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Computed Tomography Angiography From Clinical Uses to Emerging Technologies: JACC State-of-the-Art Review

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Abstract

Evaluation of coronary artery disease (CAD) using coronary computed tomography angiography (CCTA) has seen a paradigm shift in the last decade. Evidence increasingly supports the clinical utility of CCTA across various stages of CAD, from detection of early subclinical disease to the assessment of acute chest pain. Additionally, CCTA can be used to non-invasively quantify plaque burden and identify high-risk plaque, aiding in diagnosis, prognosis, and treatment. This is especially important in the evaluation of CAD in immune-driven conditions with increased cardiovascular disease prevalence. Emerging applications of CCTA based on hemodynamic indices and plaque characterization may provide personalized risk assessment, impact disease

detection, and further guide therapy. This review provides an update on the evidence, clinical applications, and emerging technologies surrounding CCTA as highlighted at the 2019 National Heart, Lung and Blood Institute CCTA Summit.

Condensed Abstract

Coronary computed tomography angiography (CCTA) can be utilized across various stages of coronary artery disease (CAD), from detection of early subclinical disease to the assessment of acute chest pain. The ability to identify high-risk plaque and quantify plaque burden positions CCTA as a unique tool for non-invasive risk stratification and treatment planning. Emerging applications of CCTA based on hemodynamic indices and plaque characterization may provide personalized risk assessment in order to further guide treatment. With more widespread availability, utilization, and further studies, CCTA may improve patient outcomes as well as our understanding of atherosclerosis and its progression.

Keywords

coronary computed tomography angiography; coronary artery disease; atherosclerosis

Introduction

Coronary computed tomography angiography (CCTA) is an effective imaging modality increasingly accepted as a first line test to diagnose coronary artery disease (CAD), and has prognostic implications for patient management (1,2). Furthermore, CCTA can be leveraged to image various stages of atherosclerosis ranging from plaque formation to plaque progression and rupture. Innovative tools derived from CCTA permit understanding of the development of atherosclerotic plaque and aid in risk stratification and medical decision-making for patients with CAD. Advancements in CCTA have allowed for minimal radiation exposure, effective coronary characterization, and detailed imaging of atherosclerosis over time. Thus, CCTA provides a central platform for a multidisciplinary approach, including immunology, pathology, radiology, and cardiology to further our understanding of CAD and to improve patient care.

In November 2019, a summit held at the National Heart, Lung and Blood Institute convened world experts on CCTA to discuss the latest developments in the field, synthesize the available evidence, and to discuss the evolving clinical applications of CCTA. In this review, we highlight the discussions put forth in this symposium, including the current understanding of atherosclerotic plaque pathology and its translation to CCTA in clinical practice. Further described are approaches to how CCTA can be utilized to characterize coronary artery plaque composition and morphology and to prognosticate cardiovascular outcomes. Finally, emerging CCTA technologies concomitant with advances in imaging acquisition, advanced techniques for analysis and characterization, and computational fluid dynamics are reviewed.

Atherosclerosis: From Plaque Pathology to CCTA

Prior to exploring the applications of CCTA, it is vital to consider the pathological basis of CAD, which CCTA seeks to detect and characterize. Atherosclerosis, a multifactorial systemic disease, is most often found at vessel branch points and areas of low shear stress that slowly evolve over time (3). Atherosclerotic lesions can be divided into early non-atherosclerotic intimal lesions including intimal thickening and xanthoma, which further progress into increasingly vulnerable and rupture-prone lesions beginning with pathological intimal thickening and leading to fibroatheroma and thin-cap fibroatheroma (Figure 1) (4). These lesions may give rise to acute thrombosis in the coronary artery, most commonly via plaque rupture, but additionally through plaque erosion and plaque fissure (5). Furthermore, as atherosclerotic lesions progress, neovascularization occurs, and histopathologic examination demonstrates increased vasa vasorum as well as macrophage and T-lymphocyte infiltration concurrent with increasing vessel stenosis and necrotic core area, demonstrating the key role of immune cells in plaque progression (5).

Intraplaque hemorrhage (IPH) is a plaque lesion most often seen in plaque rupture as compared to plaque erosion and stable CAD. Further, intraplaque hemorrhage contains high amounts of cholesterol clefts, macrophages, and an enlarging necrotic core, potentially increasing plaque vulnerability (6). However, vulnerable lesions tend to evolve over time and can transform to non-vulnerable lesions (7). An understanding of the histopathology of unstable lesions including IPH, neovascularization, and recurrent plaque healing and rupture may partially explain the rapid progression of a lesion that occurs prior to plaque rupture leading to acute coronary syndrome (ACS) (8,9).

Calcification in CAD is associated with plaque progression and can be visualized by CCTA and non-contrast computed tomography (CT) in the form of calcium scoring (10). Calcified coronary plaque can be seen histopathologically across atherosclerotic lesions beginning with early intimal microcalcifications, which progress to punctate and fragmented calcifications of fibroatheroma, followed by sheet calcium and calcified nodules (11). The progression of these calcium morphologies can be matched between histology and CCTA and may play a role in prognosis and risk stratification of rupture-prone plaques. For example, spotty calcifications on CCTA corresponding to speckled and fragmented calcification on histopathology import a greater risk of plaque rupture when compared to dense calcification such as diffuse calcium or calcium sheets (11). Further, in a recent case-control study, high density calcifications in the form of “1K” plaque, or plaque having greater than 1000 Hounsfield units (HU) on CCTA, were associated with lower risk for future ACS, suggesting that measurement of 1K plaque may improve risk stratification (12).

In addition to CCTA, histopathologic features of coronary atherosclerosis can be represented using other imaging techniques including intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near infra-red spectroscopy (NIRS). For example, quantitative analysis using IVUS and NIRS has been used to identify plaque characteristics such as the lipid-rich necrotic core (13). This “virtual histology” characterization of plaque features has been applied to CCTA and validated against histopathology as well as IVUS (14–17). However, the limited spatial and temporal resolution of CCTA have historically restricted its

ability to differentiate plaque subtypes and detect plaque rupture when compared to OCT and IVUS (17,18). Additionally, calcifications can appear falsely enlarged on CCTA and result in overestimation of stenosis due to blooming and partial volume artifacts (19). Various reports have demonstrated mixed results showing underestimation or overestimation of lumen area by CCTA when compared to IVUS (14,20,21).

These historical limitations of CCTA plaque characterization are being potentially challenged with emerging technologies to achieve tissue characterization performance comparable to catheter-based methods by patient-specific image restoration, mitigation of calcium blooming, and machine intelligence for comprehensive plaque characterization (22).

CCTA in Clinical Practice

CCTA utilization has increased in recent years in the United States (US) and around the world, driven in part by increasingly strong outcome data and similar or lower cost when compared with functional testing (23,24). Nevertheless, CCTA utilization in the US has lagged compared to Europe due to guidelines that do not yet reflect this evidence, reimbursement that does not match the resources required, and need for improved education (25). In contrast to the US, the 2016 United Kingdom National Institute for Health and Care Excellence (NICE) guidelines and 2019 European Society of Cardiology (ESC) guidelines have incorporated CCTA as a first line modality for the evaluation of chest pain patients and chronic coronary syndromes respectively (1,2).

The uses of CCTA in the United States span several settings, from evaluation of suspected ACS in the emergency setting, planning prior to cardiac surgery, to follow up of ischemic functional tests and preceding lower probability catheterization cases. CCTA can also be useful as part of cardiac evaluation prior to liver transplantation (26–28). However, in other countries such as the United Kingdom, CCTA is used to assess all patients with stable chest pain, irrespective of the pre-test probability; particularly since multiple studies have shown that the pre-test probability of obstructive CAD is often overestimated (2). This clinical utility is driven by the strong ability of CCTA to effectively rule out CAD given its high negative predictive value (e.g. >95%), which makes the modality especially useful in patients with low to intermediate risk of CAD (29–32).

