Coronary Artery Calcium and CT Angiography

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Abbreviations

CAC	Coronary artery calcification
CAD	Coronary artery disease
CT	Computed tomography
CVD	Cardiovascular disease
EBCT	Electron beam computed tomography
FRS	Framingham risk score

Introduction

Calcification of the coronary arteries is widely recognized as a marker of subclinical atherosclerosis. Dubbed as the "mammogram of the heart", calcium scoring allows for the early detection of coronary disease and prognostication of cardiovascular risk. Over the last 30 years, the field has made significant inroads with wide acceptance and implementation in preventive cardiology and guidelines [1]. Over the last decade, coronary computed tomography angiography (CCTA) has emerged as a cost-effective and powerful strategy for non-invasive evaluation of coronary arteries. Unlike functional testing, CCTA today is utilized to not only rule severe stenosis but also quantify atherosclerotic plaque burden and characterize morphology of non-obstructive and obstructive atherosclerotic plaque. In the current era, most of the patients who undergo some form of diagnostic test for chest pain are low to intermediate risk without ischemic obstructive lesions. Several studies have established association of non-obstructive CAD and future risk of cardiovascular events. Robust evidence suggests that CCTA is impactful in encouraging preventive care and leads to significant relative risk reduction of future incident MI [2–4]. Furthermore, CCTA has been utilized to monitor plaque progression to evaluate the impact of lifestyle changes and pharmacotherapy, suggesting CTA may hold future to personalize individual therapies.

The first part of this chapter will discuss the role of coronary calcification in the existing risk prediction framework, the interpretation of the calcium score, and the power of zero. It will also address the technical aspects from image acquisition to calcium quantification as well as CCTA. The second part will discuss the prognostic value of CCTA beyond CAC and compared to functional testing and role of CCTA in monitoring the efficacy of lifestyle changes and pharmacotherapy.

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Coronary Artery Calcification

Coronary Artery Disease: Risk Prediction Framework

Coronary artery disease is the leading cause of death in the developed world, accounting for an estimated 17.3 million deaths globally [5]. The 2017 American Heart Association (AHA) statistics on heart disease and stroke estimates that over 92 million adults in the United States (US) carry a diagnosis of cardiovascular disease (CVD) with nearly 44% of the US population projected to have some form of CVD by 2030 [5] (1). With advances in medical therapy, the death rates from CVD have declined by 25.3% from 2010 to 2014 [5]. However, the economic impact associated with diagnosis and management of coronary disease is substantial, approximating $165 billion in 2009 [6].

The diagnosis of CAD is complex, incorporating an understanding of disease prevalence, an assessment of individual risk factors, and recognizing pre-test probability [7]. Traditional risk factors for CAD include hypertension, hyperlipidemia, diabetes mellitus, family history, smoking history, and increasing age [8]. Clinical cardiology guidelines as recently as 2010 relied on population-based studies to predict the likelihood of cardiovascular events [9]. The Framingham Heart Study demonstrated that age, gender, smoking, diabetes, blood pressure, and cholesterol levels can be used to estimate the risk of cardiovascular events. Nearly 8500 participants were followed for a 12-year period and monitoring for outcomes of coronary heart disease and cerebrovascular disease [10]. This data led to a population-based multivariable algorithm, the Framingham risk score (FRS), to better stratify coronary disease risk in asymptomatic patients [10].

Many population-based risk assessments exist (SCORE, QRISK1, PROCAM), the most widely used being the FRS [11]. The major limitation of these risk scores is the selection of a narrow population from which the algorithm is derived and limited scope of outcome data focusing primarily on coronary heart disease. The Framingham Heart Study, for example, enrolled an exclusively white population. Because of limited applicability to diverse, real-world populations, the American College of Cardiology (ACC) and American Heart Association moved away from FRS in the 2013 revised Guideline on Assessment of Cardiovascular Risk, focusing instead on Pooled Cohort Equations based on representative cohorts of US whites and African Americans to estimate lifetime risk of atherosclerotic cardiovascular disease (ASCVD) [12]. The guideline's working group notes however that these risk assessment tools have not been formally evaluated in randomized trials and that risk estimation is based on population averages. This data has to be interpreted by the clinician in consideration of the history and focused physical exam to determine individual cardiovascular risk.

Thusly, clinicians are confronted with two key questions in assessing cardiovascular risk: (1) Is the patient at increased risk for a cardiovascular event? (2) Does my patient warrant initiation of lipid-lowering therapy? In comparison to three primary prevention cohorts (the Women's Health Study, the Physicians' Health Study, the Women's Health Initiative Observational Study), Ridker et al. found that the ACC/AHA risk prediction algorithm overestimates observed risk as much as 75–150% (Fig. 31.1). Accordingly, the addition of an additional risk marker with strong negative predictive value to the traditional risk prediction framework will enable clinicians to better adjudicate patients whom are more likely to benefit from lipid-lowering therapies and those in whom foregoing statin therapy may be considered owing to very little net clinical benefit [13, 14].

Coronary Artery Calcium (CAC)

History

Early work in coronary artery calcification (CAC) relied on cardiac cinefluoroscopy for visualization. In a report of 360 patients undergoing coronary angiography, coronary calcification was seen in 154 cases, and over 97% of these had severe coronary artery disease, defined as luminal stenosis >70% [15]. Follow-up work solidified

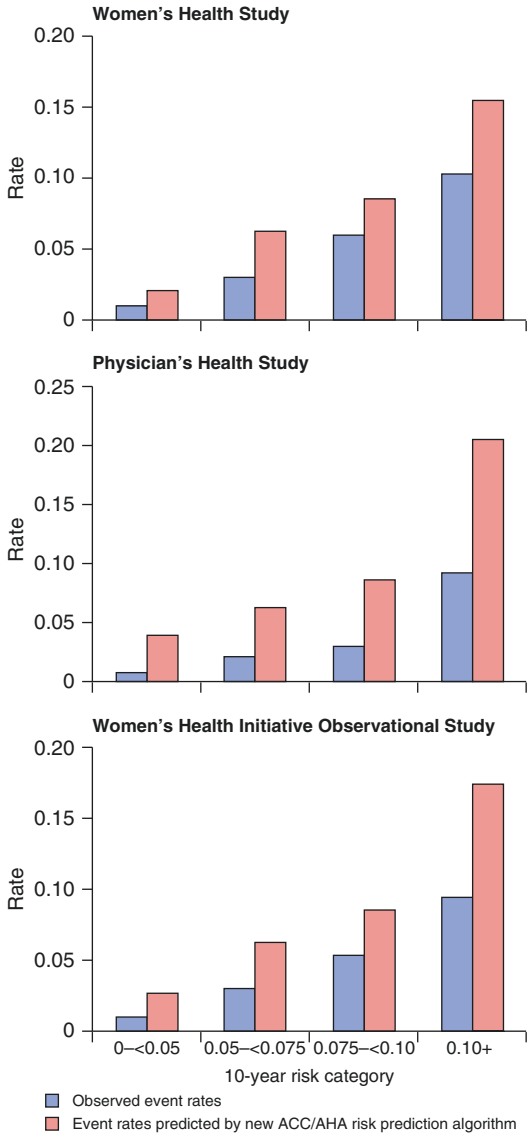

Fig. 31.1 Observed CVD event rates versus predicted rates by the 2013 ACC/AHA Pooled Cohorts ASCVD algorithm. (Adapted from Ridker and Cook [14]. With permission from Elsevier)

the association between coronary calcification and atherosclerosis in a review of clinical, post-mortem, and angiographic studies [16]. The development of electron beam computed tomography (EBCT) in 1979 enabled rapid, high-resolution image acquisition of the coronary arteries. This *ultrafast CT* was shown to be twice as sensitive as fluoroscopy in detecting coronary calcium, making it ideal for screening [17].

