhancement of the coronary lumen affects the measured attenuation values in coronary plaques, thereby affecting how plaque tissue components are classified. For this reason, this guideline does not recommend a specific absolute threshold for low-attenuation plaque. Scan-specific thresholds based on attenuation values sampled in the proximal coronary arteries have been proposed to compensate for variations in lumen opacification.[24]

5. Additional recommendations for specific situations

Considerations and recommendations for quantitative CCTA after percutaneous or surgical revascularization and the assessment of are bifurcation lesions and total coronary occlusions are listed in Table 4 and Fig. 4. Restenosis may develop following coronary interventions using metallic stents, resorbable scaffolds or drug eluting balloons. For the evaluation of in-stent restenosis (ISR), CCTA has a high negative predictive value but moderate positive predictive value.[51,52] Although CCTA is not widely recommended for clinical assessment of in-stent restenosis, quantitative CCTA has been used for longitudinal follow-up of radiolucent bio-resorbable scaffolds without a metal platform (Figs. 4 and 5).[53,54] The accuracy of CCTA for detecting bypass graft disease is very good, and excellent for complete graft occlusion.[55–57] Clinical trials that applied CCTA to assess interventions to prevent graft failure generally considered complete graft occlusion as the primary endpoint, and reported excellent diagnostic utility of CCTA.[58–60] CCTA can evaluate coronary bifurcations in terms of plaque, stenosis and the angles between the bifurcation branches (Fig. 4).[61–63] CCTA can identify characteristics of (chronic) total coronary occlusions (CTO), defined by the complete absence of lumen opacification, with modest to excellent reproducibility (Fig. 4).[5,64] Apart from single CTO features derived from CCTA, combined CT scoring systems (e.g. CT-RECTOR and KCCT scores) have been developed to predict time-efficiency of CTO percutaneous recanalization and thus to grade the CTO difficulty level prior to percutaneous coronary intervention.[65–70]

6. Quantitative CCTA in clinical research

CCTA can serve multiple purposes in clinical research. However, before CCTA derived variables can be accepted as an endpoint their technical and diagnostic validity needs to be established. Typically, the diagnostic accuracy of CT is compared to an accepted reference, e.g. histology, invasive angiography, intravascular imaging modalities. In addition, demonstration of reproducibility between scans, different scanners, acquisition and reconstruction techniques, evaluation software and/or readers are important to establish the robustness of the CT variables.

Biomarker and imaging studies, which can be cross-sectional or longitudinal in design, aim at studying associations between plaque characteristics and other individual variables, including metabolic, genomic, proteomic and any other -omics profiles. CCTA can be a screening tool to select a study population (for example, to rule out of left main stenosis in the ISCHEMIA trial). CCTA can provide (surrogate) endpoints to prospectively demonstrate the effect of an intervention: for example, restenosis after percutaneous coronary intervention or atherosclerotic plaque changes in response to a pharmacological intervention. Finally, CCTA may have multiple, overlapping roles in the same study or trial. CCTA can

Table 4
Recommendations for specific CAD situations.

