

Clinical Relevance of Coronary Computed Tomography Angiography Beyond Coronary Artery Stenosis

Klinische Relevanz der CT-Angiographie der Koronargefäße jenseits der Koronararterienstenose

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ZUSAMMENFASSUNG

Hintergrund Die Möglichkeiten der CT-Angiographie der Koronargefäße (CCTA) haben sich in den letzten 10 Jahren erheblich weiterentwickelt. Ihre Fähigkeit, stenotische Koronararterien sicher und konsistent zu erkennen, hat zu einem deutlichen Rückgang der invasiven diagnostischen Angiografie geführt. Die CCTA kann jedoch viel mehr als nur Stenosen in den Koronararterien erkennen.

Methode In dieser Übersichtsarbeit werden Anwendungen der CCTA über die Beurteilung der Koronarstenose hinaus erörtert, wobei insbesondere die visuelle und quantitative Analyse von atherosklerotischen Plaques im Mittelpunkt steht.

Ergebnisse Zu den etablierten Zeichen einer visuell beurteilten Hochrisiko-Plaques in der CT gehören positives Remodeling, Plaques mit geringer Abschwächung, fleckige Verkalkung und das Napkin-Ring-Zeichen, die mit dem histologischen

Thin-Cap-Fibroatherom korrelieren. In jüngster Zeit hat die Quantifizierung von Plaques-Subtypen die Beurteilung von Koronarplaques im CT weiter verbessert. Quantitativ bewertete Plaques mit geringer Abschwächung, die mit dem nekrotischen Kern des Thin-Cap-Fibroatheroms korrelieren, haben bei der Vorhersage des nachfolgenden Myokardinfarkts eine Überlegenheit gegenüber dem Schweregrad der Stenose und dem koronaren Kalzium-Score gezeigt. Die aktuelle Forschung zielt darauf ab, radiomische und maschinelle Lernmethoden zu nutzen, um unser Verständnis der mittels CCTA identifizierten atherosklerotischen Hochrisiko-Plaques-Subtypen weiter zu verbessern.

Schlussfolgerung Trotz des schnellen technologischen Fortschritts auf dem Gebiet der Koronar-Computertomografie-Angiografie gibt es in der täglichen klinischen Praxis, wo der Einsatz häufig auf die Lumenografie beschränkt ist, noch einen erheblichen Rückstand. Wir fassen einige der vielversprechendsten Techniken zusammen, die das diagnostische und prognostische Potenzial der CCTA deutlich verbessern.

Kernaussagen:

- Neben der Fähigkeit, den Schweregrad von Luminalstenosen zu bestimmen, liefert die CCTA durch die Beurteilung atherosklerotischer Plaques wichtige prognostische Informationen.
- Einfache Scoring-Systeme wie der Segment-Involved-Score oder der CT-adaptierte Leaman-Score können im Vergleich zu herkömmlichen Risikofaktoren wie Bluthochdruck oder Diabetes mehr prognostische Informationen über schwerwiegende unerwünschte koronare Ereignisse liefern.
- CT-Zeichen einer Hochrisiko-Plaques, einschließlich positiver Remodelierung, Plaques mit geringer Abschwächung, fleckiger Verkalkung und dem Napkin-Ring-Zeichen, sagen signifikant häufiger akute Koronarsyndrome voraus.
- Die quantitative Plaques-Bewertung kann eine präzisere Beschreibung des Volumens und der Belastung der Plaques-Subtypen liefern, und es wurde festgestellt, dass sie einen nachfolgenden Myokardinfarkt besser vorhersagen kann als kardiovaskuläre Risiko-Scores, Kalzium-Scoring und der Schweregrad der Koronararterienstenosen.
- Machine Learning hat das Potenzial, die Risikostratifizierung zu automatisieren und die Gesundheitsökonomie zu verbessern, auch wenn die derzeitigen klinischen Anwendungen begrenzt sind. In dieser Zeit der „Big Data“ sind sie ein aufregender Weg für die zukünftige Forschung.

