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Application of Quantitative Assessment of Coronary Atherosclerosis by Coronary Computed Tomographic Angiography

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Coronary computed tomography angiography (CCTA) has emerged as a pivotal tool for diagnosing and risk-stratifying patients with suspected coronary artery disease (CAD). Recent advancements in image analysis and artificial intelligence (AI) techniques have enabled the comprehensive quantitative analysis of coronary atherosclerosis. Fully quantitative assessments of coronary stenosis and lumen attenuation have improved the accuracy of assessing stenosis severity and predicting hemodynamically significant lesions. In addition to stenosis evaluation, quantitative plaque analysis plays a crucial role in predicting and monitoring CAD progression. Studies have demonstrated that the quantitative assessment of plaque subtypes based on CT attenuation provides a nuanced understanding of plaque characteristics and their association with cardiovascular events. Quantitative analysis of serial CCTA scans offers a unique perspective on the impact of medical therapies on plaque modification. However, challenges such as time-intensive analyses and variability in software platforms still need to be addressed for broader clinical implementation. The paradigm of CCTA has shifted towards comprehensive quantitative plaque analysis facilitated by technological advancements. As these methods continue to evolve, their integration into routine clinical practice has the potential to enhance risk assessment and guide individualized patient management. This article reviews the evolving landscape of quantitative plaque analysis in CCTA and explores its applications and limitations.

Keywords: Coronary computed tomography angiography; Artificial intelligence; Quantitative plaque analysis; Coronary artery atherosclerosis

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed countries. Coronary computed tomography angiography (CCTA) is a rapidly evolving diagnostic imaging modality. Multiple clinical studies have demonstrated its efficacy for diagnosing and stratifying patients with suspected coronary artery disease (CAD). Recent guidelines from American and European societies have endorsed CCTA as an initial testing modality for assessing symptomatic CAD [1,2].

One of CCTA's key strengths is its ability to characterize coronary atherosclerotic plaques. Owing to its three-dimensional (3D), noninvasive nature, CCTA enables the comprehensive assessment of coronary plaques throughout the entire coronary tree. Conventional clinical assessment using CCTA involves visual estimation and qualitative evaluations of stenosis and plaque type. However, recent advancements in image analysis and artificial intelligence (AI) techniques have enabled the comprehensive quantitative analysis of plaque composition, volume, and degree of stenosis. This quantitative plaque assessment can significantly improve the diagnosis of CAD and the prediction of subsequent cardiac events. Furthermore, serial evaluation of quantitative plaque characteristics facilitates evaluating treatment response to drugs that favorably modulate

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coronary plaques and enables effective monitoring of CAD progression.

This review provides a comprehensive overview of prior studies, future applications, and potential limitations of quantitatively assessing coronary artery plaques using CCTA.

Application of Quantitative Plaque Analysis in Stenosis Evaluation

Numerous clinical studies have consistently reported the high diagnostic accuracy of CCTA, particularly in excluding obstructive CAD among symptomatic patients with a low-to-intermediate pretest probability of CAD. However, traditional visual assessment often overestimates the degree of stenosis compared to invasive reference standards [3]. Moreover, relying solely on the anatomical evaluation of stenosis severity has demonstrated limited diagnostic accuracy in identifying hemodynamically significant stenoses [4]. Consequently, recent research has focused on addressing the limitations of CCTA for stenosis evaluation.

Quantitative Assessment of Stenosis Severity

Conventional qualitative analysis of coronary atherosclerotic lesions is based on different categories of diameter stenosis: none (no visible stenosis), minimal (1%–24% estimated stenosis of the coronary luminal diameter), mild (25%–49%), moderate (50%–69%), severe (70%–99%), or occluded (100%) [5]. Recent advances in CT workstations and specialized plaque analysis (PA) software have facilitated semi-automated or fully automated quantification of coronary artery stenosis. For example, Boogers et al. [6] demonstrated that automated quantification of stenosis severity on CCTA exhibited a good correlation with quantitative coronary angiography (QCA) and improved diagnostic accuracy compared to visual assessment alone. Furthermore, machine learning and deep learning enable a fully automated stenosis evaluation [7]. In a study by Hong et al. [8] employing a deep learning approach featuring the M-net CNN architecture, a fully quantitative assessment of area stenosis and diameter stenosis demonstrated an outstanding correlation ($r = 0.984$ for minimal luminal area and $r = 0.957$ for diameter stenosis) with expert readers with a rapid processing time of < 32 seconds. In another recent study, Lin et al. [9] developed a fully automated deep learning-based diameter and area stenosis evaluation method that employed invasive coronary angiography and intravascular ultrasound (IVUS) as the reference standard. The agreement for the minimal luminal area between the deep learning algorithm and IVUS evaluation was strong, with an interclass correlation coefficient of 0.904 (Fig. 1). In addition, Griffin et al. [10] demonstrated the effectiveness of AI-based software that enables the rapid and accurate identification and exclusion of high-grade stenosis, with good agreement with QCA. Recently, AI-based coronary stenosis quantification software exhibited a high discriminatory ability for anatomic stenosis across vessel segments, including area under the receiver operating characteristic curve (AUC) values of 0.92 and 0.93 at 50% and 70% thresholds [11]. Adopting a fully automated CT stenosis evaluation can enhance the utility of CCTA, enabling faster, more reproducible, and more accurate clinical reporting.

Quantitative Assessment of Lumen Density to Detect Hemodynamically Significant Lesion: TAG and CDD

Previous invasive studies have revealed significant disparities between angiographically and functionally significant lesions, as assessed by the fractional flow reserve (FFR) [4]. A similar gap exists between CCTA and invasive FFR. Recent developments in quantitative analysis have demonstrated the potential of CCTA to evaluate the functional significance of lesions, most notably using CT-FFR, especially in patients with intermediate stenosis, which necessitates further assessment of functional significance [12,13]. The use of CT-FFR in intermediate lesions on CCTA has a Class IIa recommendation in the American College of Cardiology/American Heart Association guidelines for patients with chest pain syndromes and a strong recommendation in the guidelines of the European Society of Cardiology [1,2]. Although CT-FFR is a widely used tool for assessing the hemodynamic significance of lesions, it has limitations. CT-FFR entails additional costs and nitroglycerin administration and requires high-quality contrast-enhanced CT images free of artifacts or noise. Furthermore, a recent multicenter observational study showed that CT-FFR has a low positive predictive value (PPV) and is associated with a higher cost than conventional stress-imaging approaches [14]. Only one vendor, HeartFlow, currently provides CT-FFR based on computational fluid dynamics. Recently, other approaches assessing the functional significance of lesions using machine learning and deep learning applied to coronary plaques have shown a high correlation with invasive FFR [15,16]. An alternative tool, CT myocardial perfusion, can also offer a functional assessment of CAD [17]. However,