CCTA may be a better predictor of obstructive CAD compared to traditional functional testing, which has been shown to be a poor predictor of obstructive CAD (33). In the Evaluation of Integrated Cardiac Imaging in Ischemic Heart Disease (EVINCI) study, a prospective study of patients with stable chest pain comparing CCTA and several function tests including single photon emission computed tomography (SPECT), positive emission tomography (PET), echocardiography and cardiac magnetic resonance (CMR), CCTA was shown to be the most accurate non-invasive imaging modality for detection of significant CAD (34).Both the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and the Scottish COmputed Tomography of the HEART Trial (SCOT-HEART) randomized controlled trials demonstrated the prognostic value and robust cardiovascular event prediction of CCTA compared to functional testing and standard care, respectively, in the setting of stable chest pain(35,36). Furthermore, five-year follow-up of the SCOT-

HEART trial demonstrated that a CCTA-first strategy significantly reduced the occurrence of myocardial infarction (MI) and coronary heart disease death without increasing invasive testing compared to standard care, although a CCTA-first strategy did not improve clinical outcomes compared to functional testing in the PROMISE trial (37,38). The prognostic superiority of CCTA in the PROMISE trial was even more pronounced in subgroup analysis of type 2 diabetes mellitus patients, further highlighting the role of CCTA as an initial diagnostic test in this population, although more prospective trials are needed to validate these findings (39). Finally, a meta-analysis of CCTA use in patients with stable chest pain compared to usual care showed a 31% relative reduction in MI and an absolute reduction in MI rates of 1.8 events per 1000 patient-years (40). In addition to diagnostic effectiveness, an approach integrating CCTA prior to selective invasive testing for suspected CAD also significantly reduces diagnostic costs while reducing the need for angiography (41).

CCTA plays a vital role in the emergency setting, where there are approximately 7 million emergency department visits annually for chest pain, accounting for 5.4% of all visits and $10 billion of spending annually (42). While most of these presentations are found to be non-cardiac in nature, missed diagnosis of acute MI accounts for significant mortality and a significant proportion (20%) of emergency medicine litigation costs (43–45). Several multicenter clinical studies in the emergency setting have demonstrated that CCTA is a safe, rapid, and effective tool for ruling out CAD in low-intermediate risk patients presenting with acute chest pain and is associated with improved time to diagnosis and reduced length of stay (46–51). Initial studies have suggested the safety of CCTA or CMR in the setting of non-ST elevation myocardial infarction (NSTEMI) as a first step prior to invasive coronary angiography, with similar rates of hospitalization, major adverse cardiac events, and complications compared to routine care. However, additional larger studies are needed to assess the role of CCTA in this setting (52). Nonetheless, as current approaches in low to intermediate risk patients may miss the culprit lesion, CCTA could also help to enhance culprit vessel identification, leading to improved treatment targets, intervention, and resource utilization (53).

CCTA offers significant advantages in the clinical setting compared to coronary artery calcium scoring (CACS) which is obtained by a non-contrast CT scan, implies the presence of atherosclerosis, and is an established predictor of future coronary events (54,55). CACS is inexpensive and reproducible with the ability to detect patients at high-risk or low risk of CAD (56). In contrast to CACS, CCTA can additionally identify coronary stenosis severity, as well as plaque composition and morphology including both calcified and non-calcified plaque (Figure 2). This is especially valuable as non-calcified plaques are associated with increased all-cause mortality when compared to calcified plaques (57). Furthermore, CCTA can capture CAD modulation with treatment and thus has the potential to be used in the clinical setting to identify treatment response (58).

However, there are patient-specific limitations to the utility of CCTA in clinical practice. Firstly, image quality may be limited in patients with dense calcifications, morbid obesity, multiple or small diameter stents, high heart rates, and non-sinus rhythm. CCTA requires the use of iodinated intravenous contrast agents which are potentially nephrotoxic. CCTA has the potential of leading to excessive downstream testing, although the recent Coronary

Artery Disease Reporting and Data System (CAD-RADS) consensus statement provides guidance on how to appropriately manage patients following CCTA (59). The utility of CCTA should also be limited in those with a high pre-test probability for CAD, where invasive angiography may be more appropriate (60).

CCTA Assessment of High-Risk Plaque Features and Plaque Features Over Time

Recent studies have implicated coronary plaque progression as one of the major determinants of future MI even when accounting for coronary stenosis severity (8). This risk is compounded by the presence of high-risk coronary plaque features associated with plaque vulnerability (9). In this context, CCTA presents a unique ability to accurately and non-invasively quantify and characterize coronary atherosclerosis (58). As a robust and validated research tool, quantitative analysis of CCTA can also be used to track coronary features over time, including to assess response to treatment and to determine plaque characteristics that are predictors of rapid plaque progression and medication non-response.

The capability to characterize coronary atherosclerosis using CCTA has led to an abundance of large-scale clinical outcomes data that directly relate plaque morphology and characteristics to adverse CAD outcomes. This includes the visual identification and discrimination of high-risk plaque features that are associated with future ACS and correlate strongly with adverse histologic and IVUS features (61,62). These features were initially based on partitioning analyses performed in histopathological samples that demonstrated the features of hierarchical importance in plaque vulnerability—namely, presence of a thin overlying fibrous cap, extent of macrophage infiltration, and size of the necrotic core (63,64). The latter two features are intimately related and can be assessed by CCTA as a low attenuation plaque (LAP) based on HU. Several high-risk features identifiable on CCTA correspond with IVUS-defined thin cap fibroatheroma and portend greater risk for rupture, including positive remodeling (PR), LAP, spotty calcifications, and the napkin-ring sign (Figure 3) (65–67).

High-risk plaques are clinically significant and robust markers of vulnerable, rupture-prone lesions. The SCOT-HEART trial demonstrated that patients with one or more characteristics of positively remodeled coronary segments or LAP have higher risk of coronary heart disease death or nonfatal MI (67). Further, a recent report from the SCOT-HEART trial demonstrated that burden of LAP quantified from CCTA using semi-automated plaque analysis software (Autoplaque, Version 2.5, Cedars-Sinai Medical Center) was the strongest predictor of MI and, further, provided incremental prediction of MI beyond standard assessments such as CACS or luminal stenosis severity (68). While these high-risk features are strongly associated with cardiovascular outcomes and have a high negative predictive value, they are limited by a low positive predictive value (69). However, Motoyama et al. demonstrated that when additional features such as significant stenosis and plaque progression are assessed alongside high-risk plaque characteristics, patients with stenotic or progressive high-risk plaques had higher event rates compared to patients with non-stenotic and non-progressive high-risk plaque, thus adding to the prognostic value of these

characteristics (70). Furthermore, the number of high-risk plaque characteristics by CCTA present in a vessel including LAP, PR, napkin-ring sign, and spotty calcification in addition to stenosis severity is significantly associated with clinical events (66,71). Despite variability in prevalence of high-risk features by CCTA between studies, studies have generally concluded that the presence of a high-risk plaque is relevant to risk assessment in patients with CAD.

Assessing high-risk features in combination with plaque characteristics by quantitative CCTA has also been utilized to identify high-risk patients especially since high-risk plaques evolve over time (72). In the Incident Coronary Events Identified by Computed Tomography (ICONIC) study, quantitative CCTA was used to compare 234 patients who developed ACS after undergoing CCTA to paired control patients. While percent diameter stenosis (%DS) was demonstrated to be a multivariable predictor of AMI in the ACS group, 65% of patients and 75% of culprit lesion precursors in the ACS group had a maximal %DS <50% at the time of CCTA. While there were no differences in total plaque volume or percent diameter stenosis between ACS and control patients, the study found significant differences in plaque composition, including increased fibro-fatty (58.7 ± 85.8 vs. 41.4 ± 62.2 mm^3, $p = 0.009$) and necrotic core plaque volume (6.5 ± 14.0 vs. 4.2 ± 8.8 mm^3, $p = 0.026$) as well as increased high-risk plaque features in patients with ACS, emphasizing the importance of both compositional and morphological plaque features by CCTA (73).

The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging (PARADIGM) study, a large, prospective study that demonstrated the role of serial quantification and characterization of CAD using CCTA, assessed the progression of coronary atherosclerosis over time in patients undergoing clinically indicated serial CCTA utilizing a semi-automated plaque analysis software (QAngioCT, Medis, The Netherlands) (74). PARADIGM demonstrated that statin use was associated with decreased progression of rupture-prone non-calcified plaque over time and increased conversion to calcified plaque, thus conferring increased plaque stability (Figure 4) (75). Determinants of plaque progression over time in the PARADIGM study were assessed using machine learning techniques, and demonstrated the superiority of quantitative CCTA characterization to clinical and qualitative measures in identifying patients at risk of plaque progression (76). Quantitative CCTA analysis has also been used to evaluate the effects of optimal medical therapy and colchicine in patients with recent ACS, demonstrating favorable effects on plaque characteristics over time independent of high intensity statin therapy (77). Future studies should further assess the effect of targeted treatment therapies on both coronary plaque composition as well as morphology including high risk features over time.