Biology of Arterial Calcification

Vascular calcification is now understood to be an active process rather than one of senility. In the coronary arterial bed, calcification is driven by a combination of metabolic and inflammatory factors. Studies have previously reported that the arterial wall has a subpopulation of cells that have the ability to undergo osteoblastic differentiation and mineralization [18]. Vascular smooth muscle cells normally express proteins that inhibit calcification [19], a process that is disrupted by inflammation and oxidized low-density lipoprotein (LDL). The presence of oxidized LDL particles upregulates osteogenic differentiation of the vascular smooth muscle cells and thus promotes vascular calcification [20].

Inflammation is a critical driving factor for atherosclerotic plaque formation and arterial calcification. The accumulation of oxidized LDL promotes endothelial dysfunction and release of pro-inflammatory cytokines. The secretion of these cytokines and adipokines from perivascular fat [21] creates a milieu that promotes the infiltration of inflammatory cells such as macrophages within the arterial wall [22]. This regional inflammation and oxidative stress further promote vascular calcification.

CAC vs. Risk Cohorts

The Framingham risk score offered an intuitive CV risk assessment based on readily available variables (age, gender, smoking, blood pressure, cholesterol). Since then, finer calibration of these risk prediction models has allowed wider applicability by including more diverse populations. The discriminative power of these models is continuously challenged by the addition of new risk factors such as C-reactive protein [23], carotid intima-media thickness test [24], and lipoprotein(a) [25]. Coronary artery calcium is an imaging biomarker that essentially provides direct visualization of coronary atherosclerosis. In a prospective, observational population-based study of 1461 asymptomatic adults with coronary risk factors, coronary calcium was shown to rank CVD risk independent of the FRS [26]. The addition of CAC score provided the greatest improvement in discrimination (Fig. 31.2). Similarly,

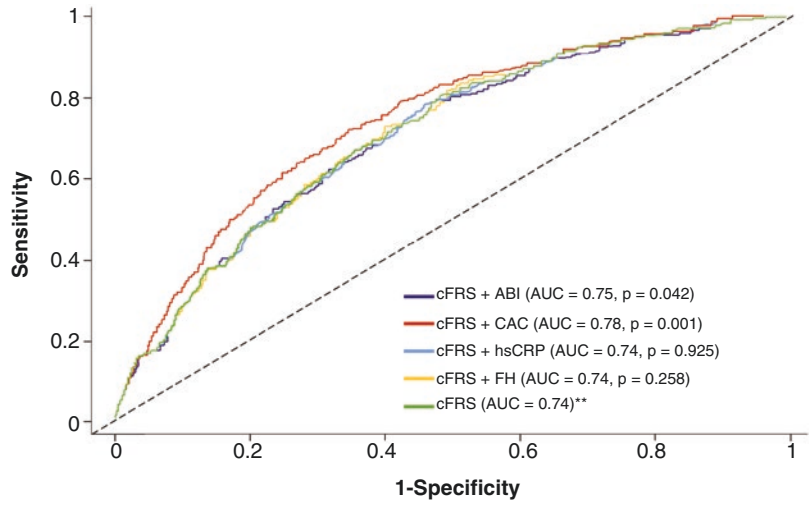

Fig. 31.2 Receiver operating characteristic curves showing the area under the curve (AUC) for calibrated FRS (cFRS) alone or plus coronary artery calcium score. ABI ankle brachial index, hsCRP high sensitivity C-reactive protein, FH family history. (Adapted from Yeboah et al. [95]. With permission from Elsevier)

Taylor et al. demonstrated that CAC independently predicts incident premature coronary heart disease over standard CV risk factors [27]. The relationship between CAC and future CV events was also studied in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. CAC scanning was performed on 6722 men and women in MESA, of which 27.6% were black, 21.9% Hispanic and 11.9% Chin*ese* [28]. Over a median follow-up period of 3.8 years, 162 coronary events were noted. Compared with participants without any coronary calcification, the risk of coronary events increased by a factor of 7.73 with CAC scores 101–300 and a factor of 9.67 with scores >300 ($p < 0.001$). Importantly, there was no difference in the predictive value of CAC across different ethnic groups. In the MESA cohort, the traditional CAD risk factors of older age, male gender, Caucasian race, hypertension, and diabetes were all associated with the development and progression of coronary artery calcification [29].

The predictive value of CAC has also been compared to the newer pooled risk cohorts. In a large Korean population of 4194 individuals without known cardiovascular disease, the odds ratios for CAC progression in low- (pooled risk 5 to <7.5%), intermediate- (7.5 to <10%), and high-risk (≥10%) groups were 1.85 (95% confidence interval (CI) 1.52–2.25), 2.63 (95% CI 2.01–3.46), and 3.58 (95% CI 2.73–4.70), respectively [30]. The study demonstrated that the newer pooled risk cohorts were predictive of the incidence and progression of CAC. However, when the pooled risk algorithm was applied to MESA, it performed suboptimally with C-statistics of 0.6–0.7, whereas the C-statistic for CAC prediction of coronary events was 0.8 [31, 32]. Thus, CAC may indeed perform more robustly than the ASCVD pooled risk algorithm alone.

An analysis of the observed versus predicted risk of cardiovascular events by DeFilippis et al. revealed that the 2013 ACC/AHA prevention guidelines overestimated CV risk in the MESA cohort (9.16% predicted vs. 5.16% observed) [33]. This discordance was noted throughout the continuum of cardiovascular risk. Risk overestimation may translate into preventive therapy such as statin drugs applied to patients who are unlikely to benefit and of course increased costs. Nasir et al. applied the pooled risk equations to 4758 statin-naive patients of the MESA cohort. By the 2013 ACC/AHA guidelines, 50% were eligible for statin therapy [34] (3). When looking at the distribution of CAC by statin eligibility, 41% of the 2377 participants recommended for moderate- to high-intensity statin by ACC/AHA guidelines had CAC = 0. CAC of zero may indeed reclassify nearly 50% patients as much lower risk than predicted by pooled cohorts and thus not favorable for statin therapy.