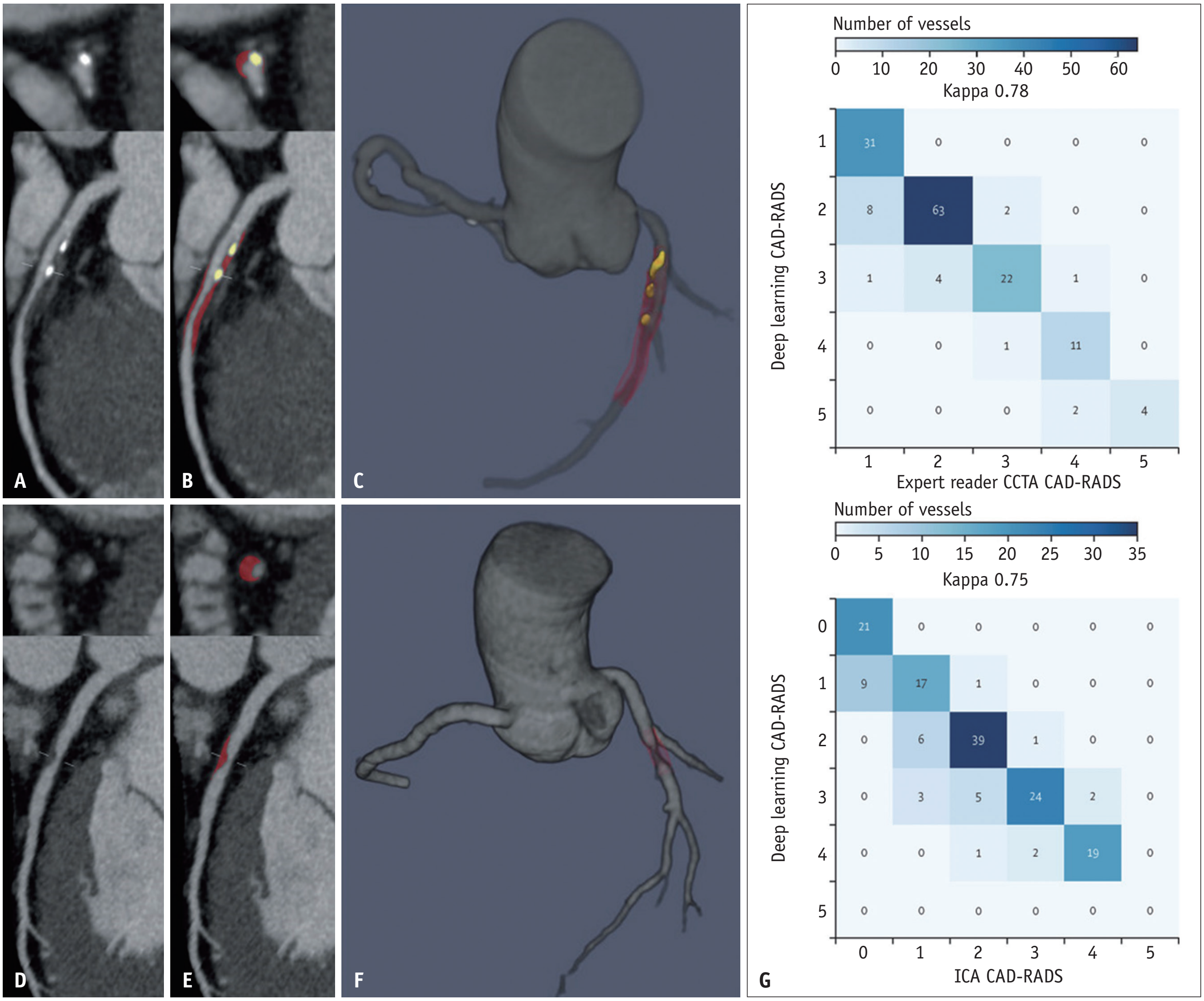

Fig. 1. Deep-learning coronary artery plaque analysis. **A-F:** Case examples of deep-learning plaque segmentation in the proximal to mid LAD **(A-C)**. Case examples of deep-learning plaque segmentation in the mid-LAD **(D-F)**. Curved multiplanar reformation CCTA images **(A, D)**. Deep-learning segmentation of calcified plaque (yellow) and noncalcified plaque (red) **(B, E)**. Three-dimensional rendered view of the coronary tree **(C, F)**. **G:** Per-vessel CAD-RADS categorization by deep learning versus expert readers and ICA. CAD-RADS categorical agreement between deep learning and experts and between deep learning and ICA was strong (unweighted Cohen's κ coefficient = 0.78 and κ = 0.75, respectively), and there was 99% (between deep learning and experts) and 97% (between deep learning and ICA) agreement within one CAD-RADS category. Adapted from Lin et al. *Lancet Digit Health* 2022;4:e256-e265, with permission of Elsevier [9]. LAD = left anterior descending, CCTA = coronary computed tomography angiography, CAD-RADS = Coronary Artery Disease Reporting and Data System, ICA = invasive coronary angiography

significant limitations constrain its widespread use in daily clinical practice, including artifacts from CT imaging such as beam hardening, misregistration, image noise, motion artifacts, and requiring a second scan using pharmacological stress, with the disadvantages of extra radiation and altered scheduling times. Alternatively, several other quantitative analysis methods, such as the transluminal attenuation gradient (TAG) and contrast density drop (CDD), have been proposed to assess coronary stenosis's functional significance by analyzing lumen density changes.

TAG is the linear regression coefficient between luminal attenuation and axial distance throughout a specific vessel, with higher TAG values associated with higher stenosis severity [18-20]. In an initial study, Choi et al. [19] investigated the value of TAG in 370 major coronary arteries, measuring 7263 intervals of 5 mm length. In correlation with CCTA and invasive coronary angiography, there was a consistent and significant decrease in TAG levels in vessels with a higher degree of stenosis. Furthermore, TAG has shown an incremental value over CCTA alone in detecting functionally significant coronary artery stenosis [21]. However, a decline in intraluminal attenuation was noted, along with a reduction in vessel diameter [22]. Prior studies have shown that TAG and transluminal diameter gradient do not offer additional diagnostic value compared to CCTA alone for detecting significant ischemia [23]. Further studies are needed to standardize and validate the TAG evaluation using a larger number of patients.

CDD, another quantitative method for assessing changes in luminal contrast density over a coronary lesion, is the maximum percentage difference in contrast densities relative to the proximal reference cross-section, with a higher CDD indicating hemodynamically significant lesions (Fig. 2) [24-26]. Dey et al. [24] compared the coronary plaque burden using CCTA in patients with acute coronary syndrome (ACS) and those with stable CAD. Their findings showed that higher CDD values reliably distinguished patients with ACS from those with stable CAD, along with plaque parameters such as noncalcified plaque (NCP), total plaque burden, and stenosis [24]. Diaz-Zamudio et al. [25] examined whether automated quantitative measurements of plaque features from CCTA could predict the presence of ischemia using myocardial perfusion imaging at various stenosis severity levels. In that study, CDD was strongly associated with ischemia in vessels with > 70% stenosis. Hell et al. [26] explored whether TAG and CDD could serve as indicators of the hemodynamic significance of coronary artery stenoses by comparing the values of invasively measured FFR. They demonstrated that the diagnostic accuracy (specificity, 75%; sensitivity, 33%; PPV, 35%; negative predictive value, 73%) of CDD was superior to TAG for identifying hemodynamically significant lesions. Furthermore, in a study using machine learning techniques to develop a model for predicting hemodynamically significant ischemia, the combination of CDD and plaque assessment showed a diagnostic performance comparable to that of CT-FFR in identifying invasive FFR-defined ischemia [27]. Despite the potential applications of CDD, certain limitations should be noted. Validation of the clinical application of the CDD is limited, and only one quantitative program can provide the required data. Additionally, imaging artifacts, such as beam hardening or metallic artifacts, and the timing of contrast acquisition can affect the assessment of changes in luminal density throughout the coronary arteries.

Application of Quantitative Analysis for Plaque Burden Assessment

An essential advantage of CCTA is its ability to assess total plaque burden. Traditionally, plaque burden has been estimated using quantitative analysis of calcified plaques in coronary artery calcification (CAC) scanning, the Agatston score, or semi-quantitative visual evaluation of plaque extent in several coronary segments. However, recent studies have demonstrated that the quantitative assessment of coronary plaques in CCTA enables a more comprehensive and