ABSTRACT

Background The capabilities of coronary computed tomography angiography (CCTA) have advanced significantly in the past decade. Its capacity to detect stenotic coronary arteries safely and consistently has led to a marked decline in invasive diagnostic angiography. However, CCTA can do much more than identify coronary artery stenoses.

Method This review discusses applications of CCTA beyond coronary stenosis assessment, focusing in particular on the visual and quantitative analysis of atherosclerotic plaque.

Results Established signs of visually assessed high-risk plaque on CT include positive remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign, which correlate with the histological thin-cap fibroatheroma. Recently, quantification of plaque subtypes has further improved the assessment of coronary plaque on CT. Quantitatively assessed low-attenuation plaque, which correlates with the necrotic core of the thin-cap fibroatheroma, has demonstrated superiority over stenosis severity and coronary calcium score in predicting subsequent myocardial infarction. Current research aims to use radiomic and machine learning methods to further improve our understanding of high-risk atherosclerotic plaque subtypes identified on CCTA.

Conclusion Despite rapid technological advances in the field of coronary computed tomography angiography, there remains a significant lag in routine clinical practice where use is often limited to lumenography. We summarize some of the most promising techniques that significantly improve the diagnostic and prognostic potential of CCTA.

Key Points:

- In addition to its ability to determine severity of luminal stenoses, CCTA provides important prognostic information by evaluating atherosclerotic plaque.
- Simple scoring systems such as the segment involved score or the CT-adapted Leaman score can provide more prognostic information on major adverse coronary events compared to traditional risk factors such as presence of hypertension or diabetes.
- CT signs of high-risk plaque, including positive remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign, are significantly more likely to predict acute coronary syndromes.
- Quantitative plaque assessment can provide precise description of volume and burden of plaque subtypes and have been found to predict subsequent myocardial infarction better than cardiovascular risk scores, calcium scoring and severity of coronary artery stenoses.
- Machine learning techniques have the potential to automate risk stratification and enhance health economy, even though present clinical applications are limited. In this era of “big data” they are an exciting avenue for future research.

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Introduction

In 1979, Godfrey Hounsfield and Allan Cormack were awarded the Nobel Prize in Physiology and Medicine for the development of computer-assisted tomography. In his Nobel Prize acceptance speech, Godfrey Hounsfield said “*A further promising field may be the detection of the coronary arteries*” [1]. In the years that followed, the challenge of capturing the beating heart has driven innovation in the field at a remarkable pace. As life expectancy throughout the world has risen, the global burden of cardiovascular disease has followed suit [2]. It is therefore fitting that coronary computed tomography angiography (CCTA) should advance to face it.

Despite many advances in the field, clinicians often focus on the ability of CCTA to predict the severity of coronary artery stenosis, perhaps oblivious to its full potential. The totality of CCTA’s capabilities is too numerous to adequately discuss in a single review. Computational fluid dynamic algorithms enable a functional assessment of stenotic lesions, with the potential to reduce unnecessary invasive angiography [3]. Mapping changes in perivascular fat attenuation has the potential to enhance cardiac risk prediction and change how we target the prescribing of preventative therapies [4]. In this review, we will focus on the ways in which CCTA can evaluate atherosclerotic plaque to

provide clinically relevant information, over and above simply answering the question “how narrow is that blood vessel?”

Basic visual assessment of plaque

Early angiographic studies demonstrated that culprit lesions in myocardial infarction were not always associated with severe stenosis [5]. Visual assessment of the coronary arteries, therefore, requires more than just an assessment of the severity of stenosis. Atherosclerosis describes the process of plaque deposition which is an immune-mediated inflammatory process, exacerbated by metabolic risk factors [6]. Plaques likely to rupture are characterized by inflamed and attenuated fibrous caps covering large and necrotic lipid cores [7, 8]. As such, along with describing the distribution of disease, a central goal of basic visual assessment is to determine the composition of the coronary plaque, as this contributes to plaque vulnerability.