In every day clinical practice, the clinician is faced with a vast amount of data with which to appropriately classify cardiovascular risk. The integration and interpretation of traditional risk factors with coronary calcification scores has to be personalized to the patient. Knowledge of the patient's pre-test probability based on traditional risk models is critically important to interpretation of the CAC score. Pletcher et al. elegantly demonstrated how the coronary artery calcium score can be integrated with conventional cardiovascular risk factors to estimate future risk [31]. The study modeled the National Cholesterol Education Panel's Adult Treatment Panel III guideline's version of the Framingham risk score in addition to race/ethnicity to estimate 10-year heart disease risk compared with CAC score. For example, a 60-year-old white male with systolic blood pressure 120 millimeters of mercury (mmHg), total cholesterol 150 mg/dL, and high-density lipoprotein (HDL) 65 mg/dL has a 10-year heart disease risk estimate based on the modeled FRS of 5% (low-intermediate risk). However, the finding of a CAC score of 101–300 increases that risk estimate to 10%, affecting clinical decision-making [31]. Similarly, a high-risk patient based on traditional FRS risk factors (≥10%) with a CAC score of zero reclassifies into a 10-year coronary heart disease risk of 2% (see section "Power of Zero"). Thus, in cases where a high CAC score might be expected based on risk factors alone, a score of zero or moderately elevated (CAC 1–100) may be reassuring to some degree. An online MESA risk calculator is available to clinicians to integrate traditional risk factors and the CAC in different ethnic groups (Caucasian, Hispanic, African American, and Chinese) – *https://www.mesa-nhlbi.org/CACReference.aspx*. The tool incorporates age; gender; ethnicity; presence of risk factors such as diabetes, tobacco use, and hypertension; as well as objective data points such as systolic blood pressure, total cholesterol, and calcium score [35].

Cost-Effectiveness of CAC

CAC scans typically range $100–200 in out-of-pocket costs. The cost-effectiveness of cardiac imaging is dependent on the prognostic capability, the finer discrimination of risk, and finally the ability to reclassify patients based on revised risk assessment. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study evaluated the clinical impact of the addition of CAC to conventional risk factors [36]. Of 2137 patients randomized to CAC scan or no scan, those who underwent calcium scanning showed improvements in blood pressure ($p = 0.02$) and LDL ($p = 0.04$) as well as a tendency toward weight loss, though statistical significance was not reached. Overall downstream testing and costs did not differ between the scan and no scan group; however, within the scan group, higher quartiles of CAC showed increased utilization of downstream testing (electrocardiogram [EKG], stress testing, coronary CTA, catheterization, revascularization, or carotid ultrasonography).

The cost-effectiveness of calcium scoring for CAD risk prediction and guiding statin allocation was evaluated in the MESA cohort [37] (4). The study simulated a model to assess the clinical and economic effects of a one-time CAC study in intermediate-risk patients. Two treatment strategies were evaluated: statin therapy for CAC ≥1 or CAC ≥100. Treating intermediate-risk patients with CAC ≥1 averted an average of 5.1 coronary events compared with 3.9 events in a treat-all strategy. Only treating patients with CAC ≥100 prevented fewer coronary events; however, it also reduced the number of patients experiencing statin-related adverse effects. Overall the study concluded that treatment on the basis of calcium score is more effective in preventing coronary events and also allows for identification of patients who would benefit from high-intensity statin therapy while also increasing medication adherence.

Power of Zero

Coronary artery calcification has been consistently shown to strongly predict cardiovascular events. CAC offers improved risk stratification where other prediction algorithms fall short – ethnic populations, women, and those at low-intermediate risk. Lakoski et al. studied over 3600 asymptomatic women in MESA who were deemed low-risk for 10-year coronary heart dis-

ease risk based on FRS [38] (5). The prevalence of CAC >0 in this cohort was 32% ($n = 870$), and compared with women with CAC = 0, this cohort had a much higher risk for coronary heart disease (hazard ratio 6.5; 95% CI 2.6–16.4) (5). The addition of CAC to traditional risk algorithms such as FRS improved the risk prediction of coronary heart disease and CVD events.

The event rate with CAC zero is substantially lower. Thus, the presence of atherosclerotic plaque or so-called vulnerable/unstable plaque is highly unlikely with cardiac event rates approaching 0.1% per year [39]. In a pooled analysis of 35,765 asymptomatic persons, Shareghi et al. demonstrated that in a subset of patients with CAC = 0, the annual event rate approached 0.027% and estimated 10-year event rate approximately 0.3% [40]. Budoff et al. provided further support for CAC as a predictor of future cardiac events, showing unadjusted Kaplan–Meier cumulative event curves for major coronary events in males and females (Fig. 31.3) [41]. Similarly, in a large registry of 25,253 persons, those with CAC = 0 scores showed survival of 99.7% over a 6.8-year period (Fig. 31.4) [42].

Role in Symptomatic Patients

The power of zero for coronary artery calcium scoring has the highest yield when applied to asymptomatic populations. When symptoms are introduced, the pre-test probability of disease increases substantially, and the negative predictive value falls. Nevertheless, the role of CAC in symptomatic patients has been previously evaluated. Higher CAC scores are associated with increased likelihood of detecting stenosis >50% [43]. In early work by Guerci et al., patients with CAC score >170 were far more likely to have obstructive coronary disease on invasive angiography regardless of number of risk factors [44]. A CAC score cutoff of 100 showed a high sensitivity and specificity for detecting high-grade stenosis (>75%) by invasive angiography, 95% and 79%, respectively [45] (6). In the multicenter PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, Budoff et al. compared the prognostic value of CAC in symptomatic patients to functional testing. CAC strongly predicted future cardiovascular events, C-statistic similar to functional testing (0.67 vs. 0.64), although functional studies were more specific [46] (Table 31.1).