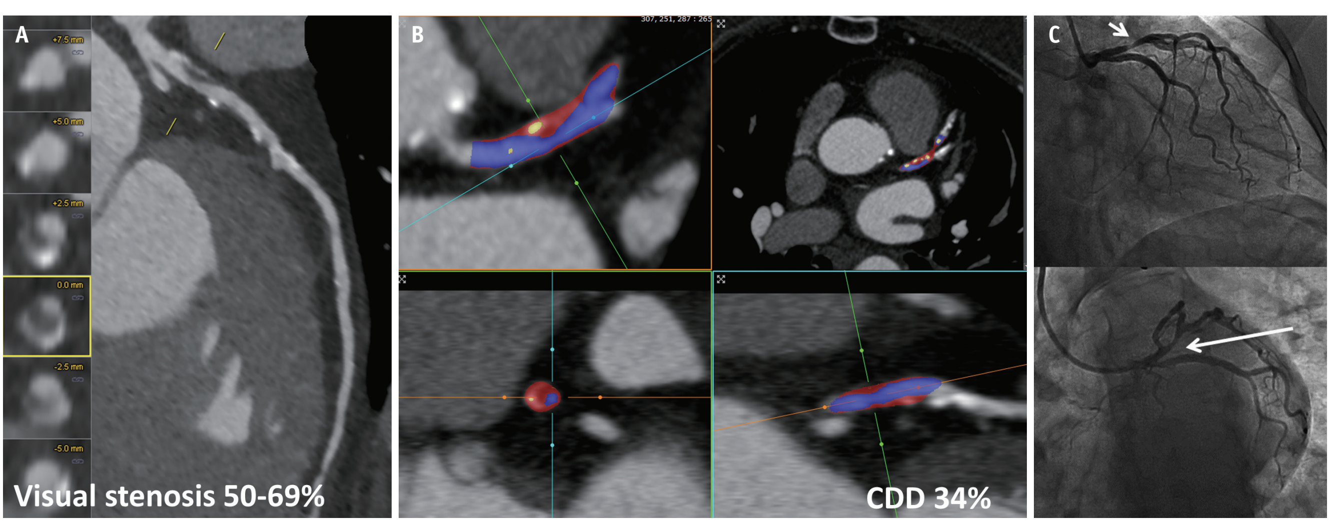

Fig. 2. Images of a 73-year-old female who presented with typical chest pain. **A:** Multiplanar reformat of CCTA demonstrating a borderline (50%–69%) stenotic lesion in the proximal LAD. **B:** Quantitative analysis of CDD using the Autoplaque software. The start and end points were selected manually, and the calculation yielded a CDD of 34. **C:** Invasive coronary angiography showing 75% stenosis of the proximal LAD (arrows). CCTA = coronary computed tomography angiography, LAD = left anterior descending, CDD = contrast density drops

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robust analysis of plaques within individual segments and across the entire coronary artery tree.

Conventional Semi-Quantitative Approach: CAC and Semi-Quantitative CCTA Scores

CAC scoring is considered an effective method for the early detection of CAD, especially in asymptomatic primary prevention populations, compared to conventional clinical risk scores such as the Framingham 10-year risk score [28,29]. The CAC plaque burden was quantified using the method described by Agatston et al. [30] and categorized as none (CAC = 0), mild (1–100), moderate (101–300), severe (301–1000), or extensive (> 1000) [5]. Although previous studies have shown that CAC is a strong and independent predictor of future adverse cardiovascular events and has incremental prognostic value in predicting CVD events [31-33], it does not account for NCP. Purely calcified plaques are stable and unlikely to cause ACS events. NCP, mainly low-density NCP, are the most rupture-prone plaques. Furthermore, the utility of serial CAC assessment is limited, given the tendency of preventive medications such as statins to potentially elevate CAC scores while simultaneously decreasing the risk of CVD.

In CCTA imaging, semi-quantitative scoring systems, such as the Segment Involvement Score (SIS), Segment Stenosis Score (SSS), and modified Duke CAD index, have been conventionally employed to assess the coronary plaque burden. The SIS provides a simple measure of the overall coronary plaque burden by assigning a score of 1 to each coronary artery segment with detectable atherosclerotic plaques, irrespective of plaque severity [34]. In contrast, the SSS and modified Duke index incorporate both the severity and extent of coronary artery plaques [35]. Although these semi-quantitative scores offer CAD plaque assessment, they only provide an approximation of the CAD burden.

Quantitative Plaque Analysis Software

Recent advancements have introduced specialized software that enables quantitative evaluation of plaques at both the lesion and patient levels. These tools measure plaque composition, volume, coronary stenosis, and positive remodeling. Various quantitative CT software options are now available, employing diverse approaches encompassing automated or semi-automated techniques for detecting the lumen border. Several FDA-approved quantitative PA software options are available, including QAngio, SUREPlaque, Autoplaque, vascuCAP, Cleerly, and automated AI-PA from HeartFlow (Table 1) [15,36-43].

The semi-automated plaque assessment process across various platforms involves several key steps. Initially, automated algorithms were used to extract the centerline of the coronary artery. Automated methods detect the boundaries of the lumen and outer vessel wall using mathematical or rule-based approaches. The lumen of a coronary artery is typically segmented based on cross-sectional CCTA images, transforming the vessel's entire length into a single volume. Subsequently, the reader manually adjusted the detected boundaries in multiplanar reconstructed or cross-sectional views, with the extent of adjustment dependent on the quality of the CCTA images. Plaque was identified as all voxels between the lumen and vessel wall boundaries, and the software automatically measured the plaque.

There is no standardized nomenclature for describing plaque volumes or components, leading to varied terminology across software vendors. Plaque size is typically measured volumetrically in cubic millimeters (mm^3), and analysis can be conducted at the per-lesion, per-coronary segment, per-vessel, or per-patient level. The plaque area on a 2D CCTA cross-section can also be determined as the plaque area (mm^2). Similar to IVUS methodology, the percentage of the overall vessel volume occupied by plaque on CCTA can be calculated as the "percent atheroma volume," "plaque burden volume ratio," or simply "plaque burden." To account for differences in patient sex and body size, plaque volume was normalized to vessel volume, reducing variability and providing a more optimal method of reporting the coronary atherosclerotic plaque burden [44]. In 2D cross-sectional PA, plaque area is indexed to vessel area (mm^2) to calculate the "cross-sectional plaque burden," typically at the site of maximal stenosis. Additional parameters automatically calculated by PA software include plaque length, plaque thickness, remodeling index, and the ratio of the maximal vessel dimension within a lesion to that at a proximal "normal" reference point.

Software vendors exhibit high heterogeneity in the terminology and thresholds used to define plaque components. Calcified plaque, or "dense calcium", is generally defined by a density ≥ 350 Hounsfield unit (HU). NCP, referred to as "fibrotic" or "medium density" plaque, is often further categorized into fibrous and fibro-fatty components. Low-density NCP, typically < 30 HU, may be labeled as "necrotic core," "lipid-rich," "lipid-rich necrotic core," or simply "low attenuation plaque" [24,45]. While

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Table 1. FDA-cleared quantitative plaque analysis softwares

Software	Vendor	FDA approval	Key features	Plaque types analyzed	Key validation studies
QAngio	Medis Medical Imaging Systems, Leiden, the Netherlands	510k 2006	Stenosis, plaque volume, vessel volume, remodeling index, plaque types	Necrotic core, fibrofatty, fibrous, dense calcium	Boogers et al. [36], de Graaf et al. [37]
SUREplaque	Canon Medical Systems, Otawara, Japan	510k 2004	Stenosis, plaque volume, vessel volume, plaque types	Low density non calcified, non-calcified, calcified	Fujimoto et al. [38], Voros et al. [39]
Cleerly	Cleerly Healthcare, New York, NY, USA	510k 2019	Stenosis, plaque volume, vessel volume, remodeling index, plaque types	Low density non calcified, non-calcified, calcified	Choi et al. [40]
vascuCAP	Elucid Bioimaging, Wenham, MA, USA	510k 2017	Stenosis, plaque volume, vessel volume, remodeling index, plaque types	Lipid rich necrotic core, matrix, calcified plaque	Sheahan et al. [41]
Autoplaque	Cedars-Sinai Medical Center, Los Angeles, CA, USA	510k 2012	Stenosis, plaque volume, composition, and burden, vessel volume, remodeling index, contrast density drop, plaque types	Non-calcified, calcified, low density non calcified, necrotic core, fibrous fatty, fibrous, dense calcium	Dey et al. [15], Dey et al. [42]
HeartFlow Plaque Analysis	HeartFlow, Mountain View, CA, USA	510k 2022	Plaque volume, vessel volume, plaque types	Low CT attenuation plaque, non-calcified, calcified	Tzimas et al. [43]

default HU thresholds are set for most software platforms, users can adjust them. Some vendors use adaptive scan-specific thresholds that are automatically adjusted based on lumen attenuation, considering their influence on the absolute HU of plaque components.

Software-based plaque measurement accuracy and reproducibility depend on image quality and reader experience. Puchner et al. [46] found that iterative reconstruction algorithms enhanced CCTA-derived cross-sectional plaque burden, correlating more strongly with IVUS than traditional methods. Stolzmann et al. [47] revealed excellent inter-reader reproducibility and a high correlation with IVUS for plaque burden using CCTA, regardless of the reconstruction algorithm used in an ex vivo study. Various software vendors have shown robust intraobserver and interobserver agreements for plaque volumes. However, there is a lack of data on inter-platform reproducibility.