	Recommendations	Parameters	Challenges
After percutaneous coronary intervention (Metallic stents, resorbable scaffolds, drug-eluting balloon)	The treated coronary segment includes 5 mm proximal and distal to the boundaries of the stent, bioresorbable scaffold or balloon. After resorbable scaffolds dissolve metal markers may remain visible in the wall.	**Area stenosis:** minimal lumen area within the treated segment proportional to the averaged reference areas outside the treated segment. **Stent dimensions:** for the expanded stent diameter/area measurements are drawn through the middle of the struts on cross-sectional images. **Neointimal thickness:** distance between the luminal border of the neointimal hyperplasia (hypodense tissue) within the stent and the middle of the stent wall. Conventional plaque and stenosis parameters apply in the absence of a metal stent (radiolucent/ resorbed scaffold or drug-eluting balloon), however, the references areas are measured outside the treated segment.	High-density artifacts obscure the lumen within metal stents, most problematic with small diameter stents (≤3.0 mm). Unless there is circumferential neointimal hyperplasia, the neointimal area cannot be delineated completely.
After bypass graft surgery	Occlusions may be limited to graft segments between anastomoses in case of sequential grafts. Graft disease location is classified as in the proximal anastomosis, the graft body or the distal anastomosis.	**Area stenosis:** minimal lumen area proportional to representative reference lumen area. Angiographically significant stenosis is defined as ≥50% diameter reduction, realizing that if the graft outsizes the dependent coronary artery this threshold will likely overestimate hemodynamic significance.	Defining reference lumen dimensions can be difficult in venous grafts with substantial natural variation in size. Interpretation of the coronary arteries may be difficult in the presence of extensive atherosclerosis.
Bifurcation lesions	Medina classification to describe the presence of ≥50% stenosis (0/ 1) at the proximal main, distal main, and side branch vessel, respectively (e.g. 1,0,1). Plaque can also be separately quantified for each of the bifurcation vessel segments.	**Angle measurements**: Proximal angle between proximal main vessel and side branch. Distal angle between distal main vessel and side branch. **Carina involvement**: the location of the plaque relative to the side branch (same or opposite side) can be defined in cross-sectional views	No dedicated CCTA software available for bifurcations.
Chronic total occlusions	A longer scan delay after contrast injection will improve opacification of the distal vessel segment.	**Occlusion length**: defined as the length of the non-opacified vessel segment between the proximal and distal end, preferably measured along the center-lumen line. **Angulation:** angles of individual bends within the occluded segment. **Proximal vessel tortuosity:** angles of individual bends in the patent vessel proximal to the occlusion. **Calcification characterization:** number and size of separate calcium spots, specifically at the proximal and distal end of the occlusion. Calcifications can be classified as large when occupying more than 50% of the cross-sectional vessel area. **Side branch at the entry or end:** defined as a ≥1.5 mm vessel ≤3 mm of the proximal or distal end of the occlusion, respectively.	Differentiation between a short total occlusion and high-grade stenoses may be challenging due to the limited spatial resolution of CT, though a longer occlusion, higher contrast density difference between the proximal and distal segment, collateral vessels, severe calcification and a blunt stump favor chronic total occlusion.

be used to select the optimal study cohort, then demonstrate the pre-specified effect of an intervention, and post-hoc identify the best responders or demonstrate associations between CCTA variables and other biomarkers to increase our knowledge and develop new hypotheses.

7. Serial imaging studies

7.1. Data acquisition and interpretation

For serial imaging studies that investigate changes in atherosclerotic disease over time, it is crucial to image consistently so that the CT measurements can be compared accurately. Serial and re-scan studies show that plaque quantification can be reproducible using semi-automated tools if scans are performed on the same scanner (Table 5).[28] The mean differences for total plaque volume are typically below 5%, however, substantial variance has been reported for calcified and low-attenuation plaque.[29,71] Based on the observed inter-scan reproducibility between the same and different CT systems, Symons et al., estimated that an intervention trial using non-calcified plaque as an endpoint would need a threefold larger population if individuals have baseline and follow up CT on different scanners.[72] There is considerable variability between CT platforms, and for coronary plaque quantification serial scans should ideally be performed on the same CT system at each time point, using the same pre-defined imaging protocol.[82] Similarly, (semi-) automated plaque quantification software tools provide reproducible plaque measurements, but results are not necessarily concordant between different software applications. Even dedicated software packages require manual modification or other operator-dependent decisions. Particularly for serial studies, a detailed pre-specified description of interpretation procedures is important. Interpretation consistency also improves if the number of readers is limited. Side-by-side interpretation of serial samples may be the most practical approach to minimize intra-observer variability.