On CCTA, atherosclerotic plaques can be classified as calcified, non-calcified, or mixed plaques. While calcified plaque has always been easy to detect, detecting non-calcified plaque accurately has only been possible in the era of multi-slice CT scanning [9, 10]. Kopp et al. were the first to demonstrate the ability of CT to noninvasively characterize lesion morphology and composition

[11]. Multiple studies have since demonstrated the excellent correlation between CT attenuation density and plaque characterization as determined by intravascular ultrasound [12, 13]. Culprit lesions in acute coronary syndromes are more likely to be non-calcified than calcified [14]. There are also interesting sex-based differences in plaque type with women having more non-calcified plaques and men having more calcified plaques [15, 16]. However, the prognostic implications of basic plaque classification are less certain. In 458 patients presenting with acute chest pain but without an acute coronary syndrome, Nance et al. found that the occurrence of MACE (major adverse cardiovascular events) at 13 months was higher in those with mixed plaques rather than non-calcified or calcified plaques [17]. However, in 1584 stable patients undergoing CCTA for suspected coronary artery disease, Hadamitzky et al. found that plaque classification as non-calcified, calcified, or mixed did not improve risk stratification over assessment of stenosis severity [18]. One of the important limiting factors of this form of plaque assessment is that observer variability for visual plaque analysis has been shown to be poor [19]. Moreover, this basic assessment does not allow for quantification of the extent of disease.

Semiquantitative assessment of plaque burden

A distinct advantage of CCTA over other noninvasive imaging modalities is the ability to derive a measure of atherosclerotic burden throughout the coronary tree. This is particularly important as Maddox et al. found that those with multi-vessel nonobstructive disease have a similar prognosis to those with single vessel obstructive disease [20]. A variety of semi-quantitative scores have been proposed which aim to summarize the results of CCTA into a single metric that communicates plaque burden (► **Table 1**) [21].

The “Segment Involved Score” (SIS) is a semi-quantitative measure of the extent of coronary artery disease throughout the coronary tree. In the SIS, segments are scored 0 or 1 based on the presence or absence of plaque, irrespective of the degree of stenosis. Meta-analyses have established extent of disease as determined by the SIS is a strong and independent predictor of cardiovascular mortality [22]. Moreover, recent results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry suggest that an SIS > 5 provides more prognostic information for MACE than traditional cardiovascular risk factors such as hypertension or diabetes [23]. Despite this, the SIS is limited due to the lack of consideration given to stenosis severity. Recently, more comprehensive scores such as the CT-adapted Leaman score have been shown to improve prognostic stratification. In accounting for lesion locale, plaque composition, and degree of stenosis, the CT-adapted Leaman score performs considerably better than SIS [24]. However, these scores do not account for more advanced visual assessment of high-risk plaque and only provide an estimate of plaque burden rather than true quantification.

Visual assessment of high-risk plaque

While the extent of disease and severity of stenosis are undoubtedly important, they do not provide any information on the vulnerability of a plaque to rupture. Autopsy studies have established the thin cap fibroatheroma as the histological precursor of plaque rupture [25]. CCTA correlates of the thin-cap fibroatheroma include positive remodeling (a positive change in vessel diameter at the plaque site compared to a normal-appearing proximal segment), low attenuation plaque (< 30 Hounsfield units), spotty calcification (calcification < 3 mm in size) and the “napkin-ring sign” (► **Fig. 1**). These have been established by correlating CCTA findings to intravascular ultrasound (IVUS) and optical coherence tomography (OCT) findings [26, 27]. Early work by Motoyama et al. demonstrated the significant association of positive remodeling, low attenuation plaque, and spotty calcification with plaque rupture events in patients who had suffered an acute coronary syndrome [28]. Moreover, in their follow-up study, they demonstrated that positively remodeled segments with low-attenuation plaque were significantly more likely to result in acute coronary syndromes [29, 30]. As an individual plaque feature, the “napkin-ring sign” correlates with histological findings of central necrotic lipid cores surrounded by fibrous tissue [31] and demonstrated excellent specificity in identifying advanced lesions [32].