Role of CCTA in Immune-driven Phenotypes

Inflammation is critical to the development and progression of atherosclerosis (78). The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial further demonstrated the critical role of inflammation in atherogenesis by highlighting that canakinumab, an interleukin-1B inhibitor, led to a decrease in recurrent cardiovascular events compared to placebo in patients with residual inflammatory risk as assessed by history of prior MI and high-sensitivity C-reactive protein level of 2 mg/L or greater (79).

Furthermore, several chronic inflammatory conditions such as human immunodeficiency virus (HIV), psoriasis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) have high systemic inflammation and increased cardiovascular disease prevalence, providing natural disease models for studying the effects of systemic inflammation and immune activation on CAD (80–83).

The importance of studying HIV-associated CVD is highlighted by a dramatically increased rate of incident MI among patients with HIV compared to non-HIV patients, especially as widespread access to antiretroviral therapy has led to prolonged survival and shifted focus to chronic disease management (84). Furthermore, HIV-associated CVD has tripled globally over the past two decades, representing a major public health problem with residual inflammation and immune dysfunction playing a major role in the progression of CAD (85–88). Quantitative CCTA analysis has demonstrated increased non-calcified plaque burden and high-risk plaque features including LAP and PR in relatively young HIV patients, tying together plaque morphology in both HIV and non-HIV patients in terms of cardiovascular risk profile (89). The vascular inflammation and high-risk plaque morphology in HIV have been assessed together in registered ^{18}FDG-PET and CCTA images which demonstrated a positive relationship between arterial inflammation and high-risk plaque features of LAP and PR (90). Response to statin therapy in the HIV population measured by quantitative CCTA has been assessed in a longitudinal randomized controlled trial, which demonstrated reduced non-calcified plaque volume and high-risk plaque features in HIV patients receiving statin therapy.

Similarly, psoriasis is a chronic inflammatory disease with increased cardiometabolic disease burden compared to the general population (91). Quantitative CCTA has demonstrated that young psoriasis patients have increased non-calcified coronary artery plaque burden as well as high-risk plaque features compared to 10-year-older hyperlipidemia patients and healthy controls (92). Serial imaging in an observational cohort study of psoriasis patients has allowed for monitoring of disease using quantitative CCTA. For example, it has been demonstrated that biologic therapy for severe psoriasis is associated with favorable modulation of plaque characteristics including a 6% reduction in non-calcified coronary artery plaque burden and reduction in necrotic core volume by CCTA at one-year follow up (Figure 5) (93). Future trials are being planned to test the effect of different anti-inflammatory therapies on CAD progression in this patient population.

Finally, patients with other chronic inflammatory diseases such as rheumatoid arthritis and SLE also have increased prevalence of non-calcified coronary artery plaque burden as captured by CCTA compared to the general population (94,95). Thus, CCTA has helped to characterize coronary artery disease in patients across a wide spectrum of immune-driven conditions and may aid in early identification of patients at risk of CVD.

Emerging CCTA Technologies

Despite the widespread applications of quantitative CCTA and high-risk features previously described, there are many challenges associated with visual plaque assessment, including observer variability, need for expert opinion, and the time-consuming nature of assessing

these features. Thus, software applications dedicated to increasing automation of identifying high-risk plaque have emerged, and technologies including Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography (FFR_{CT}), perivascular fat attenuation index (FAI), and wall shear stress (WSS) show promise in understanding both the anatomic and physiologic significance of plaque and improving risk stratification (Figure 6) (96).

Advancements in CCTA technology, including improvements in acquisition quality, spatial and temporal resolution, radiation exposure, and application-based analysis alongside data supporting its clinical and prognostic utility have positioned CCTA as a leading modality in cardiac imaging. Additionally, the application of non-invasive comprehensive hemodynamics, 3D-plaque assessment, and machine learning algorithms promise to optimize coronary imaging through improved diagnosis and prognostication, prediction of treatment response, and non-invasive physiologic assessment. Furthermore, integration of these technologies into the standard reporting of CCTA may allow personalized risk assessment with major impacts on primary and secondary prevention.

One major concern with the widespread use of CCTA is radiation exposure, as long-term exposure to low levels of radiation has been associated with increased cancer risk in epidemiological studies (97). Furthermore, a 2007 study demonstrated a nonnegligible increased lifetime attributable risk of cancer incidence associated with the radiation exposure from a CCTA study (98). In recent years, several initiatives have focused on reducing radiation exposure from CCTA, with initially expressed goals of achieving submillisievert scans (99). Radiation reduction strategies involve optimization of CT scanners for image acquisition, involving a complex interplay between patient preparation, x-ray beam peak tube voltage, tube current, collimation, focal spot size, gantry rotation time, pitch and field of view/wedge selection, as well as improved electrocardiogram (ECG) scan acquisition modes and image processing.

Advances in image reconstruction and computing power have also enabled reductions in radiation dose with progression from iterative reconstruction methods to next generation technology utilizing convolution neural networks and artificial intelligence (Figure 7). At the NHLBI, routine submillisievert CCTA while maintaining image quality has been demonstrated since 2013 (100). Studies published in 2018 have demonstrated a nearly 80% worldwide reduction in radiation exposure from CCTA compared to 2007, although there remains significant variability between centers (101). Consistently low radiation exposure from CCTA creates new opportunities to serially evaluate CAD while minimizing risk to the patient.

Beyond improved acquisition and optimization of radiation, recent developments have led to the development of new imaging biomarkers from CCTA such as perivascular FAI, which provides visualization and quantification of inflammation in the coronary arteries. FAI may further aid in identifying vulnerable plaques as well as vulnerable patients, helping predict future heart attacks (102). This novel radiotranscriptomic biomarker is based on the principle that vascular inflammation precedes atherosclerosis, triggers atherosclerosis development, and induces plaque rupture, and that adipocytes in perivascular fat “sense” vascular inflammation and respond via phenotypic changes that inhibit adipogenesis

(103,104). These phenotypic changes can then be detected on CCTA as FAI, capturing the three-dimensional spatial changes in the perivascular space as well as texture changes such as angiogenesis and fibrosis, and have been shown to enhance cardiac risk prediction and restratification as an indicator of increased cardiac mortality beyond the current state of the art (102). FAI can also be used to track changes in inflammation over time independent of the presence of a coronary plaque. For example, psoriasis patients undergoing serial CCTA had reduced coronary inflammation by FAI in response to biologic therapy, demonstrating the feasibility of tracking response to intervention using this novel biomarker (105).

In addition to imaging biomarkers, it has been suggested that effective, personalized diagnostic tools for detecting early subclinical coronary artery disease may allow for interventions aimed at preventing the progression of coronary plaque and reducing coronary events (9). Emerging technology such as the commercial software application vascuCAP (Elucid Bioimaging, Boston, MA) utilizes histologically validated, application-based tissue quantification to characterize atherosclerosis. This technology could allow for earlier detection of CAD, capitalizing on machine intelligence for interpretation and increased automation compared to contemporary quantitative CCTA approaches (106). While a multitude of studies have utilized software-based approaches for plaque characterization, many of these applications are limited by pre-specified thresholds that do not consider various technical limitations including different scanners and scan protocols. However, model-based quantification algorithms as utilized by vascuCAP claim to reduce inter-scan and observer variability and allow for detailed characterization of morphological features including PR, lipid-rich necrotic core, and coronary artery plaque burden (107). The potential granularity of morphologic assessment provided by automated software applications may help further elucidate mechanisms of CAD and enable earlier interventions or tailored therapeutics based on treatment response.

Emerging applications of CCTA have allowed for non-invasive assessment of the functional significance of atherosclerotic lesions from CCTA-derived models, as CCTA alone does not effectively define the hemodynamic significance of coronary lesions (108). While fractional flow reserve (FFR), the gold standard for assessing functional significance of CAD, involves invasive measurement of pressure in the coronary arteries at the time of cardiac catheterization, a large retrospective study found that less than 40% of patients undergoing coronary angiography had anatomically-obstructive CAD (109). Furthermore, in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, only 35% of patients with anatomically-obstructive CAD on angiography had FFR-positive lesions (110). Thus, the ability to identify patients with both anatomically and functionally significant CAD prior to catheterization using non-invasive testing could dramatically reduce the need for invasive testing while improving its diagnostic yield.