7.2. Selection of CCTA-derived study endpoints

There are various aspects to consider when selecting a CT-based endpoint as a surrogate marker of treatment effect. Tables 1 and 2, Supplement Table 3. First, the CT variable should be affected by the intervention under investigation, and changes in the imaging endpoint should be clinically relevant. Ideally, the endpoint is specific and shows consistent change with low temporal variability within individuals. Finally, measurements by CT should be reproducible between scans, analysis software and readers. The total plaque volume is a global

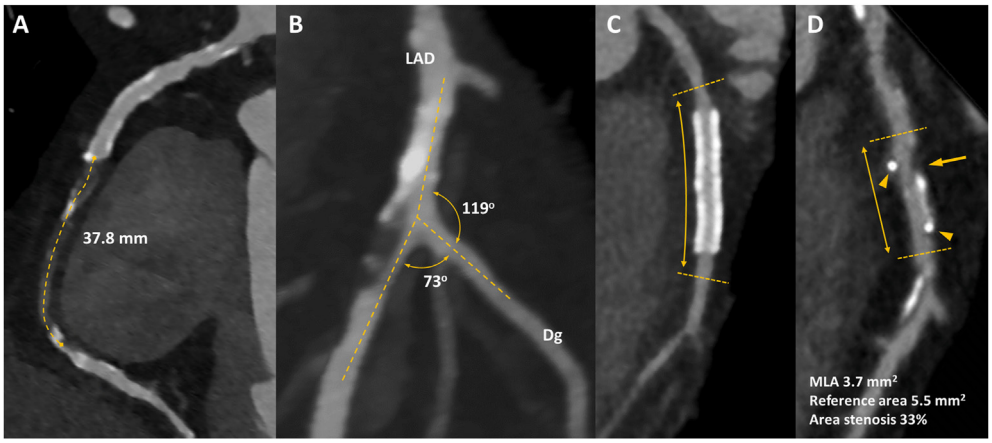

Fig. 4. Chronic total occlusion, coronary bifurcations, stented segment and bioresorbable examples
A) Chronic total occlusion with occluded segment of 37.8mm measured along the curved reconstruction. B) Bifurcation disease (Medina classification 1, 1, 0) consisting of both predominantly calcified (proximal) and pre-dominantly non-calcified plaque (distal to the bifurcation), and measurement of the angles between the proximal left anterior descending coronary artery (LAD) and diagonal branch (Dg) and the diagonal branch and distal LAD (B). C) Metal stent in a coronary artery with no obvious in-stent disease within the treated segment (between dashed lines which are 5 mm away from the edges), although blooming and beam hardening prevent accurate evaluation of the lumen within the stent. D) Quantitative CCTA after treatment with a bioresorbable scaffold, indicated by the remaining platinum markers (arrow heads), demonstrating partially calcified plaque at the proximal edge. Area stenosis is calculated as the percentage lumen reduction at the narrowest section (minimal lumen area (MLA), arrow) relative to the averaged reference areas measured outside the treated segment (≥5 mm beyond the marker).

measure of all coronary plaque and should therefore be a sensitive endpoint to systematic treatment of CAD. Percent plaque volume (%PV) is defined as the total plaque volume divided by the total vessel volume encompassing each coronary artery of >2 mm in diameter in the coronary artery tree (Table 2). The %PV has been commonly used in order to account for vessel size and exclusion of non-diagnostic segments. Of note, quantifying plaque in small coronary branches is less accurate and more susceptible to inconsistent scan conditions. Alternatively, selective interrogation of large vessels or large plaques will be more accurate and will provide smaller, but potentially more specific and reproducible changes. Sampling errors can be minimized by using standardized, volumetric or volume averaged measurements and image co-registration. Clinically relevant features of CAD (stenosis, global plaque burden) do not (yet) fully overlap with features typically used as surrogate markers in intervention trials. As noncalcified and low-attenuation plaque are thought to be the most biologically active and deleterious forms of plaque, recent plaque progression studies have focused on these two components.[83] A drawback of selectively measuring low-attenuation, non-calcified plaque is a higher susceptibility to variations caused by differences in scan conditions (heart rate, lumen contrast concentration, image noise, reconstruction filters see Table 3). In addition, the amount of low-attenuation plaque is proportionally small in most patients. Pharmacological interventions as well as time may transform plaques from low-to high attenuating tissue, without necessarily reducing total plaque volumes.