Several studies have subsequently built on these findings (► **Table 2**). The ICONIC (Incident COroNary Syndromes Identified by Computed tomography) case-control sub-study of the CONFIRM registry found that high-risk plaque features predict future acute coronary syndromes independent of, and better than, atherosclerotic plaque burden and the number of obstructed vessels [33]. The ROMICAT-2 (Rule Out Myocardial Infarction using Computer-Assisted Tomography) trial found in troponin- and electrocardiogram-negative patients presenting with chest pain to the emergency department, the presence of high-risk plaque on CCTA increased the likelihood of myocardial infarction independent of clinical risk assessment and extent of coronary disease [34]. In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, of the 4415 patients with stable chest pain who underwent CCTA, 15% had high-risk plaques [35]. Patients with high-risk plaques had an increased risk of MACE (hazard ratio 2.73, 95% confidence interval, 1.89 to 3.93), which was independent of cardiovascular risk score and the presence of significant stenosis. Interestingly, the presence of high-risk plaque was a more important predictor of events in women and younger patients. In a prospective cohort study of 1469 patients, Feuchter et al. found that the strongest predictors of cardiovascular events over an 8-year period were low-attenuation plaque and the napkin-ring sign [36]. Together these studies show that high-risk plaque features provide important prognostic information, over and above traditional assessments, and they are now part of the Society of Cardiovascular Computed Tomography CAD-RADS reporting guidelines [37].

However, the inter-observer variability for the identification of high-risk plaque features has been shown to be only fair, which limits their use in clinical practice [19]. In the Scottish Computed Tomography of the HEART (SCOT-HEART) trial, patients with posi-

► **Table 1** Comparison of semiquantitative score progression.

► **Tab. 1** Vergleich des semiquantitativen Score-Verlaufs.

Score	Explanation	Sample case: patient with one 70 % lesion in the left main stem
Coronary Artery Disease – Reporting and Data System (CADS-RADS)	score 0–5 depending on the severity of the worst stenosis: <ul style="list-style-type: none"> ▪ 0–0 %, no CAD ▪ 1–1–24 %, minimal non-obstructive ▪ 2–25–49 %, mild non-obstructive ▪ 3–50–69 %, moderate stenosis ▪ 4–70–99 %, severe stenosis <ul style="list-style-type: none"> – A – > 50 % LMS – B – 3-vessel ≥ 70 % ▪ 5–100 %, total coronary occlusion 	CAD-RADS Score: 4
Segment Involved Score (SIS)	score depending on the absolute number of segments with any disease based on the 17-segment coronary tree model. <ul style="list-style-type: none"> ▪ 0 – no coronary artery disease ▪ 1 – coronary plaque present ▪ continuous score, range: 0–16 	SIS Score: 1
Segment Stenosis Score (SSS)	score depending on severity of stenosis in each segment based on the 17-segment coronary tree model. <ul style="list-style-type: none"> ▪ 0 – no coronary artery disease ▪ 1 – mild plaque ▪ 2 – moderate plaque ▪ 3 – severe plaque ▪ continuous score, range: 0–48 	SSS Score: 3
CT-adapted Leaman Score (CT-LeSc)	weighted score based on: <ol style="list-style-type: none"> 1. location of coronary plaque <ul style="list-style-type: none"> ▪ 5.0–6.0 for LMS depending on dominance ▪ 1.0–3.5 for LAD segments and branches depending on dominance ▪ 0.5–2.5 for LCx segments depending on dominance ▪ 0.5–1.0 for RCA segments depending on dominance 2. severity of stenosis <ul style="list-style-type: none"> ▪ multiply score by 1 for obstructive ▪ multiply score by 0.615 for non-obstructive 3. coronary plaque composition <ul style="list-style-type: none"> ▪ multiple score by 1.5 for non-calcified or mixed plaque ▪ multiple score by 1.0 for calcified plaque 	CT-LeSc Score if right dominant: <ul style="list-style-type: none"> ▪ 5 if calcified ▪ 7.5 if non-calcified CT-LeSc Score of left dominant: <ul style="list-style-type: none"> ▪ 6 if calcified ▪ 9 if non-calcified

CAD- coronary artery disease, LMS- left main stem, LAD- left anterior descending artery, LCx- left circumflex artery, RCA- right coronary artery.

tive remodeling or visually assessed low-attenuation plaque had a three-fold increase in the rate of fatal or non-fatal myocardial infarction (hazard ratio 3.01, 95 % confidence interval 1.61 to 5.63, $p = 0.001$). [38] However, this was not independent of the coronary artery calcium score, a surrogate marker of the overall plaque burden. It is likely that these high-risk plaque features are of particular importance early on after imaging, but they continue to evolve and potentially stabilize with time. In addition, these high-risk plaques are common on CCTA, occurring in 15 % to 50 % of patients depending on their presenting symptoms [33, 35, 38]. Thus, the presence of visually assessed high-risk plaque can be used to identify patients at an increased risk of myocardial infarction, but not all patients with high-risk plaque will undergo myocardial infarction.

