Coronary atherosclerosis is a complex inflammatory process that involves, in part, endothelial damage, deposition of oxidized low-density lipoprotein into the intima, smooth muscle cell proliferation, and macrophage infiltration and activation.1–5 Several inflammatory mediators and chemokines contribute to plaque initiation, growth, and rupture, which is the most common proximate event behind sudden coronary thrombotic events that result in acute coronary syndrome.2 Among the plaque constituents, coronary calcium fares prominently and is virtually pathognomonic for atherosclerosis5 (Figure 1). Calcium phosphate in a hydroxypatite form accumulates in intimal atherosclerotic lesions.7 Calcification of atherosclerotic plaque first appears in the lipid core of the atheroma, juxtaposed to inflammatory cells and occurs by an active process resembling bone formation, under the control of complex enzymatic and cellular pathways.8 This formation involves osteoblast-like cells, cytokines, transcription factors, and bone morphogenetic proteins (such as bone morphogenetic protein 2A, osteoprotegerin, osteopontin, osteocalcin, and osteonectin) and is characterized by inflammation, lipoprotein and phospholipid accumulation, apoptosis, and finally hydroxyapatite deposition.9 The inciting mechanisms are not definitively understood, but apoptosis of smooth muscle cells seems to be an important step, which then serves as a nidus for calcification. There is a linear relationship between coronary calcification and total coronary plaque burden on a segmental and entire coronary vessel basis. Based on histomorphometric studies, ≈20% of atherosclerotic plaque burden in the coronary vascular bed is calcified, and these macrocalcifications can be identified by noncontrast-enhanced computed tomography (CT).7,9,10

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Methods of Measurement of Coronary Artery Calcium

The identification and quantification of coronary artery calcium (CAC) by CT was first performed using electron beam computed tomography in the 1980s.11 Since then, advances in CT technology have allowed for more accurate and reproducible measurement of CAC. CAC can be measured using different CT protocols, including electron beam CT, multislice CT, and CT angiography. The most widely used protocol is electron beam CT because it provides high spatial resolution and signal-to-noise ratio, which are important for accurately measuring CAC. The CAC score is calculated using a scoring system that assigns points based on the number and size of calcified plaques. The CAC score is a powerful predictor of future cardiovascular events, independent of traditional risk factors. The CAC score is also useful in risk stratification, as patients with high CAC scores are at increased risk for future cardiovascular events.
CT, a technology that provides the high temporal resolution needed to image the perpetually moving coronary arteries. This temporal resolution is facilitated by a CT scanner with a nonmoving gantry using an electron beam steered electromagnetically onto tungsten rings to produce x-rays, which are then swept across the patient’s heart and detected on 2 parallel static detector rings.11 With the recent introduction of multidetector row CT, however, electron beam CT has been generally supplanted by a scanner with superior spatial resolution. By either method, the radiation dose to detect and quantify coronary calcification is low. Radiation exposure of CAC scoring (CACS) is ≈1 mSv, which is comparable with that of a screening mammogram (0.7 mSv).12 With rapidly occurring further improvements in scanner hardware and software, radiation exposure will go down even further, to <0.5 mSv.

An array of scores has been used to quantify coronary calcium content, among which the Agatston score remains the most commonly used.11 In this method, calcified lesions above a threshold value of 130 Hounsfield units (HU) and area >1 mm² (3 adjacent pixels) are detected based on their density and area. The area of calcification in each of the slices is calculated and multiplied by a weighting factor (eg, for 130–200 HU, a factor of 1 is assigned; for 201–300 HU, a factor of 2 is assigned; for 301–400 HU, a factor of 3 is assigned; and so on). All axial scores are then summed (Figure 2). One caveat is that the Agatston score is prone to overestimation of coronary calcium content, because it is susceptible to partial volume effects, motion, arrhythmias, image noise, and artifacts from metallic clips and implanted defibrillator leads. To overcome these limitations, Callister et al13 proposed a volume score because the Agatston score does not take into account the depth of calcium, but rather the area only. Thus, an increase in the Agatston score over time may occur from an increase in the amount of plaque, but may also occur as a result of increased plaque attenuation (density) rather than a true increase in plaque size. In contrast, the calcium volume score is independent of image overlap and slice thickness.13 In the Multi-Ethnic Study of Atherosclerosis (MESA) study, each participant underwent an electron beam CT and multidetector row CT 2