The QAngio software (Medis Medical Imaging Systems, Leiden, the Netherlands) was validated against IVUS, demonstrating a strong correlation between lumen area stenosis and plaque burden. Moreover, the quantification of plaque subtypes, including fibrofatty, fibrous, and calcified volumes, exhibited excellent correlation with those assessed by IVUS. The well-established (Progression of AtheRosclerotic PlAque DetermIned by Computed Tomographic Angiography Imaging) PARADIGM registry examined serial changes in plaque components using Medis QAngio for at least 2 years between baseline and follow-up scans for over 2000 patients. The findings of multiple substudies revealed important factors modulating plaque progression, including baseline plaque burden and statin therapy [48,49].

SUREplaque (Canon Medical Systems, Otawara, Japan) was also validated against IVUS in a prospective study focusing on the accuracy of 3D quantitative PA using CCTA compared to IVUS with radiofrequency backscatter analysis. Although there was a wide limit of agreement, the overall mean differences in the total plaque assessment were minor [39]. Furthermore, low-density NCP correlated with the necrotic core and fibrofatty tissue on IVUS. Compared to the invasive coronary angiography findings of the culprit lesion, CCTA features of plaque disruption in patients with unstable angina demonstrated good sensitivity (53%–81%) and specificity (82%–95%) [50].

Cleerly Healthcare (New York, USA) offers AI-based, fully automated CCTA analysis with manual adjustment, if necessary. The software has been validated primarily through studies comparing it with expert plaque quantification or QCA analyses. Initial validation studies reported excellent diagnostic performance for detecting > 70% and > 50% stenosis compared to the consensus of three level-3 expert CCTA readers [40]. In a sub-study of the PARADIGM registry, the software proved effective in evaluating a large patient population for detecting small changes in plaque burden and reducing measurement variability compared with the initially

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used software [51].

vascuCAP (Elucid Bioimaging, Wenham, MA, USA) is another plaque quantification software initially validated against carotid CT imaging histopathological findings. This study demonstrated a strong correlation between calcification and lipid-rich necrotic core [41]. The software was also applied in the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) randomized trial, which assessed changes in plaque morphology in a trial evaluating the efficacy of icosapent ethyl in patients with hypertriglyceridemia. Evaluation at three time points, baseline, 9 months, and 18 months of follow-up, showed potential in assessing plaque changes early in follow-up at 9 months [52]. Furthermore, this study suggests that assessing more detailed changes in plaque characteristics, such as maximal wall thickness and increases in cap thickness, might be feasible.

Autoplaque (Cedars-Sinai Medical Center, Los Angeles, CA, USA) is widely used and was initially validated and compared with IVUS, showing an excellent correlation of quantified NCPs between the software and IVUS. The software, utilized in large multicenter clinical trials, such as the Scottish Computed Tomography of the HEART (SCOT-HEART) and Rapid Assessment of Potential Ischemic Heart Disease with computerized tomography coronary angiography (RAPID CTCA), demonstrated its capability to improve the identification of patients at high risk for adverse CVD events. Furthermore, quantitative plaque burden assessment improved the assessment of lesion-specific ischemia and predicted lesions requiring revascularization by implementing machine-learning techniques [15,53]. Most recently, the application of a rapid AI tool enabled fully automated plaque quantification, showing good-to-excellent agreement between automated plaque and expert reader measurements of the total plaque volume and diameter stenosis [9].

HeartFlow (Mountain View, CA, USA) offers an automated AI-PA that was validated against expert reader plaque quantification using Autoplaque software. Pearson's correlation coefficient demonstrated a highly significant correlation between AI-PA and CT readers when the overall total atherosclerotic plaques were assessed [43]. The tool's accuracy was also compared with that of IVUS, demonstrating that the total plaque volume, vessel, lumen, and plaque subtype volumes derived from the AI-PA tool were highly correlated with those derived from IVUS in per-lesion analysis.

Clinical Application of Quantitative Plaque Assessment

Risk Prediction

Total Plaque Burden

The total plaque burden derived from CCTA has demonstrated a predictive value for subsequent cardiac events [54,55]. In a prospective study analyzing the results of the PARADIGM registry involving 1345 patients, the additional value of semiautomated quantitative total plaque volume over qualitative CCTA evaluation methods improved the prediction of rapid plaque progression and adverse clinical outcomes [56]. More recently, Lin et al. [9] demonstrated that a deep learning-based plaque quantification system could predict the risk of myocardial infarction.

Plaque Subtypes

A growing body of evidence suggests that the specific plaque phenotypes are more strongly associated with the risk of plaque rupture and increased cardiovascular events. In quantitative PA using CCTA imaging, the plaque subtype was differentiated based on HU. The CT findings of low-HU attenuation plaques signified the presence of high intraplaque lipid content. Quantification of LAP holds promise as a marker of high-risk plaques and a prognostic indicator. Previous studies have shown that increased low-density NCP increases the risk of plaque rupture and myocardial infarction. For example, Chang et al. [54] performed quantitative PAs in 234 patients with ACS and 234 matched controls in the Incident Coronary Syndromes Identified by Computed Tomography (ICONIC) sub-study of the Coronary CT Angiography Evaluation for Evaluation of Clinical Outcomes: An International Multicenter Registry (CONFIRM) registry. They found that the total, calcified, and fibrous plaque volumes did not differ significantly between patients with ACS and controls. In contrast, the fibrofatty plaque and necrotic core volumes were substantially higher in patients with ACS than in controls. In addition, in the SCOT-HEART trial, LAP burden was the strongest predictor of fatal or nonfatal myocardial infarction beyond the cardiovascular risk score, CAC score, or obstructive coronary artery stenoses [55]. They found that patients with an LAP burden > 4% had a nearly five times higher risk of myocardial infarction (Fig. 3). Similar observations were reported for RAPID-CTCA. In patients with suspected ACS, LAP burden is a significant predictor of 1-year death or recurrent myocardial infarction [57]. Patients with an

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LAP burden above the median had an approximately 8-fold increased risk of adverse CVD outcomes, outperforming conventional stenosis-based approaches.

In contrast to low-density plaques, high-density calcium is considered a stabilized plaque phenotype associated with low CVD risk. Early studies using noncontrast CAC scoring CT scans have shown that calcium density is inversely related to coronary heart disease and CVD risk at any CAC volume level [58]. This density assessment can also be applied to quantitative CCTA based on the HU threshold. In a substudy of ICONIC, van Rosendael et al. [59] showed that patients who experienced subsequent ACS events had not only a high burden of low-density NCP but also a significantly low burden of high-density calcium, defined as > 1000 HU, compared with those without ACS events. Moreover, statin treatment is associated with an increased volume of high-density calcified plaques, suggesting that increased calcium densification may be related to plaque healing and a reduced risk of plaque rupture [48].