Quantitative plaque assessment

While semi-quantitative scores provide important prognostic information, they remain a surrogate for actual measurements of plaque volume and burden. With advances in computing technology, we are now able to quantitatively assess plaque subtypes on CCTA based on their attenuation density. Total plaque volume can be measured as well as plaque subtypes including calcified and noncalcified (fibrous, fibrofatty, and necrotic or low-attenuation) plaque. This technology could be used to identify patients with an increased plaque burden or an increased burden of particular high-risk plaque subtypes (► **Fig. 2**). In addition, assessing the progression of plaque subtypes in such detail can facilitate our understanding of the impact of medications on the atherosclerotic process.

Early iterations of plaque quantification software were time-consuming, manual processes that could not differentiate

► **Table 2** Key studies assessing quantitative and qualitative plaque on CCTA.

► **Tab. 2** Wichtige Studien zur Bewertung der quantitativen und qualitativen Plaque mit CCTA.

Visual assessment of high-risk plaques		Quantitative assessment of plaque	
Author, date	Findings	Author, date	Findings
Motoyama et al., 2007 [29]	HRP is an independent predictor of acute coronary syndrome	ROMICAT, 2012 [43]	ACS patients have a higher volume of plaque with low CT density (<90 HU)
ROMICAT-2, 2014 [33]	HRP in troponin-negative and ECG-indeterminate patients with chest pain increased the likelihood of MI independent of clinical risk assessment and atherosclerotic plaque burden	ROMICAT II, 2015 [44]	ACS patients have a higher volume of plaque with a low CT density (<30HU and <60 HU)
Motoyama et al., 2015 [56]	HRP is an independent predictor of acute coronary syndrome at 4 years. Plaque progression by serial CCTA is an independent predictor of acute coronary syndrome	Nadjiri et al., 2016 [47]	non-calcified plaque volume and low-attenuation plaque volume are predictive of MACE at 5 years
Feuchtner et al., 2016 [35]	High-risk low-attenuation plaque and the napkin-ring sign are the most powerful predictors of MACE over long-term follow-up (8 years)	ICONIC, 2018 [32]	cross-sectional plaque burden, fibro-fatty and necrotic core volumes were higher in ACS patients than controls. All three were significant predictors of ACS
PROMISE, 2018 [34]	HRP is associated with an increased risk of MACE after adjustment for cardiovascular risk and presence of significant stenoses	PARADIGM, 2018 [49]	progression of atherosclerosis is slowed by statin therapy. Females are more responsive to statin compared to men
ICONIC, 2018 [32]	HRP predicted future ACS independent of and better than number of obstructive vessels and atherosclerotic plaque burden	de Knecht, 2019 [45]	ACS patients have a higher plaque volume, with more fibro-fatty plaque and less densely calcified plaque
SCOT-HEART, 2019 [37]	HRP is associated with a worse prognosis but not independent of coronary calcium score	SCOT-HEART, 2020 [48]	low-attenuation plaque burden is the strongest predictor of fatal or non-fatal myocardial infarction

ACS, acute coronary syndrome; ECG, electrocardiogram; HRP, high-risk plaque; MACE, major adverse cardiovascular event; MI, myocardial infarction.