Caution must be exercised in applying the "power of zero" to clearly symptomatic patients. Applying the Bayes theorem, which invokes that the efficiency of a diagnostic test is reliant on the frequency of disease in the population tested, clinicians must be wary of using a CAC = 0 to rule

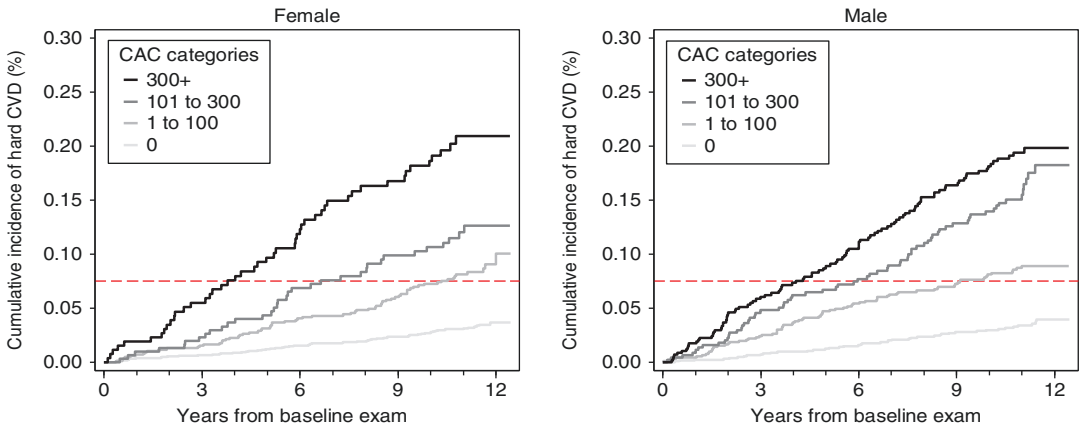

Fig. 31.3 Unadjusted Kaplan–Meier cumulative incidence of major coronary events stratified by CAC score and sex. (Adapted from Budoff et al. [41])

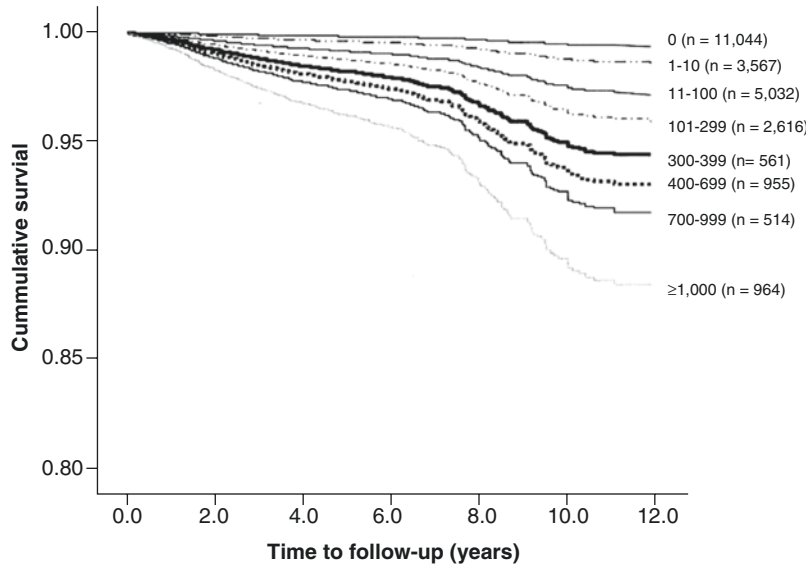

Fig. 31.4 Cumulative survival stratified by CAC subsets from 0 to >1000. Increasing calcium scores are associated with worsened survival. (Adapted from Budoff et al. [42]. With permission from Elsevier)

Table 31.1 Summary of existing guidelines and expert consensus statements on the addition of CAC scoring to traditional cardiovascular risk assessment tools in asymptomatic persons

Guideline/statement	Summary	COR	LOE
2010 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [7]	Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10–20% 10-year ASCVD risk)	IIa	B
2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [8]	Coronary artery calcium scoring may be considered as a risk modifier in CV risk assessment	IIb	B
2018 United States Preventive Services Task Force [9]	In asymptomatic adults, the current evidence is insufficient to assess the balance of benefits and harms of adding CAC score to traditional risk assessment of CV disease prevention	I	
2018 Guideline on the Management of Blood Cholesterol [10]	In adults 40–75 years of age without diabetes mellitus and LDL levels ≥70–189 mg/dL, at a 10-year ASCVD risk of ≥7.5–19.9%, if a decision about statin therapy is uncertain or selected borderline risk (5% to <7.5% 10-year ASCVD risk), consider measuring CAC. A CAC score of 1–99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated	IIa	B-NR
2017 Expert Consensus Statement from the Society of Cardiovascular Computed Tomography [11]	It is appropriate to perform CAC testing in the context of shared decision-making for asymptomatic individuals without clinical ASCVD who are 40–75 years of age in the 5–20% 10-year ASCVD risk group and selectively in the <5% ASCVD group, such as those with a family history of premature coronary artery disease		

CAC coronary artery calcium, *CV* cardiovascular, *AHA* American Heart Association, *ACC* American College of Cardiology, *COR* class of recommendation, *LOE* level of evidence, *ASCVD* atherosclerotic cardiovascular disease, *LDL* low-density lipoprotein, *NR* nonrandomized

out obstructive coronary disease in a symptomatic, higher-risk population [47]. Results from the Core64 substudy which consisted of primarily intermediate to high pre-test probability of obstructive CAD demonstrated that while CAC = 0 reduced the likelihood of obstructive disease on invasive angiography (15% for CAC = 0, 58% for CAC >10), it cannot be used to exclude CAD in a high-risk, symptomatic cohort [48].

However, there may be a role for assessing coronary calcium in the low-risk symptomatic patient presenting to the emergency department. Current expert consensus statements advocate for the use of CAC in triaging chest pain patients in the emergency department. The authors argue that CAC = 0 has sufficiently high sensitivity (98%) such that a low-risk symptomatic patient with a score of zero can be safely discharged without further testing [49]. Such a fast rule-out model applied to the right patient population may translate to significant cost savings on the healthcare system.

Guidelines

A summary of current guidelines and expert consensus statements on the use of coronary artery calcium scoring is provided in Table 31.1. The 2018 Guideline on the Management of Blood Cholesterol incorporated CAC assessment to determine need for statin therapy, moving to a class IIa recommendation for any adult 40–75 years of age with CAC >100 [10, 50]. A recent study from Walter Reed Army Medical Center evaluated the impact of statins on ASCVD outcomes stratified by CAC score. Over a median follow-up period of 9.4 years and enrollment of 13,644 patients, the investigators found that statin therapy reduced MACE events in patients with CAC (adjusted subhazard ratio 0.76; 95% CI 0.60–0.95; $p = 0.015$) but not in patients without coronary calcification (adjusted subhazard ratio: 1.00; 95% CI 0.79–1.27; $p = 0.99$) [12]. The number needed to treat (NNT) in patients with CAC >100 was 12 ($p < 0.0001$), whereas CAC 0 showed no significant effect and CAC 1–100 showed NNT 100 ($p = 0.095$) [51].

Technical Aspects

Image Acquisition

In current modern-day, multi-detector CT scanners, the acquisition of coronary artery calcium scans is standardized across vendors and imaging centers. Images are acquired prospectively with EKG gating at a slice thickness of 2.5–3 mm [52]. CAC scans are acquired without the use of intravenous contrast. Scanner settings can alter the density of calcified plaque through increased blooming artifact. Nonetheless, image acquisition time remained too slow for imaging rapidly moving heart to accurately assess the coronary arteries, until the early 2000s, when faster CT systems with capability to acquire thin slices were introduced. For example, 64-slice CT system was available around 2005 with rotation time of 330 milliseconds (ms) and slice thickness of 0.6 millimeter (mm) with the capability to cover the entire heart in three partial rotations. Some of the latest scanners have 256/320 rows of detectors. They provide a rotation speed of 280/300 ms. At a collimated slice thickness of 0.6/0.5 mm, scan volume of 16 cm can be covered, sufficient to cover the heart in one single partial resolution. The Society of Cardiovascular Computed Tomography (SCCT) has specified CAC and CCTA scan acquisition at a voltage of 120 kVp with tube current variable based on body habitus [53].