Plaque Distribution

In addition to the evaluation of plaque morphology

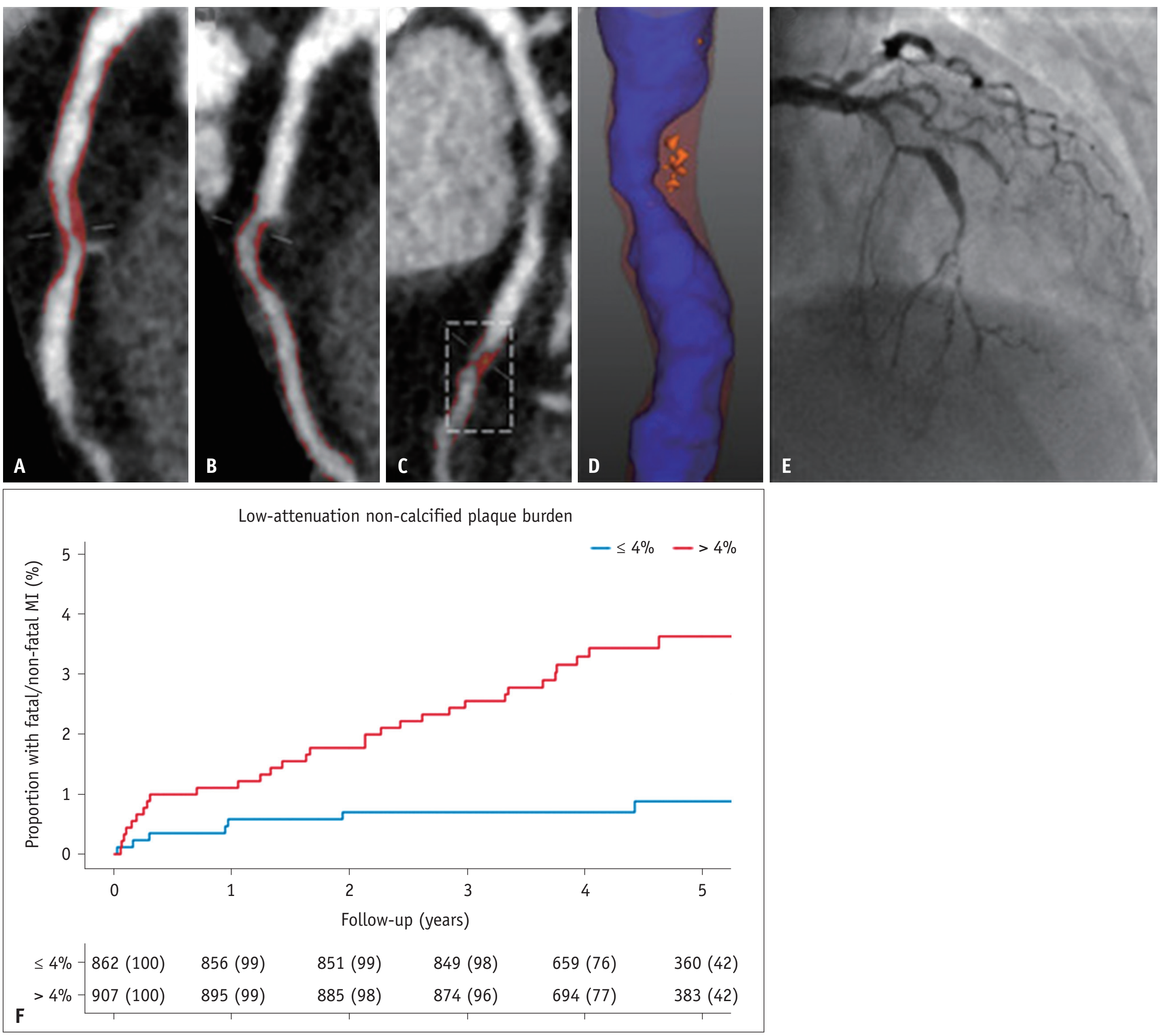

Fig. 3. Plaque characteristics. **A:** Proximal LAD. **B:** First diagonal. **C:** Mid LAD. **D:** Mid-LAD plaque with blue lumen, red noncalcified plaque, and orange LAP. **E:** Invasive coronary angiography. **F:** Cumulative incidence of MI in patients with and without a LAP burden greater than 4%. Adapted from Williams et al. *Circulation* 2020;141:1452-1462, with permission of Wolters Kluwer Health [55]. LAD = left anterior descending, LAP = low attenuation plaque, MI = myocardial infarction

and burden, CCTA permits the accurate determination of plaque distribution and vessel curvature. The quantitative assessment of these geometric characteristics has improved the risk prediction of future CVD events. In a serial CCTA study of 1478 patients, proximally located lesions tend to have more significant lipid-density plaque components and progress rapidly [60]. Another study investigated the incremental prognostic values of quantitative adverse geometric characteristic assessments, including ostial to plaque distance, vessel tortuosity, and lesion at bifurcation, for future ACS in a sub-study of the ICONIC study [61]. This study found that CCTA-derived adverse geometric characteristics were significantly associated with the risk of future ACS-causing culprit lesions and conventional CCTA assessments, including diameter stenosis, adverse plaque characteristics, and quantitative plaque characteristics.

Plaque Radiomics

Radiomics is a method for extracting imaging features (radiomic features) from medical images using data characterization algorithms. This serves as a potential quantitative approach to enhance the precise phenotyping of diseases. Several studies have shown that applying radiomics to CCTA can improve the identification of vulnerable plaque characteristics. Kolossváry et al. [62] compared radiomics-based ML models with visual and histogram-based assessments of ex vivo CCTA, using histological examination as a reference standard for detecting advanced atherosclerotic lesions. This study showed that the radiomics-based ML model improved the discrimination of plaques from advanced atherosclerotic lesions, which are associated with a higher risk of future myocardial infarction. In addition, Lin et al. [63] found distinct radiomic features in culprit lesions in acute myocardial infarction compared to nonculprit lesions in the same patients and with lesions in stable CAD patients. Recent studies have also suggested that the CCTA-derived radiomic signature of coronary plaques enables better identification of rapid plaque progression and improved prediction of future adverse cardiac events compared to conventional morphological plaque parameters [64,65]. Integrating radiomic analysis with AI-based plaque assessment can enhance the detection of patients at an elevated risk of future cardiovascular events, potentially warranting more aggressive preventive interventions. Nevertheless, the clinical application of radiomics in CCTA PA is in its early phases, and additional studies are required to validate its efficacy. The development of standardized radiomics approaches is essential to ensure consistency and reliability across research settings and clinical practices.

Monitoring Medical Therapy with Serial CCTA Scans

An essential advantage of the quantitative analysis of plaque composition is that plaque changes over time can be assessed as objective indicators through serial CCTA. Table 2 summarizes previous studies that explored the association between conventional clinical risk factors and changes in quantitative plaque characteristics using serial CCTA analysis [66-85]. Previous studies on patients who underwent serial CCTA examinations have reported associations between clinical factors, laboratory values, and changes in quantitative plaque characteristics. For example, the presence of conventional risk factors such as diabetes or high low-density lipoprotein (LDL) cholesterol levels is associated with accelerated plaque progression [66,67,69,71-74]. Patients at high risk of atherosclerotic cardiovascular disease (ASCVD) with an increased ASCVD risk score demonstrated more rapid plaque progression, including calcified plaques, fibrofatty plaques, and LAP, and exhibited more newly developed adverse plaques [77]. Plaque changes exhibited sex-related distinctions, indicating more favorable alterations in women. Women demonstrate slower NCP progression and faster calcified plaque progression than men [75,76]. Otaki et al. [68] also showed that a reduction in LDL-cholesterol level was associated with a reduction in all components of the NCP, including LAP.

Furthermore, a recent study showed that higher lipoprotein(a) levels are associated with accelerated progression of coronary LAP [83,85]. Beyond the established risk factors, research has explored the link between plaque progression and variables such as triglyceride levels, hemoglobin changes, and blood pressure control maintenance [79-81]. Consistent with the established link between CVD risk factors and plaque modification, changes in these risk factors can induce favorable changes in plaque characteristics, potentially mitigating the risk of future CVD events.

Table 3 summarizes prior research using serial CCTA quantitative analysis to assess changes in coronary artery plaques in response to therapies [48,49,86-108]. Studies have consistently shown that statin use is associated with reduced or slower progression of the overall coronary plaque volume and reduced high-risk plaque features, while accelerating the progression of calcified plaque volume in patients with

Table 2. Studies exploring the association between clinical risk factors and serial plaque changes