Several recent reports have examined the relationship between various CCTA-derived plaque characteristics and the ability to predict ischemia as measured by various techniques including myocardial perfusion and FFR. In the Combined Non-invasive Coronary Angiography and Myocardial Perfusion Imaging Using 320 Detector Computed Tomography (CORE320) study, CCTA-derived features including percent stenosis, percent atheroma volume and the impression of “vulnerable plaque” independently predicted

provocable myocardial ischemia by SPECT (111). Additionally, Gaur et al. investigated 254 patients and reported that non-calcified plaque volume predicted FFR ≤0.80, independent of stenosis severity (112). Park et al. demonstrated that established high-risk plaque features (i.e., PR and LAP) and aggregated plaque volume were independently related to invasive FFR (113). These results were confirmed by a recent post-hoc analysis from the single center Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CCTA with Invasive Coronary Angiography (PACIFIC) trial showing that PR and non-calcified atherosclerotic plaque volume were associated with decreased absolute myocardial blood flow by $[^{15}O]H_2O$ PET and invasive FFR (114).

Capitalizing on this ability of CCTA to predict physiologic consequences of CAD, FFR_{CT} (HeartFlow, Redwood City, CA) is a technology whereby patient-specific models of blood flow are constructed from CCTA images and used to non-invasively estimate FFR. The technology utilizes deep learning algorithms to extract lumen boundaries from CCTA using an approach validated against OCT, and creates a patient-specific physiologic model based on form-function principles and computational fluid dynamic analysis to compute the blood flow solution (115,116). The Analysis of Coronary Blood Flow using CT Angiography: Next Steps (NXT) trial demonstrated that the diagnostic accuracy of FFR_{CT} (AUC under the receiver operating curve: 0.90 (95% confidence interval [CI]: 0.87 to 0.94) was significantly greater than CCTA alone (0.81 (95% CI: 0.76 to 0.87) (117). In addition, the PACIFIC study compared diagnostic accuracy of various modalities using invasive FFR as the gold standard, and found AUC on a per-vessel basis was significantly greater for FFR_{CT} (0.94) in comparison with CCTA (0.83), SPECT (0.70) and PET (0.87) (118).

Like FFR_{CT}, myocardial perfusion by cardiac CT (stress-CTP) also allows for non-invasive assessment of the physiologic consequences of stenoses in CAD (119,120). Stress-CTP combined with CCTA has been demonstrated to detect functionally relevant stenoses with greater diagnostic accuracy, specificity, and positive predictive value when compared with CCTA alone, and comparable to FFR_{CT} combined with CCTA (121). The increased diagnostic accuracy of stress-CTP over CCTA alone was recently demonstrated in patients with previous stent implementation and suspected in-stent restenosis or CAD progression, suggesting its utility in stent evaluation (122). However, clinical utility and outcome data with stress-CTP have not been reported.

Several follow-up studies have demonstrated the prognostic utility of FFR_{CT} in predicting outcomes from one year to five years (123–127). Additionally, a percutaneous coronary intervention (PCI) planner tool derived from FFR_{CT} has been developed which can estimate the FFR contribution of an individual stenotic lesion in a vessel, allowing for prediction of the effects of revascularization of a stenosis (128). The real-world utility of FFR_{CT} in clinical practice is exemplified by the Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) registry which demonstrated that a decision- making pathway utilizing CCTA and FFR_{CT} results in decreased negative invasive angiography and helped predict subjects at low risk of adverse cardiac events (129). Two large randomized controlled trials, Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) and

Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE) on FFR_{CT} are currently underway.

The application of machine learning algorithms to assess FFR by CT may significantly improve computation speeds with diagnostic accuracy comparable to workstation-based computational fluid dynamics modeling approaches, although clinical utility and outcomes have not been established (130,131). The accuracy of these deep learning models was further evaluated by results from the MACHINE consortium which also demonstrated correct reclassification of false positive CCTA results with the addition of machine learning based assessment of FFR by CT (132).

However, evaluating values of any test, including FFR_{CT} and invasive FFR, as they approach a threshold invariably leads to lower reported accuracy, also known as a diagnostic “gray zone” (133). Further development and large, randomized controlled trials of FFR_{CT} may increase its utility in planning PCI, evaluating risk of rupture of coronary plaques, computing the myocardial territory affected by ischemic lesions, and assessing functional significance of diffuse atherosclerosis.

Finally, wall shear stress (WSS) is a computational fluid dynamics (CFD) metric that may help to explain the implications of an atherosclerotic coronary plaque and can be derived using invasive techniques or non-invasively from CCTA. WSS represents the tangential frictional force of blood acting on the coronary vessel wall (134). Vascular biology has long linked WSS to coronary atherosclerosis via alterations in endothelial cell pathways, including the demonstrated relationship between low shear stress and vascular cell adhesion molecule (VCAM), a critical molecule in the pathogenesis of atherosclerosis (135–139).

WSS derived from CCTA has also been shown to aid in identification of high-risk plaque beyond percent stenosis alone, and is independently related to increases in coronary plaque burden (140–142). Furthermore, in the EMERALD study, integration of various hemodynamic indices including WSS from CCTA, FFR_{CT}, change in $FFR_{CT,}$ and axial plaque stress demonstrated incremental prognostic value in addition to anatomic stenosis severity and CCTA-derived plaque characteristics, suggesting that assessment of WSS may also help identify future lesions leading to ACS and functionally significant plaques with high-risk features (143). Similar findings have been reported in WSS derived from IVUS, which has been shown to predict progression of atherosclerotic features and development of high-risk features including PR (96). Thus, the consideration of WSS in CCTA analysis may have the potential to identify at-risk patients and guide management strategies for patients with CAD.

Future Directions and Unmet Needs

Clinical utilization of CCTA has seen a surge in cardiovascular care and research. The technology is in its prime for understanding atherosclerosis as well as the effects of interventions on atherosclerosis progression. CCTA captures a wide field of view and thereby may be better positioned to characterize disease as well as to track it longitudinally compared to other techniques. Furthermore, outcomes beyond total atheroma burden, plaque

volume, and plaque progression are ready to test in larger trials. Indeed, improved understanding of early atherosclerosis features from CCTA may provide targets to reduce disease progression and development of high-risk features. This may help to assess more sensitive outcomes in the era of statin therapy and maximal secondary prevention efforts. Endpoints for trials utilizing CCTA are a dynamic field of study and with more widespread availability, CCTA will continue to contribute to improved patient outcomes and understanding of coronary artery disease.

Without effective mitigation, there remain important limitations to the use of CCTA, some of which have been mentioned previously. CCTA is still limited in spatial and temporal resolution compared to invasive methods including coronary angiography, which may be better suited for high risk patients with extensive calcifications or those that have multiple stents. Moreover, in patients who have lesions of uncertain hemodynamic significance, other functional testing approaches may be preferable (32,59,60). Furthermore, interpretation of CCTA requires highly trained readers to ensure diagnostic accuracy and minimize inter-observer variability. Additionally, CCTA based outcomes as well as emerging technologies have not been validated in randomized controlled trials with well-defined outcomes, which are needed to validate the clinical benefit of many applications of CCTA, from assessment of high-risk plaque to emerging technologies like FAI and WSS.

Conclusions

CCTA is emerging as a first-line diagnostic modality for CAD with a strong basis in histopathology and strong clinical applicability driven by excellent negative predictive value. The ability of CCTA to quantify coronary plaque composition and identify coronary plaque morphology including high-risk plaque morphology will help inform monitoring of therapy and may one day become a cornerstone in personalizing treatment. Emerging technologies which capitalize on reduced radiation doses, advances in feature extraction, and computational fluid dynamics have increased the prognostic value of CCTA and further integrated CCTA into clinical practice.