Radiation

The ALARA (as low as reasonably achievable) principle applies to coronary artery calcium scans just as with any other medical imaging that utilizes ionizing radiation. The lifetime risk of cancer relates to the cumulative radiation dose, making it all the more important to keep dose low in each study when possible. The SCCT requires that all CT laboratories record radiation dose in each patient as dose-length-product (DLP; units of milligray*cm) and effective radiation dose (millisievert [mSv]) [53]. The average DLP should not exceed 200 mGy*cm with effective radiation dose averaging 1.0–1.5 mSv [53]. Importantly, there has been dramatic reduction in

radiation doses since the last decade for CCTA as well. Median effective dose estimates were 12.4 mSv in 2007 decreasing to 2.7 mSv by 2017, resulting in 78% reduction in radiation doses according to large prospective multicenter trial. Notably, the number of non-diagnostics coronary CTAs did not increase [54]. Low radiation with capability to not only rule out obstructive disease but characterize atherosclerotic plaque severity and morphology makes CCTA a unique and attractive non-invasive imaging modality.

CAC Scoring

Several methods exist for quantifying coronary artery calcification (Fig. 31.5). Each has its own benefits and limitations; however, quantifying the degree of coronary calcification is essential to its predictive value for cardiovascular disease.

The Agatston score is the most widely used scoring system in clinical practice and remains the reference standard since introduction by Dr. Arthur Agatston in 1990 [17]. The per-lesion score is the product of area (mm^2) and lesion density weighting factor (DWF). The density weighing factor is obtained from the maximal CT attenuation of a given lesion where 130–199 Hounsfield Units (HU) =1, 200–299 HU = 2, 300–399 = 3, and >400 = 4. The total Agatston score is the summed score of all calcified lesions.

Alternate methods for describing coronary calcium burden include a volume-based score that relies upon similar scanning protocols as the Agatston score. The number of voxels exceeding a cutoff of 130 HU and area ≥1 mm^2 multiplied by the volume per voxel yields the per-lesion volume score [55]. This methodology does not account for density of a particular plaque. Another method for scoring calcium burden is to measure the total mass of coronary calcium. This method involves the use of phantoms for calibration and is not widely used. Finally, the density score is another scoring system that has gained increased attention. This method uses the Agatston score and the total volume score to back-calculate the average density factor. In MESA, Criqui et al. demonstrated that CAC density showed an inverse relationship with CVD events. Consideration of calcium density may be of most value in extremes of age – younger patients with low calcium density in whom intermediate Agatston scores may underestimate risk or older patients in whom highly dense lesions with borderline Agatston scores may lower risk estimates [13, 55].

Regardless of scoring methodology, high-quality image acquisition is paramount to high reproducibility and accuracy of calcium scoring. Motion can result in overestimation of calcium, particularly in the right coronary artery which is prone to such artifact. Similarly, poor spatial res-

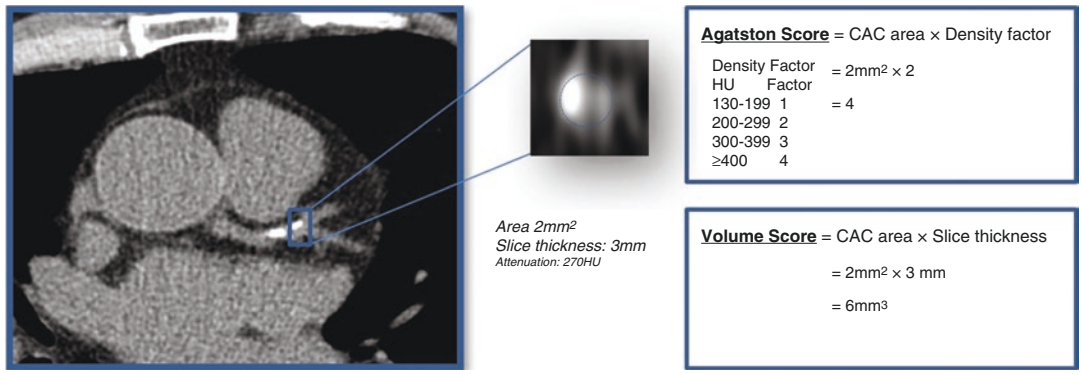

Fig. 31.5 Quantification of coronary calcification using the Agatston score and volume-based score. CAC coronary artery calcification, HU Hounsfield units

olution and noisy images may underestimate the total calcium score. Calcification outside the coronary arteries, such as valvular calcification, mitral annular calcification, and aortic root calcification, can all contribute to overestimation of the calcium score and must be excluded. Vessel segments with stents must also be excluded from analysis.

CAC from Nongated Chest CT

On average in the United States, 14,000,000 chest CT scans are obtained annually for non-coronary purposes [56]. While vascular calcification may be noted on formal reports, quantification of CAC is typically not undertaken. This presents a tremendous opportunity to screen and identify patients at risk for future cardiovascular events and, importantly, capture this data across a variety of clinical settings (i.e., primary care, emergency department) and for myriad indications (lung cancer screening, chronic obstructive pulmonary disease). Prompt implementation of secondary prevention strategies from cholesterol reduction to risk factor modification could have a significant impact on population-based cardiovascular risk. Recent work from our lab demonstrated a strong correlation in Agatston score between gated calcium scans and nongated chest CTs with a weighted Cohen's kappa = 0.86 (95% CI: 0.84–0.89). Measurement of coronary calcium from nongated chest CTs presents an opportunity for earlier identification of coronary disease and implementation of targeted primary prevention measures.

CT Angiography

Prognostic Value of Coronary CT Angiography

Semi-quantitative CT Measures

Atherosclerotic plaque is assessed on per segment basis on CCTA. Coronary arteries usually >2 mm are evaluated. Coronary plaques are defined as structures >1 mm^2 within and/or adjacent to the coronary lumen, which could clearly be distinguished from the surrounding pericardial fat tissue and contrast-enhanced vessel lumen. Normal coronary arteries are defined as absence of obstructive or non-obstructive atherosclerotic plaque [57]. The parameters that are used for semi-quantitative analysis on cardiac CT are as follows.