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
LDL-C								
Shin et al., 2017 [66]	147	Participants who underwent serial CCTA	Prospective observational	F/u LDL-C < 70 mg/dL: 37 F/u LDL-C ≥ 70 mg/dL: 110	QAngio	PV, dense calcium	3.2 years	Patients with LDL-C below 70 mg/dL displayed a significant attenuation in PP
Svanteson et al., 2019 [67]	68	Patients with IJD and carotid artery plaque(s) underwent CCTA before and after statin treatment	Prospective observational	RA 45 AS 15 Psoriatic arthritis 8	Plaque Analysis, Comprehensive Cardiac, Philips Healthcare	TP, CP, MP	4.7 years	Patients who had obtained the LDL-C treatment target at follow-up, experienced reduced progression of both CAC and TP volume
Otaki et al., 2019 [68]	154	Patients with serial CCTA	Retrospective observational	LDL-C decrease 85 No LDL-C decrease 69	Autoplaque	TP, NCP, LAP	4 years	There was interval reduction in TP, LAP, MLAP, and MAP volumes in patients with LDL-C decrease
Shi et al., 2022 [69]	208	DM patients	Retrospective observational	LDL controlled 75 LDL uncontrolled 133	cvi42, Circle Cardiovascular Imaging	TP, CP, NCP, LD-NCP	Unavailable	Increase in CACs was independently associated with the annual change of NCPV and LD-NCPV in LDL-C uncontrolled patient
Sun et al., 2022 [71]	240	Patients over 60 years old	Retrospective observational	Intensive lipid lowering 66 Lipid lowering 110 Control 64	QAngio	TP, CP, NCP, Fibrous, FF, lipid rich plaque	2 years	Intensive lipid-lowering group demonstrated a higher progression in calcified PV, CACS, and PCPV, and a significantly greater attenuation in FF and lipid-rich PV
Hirai et al., 2023 [70]	81	ACS patients	Retrospective observational	LDL-C < 70 48 LDL-C ≥ 70 33	Vitrea, Canon	TP, CP, LAP, Fibrous	1 year	CP volume was significantly increased in the LDL-C < 70 group Percent change in LAP volume in the LDL < 70 group was significantly lower than in the LDL-C ≥ 70 group
Diabetes								
Nakanishi et al., 2016 [73]	142	Patients who were clinically referred for serial CCTA	Propensity-matched study	DM 71 Non-DM 71	QAngio	TP, NCP, CP, Fibrous, FF, LAP	3.4 years	Diabetic patients showed a 2-fold greater progression in normalized TPV than non-diabetes patients. DM was associated with normalized TP and NCP progression

Table 2. Studies exploring the association between clinical risk factors and serial plaque changes (continued)

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
Kim et al., 2018 [72]	1602	PARADIGM	Prospective observational Propensity score matching	No DM 326 DM 326	QAngio	PV, CP NCP, LAP, FF, NC	3.8 years	Percent changes in overall PV and NC volume were significantly greater in those with DM
Won et al., 2019 [74]	1296	PARADIGM	Prospective observational	According to glycemic status: normal, pre-DM, and DM	QAngio	TP	3.2 years	Adjusted OR for PP was higher in DM than non-DM
Sex difference								
Lee et al., 2020 [76]	1255	Suspected CAD	Prospective observational	Women 543 Men 712	QAngio	TP, CP, NCP, LAP	2 years	Women was associated with greater calcified PV progression but slower noncalcified PV progression than in men
El Mahdiui et al., 2021 [75]	211	Patients underwent CCTA	Prospective observational	Men 146 Women 65	QAngio	TP, CP, NCP, Fibrous, FF, NC	6.2 years	Women under 55 years demonstrated significantly greater reduction in fibrous and non-calcified PAV over time compared to age-matched men
Other risk factors								
Han et al., 2020 [77]	1005	PARADIGM without known CAD	Prospective observational	ASCVD risk Low 463 Intermediated 373 High 169	QAngio	TP, CP, NCP, LAP	3.3 years	Annualized progression rate of PAV for TP, CP, and NCP was associated with increasing ASCVD risk score
Weber et al., 2020 [78]	350	Patients underwent serial CCTA	Retrospective observational	-	QAngio	TP, CP, NCP, LAP	3.6 years	Men and typical angina were identified as risk factors for fast TPV progression, while HDL-C had a protective effect
Won et al., 2020 [80]	1143	PARADIGM with available data on TyG index and diabetic status	Prospective observational	TyG index Lowest 382 Middle 388 Highest 373	QAngio	TP, CP, Fibrous, FF	3.2 years	Risk of PP and rapid PP was increased in highest TyG index compared to that in lowest TyG index
Won et al., 2022 [79]	830	PARADIGM	Prospective observational	Baseline hemoglobin	QAngio	TP	3.2 years	Hemoglobin change was independently associated with a decrease in annualized total PVC
Won et al., 2022 [81]	95	PARADIGM	Prospective observational	Normal SBP 40 Elevated SBP 55	QAngio	TP, CP, Fibrous, FF, NC	3.5 years	SBP maintain ≥ 118.5 mm Hg and baseline total PV independently influenced coronary PP

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Table 2. Studies exploring the association between clinical risk factors and serial plaque changes (continued)

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
Ben Zekry et al., 2022 [84]	1234	PARADIGM	Prospective observational	East-Asian 955 Caucasian 279	QAngio	TP, CP, Fibrous, FF	8.5 years	East Asians with PP had more clinical risk factors and higher plaque burden at baseline
Li et al., 2020 [82]	396	T2DM patients	Prospective Observational	Non-progression 253 Progression 143	-	TP	2.3 years	Long-term glycemic variability is associated with accelerated PP
Wang et al., 2021 [83]	116	Serial CCTA without prior CAD history	Retrospective, observational	PP (-) 84 PP (+) 32	Syngo.via VB10B	TP	30.8 months	Elevated baseline Lp(a) level was an independent risk factor for PP
Kaiser et al., 2022 [85]	191	Sable CAD, serial CCTA at baseline and 1 year	A substudy of randomized controlled trial	Lp(a) ≥ 70 43 Lp(a) < 70 148	Autoplaque	TP, CP, NCP, FF, low density plaque	1 year	Lp(a) is associated with accelerated progression of coronary LAP

*The mean or median values.
CCTA = coronary computed tomography angiography, F/u = follow up, LDL-C = low density lipoprotein cholesterol, PV = plaque volume, PP = plaque progression, IJD = inflammatory joint diseases, RA = rheumatoid arthritis, AS = ankylosing spondylitis, TP = total plaque, CP = calcified plaque, MP = mixed plaque, CAC = coronary artery calcium, NCP = non-CP, LAP = low attenuation plaque, MLAP = medium LAP, MAP = medium attenuation plaque, DM = diabetes mellitus, LD-NCPV = low-density noncalcified PV, FF = fibro-fatty, ACS = acute coronary syndrome, NC = necrotic core, CAD = coronary artery disease, PAV = percentage atheroma volume, ASCVD = atherosclerotic cardiovascular disease, HDL = high density lipoprotein, TyG = triglyceride glucose index, PVC = plaque volume change, SBP = systolic blood pressure, Lp(a) = lipoprotein(a)

suspected CAD [49,86-88,91,93], acute myocardial infarction [90] and human immunodeficiency virus [89,92,94]. These findings suggest that the benefits of statins and lowering LDL cholesterol levels in CVD risk reduction can be evaluated by serial monitoring of quantitative CT PA, namely, favorable modification of plaque subtypes (Fig. 4).

Studies have also shown that serial CCTA can monitor plaque changes in patients receiving other lipid-lowering therapies [95-99]. As noted above, the EVAPORATE study revealed that icosapent ethyl was associated with a significant regression of LAP volume compared to placebo over 18 months [98]. More recently, the Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition (ARCHITECT) study demonstrated that treatment with the PCSK9 inhibitor alirocumab and a high-intensity statin for 78 weeks in patients with familial hypercholesterolemia induced significant plaque regression of the coronary artery and plaque stabilization with an increase in calcified and fibrous plaques, accompanied by a reduction in fibrofatty and necrotic plaques [99].

Several studies have examined the effects of medication on plaque modification. The ongoing WARRIOR CCTA (NCT 05035056) sub-study evaluating plaque changes by serial CCTA, in which symptomatic women with nonobstructive CAD are randomized to usual care or intensive medical therapy (statins, angiotensin-converting enzyme inhibitors, aspirin), may shed further light on the effects of renin-angiotensin-aldosterone system inhibitors on the atherosclerotic process in addition to ACS, stroke, and cardiac mortality. In another study, the impact of evolocumab on coronary artery plaque volume and composition by CCTA and microcalcification by 18F-sodium fluoride (18F-NaF) PET (EVOLVE study, NCT03689946) was studied to determine the effects of evolocumab on changes in coronary plaque volume, as measured by serial CCTA and microcalcification activity using serial 18F-NaF PET. Future studies will provide critical mechanistic insights into plaque characteristics that may inform clinical trials of novel lipid-lowering agents or other preventive strategies for reducing the risk of CVD.