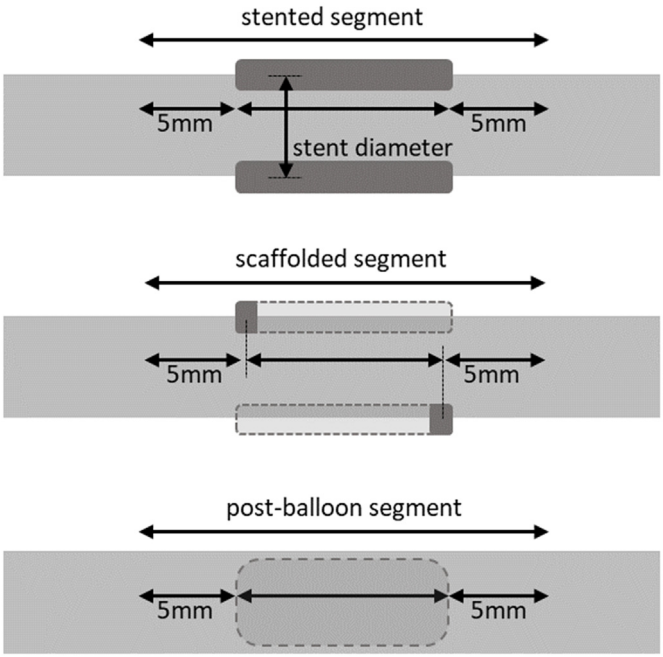

Fig. 5. Interpretation of intervened coronary arteries.
The treated coronary segment includes 5 mm proximal and distal to the boundaries of the stent, bioresorbable scaffold or balloon. In this example the bioresorbable scaffold has radiopaque markers at each edge (the previous site) of the scaffold.

For serial assessment of angiographic CAD (lumen narrowing), area measurements have methodological advantages over diameters. Reproducibility of the MLA decreases as the (residual) lumen becomes smaller. Relative (diameter) stenosis severity is more intuitive and relatable to clinicians, however, selection of the reference site by the reader introduces variability.

A study protocol should clearly outline the imaging endpoints as per Tables 1 and 2 Changes can be evaluated at several different levels, including:

A Plaque level analysis: plaques are identified at baseline and the same anatomical location is evaluated on follow up CCTA. Co-registration should be done considering anatomical landmarks such as side branches and calcifications. Every attempt should be made to do this by having the imaging datasets side-by-side and preferably blinded to the relative timing of the exams (i.e. without knowing which is baseline and follow-up). When there are no neighboring landmarks, distance from the coronary ostium could be used.
B Vessel level analysis: this approach resembles the intravascular ultrasound progression/regression clinical studies. Typically, most of the length of one of the major coronary epicardial vessels is included. For CCTA the interpreted length of the vessel is generally restricted to

Table 5
Key considerations for serial plaque imaging studies.

Study design	Study site selection
	Time interval between studies
Endpoint selection	Association with a relevant clinical endpoint
	Potential target for intervention
	Prevalence of the variable and natural variation over time
	Accuracy and reproducibility of acquisition and analysis
Scan protocol	General optimization of the procedure: training, patient preparation, heart rate modulation.
	Optimization targeted to the variable of interest (e.g. coronary lumen attenuation)
	Consistency of hardware, software, protocols, etc.
Image reconstruction	Optimization to the variable of interest
	Consistency of reconstruction parameters, including slice thickness, overlap, kernels, field of view
Image interpretation	Consistency of analysis software and readers
	Clearly defined vessel/segment of interest or plaque boundaries
	Co-registration for side-by-side interpretation
Procedural	Detailed protocols (SOPs) of methods and definitions

Based on isolated modifications and fixed HU-thresholds for segmentation of inner and outer vessel boundaries and plaque components.

a minimal vessel diameter and multiple vessels can be included per patient. If only one vessel is included, typically the vessel with the largest (non-calcified) plaque may be preferred. At follow-up, the same vessel section is compared with the baseline measurements.