Segment involvement score (SIS)- is determined by adding the number of segments with any coronary lesion, providing a number of segments of the coronary tree with stenosis present. The Total Plaque score (TPS) is derived by the amount of plaque in each segment. Plaque is quantified as mild (score-1), moderate (score of 2), or severe (score of 3). Total plaque score is determined by summation of the severity of plaque in each coronary segment. Segment stenosis score (SSS): Severity of stenosis for each segment is determined as score of 0 for normal, 1 for 1–49% stenosis, 2 for 50–69%, and 3 for >70% stenosis. SSS is calculated as the sum of the maximal stenosis score in each segment [57, 58].

Furthermore, morphology of coronary artery plaques is determined visually. Non-calcified plaques are defined as those with no calcifications, while partially calcified or mixed plaques have <50% calcification and calcified plaques as presence of >50% calcifications [58] (Fig. 31.6).

The earlier studies evaluated the prognostic value of CCTA mostly utilizing the worst lumen stenosis [59, 60]. A meta-analysis of 9592 patients showed that the presence of >50% stenosis on CCTA had incidence of death or MI 3.2% as compared to 0.15% in those without CAD [61]. Moving beyond stenosis, subsequent studies evaluated the prognostic value of CTA utilizing several other markers such as SIS, TPS, and SSS as described above. CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry which comprises 27,125 consecutive patients from 12 cluster sites in 6 different countries has played a pivotal role in establishing prognostic value of CCTA. It comprises patients with known coronary artery disease (CAD), patients with suspected but without known CAD, or asymptomatic persons undergoing CTA [58].

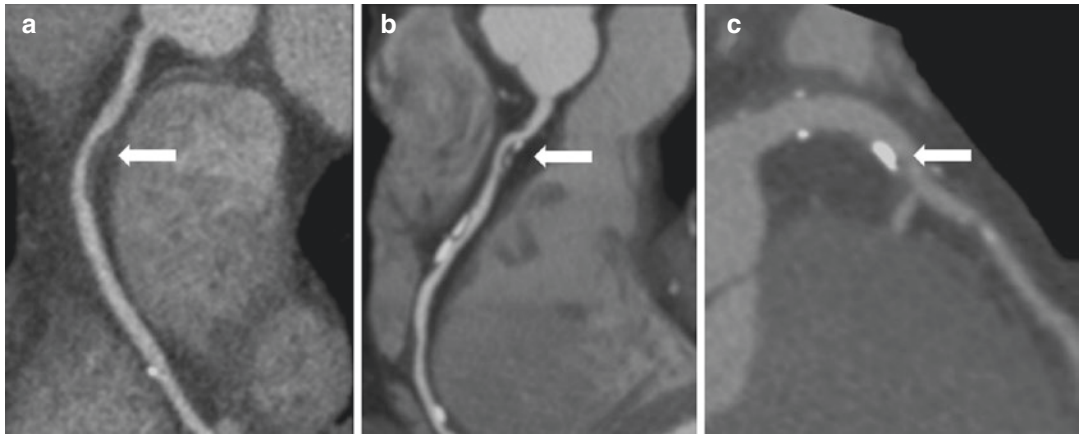

Fig. 31.6 Examples of atherosclerotic plaque types, (**a**) non-calcified plaque, (**b**) mixed plaque, and (**c**) calcified plaque

In CONFIRM Registry, individuals without prior CAD and with no known medically modifiable CAD risk factors including hypertension, dyslipidemia, diabetes mellitus, and family history were evaluated. Non-obstructive disease defined as >1 coronary segment involved was associated with increased mortality as compared to those with no atherosclerosis (9.48% vs. 3.95%, $p < 0.001$) over a mean long-term follow-up of 5.6 years. In this cohort of patients with no-modifiable risk factors, 92% were classed as either low or intermediate pre-test likelihood of obstructive CAD, according to the Diamond and Forrester model. However, 24% patients had obstructive CAD and 26.3% non-obstructive CAD, highlighting the inconsistency in clinical assessment of CAD and extent of atherosclerosis on coronary CT [62].

CONFIRM investigators created a CONFIRM score based on test sample of 17,792 patients and validation sample of 2506 patients. It integrated the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III score, with assessment of most predictive CCTA parameters including plaque and stenosis in proximal segments. Proximal segments include proximal and mid left anterior descending, proximal and mid right coronary artery, proximal left circumflex, and first obtuse marginal. Deseive and colleagues showed that among all clinical risk scores, NCEP ATP III performed better (c-index 0.675), followed by the Framingham score (c-index 0.661) and Morise score (c-index 0.606) for all-cause mortality. However, CONFIRM score provided best prediction for all-cause mortality (c-index 0.69) with reclassification of 34% of patients when compared with the NCEP ATP III score. Furthermore, the authors conducted subgroup analyses in women and asymptomatic individuals. Predictive value of CONFIRM scores remained robust in these subgroups. This study underscores the importance of utilizing CCTA parameters, which could potentially reclassify around one third of patients. The CONFIRM score also provided significantly better prediction for all-cause mortality in comparison to other CCTA-based parameters, and c-indices for SIS, SSS, and Leaman score were 0.648, 0.653, and 0.646 ($P < 0.001$) for all-cause mortality [63].

Recent guidelines recommend deferring statins in patients with CAC-0 in general population except in individuals with specific conditions such as diabetes. There are reports that CCTA provides an added prognostic value over CAC in asymptomatic individuals with diabetes. Min et al. reported age, gender, and CACS in asymptomatic diabetics provided c-index of 0.64, which improved by the addition of CCTA parameters such as SSS (c-index 0.78) [64]. However, two meta-analyses showed a conflicting result about predictive value of coronary CTA as a screening test in asymptomatic diabetics [65, 66].

Currently, CCTA is not recommended as screening test, but CTA may hold a place in screening high-risk patients with diabetes and those with chronic inflammatory conditions such as HIV and rheumatoid arthritis. Nonetheless, more work would need to be done before making screening CTA a routine in these groups.

Quantitative Volumetric Analysis

Invasive imaging tools such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) offer the closest information to match histopathology of atherosclerotic plaque information [67–70].

However, their invasive nature precludes their utilization for cardiovascular risk assessment. Volumetric nature of CCTA provides an opportunity to assess the atherosclerotic plaque burden in the entire coronary artery tree, thus making it unique among various imaging modalities (Fig. 31.2). CCTA identifies twice as many atherosclerotic plaques compared to invasive coronary angiography [71, 72]. Submillimeter isotropic resolution of CCTA allows the assessment of morphology of coronary atherosclerosis. Several studies have shown that plaque detection and characterization evaluated on CCTA correlate well with IVUS [67, 68, 73]. Motoyama et al. [74] showed that total atheromatous plaque volume progression over time on a volumetric basis was an independent predictor of future acute coronary syndrome (ACS) as compared to non-progressors (14.3% vs. 0.27%) over a median follow-up of 4 years. In a case-control study, M.M Hell et al. [75] showed that total plaque volume >179 mm^3, non-calcified plaque volume >146 mm^3, and low-attenuation plaque >10.6 mm^3 were significant predictors of cardiac death over a mean 5-year follow-up period [75]. Similarly, several other studies have shown that software-based objective assessment of plaque burden, specifically non-calcified plaque, is associated with future major adverse cardiovascular events [76]. Verteylen et al. [76] showed that volumetric plaque quantification and characteristics provided additional prognostic value over clinical risk factors and conventional CT reading (including CAC, segment stenosis, lesion severity, and number of segments with non-calcified plaques (AUC 0.64–0.79, $p = 0.047$)). Currently plaque quantification and characterization using semi-automated software takes on average 20–30 minutes making it hard to incorporate in routine clinical practice. Nonetheless, with machine learning algorithm getting better might make plaque quantification part of routine clinical algorithm [75].