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Abbreviations

CCTA	coronary computed tomography angiography
CAD	coronary artery disease
CVD	cardiovascular disease
IPH	intraplaque hemorrhage
NIRS	near infra-red spectroscopy
IVUS	intravascular ultrasound

CAC	coronary artery calcification
ACS	acute coronary syndrome
AMI	acute myocardial infarction
FFR_{CT}	Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography

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Highlights

- CCTA is a non-invasive first-line modality for the assessment of CAD.
- CCTA can be used to characterize disease burden, add prognostic value, and guide patient management.
- CCTA-derived characteristics can be leveraged to predict plaque evolution, rupture, and to predict ischemia.
- Further clinical trials are needed to validate clinically relevant endpoints and increase utilization of CCTA.

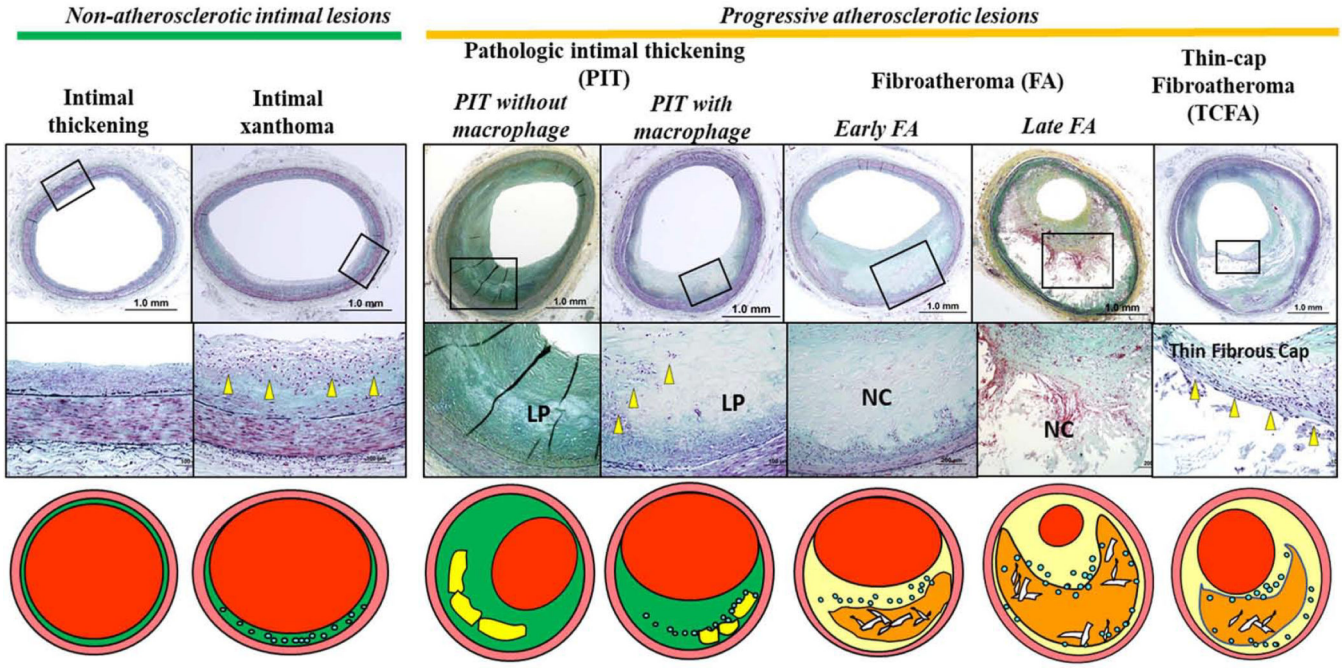


Figure 1. Progression of human coronary atherosclerosis.

Non-atherosclerotic lesions including intimal thickening and intimal xanthoma progress into atherosclerotic lesions beginning with pathologic intimal thickening and leading to fibroatheroma and thin-cap fibroatheroma. Reproduced with permission from Yahagi et al (4).

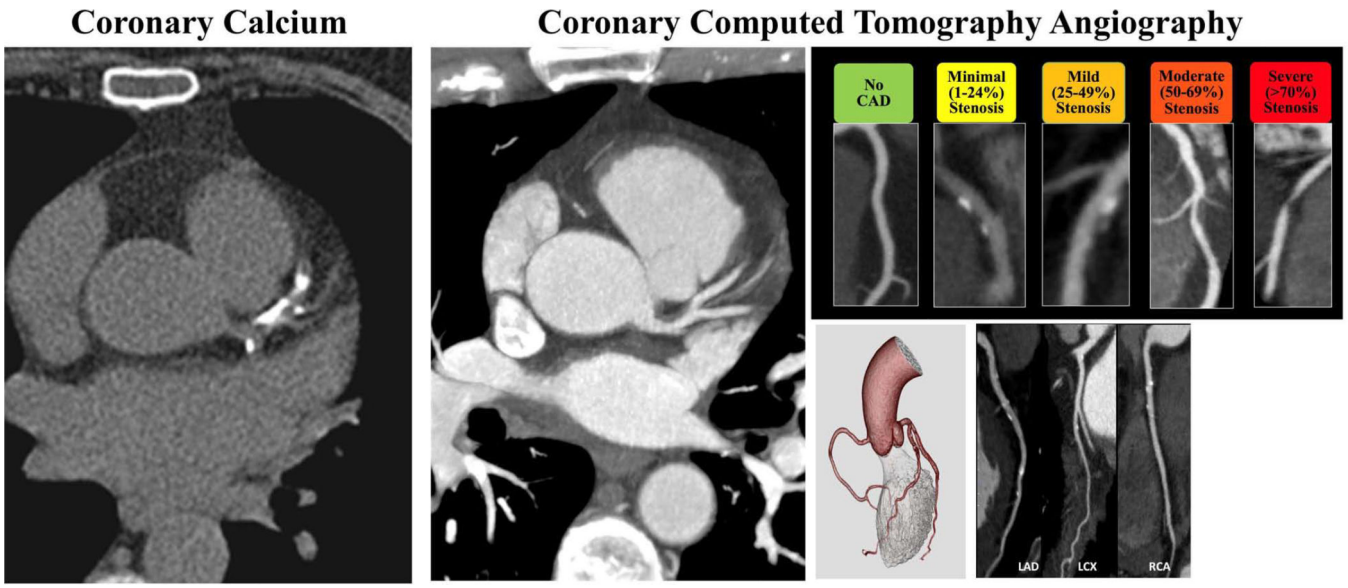


Figure 2. Coronary artery calcium scoring compared to Coronary Computed Tomography Angiography.

Coronary artery calcium scoring (CACS) is quick, reproducible, does not require contrast, and provides strong prognostic data (left). Coronary computed tomography angiography (CCTA) (right) provides unique practical advantages over CACS, including high resolution of plaque features such as non-calcified, rupture-prone plaque and characterization of stenosis severity.