C Patient level analysis: Plaque analysis is performed on all segments/vessels that meet a minimal vessel size and can be assessed on both baseline and follow up CCTA. Results are summed on a per patient basis.

8. Future directions

The demand for quantification of CAD is expected to greatly expand in the future for both clinical and research purposes. To test the effectiveness of mechanical or pharmacological interventions for the management of CAD, trialists have traditionally relied on surrogate endpoints provided by invasive imaging modalities (selective angiography, IVUS, OCT, FFR). While catheter-based techniques remain superior in terms of accuracy and reproducibility for several plaque measures, non-invasive techniques offer lower burden and risk to study participants, and thereby higher participant retention. Costs of noninvasive imaging techniques are lower, and CT generally provides more complete coronary coverage compared to intravascular imaging. Wider availability of automated plaque analysis software tools and services is expected to encourage reporting of quantitative plaque characteristics. For individual patients, however, prospective evidence is currently lacking whether quantitative CCTA outperforms qualitative interpretation of CAD in terms of decision-making or clinical outcomes.

Technical innovation will continue to improve the robustness, quality and reproducibility of cardiac CT. All vendors have developed spectral imaging techniques, which improves differentiation of tissue types by comparing attenuation characteristics at different tube potentials. The anticipated benefits of spectral imaging for plaque characterization and calcium artifact reduction have so far not come to full fruition. Photon-counting CT represents a major leap forward in scanner technology and is expected to further improve spatial resolution and tissue differentiation.[73]

On the software side there are rapid developments in the automated analysis of CT images and the discovery of new image features with clinical relevance. Radiomics refers to the process of extracting many quantitative imaging features from a given region of interest to create big data in which each abnormality is characterized by hundreds or thousands of quantitative parameters (statistical, shape, texture) extending far beyond those that can be characterized by the human eye. Radiomics approaches have been investigated for the detection of rupture-prone coronary plaque and in the future radiomics-based features may extend the quantitative tool set if reproducibility can be demonstrated.[74]

This document focused on established, morphological features of atherosclerosis obtained by CCTA. Outside the scope of this document, cardiac CT offers a number of approaches to quantify the functional severity of CAD. CT-derived fractional flow reserve (CT-FFR), i.e. the computation of FFR values from CT images using computational fluid dynamics or other computational techniques, can estimate the functional significance of coronary lesions, guide revascularization decision making, and its clinical use is supported by recent clinical guidelines.[75] CT-FFR has not yet been extensively used as an endpoint in clinical trials, however, biomechanical features derived from computational fluid dynamics, which also include for instance wall shear stress and plaque structural stress, are expected to play a more prominent role in the future.[43,76] Cardiac CT scanners can be used for stress perfusion imaging and calculate various parameters of myocardial perfusion (blood flow, perfused capillary blood volume, first-pass distribution volume).[77,78] CT myocardial perfusion imaging can identify inducible myocardial ischemia and guide revascularization decisions. Reproducibility of quantitative perfusion imaging, and its value for serial imaging, requires further investigation.

9. Conclusion

Quantification of CAD on CCTA images is technically feasible, increasingly automated, and in more demand for research as well as clinical patient care. Standardization of acquisition methods and measurement techniques and transparent reporting enhance the validity and acceptance of CCTA-defined endpoints in clinical trials. Methodological rigor is essential for comparison of results between different studies.

Declaration of competing interest

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Maksymilian P. Opolski reports institutional grant support from B. Braun; consulting for Boston Scientific and proctorship for Boston Scientific, Terumo and Biotronik.

Michelle Williams has given talks for Canon Medical Systems, Siemens Healthineers and Novartis.