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Figure 1. Diagram depicting the progression of coronary atherosclerosis with age. By the teenage years, there is almost universal appearance of type 3 lesions in the aorta.6 With increasing number of risk factors and age and ensuing endothelial damage, there is progressive growth in atheroma size. Calcification occurs in some of these lesions and leads to increasing calcium deposition with time, which is readily appreciated by noncontrast cardiac computed tomography. CAC indicates coronary artery calcium.
minutes apart; volume scores showed better reproducibility compared with Agatston scores. A third method of measuring coronary calcium content is the mass score, a technique that multiplies the lesion volume, the average CT density, and a calibration factor. The method of CACS requires an external standard calibration phantom, but is the most reproducible value because it is independent of hardware or scanning protocols. Nonetheless, these newer scores have a smaller prognostic evidence base of studies, and despite its aforementioned limitations, the Agatston score has been studied extensively for risk assessment in various large population-based studies, and despite its aforementioned protocols. Nonetheless, these newer scores have a smaller prognostic evidence base of studies, and despite its aforementioned limitations, the Agatston score has been studied extensively for risk assessment in various large population-based studies and continues to enjoy the greatest popularity of use.

Risk Stratification, Discrimination, and Reclassification of At-Risk Individuals Based on Coronary Artery Calcium Prevalence and Extent

An online arterial age calculator (www.mesa.nhlbi.org) is available to estimate the percentile ranking of a patient compared with the MESA data after taking into account age, sex, ethnicity, and smoking status. This method, although often clinically used, does not effectively identify at-risk individuals. Indeed, an absolute value of CACS of $\geq 300$ or $400$ is more predictive of major adverse cardiac event (MACE) rather than a percentile score.

This is especially true in younger patients where the percentile score informs relative risk, whereas the absolute score gives the lifetime risk. CACS increases with increasing age and male sex. In general, CACS in women lag behind men by $\approx 10$ years. The prognostic value of CACS is retained in elderly patients.

Furthermore, the pattern of coronary artery calcification is also important, with greater risk of adverse clinical events occurring in the setting of greater numbers of calcified plaques and more coronary vessels involved, particularly if the calcification is in more proximal segments. A newly developed calcium coverage score incorporates the distribution and dispersion of calcium throughout the coronary tree. In a recent analysis of the MESA database with 3398 patients followed for a median of 7.6 years, the calcium volume score was associated with MACE, but calcium density was inversely associated with MACE, and it is feasible that more calcium-dense plaques might be protective because of a decrease in vulnerability. At this time, there are no data showing that preventive treatment of patients with high CACS is associated with improved cardiovascular outcomes, although it is likely that it does so and that such demonstration will require a large trial with a long follow-up period.

An Agatston CACS of $1$ to $99$ identifies a mild amount of plaque burden, $100$ to $399$ is moderate, $>400$ is high, and $>1000$ is severely elevated. A score of $0$ carries an excellent prognosis in asymptomatic patients. Pooled analysis from 6 studies from 2003 to 2005 with 27,622 asymptomatic patients showed that $43\%$ had a CACS of $0$ and a low rate of MACE of $0.4\%$ during a $3$- to $5$-year follow-up. The risk ratio for MACE increased to $7.2$-fold for a CACS between $400$ and $1000$ and to $10.8$-fold for a score $>1000$, therein demonstrating a continuous graded relationship between CACS and MACE. Survival rates have also been shown to have a similar graded relationship: from a large observational study of 25,253 patients with a mean follow-up of $6.8 \pm 3$ years, cumulative 10-year survival was $99.4\%$ for a CACS of $0$, which dropped to $87.8\%$ for a score $>1000$. In a systematic review of 13 studies with a total of almost 65,000 patients, $45\%$ had a CACS of $0$, and their event rate was $0.56\%$ during $4.25$ years of follow-up. Longer-term follow-up of $\approx 12$ years showed a mortality rate of only $0.4\%$. Thus, CACS=$0$ now allows for an intermediate-term warranty period that is more predictive of salutary outcomes, as compared with other methods of risk stratification, such as a negative stress nuclear perfusion study or carotid intima-media thickness. Importantly, although the noncontrast CACS does not permit direct visualization of coronary stenosis, the probability of coronary stenosis increases as the CACS increases (Figure 3).