Adverse Plaque Features

Three coronary atherosclerotic plaque characteristics – positive remodeling, low-attenuation plaque, and spotty calcification – have been identified as high risk of coronary CTA (Fig. 31.7). Motoyama et al. [77] studied 38 patients with ACS and compared them with 33 patients with stable chest pain. The presence of positive remodeling, spotty calcification, and low-attenuation plaque was significantly more in ACS lesions. In a nested case-control ICONIC (Incident COronary EveNts Identified by Computed Tomography) study, patients with high-risk plaque features, defined as ≥2 of the above-described features, had 60% increased risk of future acute coronary syndrome [78]. Interestingly, 75% of acute coronary syndrome culprit lesion precursors at baseline showed <50% stenosis [79]. In patients who experienced ACS versus those who did not, adverse plaque features were present in 52% and 33%, respectively, implying the dynamic evolving nature of plaque and that even stable asymptomatic patients may have these underlying high-risk plaque features that makes them vulnerable. Furthermore, recent analysis from Scottish COmputed Tomography of the HEART Trial (SCOT-HEART) [80] showed that adverse plaque features were predictive of MACE over a 2-year but not at 5 years' follow-up, suggesting that these plaque features might identify patients at near-term risk.

CTA Versus Standard of Care in Patients with Stable Chest Pain

Two large prospective multicenter randomized trials compared initial strategy of CCTA versus traditional strategy of functional testing or usual

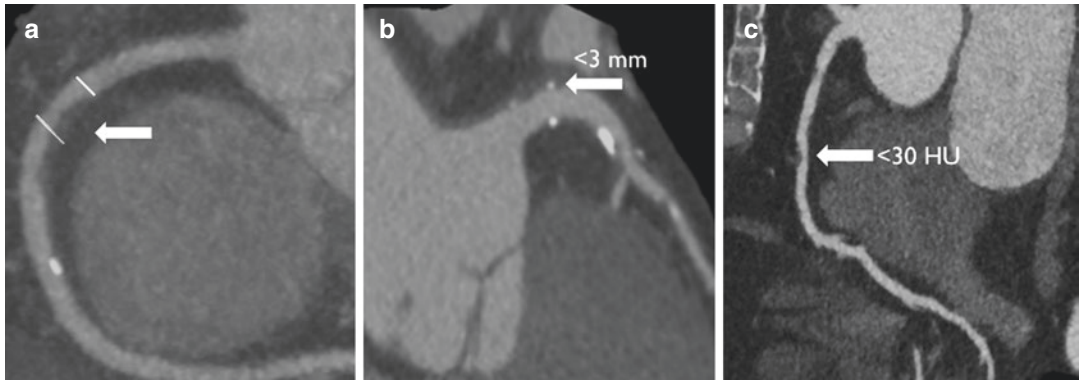

Fig. 31.7 CCTA-based examples of adverse plaque features. (**a**) Positive remodeling characterized by ratio of vessel diameter at lesion (white arrow) site to reference vessel >1.05. (**b**) Spotty calcification (white arrow) characterized by <3 mm calcification. (**c**) Low-attenuation plaque (arrow) characterized by <30H

care in patients presenting with stable chest pain. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study showed there was no significant decrease in MACE in CCTA arm as compared to functional testing. However, there was a significant reduction of the number of patients receiving invasive catheterization without obstructive disease in CTA versus functional strategy (28% vs. 52%) [81]. However a priori planned subgroup analysis showed that patients with diabetes who underwent CCTA had a lower risk of death/MI compared with functional testing (CCTA: 1.1% vs. stress testing: 2.6%; a; $p = 0.01$ [82]). A recent landmark 5-year clinical outcome result for SCOT-HEART showed a 40% reduction of coronary heart disease death or non-fatal MI in CCTA arm compared to standard of care [83]. There is an evidence that these results are likely due to initiation or intensification of preventive therapies in patients undergoing CTA [4]. The capability of CCTA to see and quantify atherosclerosis leads to post-care pattern that is quite dissimilar from that of functional testing [3].

CTA Versus Standard of Care in ER

Four large randomized trials (CT-COMPARE, ROMICAT II, ACRIN-PA, and CT-STAT) compared current standard including stress testing with CCTA strategy [84–87]. These trials demonstrated that patients who underwent CCTA had shorter length of stay and shorter time to discharge. Importantly these trials demonstrated the safety of a negative CCTA with very low subsequent events (<1%). It is estimated that more than 6 million people in the United States alone go to emergency departments due to acute chest pain. Very few percentages of these patients have obstructive coronary artery disease. In majority of these patients, CP is unrelated to heart. Along with faster discharge, CCTA provides an opportunity to initiation and intensification of preventive therapies in patients with non-obstructive coronary artery disease on CTA (Fig. 31.8).

Monitoring Therapy with Serial Coronary CT Angiography

Serial studies utilizing IVUS and coronary angiography provided an insight into natural history of atherosclerotic coronary artery disease. Besides, serial measurements of coronary plaque volume using IVUS have served as remarkable tool to gauge drug efficacy in atherosclerosis progression [69, 88]. Nonetheless, invasive nature of IVUS limits the routine use of this modality. Given the capability of CCTA to assess the plaque morphology. Several studies have utilized serial CCTAs to evaluate changes in morphology and progression of plaque after a specific therapy [69] (Fig. 31.9). Shin et al. [89] performed semi-automated quantitative coronary CT plaque assessment in 467 patients with median scan