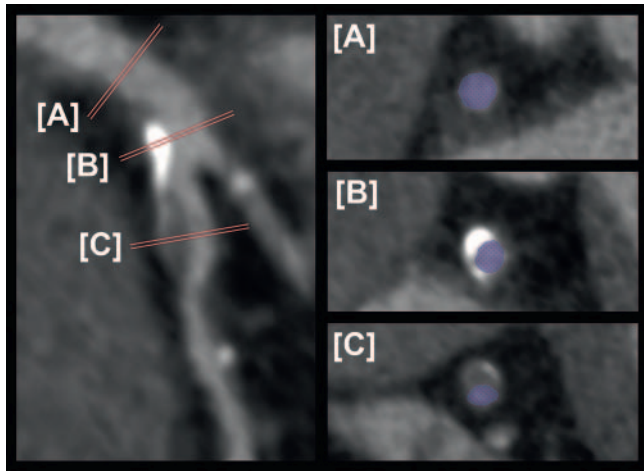
between low-attenuation and non-calcified plaques [39]. Accordingly, semi-automated software has now been developed that significantly reduces the time needed to quantify plaque burden. The software demonstrates improved repeatability and reproducibility over manual quantification, especially in patients with low to intermediate disease burden [40, 41]. Moreover, improved algorithms allow for more a precise description of low-attenuation plaque burden which correlated better with intravascular ultrasound [42, 43]. These advances have streamlined our ability to measure plaque burden and progression on serial imaging.

In patients with acute chest pain, the ROMICAT [44] and ROMICAT II [45] studies found that patients with acute coronary syndromes had a larger volume of plaque with a low attenuation density. De Knecht et al. showed that compared to asymptomatic patients and patients with acute chest pain without acute coronary syndrome, patients with acute coronary syndromes had a higher total plaque volume and volume of fibrofatty and necrotic core plaque, but a lower volume of densely calcified plaque [46]. These studies highlight the differences in plaque subtypes found in patients with different clinical presentations.

Several studies have established the particular importance of low-attenuation plaque, associated with the necrotic core of the thin-cap fibroatheroma. In the ICONIC sub-study of the CONFIRM

trial, increased cross-sectional plaque burden, fibrofatty plaque volume, and necrotic core volume were all associated with increased risk of subsequent acute coronary syndrome in 234 patients with acute coronary syndrome compared to matched control pairs [33]. Interestingly, they found that there were no sex-based differences in calcified plaque volume, but women had lower fibrous and fibrofatty plaque volume compared to men [47]. Nadjiri et al. found that in 1168 patients undergoing CCTA for suspected coronary artery disease the volume of non-calcified plaque and low-attenuation plaque was higher in patients that experienced MACE during 5 years of follow-up [48].

Recently, a post hoc analysis of the SCOT-HEART trial showed the primacy of low-attenuation plaque burden in the prediction of future fatal or non-fatal myocardial infarction [49]. The total plaque burden and the burden of all sub-types of plaque were higher in patients who suffered subsequent myocardial infarction after 4.7 years of follow-up. Low-attenuation plaque burden was the strongest predictor of subsequent myocardial infarction (adjusted hazard ratio per doubling 1.60, 95% confidence interval 1.10 to 2.34, $p = 0.014$), over and above the cardiovascular risk score, coronary artery calcium score, and coronary artery stenoses. Patients with a low-attenuation plaque burden above 4% were at a particularly high risk for subsequent myocardial infarction.