As an example, Shareghi et al observed that among 3529

Figure 3. As the Agatston score increases, the proportion of patients with more obstructive stenoses on cardiac computed tomographic angiography (CCTA) increases. CAC indicates coronary artery calcium.
asymptomatic subjects of the Framingham Offspring Cohort, a zero CACS, although not excluding the presence of noncalcified plaque, virtually excluded the presence of significant atherosclerosis with a high negative predictive value for stenosis as well as event risk. Patients within this study experienced an annualized event rate of 0.6% for 5 years.

A major strength of CACS has been in its ability to improve reclassification and discrimination of patients into low-, intermediate- and high-risk states. As alluded to previously, the traditionally used Framingham Risk Score (FRS) and Adult Treatment Panel III schema misclassify a significant proportion of low- and intermediate-risk individuals. In 1 study, 4129 subjects without known coronary artery disease (CAD) were followed for 5 years. When CACS was applied to refine the FRS risk estimate, 21.7% were reclassified into the low-risk category and 30.6% were reclassified into the high-risk category. CACS, therefore, increased the receiver operating curve statistic area under the curve from 0.681 to 0.749 compared with FRS, and from 0.653 to 0.755 compared with Adult Treatment Panel III. Adding CACS to traditional risk factors in the MESA cohort, including age, sex, tobacco use, systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein-cholesterol, race, and ethnicity, resulted in a net reclassification index of 0.25, implying that 25% of patients were correctly reclassified into a different risk group.

Notwithstanding the oft-observed discordance between CACS and traditional risk factors of coronary heart disease (CHD), there is a significant continuous graded relationship among the prevalence of coronary calcium, mean CACS, and the number of risk factors. In a recent investigation, 40% of asymptomatic men aged <40 years showed calcium deposits, whereas the prevalence was 74% in men aged >60 years with ≥3 risk factors. This relationship between coronary calcification and risk factors becomes diluted in men aged >60 years, where the prevalence of coronary calcium deposits >80% and is not as tightly dependent on the number of risk factors. A family history of premature CHD also increases the likelihood of coronary calcification in the offspring. In the Coronary Artery Risk Development in Young Adults (CARDIA) study in younger adults aged 18 to 30 years, a higher number of risk factors was associated with higher CACS. As a general rule, sex differences are significant for CACS, with women, in general, lagging 10 years behind men in their plaque burden and CACS.

Current guidelines on CACS recommend it as reasonable (class IIa recommendation) for risk assessment in asymptomatic adults at intermediate risk (10-year risk of 10% to 20%) and in patients with diabetes mellitus, and that it may be reasonable (class IIb) for patients at low to intermediate risk (6–10% risk). They recommend against screening (class III) for high- (>20%) or low-risk (<6%) patients because CACS results will not demonstrably alter the reclassification or discrimination of these patients for risk prediction. With respect to the latter group, there is 1 exception: the appropriate use criteria committee judged it to be appropriate for low-risk patients who also had a family history of premature CAD. In fact, the clinical use of CACS has also been studied in a myriad of patient subsets. The prognostic value of CACS holds true for patients with diabetest mellitus who traditionally are thought to have a high burden and risk of CAD. In 900 patients with diabetes mellitus and a CACS=0, survival was similar to nondiabetic patients with a score of 0 (98.8% versus 99.4%). Likewise, in the MESA study of 2600 asymptomatic women with a median Agatston score of 0, the receiver operating curve area under curve for CAD was increased from 0.8 to 0.835 with the addition of CACS. Similar data exist for elderly patients and smokers as well. One notable exception is patients with chronic kidney disease, which is associated with increased total body calcium and increased CACS as well.

In the Chronic Renal Insufficiency Cohort (CRIC) study of coronary calcification in patients with chronic kidney disease, the degree of coronary calcification and cardiac event rate increased in a graded manner with worsening of renal function as measured by the glomerular filtration rate. A glomerular filtration rate <30 carried an odds ratio of 1.53 in multivariate analysis. In the Hisayama study of Japanese patients, there was a strong correlation between both CAC and atherosclerotic plaque burden and chronic kidney disease. Furthermore, patients on hemodialysis have much higher CAC compared with age-matched individuals and have a faster rate of CAC progression. At initiation of dialysis, 50% to 60% of patients show CAC, with even higher rates in the subset of those with diabetes mellitus.