Studies have also shown changes in coronary artery plaques when treating conditions unrelated to cholesterol treatment. Budoff et al. [102] investigated the effects of testosterone treatment on coronary plaques in older men with low testosterone levels in a double-blinded, placebo-controlled trial. They found that 1 year of testosterone gel treatment was associated with an increased volume of noncalcified coronary artery plaques without changes in the

Table 3. Studies assessing quantitative plaque changes on serial CCTA in response to therapies

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
Statin								
Hoffmann et al., 2010 [86]	63	Serial CCTA studies	Retrospective observational	Statin*	Vitrea	TP, NCP, MP, CP	25 months	Statins significantly slowed the growth of NCP but did not significantly affect the growth rate of MP or CP
Inoue et al., 2010 [87]	32	Suspected CAD, no baseline statin	Prospective observational	Statin 24 No statin 8	SUREPlaque	LAP, intermediate, calcified based on HU	12 months	Statin treatment results in significant reduction of TP and LAP volumes
Zeb et al., 2013 [88]	100	No history of CAD and serial CCTA at an interscan interval of 1 year	Retrospective observational	Statin 60 No statin 40	Vitrea	TP, NCP, MP, CP, LAP	406 days	Mean plaque volume difference between statin and non-statin users was statistically significant for both LAP and NCP volumes
Lo et al., 2015 [89]	40	HIV-infected patients on stable ART, and LDL-C between 70–130 mg/dL	Prospective randomized	Atorvastatin 19 No statin 21	Aquarius iNtuition, Terarecon	TP, NCP	1 year	Atorvastatin reduced NCP volume relative to placebo
Auscher et al., 2015 [90]	96	Acute MI patients	Prospective randomized	Intensive statin 48 Standard statin 48	QAngio	TP, NC, FF, Fibrous, CP	1 year	Plaque composition changed over 1 year with an increase in total dense calcium volume in the intensive care group and a decreased in the usual care group
Li et al., 2016 [91]	206	Suspected CAD	Prospective observational	Intensive 55 Moderate 85 No statin 66	CardIQ Xpress 2.0	LAP, TP, PPV	18 months	LAP volume, TP volume, and PPV showed significant regression among intensive-statin compared with no-statin group
Nou et al., 2016 [92]	40	HIV-infected patients on stable ART with subclinical coronary atherosclerosis and LDL-C less than 130 mg/dL	Prospective randomized	Atorvastatin 19 Placebo 21	-	TP, NCP, CP	12 months	Change in oxLDL significantly correlated with changes in NCP volume, TP volume
Lee et al., 2018 [49]	1255	serial CCTA at an interscan interval of ≥ 2 years	Prospective observational	Statin naïve 474 Statin taking 781	QAngio	PV, CP NCP, LAP, FF, Fibrous	3.4 years	Lesions in statin-taking patients displayed a slower rate of overall PAV progression but more rapid progression of calcified PAV

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Table 3. Studies assessing quantitative plaque changes on serial CCTA in response to therapies (continued)

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
Smit et al., 2020 [93]	202	Suspected CAD	Prospective observational	Statin (+) 161 Statin (-) 41	QAngio	TP, CP, NCP	6.4 years	Statin use showed an independent association with annual progression of CP. Statin use was borderline significantly associated with a reduced progression of NCP
Foldyna et al., 2020 [94]	40	HIV-infected patients	Prospective randomized	Atorvastatin 19 Placebo 21	Aquarius iNtuition, TeraRecon	TP, CP, FF, Fibrous	12 months	Statins suppressed progression of fibrotic plaque, with a trend towards reducing fatty plaque and no significant effect on CP
van Rosendael et al., 2021 [48]	857	PARADIGM	Prospective observational	Statin (+) 548 Statin (-) 309	QAngio	LAP, FF, Fibrous, low-density calcium, high-density calcium	3.4 years	Statin therapy was associated with volume decreases in LAP and FF plaque and greater progression of high-density CP and 1K plaque
Other lipid lowering treatment								
Alfaddagh et al., 2017 [96]	285	Stable CAD on statins	Prospective randomized	Omega-3 ethyl ester 143 Control 142	SUREPlaque	TP, CP, NCP, FF, Fibrous	30 months	No difference was observed in NCP volume, between the 2 treatment groups
Budoff et al., 2020 [98]	80	Patients with stenoses with ≥ 20% persistently elevated TG levels	Prospective randomized	IPE 31 Placebo 37	QAngio	TP, NCP, LAP, FF, CP	18 months	IPE demonstrated significant regression of LAP
Motoyama et al., 2022 [95]	210	ACS patients	Retrospective observational	No EPA/DHA 69 Low dose EPA + DHA 51 High dose EPA + DHA 20 High dose EPA alone 70	QAngio	TP, CP, NCP, LAP, Fibrous, FF	24 months	Addition of high-dose EPA to statin therapy was associated with a lower rate of plaque progression
Baumann et al., 2022 [97]	23	Patients underwent CCTA	Prospective observational	PCSK 9 inhibitor	Syngo VE36A	TP, CP, NCP	1 year	TPV, CPV, NCPV, lumen volume, and functional plaque parameters did not change significantly
Pérez et al., 2023 [99]	104	Familial hypercholesterolemia without ASCVD	Phase IV clinical trial	Alirocumab, PCSK9 inhibitor	QAngio	TP, CP, Fibrous, FF, NC	78 weeks	Alirocumab + high-intensity statin induced increased calcified, fibrous plaque, and decreased FF, necrotic plaque
Biology therapy in psoriasis patients								
Elnabawi et al., 2019 [100]	290	Severe psoriasis	Prospective observational	TNF-a, IL 12/23, IL 17 inhibitor vs. placebo	QAngio	TP, NCP, CP, LAP	1 year	Biology therapy is associated with decreased NCP, FF, necrotic burden

Table 3. Studies assessing quantitative plaque changes on serial CCTA in response to therapies (continued)

Study	Patients (n)	Population	Study type	Intervention (groups)	Software	Plaque measures	Follow up*	Results
Choi et al., 2020 [101]	209	Biologic naïve psoriasis patients	Prospective observational	Mild to moderate psoriasis 212 Severe psoriasis 77	vascuCAP	LRNC	1 year	Biologic therapy had a reduction in LRNC
Other medication								
Budoff et al., 2017 [102]	138	Symptomatic hypogonadism	Prospective randomized	Testosterone treatment 73 Placebo 65	QAngio	TP, NCP, LAP, FF, CP	1 year	Treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in NCP volume
Lee et al., 2017 [103]	40	DM patients	Prospective randomized	Sarpogrelate + aspirin: 20 Aspirin: 20	Brilliance Workspace V4.5; Philips Healthcare	TP, NCP, CP	6 months	Sarpogrelate treatment may decrease coronary artery plaque volume, particularly the NCP, in DM patients
Matsumoto et al., 2017 [104]	54	Recent ACS patients	Prospective randomized	One of 3 VIA-2291 doses (25 mg, 50 mg, 100 mg) or placebo	SUREPlaque,	LAP, FF, Fibrous, dense calcium	6 months	VIA-2291 resulted in slowed PP compared with placebo across different plaque subtypes in patients with recent ACS
Vaidya et al., 2018 [105]	80	Recent ACS (< 1 month)	Prospective observational	Colchicine + OMT 40 OMT alone 40	GE Advantage workstation v4.5	CP, NCP, LAP, TAV	12.6 months	Colchicine therapy significantly reduced LAPV
Shaikh et al., 2020 [106]	66	DM patients	Prospective randomized	Aged garlic extract 37 Placebo 29	QAngio	TP, NCP, CP, LAP	1 year	Aged garlic extract group exhibited a statistically significant regression in normalized LAP
Aldana-Bitar et al., 2023 [107]	74	Patients with nonvalvular atrial fibrillation using apixaban or rivaroxaban	Prospective randomized	Apixaban 29 Rivaroxaban 45	AW 4.6 GE Healthcare	TP, CP, NCP	12 months	Significantly lower CP progression in the apixaban group
Heinsen et al., 2023 [108]	204	Asymptomatic DM patients	Prospective observational	Liraglutide (+) 55 Liraglutide (-) 149	QAngio	TP, CP, Fibrous, FF, NC	1 year	A greater increase in fibrous plaque volume was seen in the Lira+ vs. the Lira- group

*The mean or median values.