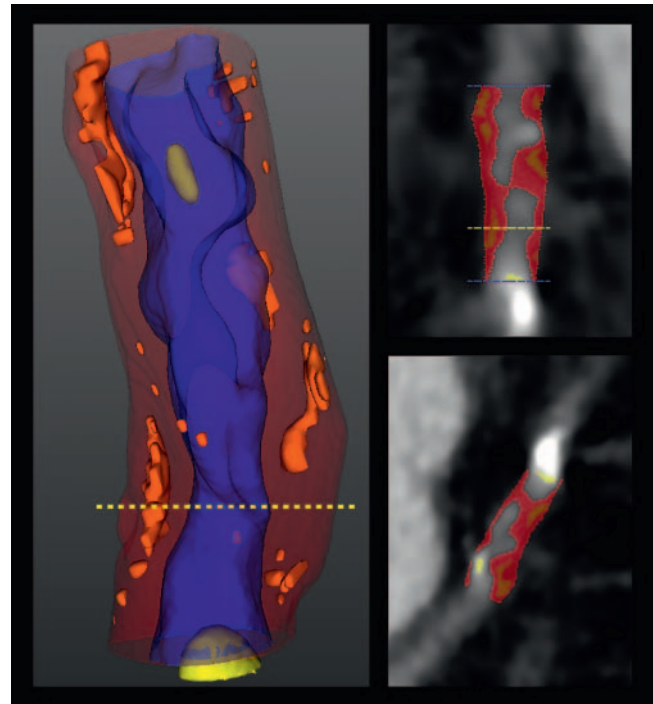
► **Fig. 1** CT coronary angiogram of diseased coronary artery, lumen highlighted in blue. **A** Normal proximal left main stem measuring 5.1 mm × 5.4 mm. **B** Calcified lesion distal to the left main stem, positively remodeled, measuring 6.5 mm × 5.8 mm. **C** High-risk plaque (napkin-ring sign) in the proximal left anterior descending artery, vessel measuring 6.2 mm × 5.7 mm.

► **Abb. 1** CT-Koronarangiogramm einer erkrankten Koronararterie, Lumen blau hervorgehoben. **A** Normaler proximaler linker Hauptstamm mit den Abmessungen 5,1 mm × 5,4 mm. **B** Verkalkte Läsion distal des linken Hauptstamms, positiv remodeliert, mit Abmessungen von 6,5 mm × 5,8 mm. **C** Hoch-Risiko-Plaques (Serviettenring-Zeichen) in der proximalen linken anterioren absteigenden Arterie, Gefäßgröße 6,2 mm × 5,7 mm.

tion (hazard ratio 4.65, 95% confidence interval 2.06 to 10.5, $p < 0.001$). Thus, in patients presenting with stable chest pain, quantitative plaque burden provides better prognostic information than classic markers of cardiovascular risk.

The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography) trial was a large, prospective, observational study that evaluated temporal changes in plaque characteristics utilizing semi-automated plaque quantification software [50]. This trial demonstrated that statins not only resulted in slower rates of progression of non-calcified plaque volume, but also reduced the risk of positive remodeling and high-risk plaque formation. Importantly, they were able to quantitatively assess the impact of statins on the whole coronary tree. Progression of subclinical atherosclerosis was slowed in vessels beyond the proximal segments that are usually assessed by intravascular ultrasound [50]. The authors were also able to describe sex-based differences in plaque composition (high-risk plaque was more common in men than women) and plaque progression (female sex was associated with greater progression of calcified plaque and reduced progression of non-calcified plaque) [51].

Together these studies show the power of quantitative plaque assessment in identifying patients at risk for subsequent cardiac events and the impact of medications on plaque progression. However, as the quantification of plaque is based on CT attenuation density, it is limited by scan image quality, including motion artifacts, image noise, and stair-step artifacts. Its use in advanced,



► **Fig. 2** Quantitative plaque assessment (Autoplaque, Los Angeles, US) of a stenotic mid left anterior descending artery. Blue represents the lumen, calcified plaque volume (highlighted in yellow) 3.0 mm³, non-calcified plaque volume (highlighted in red) 154.3 mm³, low attenuation plaque volume (highlighted in orange) 8.0 mm³.

► **Abb. 2** Quantitative Plaque-Bewertung (Autoplaque, Los Angeles, US) einer stenotischen mittleren linken anterioren absteigenden Arterie. Blau repräsentiert das Lumen, verkalktes Plaquevolumen (gelb hervorgehoben) 3,0 mm³, nicht verkalktes Plaque-Volumen (rot hervorgehoben) 154,3 mm³, gering verkalktes Plaque-Volumen (orange hervorgehoben) 8,0 mm³.

calcific disease and the primary prevention populations have yet to be evaluated. Although plaque quantification does not require new hardware or special scanning techniques, dedicated software is required, and individual readers require training to be able to adjust vessel and plaque contours if required. At present, quantitative plaque analysis remains a valuable research technique. Current research studies have shown that quantitative plaque assessment can be used as an endpoint in drug trials. Future research studies will assess whether management based on quantitative plaque analysis can improve outcomes.