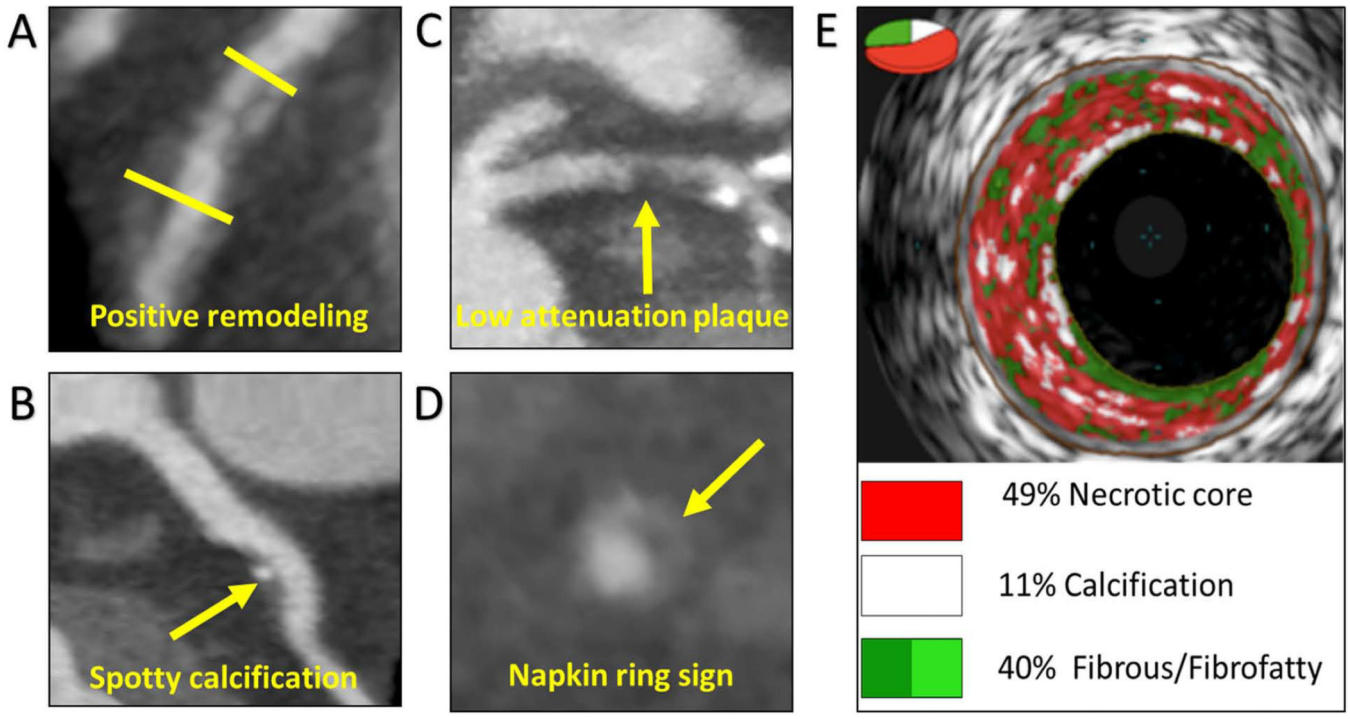


Figure 3. Coronary Plaque Features on Coronary Computed Tomography Angiography and Intravascular Ultrasound.

Coronary atherosclerotic plaque features associated with increased vulnerability including (A) positive remodeling, (B) low attenuation plaque, (C) spotty calcification, and (D) napkin-ring sign from the Scottish COmputed Tomography of the HEART Trial (SCOT-HEART) trial are visualized on coronary computed tomography angiography (CCTA). (A) Positive remodeling was defined as an outer vessel diameter (yellow line) that was 10% greater than the mean diameter of the segments immediately proximal (short yellow line) and distal to the plaque. (B) Low attenuation plaque was defined as a focal central area of plaque with an attenuation density of <30 Hounsfield Units (yellow arrow). (C) Spotty calcification was defined as focal calcification within the coronary artery wall that measured <3 mm in maximum diameter (yellow arrow). (D) The “napkin ring” sign was defined as a central area of low-attenuation plaque with a peripheral rim of high attenuation (yellow arrow). (E) Correspondingly, features of vulnerable plaque such as necrotic core can be visualized on virtual histology from intravascular ultrasound. Reproduced with permission from Williams et al. and Joshi et al (66,67).

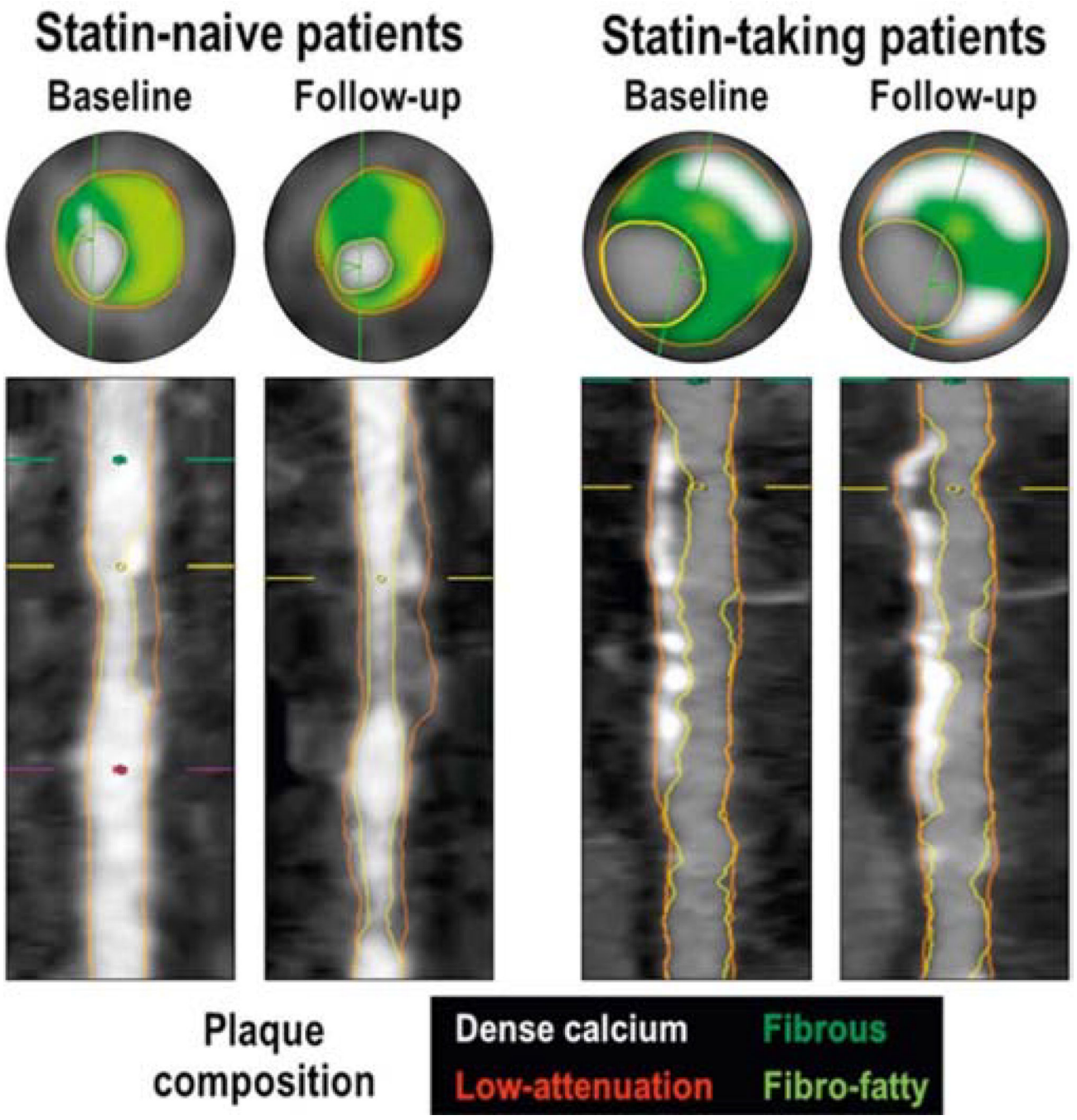


Figure 4. Temporal coronary computed tomography angiography assessment of coronary artery plaque characteristics according to statin use.

Coronary computed tomography angiography (CCTA) images of coronary artery lesions at baseline and follow-up from the Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging (PARADIGM) study demonstrate favorable modulation of rupture-prone non-calcified burden in statin-taking patients when compared to non-statin taking patients, demonstrating the utility of coronary computed tomography angiography in assessing treatment response. Reproduced with permission from Lee et al (75).