CCTA = coronary computed tomography angiography, TP = total plaque, NCP = noncalcified plaque, MP = mixed plaque, CP = calcified plaque, CAD = coronary artery disease, LAP = low attenuation plaque, HU = Hounsfield unit, HIV = human immunodeficiency virus, ART = antiretroviral therapy, LDL-C = low density lipoprotein cholesterol, MI = myocardial infarction, NC = necrotic core, FF = fibro-fatty, PPV = percent plaque volume, oxLDL = oxidized LDL, PAV = percentage atheroma volume, IPE = icosapent ethyl, ACS = acute coronary syndrome, EPA = epicosapentaenoic acid, DHA = docosahexaenoic acid, ASCVD = atherosclerotic cardiovascular disease, LRNC = lipid rich necrotic core, DM = diabetes mellitus, OMT = optimal medical therapy

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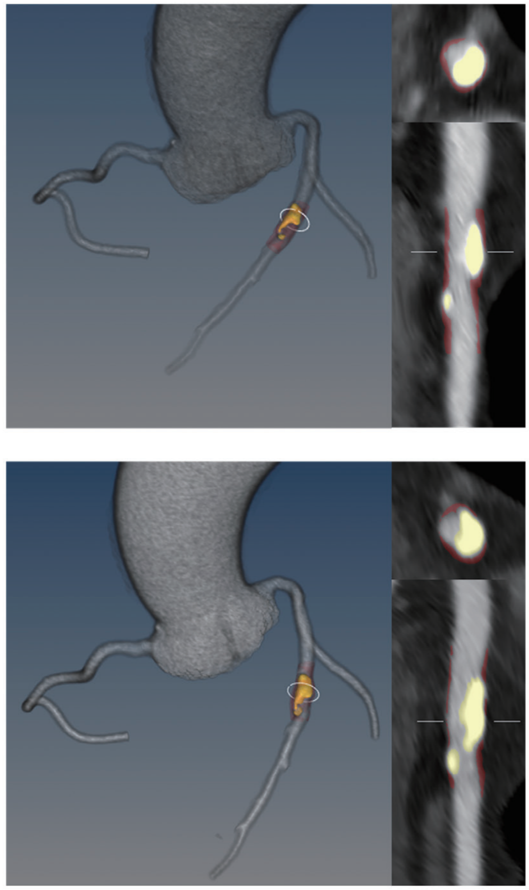

Baseline

Per-patient plaque analysis

Plaque volume (mm³)	
Total	134
CP	44
NCP	90
LD-NCP	7
Plaque burden (%)	
Total	48
CP	16
NCP	32
LD-NCP	2

Follow-up

Per-patient plaque analysis

Plaque volume (mm³)	
Total	119
CP	52
NCP	67
LD-NCP	1
Plaque burden (%)	
Total	42
CP	19
NCP	24
LD-NCP	0

Fig. 4. 3D rendered view of the coronary tree and quantitative plaque volume from a 64-year-old woman who was treated with high-intensity statins. The interscan interval is 2.3 years. CP increased (yellow overlay in 3D and 2D images), and noncalcified and LD-NCPs decreased (red overlay). Changes in plaque volume and burden are presented in tables. D = dimensional, CP = calcified plaque, LD-NCP = low-density NCP, NCP = noncalcified plaque

CAC score, as measured by serial CCTA scans. Elnabawi et al. [100] evaluated the changes in coronary artery plaques in psoriasis patients treated with biologic therapies, such as anti-tumor necrosis factor, anti-interleukin (IL) 12/23, and anti-IL 17. They observed a favorable modification, primarily a reduction in the NCP burden, without significant changes in calcified plaques. The study noted diminished inflammatory phenotypes, including fibrofatty plaques and necrotic cores, and biomarkers in patients with psoriasis receiving biological treatment. Furthermore, studies have explored the influence of drugs such as sarpogrelate [103], colchicine [105], aged garlic extract [106], and liraglutide [108] on modifications in plaque composition. These findings suggest that serial CCTA can be expanded to evaluate overall CVD risk assessment in patients with various conditions that may facilitate CVD progression and are at high risk for CVD.

Limitations and Barriers to Implementation

One challenge in implementing quantitative analysis in clinical practice is the time required for the analysis. Most methods are semi-automated and need human interaction to refine the detected vessel contours. Significant time investment is necessary when handling cases with high plaque burden and poor image quality. Consequently, much of this software has been primarily applied in research because its speed and labor-intensive nature are significant barriers to its clinical deployment. Recently, several AI-based CCTA PA software programs, which rapidly perform with minimal subjective adjustment, have been approved by the FDA for clinical use. Accelerating the speed of analysis and improving access to these software tools are essential factors in promoting their broader adoption in clinical practice.

Furthermore, despite validation using invasive imaging or expert manual measurements, each software platform may yield very different results for plaque volumes. Head-to-head comparisons of the latest technologies have yet to be conducted.

The quality of CT images, and consequently, the accuracy of quantitative plaque measurements, can be influenced by various factors, including CCTA and clinical parameters such as imaging protocol, contrast timing, scan parameters, reconstruction technique, temporal and spatial resolution, heart rhythm variability, and patient-specific factors [109-111]. Addressing these limitations requires the establishment of standardized imaging protocols, guidelines, and quality assurance measures to ensure the consistency and comparability of results in clinical practice and research involving CCTA. In addition, validating quantitative analysis software across multiple CT vendors and diverse patient cohorts, including populations with varying clinical and imaging characteristics, is essential to address validity concerns and enhance the reliability of the findings.

The principal limitation of the practical clinical use of various quantitative plaque measurements is that physicians do not yet know how to use these data to guide patient management. Some studies have attempted to establish a reference threshold for quantitative plaque volume based on CCTA. HeartFlow AI-PA recently established age- and sex-based nomograms for plaque volumes derived from a large cohort of 11808 patients who underwent clinically indicated CCTA [43]. A staging system was proposed for absolute total plaque volume and percentage atheroma volume based on lesions' anatomical and functional significance on invasive QCA and FFR [112]. Although plaque measurements have been shown to add predictive information regarding cardiac events, there currently needs to be a consensus on applying these findings to individual patient management. One straightforward application is the assessment of therapy effectiveness through consecutive measurements from serial CCTA studies. Nonetheless, as AI methods continue to improve the various software used for quantitative plaque measurement, these assessments will soon be widely used in the practical care of patients with coronary atherosclerosis.

CONCLUSION

The paradigm of CCTA image analysis has moved beyond the visual assessment of coronary artery stenosis to include the characteristics and quantitative analysis of coronary plaques. CCTA-derived plaque volume and composition measurements can now be efficiently performed using semi-automated software, demonstrating strong correlations with IVUS results. Quantitative analysis of coronary plaques improves subsequent cardiac event prediction and enables a more precise assessment of temporal plaque changes on serial imaging. Moreover, applying AI techniques such as deep learning will facilitate the complete automation of coronary plaque and stenosis quantification. Furthermore, there is the potential to identify new "high-risk" plaque phenotypes through ongoing software and AI advancements. Integrating quantitative PA with factors such as stenosis severity and high-risk plaque characteristics may contribute to a more comprehensive cardiovascular risk assessment in patients undergoing CCTA. However, for these analyses to be incorporated into clinical practice, conducting studies demonstrating how changes in plaque properties lead to improved outcomes is essential.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Donghee Han. Data curation: Su Nam Lee, Donghee Han. Formal analysis: Su Nam Lee, Donghee Han. Funding acquisition: Donghee Han, Damini Dey, Daniel S. Berman. Investigation: Su Nam Lee, Donghee Han. Methodology: Su Nam Lee, Andrew Lin. Project administration: Su Nam Lee, Donghee Han. Resources: Su Nam Lee, Andrew Lin, Donghee Han. Software: Andrew Lin, Damini Dey, Donghee Han. Supervision: Damini Dey, Daniel S. Berman. Validation: Andrew Lin, Damini Dey, Donghee Han. Visualization: Andrew Lin, Damini Dey, Donghee Han. Writing—original draft: Su Nam Lee, Donghee Han. Writing—review & editing: all authors.

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