Functional assessment of coronary stenosis – Computed Tomography Fractional Flow Reserve

A common criticism of coronary assessments made by CCTA is the lack of associated functional information. When this is combined with the tendency to overestimate the severity of calcified lesions, patients may require more “downstream” noninvasive imaging to clarify the significance of a particular lesion on CCTA [52]. Frac-

tional flow reserve (FFR) measures the change in pressure across a coronary lesion under pharmacological stress using specially designed pressure-sensitive wires. Multiple randomized controlled trials have demonstrated that when such physiological measurements are used to guide coronary revascularization, outcomes are improved and unnecessary coronary interventions are reduced [53, 54].

CTFFR (computed tomography fractional flow reserve) utilizes computational fluid dynamics and models physiological conditions of hyperemia to produce an estimate of the invasive FFR. The diagnostic accuracy of these calculations was directly confirmed in several trials, where CTFFR results were compared directly to invasive FFR [55, 56]. Correlation between both were good, and moreover the diagnostic accuracy of CTFFR was significantly better than with CCTA alone for the identification of hemodynamically significant lesions. The PLATFORM study (Prospective Longitudinal Trial of FFRct: Outcome and Resource Impacts) went on to demonstrate a 61% reduction in non-obstructive coronary arteries on invasive angiography and a significant reduction in costs compared to usual care with equivalent clinical outcomes [3]. The advantages of CTFFR over other noninvasive tests are clear, in that it provides anatomical and functional information, without the requirement to perform additional imaging or radiation exposure. However, at present its use remains limited due to the need for careful selection on the basis that image quality can greatly affect the reliability of results [57].

Future developments – Radiomics & machine learning

Fundamentally, radiological images are large 3-dimensional vaults of data, with each voxel representing unique tissue-dependent measurements. As we image structures with higher resolution, these datasets have grown exponentially in size, providing us with ever increasing quantities of information. Radiomics aims to extract further information from these datasets by using mathematical techniques to extract higher dimension data such as spatial interrelationships and textural information. Machine learning, a branch of artificial intelligence, can be used to mine these datasets to identify radiomic patterns associated with an increased risk of cardiac events. Kolossvary et al. showed that radiomic features can identify high-risk plaques with good diagnostic accuracy compared to IVUS and 18F-sodium fluoride PET, better than visual assessment alone [58].

There are numerous applications of both supervised and unsupervised machine learning in CCTA, including the identification and quantification of atherosclerotic plaque. The identification of calcified plaque on CT using deep learning has been widely studied, particularly on non-contrast images, but the automatic identification of non-calcified and high-risk plaque subtypes is more challenging [59]. Recently, a deep learning algorithm that identified CCTA without calcification has been proposed as a method to help prioritize work lists [60]. Further advancements in machine learning to automate plaque analysis will reduce the time to perform this analysis and increase its application in clinical practice.

Machine learning techniques can also be used to analyze the complex interactions between multiple parameters in large datasets. For example, when machine learning was used to combined clinical and CCTA data from the CONFIRM registry, it performed significantly better than clinical risk scores (Framingham) and CCTA severity scores (SIS and SSS) at predicting all-cause mortality ($p < 0.001$ for all) [61]. In another example, machine learning was used to integrate quantitative CCTA plaque metrics including plaque measurements, diameter stenosis, and contrast density difference (maximal difference in luminal attenuation per unit area) and was shown to be better at predicting ischemia by FFR over any individual measure [62].

The potential applications of machine learning include precision diagnostics, automated risk stratification and enhanced health economy, thus reducing healthcare costs by saving clinicians valuable time. At present, the clinical applications are limited, but machine learning is an exciting avenue for future research and is likely to become an integral part of clinical practice over the coming decades.

Conclusion

The technological advances both in how we acquire and how we interpret CCTA images have undergone rapid and sustained innovation, particularly in the last decade. However, there is a considerable lag in routine clinical practice for CCTA which remains largely based on lumenogram. While stenosis severity is one important variable, this review highlights the critical importance of quantifying and classifying coronary artery plaque to substantially improve the diagnostic and prognostic potential of CCTA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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