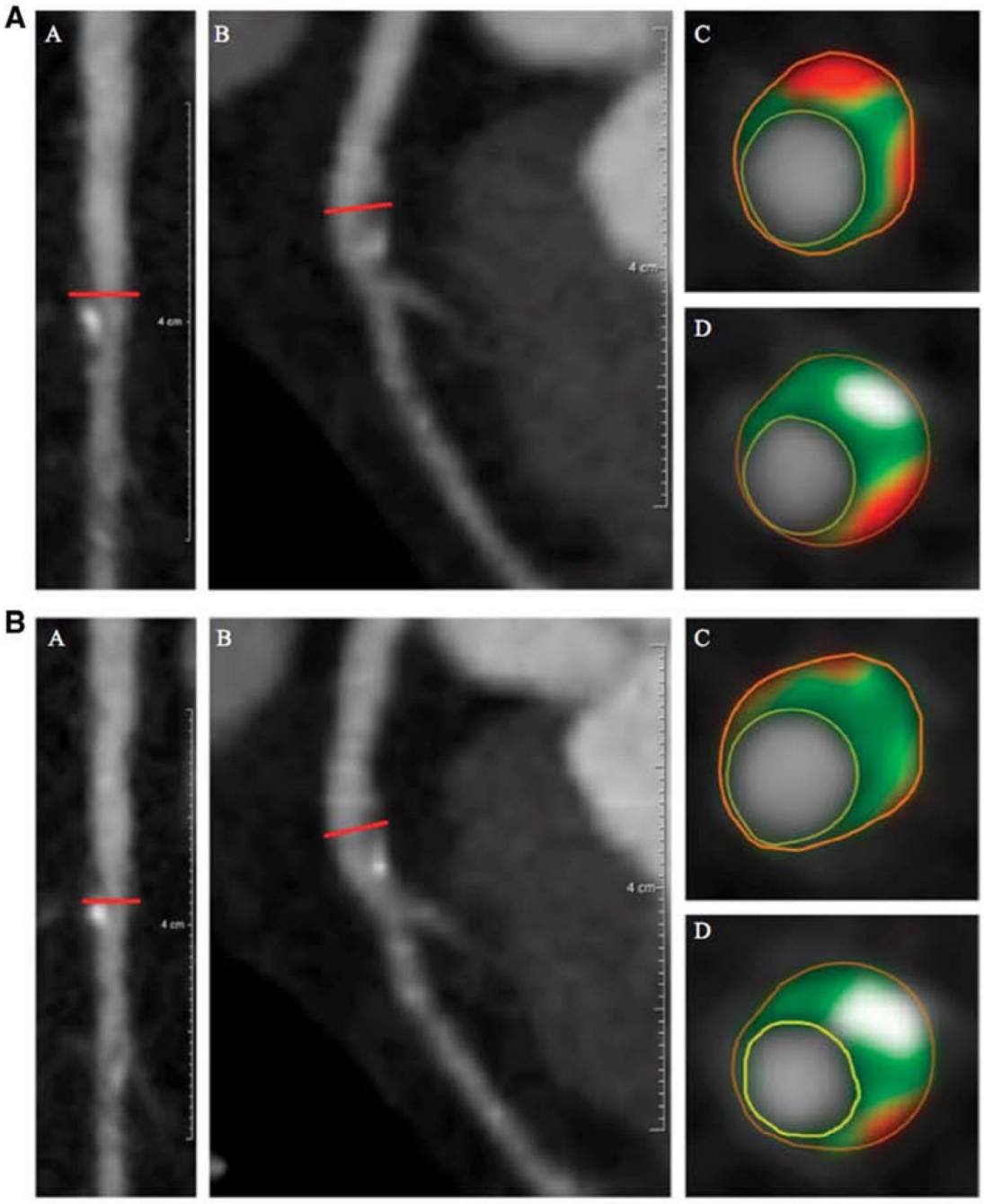


Figure 5. Coronary computed tomography angiography demonstrates favorable modulation of coronary plaque characteristics in response to treatment with biologic therapy in psoriasis.

Left anterior descending artery plaque in a psoriasis patient identified before (2A) and after (2B) biologic therapy, demonstrating a reduction in non-calcified plaque burden and total atheroma volume. (A) (a) Longitudinal planar and (b) curved planar reformat. (c and d) Representative cross-sectional views with color overlay for plaque subcomponents. Lumen is encircled in yellow, vessel wall in orange with subcomponents in between, including fibrous (dark green), fibro-fatty (light green), necrotic (red), and dense-calcified (white). Non-calcified plaque burden = 1.03 mm^2 and total atheroma volume = 99.2 mm^3. (B) (a)

Longitudinal planar and (b) curved planar reformat. (c and d) Representative cross-sectional views with color overlay for plaque subcomponents. Lumen is encircled in yellow, vessel wall in orange with subcomponents in between, including fibrous (dark green), fibro-fatty (light green), necrotic (red), and dense-calcified (white). Non-calcified plaque burden = 0.85 mm^2 and total atheroma volume = 80.6 mm^3. Reproduced with permission from Elnabawi et al (93).

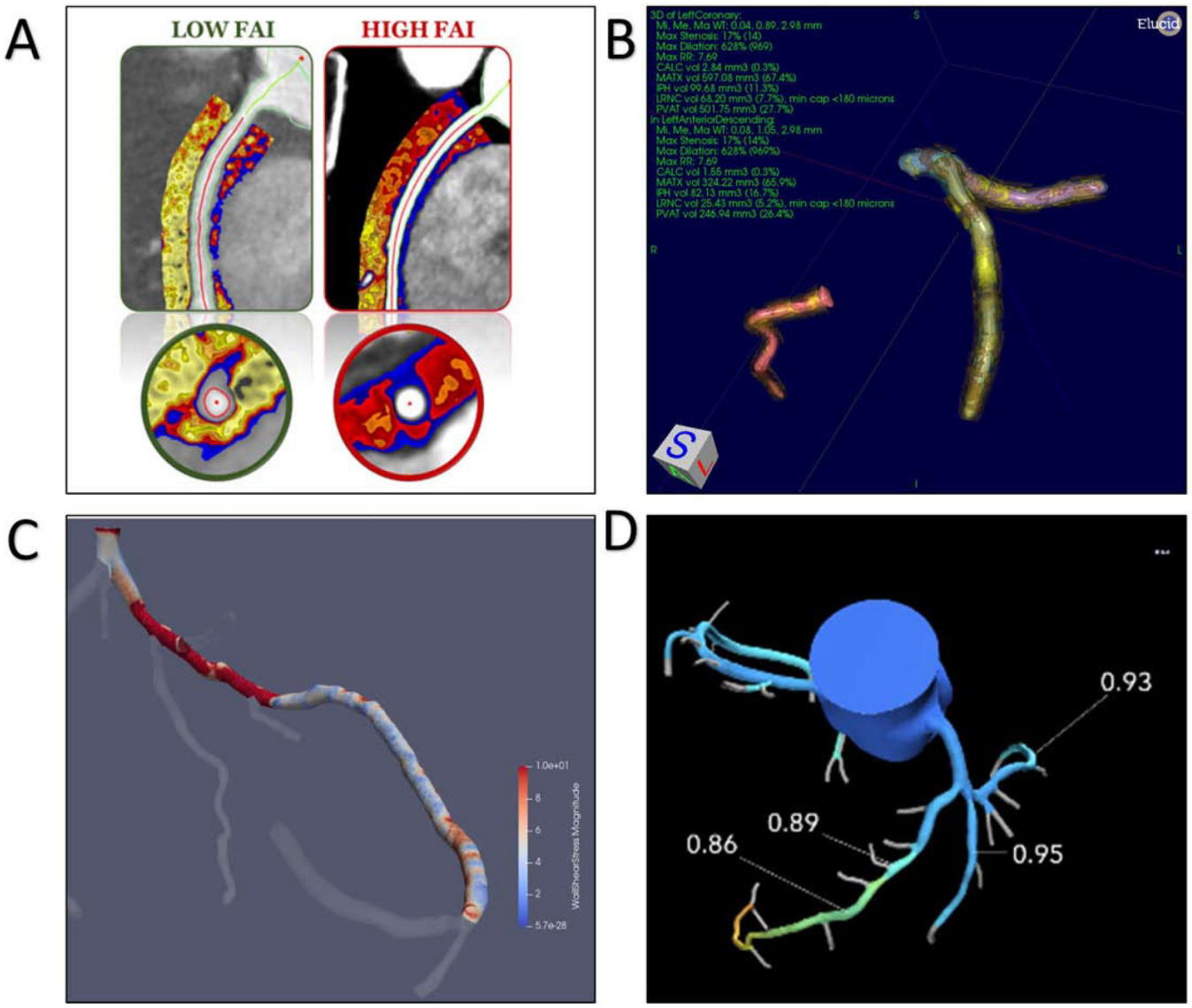


Figure 6. Emerging technologies derived from Coronary Computed Tomography Angiography.

(A) Two patients with high and low perivascular fat attenuation index (FAI) identified on coronary computed tomography angiography (CCTA) are shown. (B) Plaque quantification and characterization from CCTA using vascuCAP (Elucid Bioimaging) is shown in a 3-dimensional view of the left and right coronary arteries. (C) Example of a wall shear stress (WSS) profile superimposed on a coronary artery tree from CCTA. Reproduced with permission from Samady et al (96). (D) FFR_{CT} calculations (HeartFlow) are superimposed on a coronary artery tree extracted from CCTA.