Damini Dey has received software royalties from Cedars-Sinai Medical Center and is supported by grants from the NIH/NHLBI (1R01HL148787-01A1 and 1R01HL151266).

Jonathon Leipsic is a consultant and holds stock options in HeartFlow Inc., is a consultant to Circle CVI and has received modest corelab personal fees from Arineta and has received modest speaking fees from GE Healthcare and Philips HealthCare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2024.05.232.

Appendix 1

Author relationships with industry: Standards for Quantitative Assessments by Coronary Computed Tomography Angiography (CCTA): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT).

Writing Group Member	Employment	Consultant/ Honoraria	Speakers Bureau	Ownership interest/ Stock and stock options	Grants and research support	Patents	Royalties
Koen Nieman (co-chair)	Stanford University	Artrya; Cleerly; Novartis; Siemens			Bayer; HeartFlow; Novartis; Siemens		
Hector M Gracia-Garcia (co-chair)	MedStar Washington Hospital Center	Boston Scientific, Abbott, Medis, Biotronik, Terumo			Boston Scientific, Abbott, Medis, Biotronik, Terumo, Cordis, Corflow, Neovasc, Sprectawave, Pulse, Phillips		
Stephan Achenbach	Friedrich-Alexander-University Erlangen-Nürnberg						
Pablo Javier Blanco	National Laboratory for Scientific Computing			FLOUIT			
Nico Bruining	Erasmus Medical Center						
Carlos Collet	OLV Aalst	HeartFlow; Pie Medical			GE Healthcare; HeartFlow; Medis; Pie Medical		
Damini Dey	Biomedical Imaging Research Institute, Cedars-Sinai Medical Center				patent, research grants from NIH/ NHLBI		software royalties from Cedars Sinai Medical Center
Maros Ferencik	Knight Cardiovascular Institute	Elucid; HeartFlow; Siemens Healthineers; Cleerly; BioMarin		Elucid			
Alexandre Hideo-Kajita	Hospital Nove de Julho						
Pal Maurovich-Horvat	Semmelweis University		Siemens Healthineers	InterSynk Solutions	Siemens Healthineers		
Jonathon Leipsic	University of British Columbia	Circle CVI; Heartflow; MVRX	GE Healthcare; Philips HealthCare	Circle CVI; Heartflow			
Michael T Lu	Massachusetts General Hospital & Harvard Medical School				AstraZeneca; Ionis; Johnson & Johnson Innovation; Kowa; MedImmune		
Maksymilian P Opolski	National Institute of Cardiology	Boston Scientific	Proctorship: Asahi Intecc, Biotronik; Boston Scientific; Terumo				
Francesca Pugliese	Queen Mary University of London & Barts Health NHS Trust				Siemens Healthineers		
Jan GP Tijssen	Academic Medical Center						
Gaby Weissman	MedStar Washington Hospital Center				Abbott; Boston Scientific; Medtronic; NeoVasc; Ancora Heart		
Michelle C Williams	University of Edinburgh		Canon Medical Systems; Novartis; Siemens Healthineers				

Appendix 2

REVIEWER RELATIONSHIPS WITH INDUSTRY — Standards for quantitative assessments by coronary computed tomography angiography.

Reviewer	Employment	Consultant/ Honoraria	Speakers Bureau	Stock and stock options	Grants and research support	Royalties
Cristina Fuss	Yale New Haven Hospital	Elsevier; Siemens				Elsevier
Abdul Rahman Ihdayhid	Harry Perkins Institute of Medical Research, Curtin University, Fiona Stanley Hospital	Artrya; Abbott Medical		Artrya		
Mahadevappa Mahesh	Johns Hopkins University School of Medicine					
Renu Virmani	CVPath Institute Inc.	Abbott Vascular; Boston Scientific; Celenova; Edwards Lifesciences			NIH Recover480; RECOVER Initiative (OT2HL161847-01)	
Jeannie Yu	Tibor Rubin VA Medical Center at Long Beach					

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