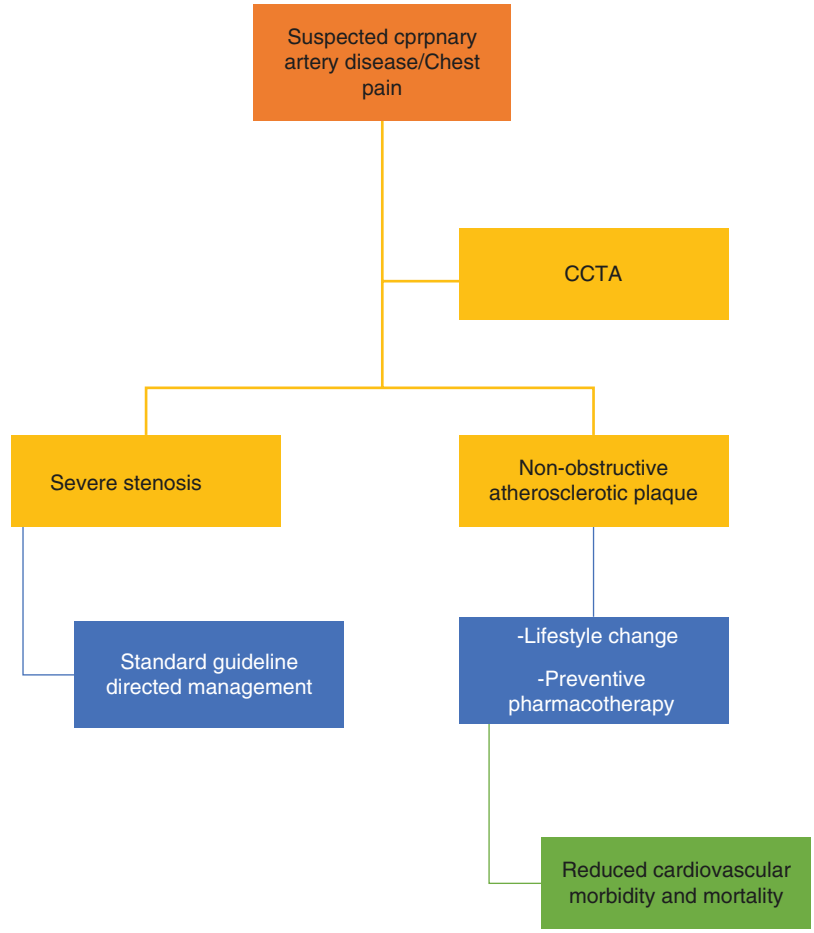

Fig. 31.8 Pathway to improve outcomes in patients who underwent CT for acute chest pain or stable chest pain of suspected coronary origin

period of 3.2 years. Patients who achieved LDL-C of <70 were compared to those with >70. Patients with LDL-C levels below 70 had significantly less progression of plaque as compared to those with >70 mg/dl (12.7 + 38.2 vs. 44.2 + 73.6 mm, respectively = 0.014).

Kaivan et al. [90] performed serial coronary CT study to assess the impact of colchicine on plaque over a mean follow-up of 12.6 months. They showed that colchicine therapy significantly reduced LAPV as compared to control group (mean 15.9 mm [−40.9%] vs. 6.6 mm [−17.0%]; p = 0.008). In a serial prospective study of 32 patients, 24 on statins and 8 not on statins, Kaori et al. [91] assessed the efficacy of fluvastatin. Serial CTAs were performed after a median follow-up of 12 months. In the fluvastatin-treated patients, total plaque volume and low-attenuation plaque volume were significantly reduced over time (92.3 ± 37.7 vs. 76.4 ± 26.5 mm, $p < 0.01$) and (4.9 ± 7.8 vs. 1.3 ± 2.3 mm, $p = 0.01$), respectively. Control subjects had no change in total atheroma plaque volume and LAP. Other studies utilizing serial coronary CTA showed the less coronary plaque progression in patients treated with statins, in concordance with previous IVUS literature. Budoff et al. [92] recently evaluated impact of testosterone on coronary atherosclerosis. Testosterone treatment compared to placebo was associated with a significant increase in non-calcified plaque volume from baseline to 12 months as compared to placebo (estimated difference 47 mm 3; 95% CI, 13–80 mm; $P = 0.006$).

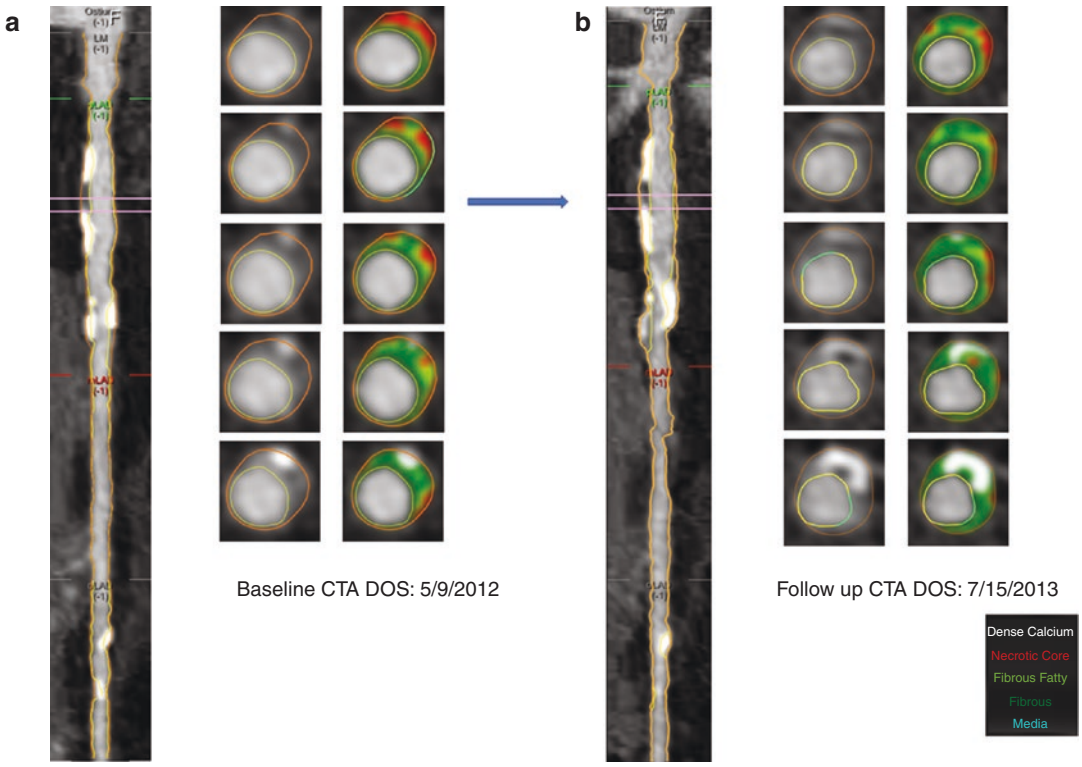

Fig. 31.9 Volumetric assessment of coronary plaque, (**a**) plaque burden at mid left anterior descending artery and (**b**) plaque progression at follow-up scan over a year later

Our lab and others have evaluated the efficacy of alternative therapies in halting coronary plaque progression over time. For example, aged garlic extract compared to placebo was shown to cause regression in low-attenuation plaque volume on serial coronary CT over a period of 1 year in patients with metabolic syndrome and diabetes [93, 94]. There was 20% reduction in LAP in participants taking aged garlic extract as compared to those on placebo [93].

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