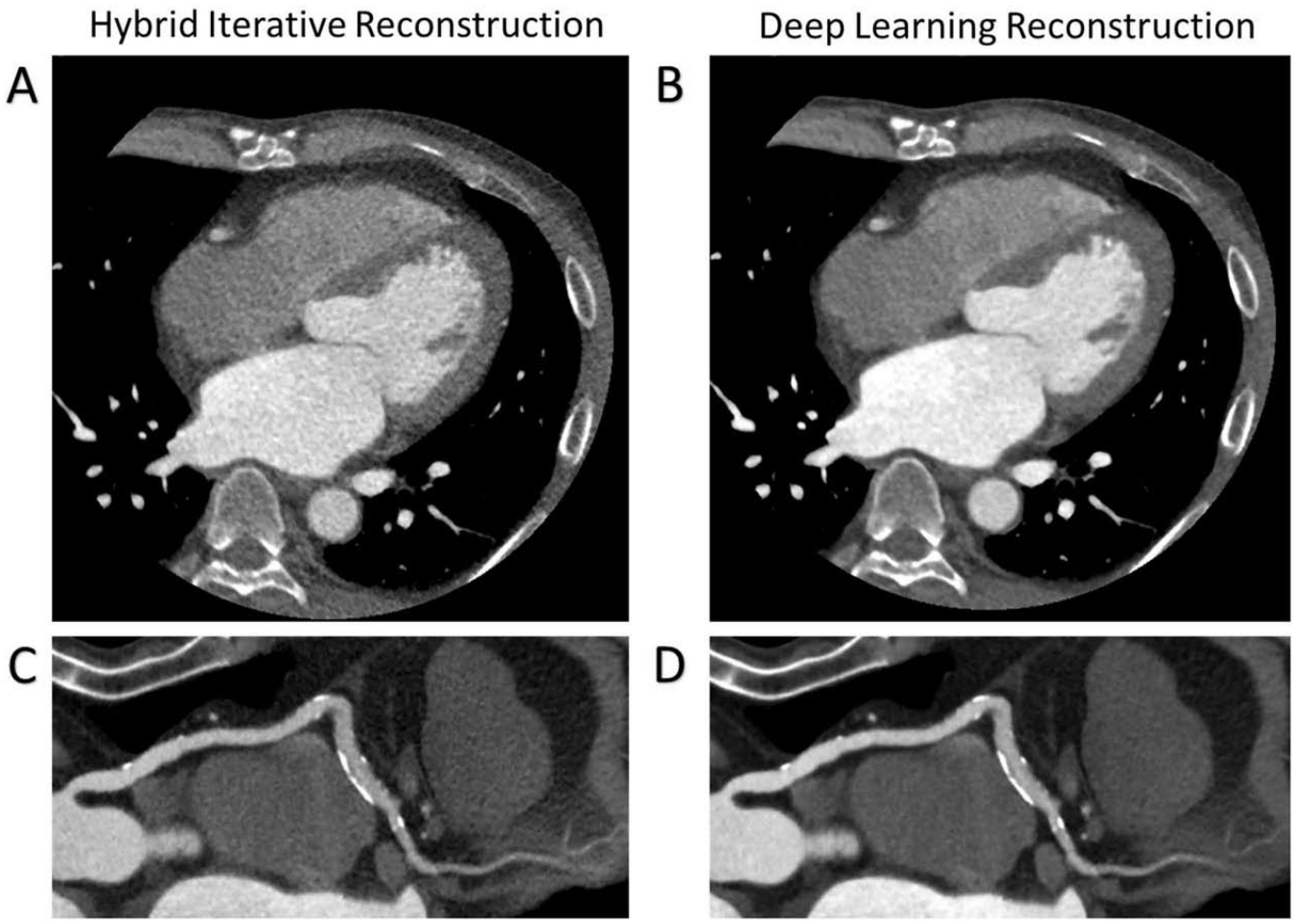
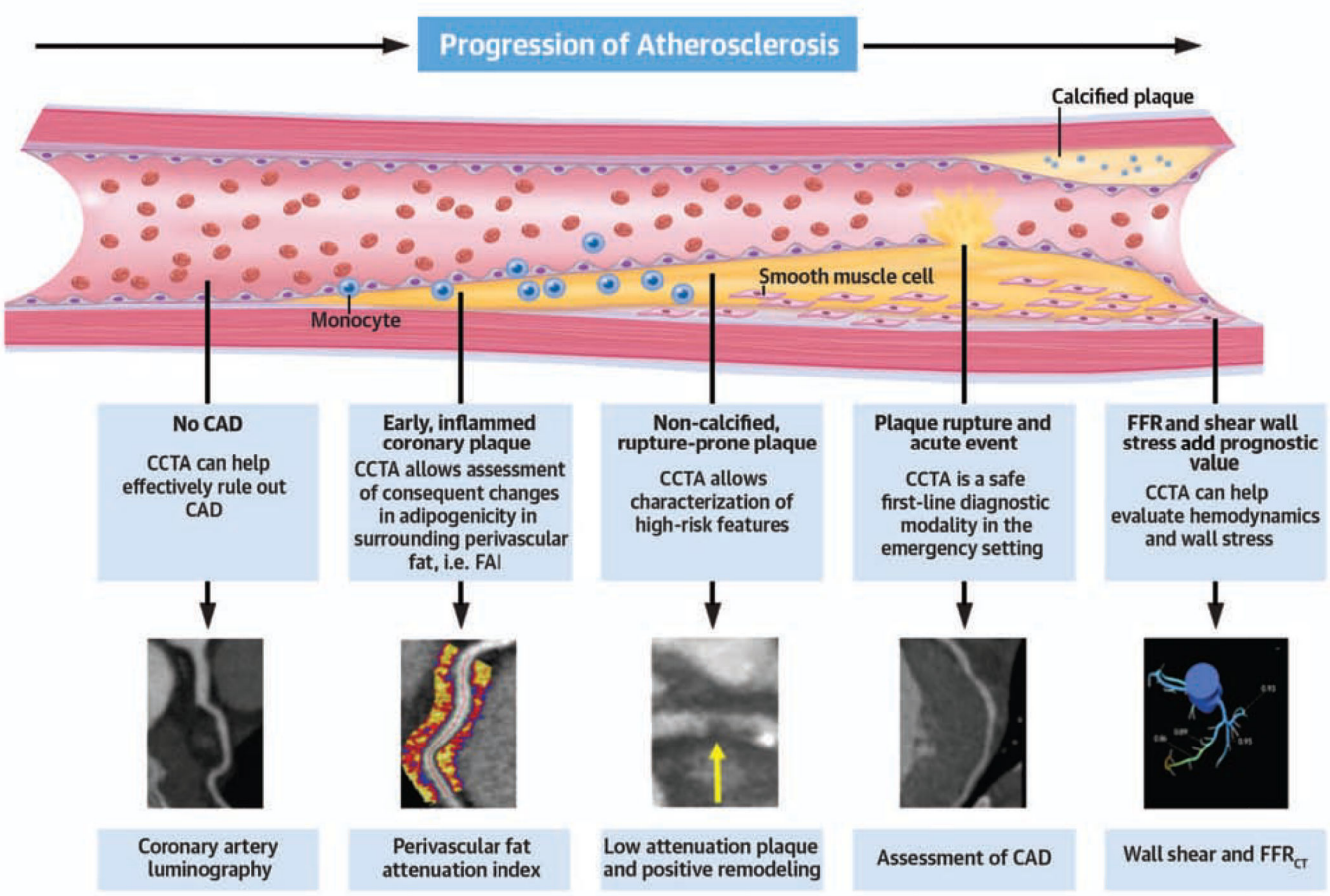


Figure 7. Reconstruction techniques for radiation reduction and coronary computed tomography angiography image quality.

Coronary computed tomography angiography (CCTA) radiation dose can be reduced while maintaining high image quality using deep learning reconstruction techniques, which provide superior image quality compared to hybrid iterative reconstruction techniques. Axial CCTA sections reconstructed using (A) hybrid iterative and (C) deep learning techniques are shown, as well as multiplanar reformatting of the right coronary artery using (C) hybrid iterative reconstruction and (D) deep learning reconstruction.



Central Illustration. Utility of coronary computed tomography angiography in coronary artery disease.

Coronary Computed Tomography Angiography is a powerful clinical tool that can be used to detect and characterize coronary artery disease across various stages from early, subclinical disease to myocardial infarction.