Role of CACS in Symptomatic Patients With Acute Chest Pain

In symptomatic patients, a CACS=0 portends a favorable prognosis, although in this population the negative CACS may be associated with a small but nonnegligible prevalence of noncalcified plaque, a finding predictive of higher adverse clinical event rates (3.6%). Thus, although current National Institute for Health and Clinical Excellence guidelines recommend CACS as the initial workup test in patients with acute chest pain with a low pretest probability, this strategy will miss a small proportion of patients whose CACS=0 but, nonetheless, possess high-grade noncalcified plaque. In a series studying these populations, 6% to 12% of patients have only noncalcified plaque. This strategy may be most useful in the low-risk population, as evidenced by a study of 1031 patients with chest pain evaluated in the emergency department, where 61% had a CACS of 0 and were discharged home. Of these, only 0.3% had events during 6 months of follow-up. A CACS of 0 was also correlated with a normal, follow-up single-photon emission CT perfusion scan. However, there is the possibility of missing high-grade stenosis from noncalcified plaque by the use of CACS only. Because calcified plaque represents ≥20% of all plaque burden, despite the above reassuring data, there continues to be some controversy whether a CACS of 0 can be used to make discharge decisions in patients with acute chest pain.

Germaine to these findings, the sensitivity and specificity for a CACS >0 for predicting any stenosis >50% is 91% and 49%, respectively. However, the negative predictive value to exclude high-grade stenosis is high in the setting of a CACS=0, where the probability of >50% stenosis is <1%. As the CACS increases, the probability of obstructive CAD increases; for example, for a CACS ≥400, the likelihood of a >50% stenosis is >60% (Figure 3).
Progression of CACS

In the MESA study, conversion from a CACS=0 occurred annually in 5% of 50-year-olds and in >12% of 80-year-olds. In those patients, CAC progression was associated with 1.5-fold increased risk of hard CHD events. Among patients with CAC at baseline, event risk was 6-fold higher when the progression rate was >300 units per year.\(^53\) CAC progression rates were associated with conventional CHD risk factors, such as age, male sex,\(^44\) smoking,\(^23\) hypertension, fasting plasma glucose,\(^46,47\) family history of premature CAD,\(^48\) and diabetes mellitus.\(^49,50\) Novel markers of risk for CHD were also investigated. Although microalbuminuria,\(^51\) carotid intima-media thickness,\(^52\) white race,\(^53\) and polymorphisms of the renin–angiotensin system genes\(^53\) predict progression of subclinical coronary atherosclerosis, the C-reactive protein did not.\(^54,55\) Interestingly, although abdominal obesity,\(^56\) body mass index,\(^57\) and metabolic syndrome\(^58\) were associated with the progression of CACS, the levels of low- and high-density lipoproteins were related just with the incidence and not with the progression of preclinical atherosclerosis disease.\(^43\)

It has been described in a community-based screening cohort that calcium screening led to a 3- to 7-fold increase in the use of aspirin, statins, and lifestyle changes over 6 years.\(^58,59\) However, data on the effect of lipid-lowering therapy on the rate of progression of CACS has been still conflicting. Previous studies described positive correlation between statin treatment, serum lipid levels, and coronary calcium progression.\(^13,60-62\) More recently, however, several studies demonstrated that statin treatment was not able to reduce the progression of CACS,\(^63-66\) independently from the serum-level reduction of cholesterol and low-density lipoprotein.\(^63,64\) St Francis Heart Study is the largest prospective trial evaluating lipid-lowering therapy on CAC progression.\(^64\) It randomized 1005 patients with CAC equal to or greater than the 80th percentile for age and sex to statin treatment (20 mg atorvastatin daily) versus placebo and followed them prospectively with a repeat CACS in 4.3 years. Although it demonstrated a reduction in the low-density lipoprotein by 43% from baseline (146 mg/dL), the CACS increased from 528 to 846, and the 3% absolute risk reduction in the composite MACE end point in treated patients versus placebo did not reach statistical significance (\(P=0.08\); trend toward significance). Remarkably, in the subgroup of patients with a baseline CACS >400 (almost half of the study population), MACE was reduced by 42% (\(P=0.046\)). This discrepancy between CACS progression and MACE reduction may be explained on the basis of plaque stabilization by statins that involves depletion of lipid core and reduction in plaque macrophage content and inducing a fibrovascular transformation of thin-cap fibroatheroma (TCFA).\(^3\) Thus, although the plaque may become less vulnerable and the plaque volume may regress, the relative proportion of calcium may actually increase, accounting for these observations.

A continued increase of CAC may indicate inefficacy of the lipid-lowering therapy, and a rapid increase in the score is associated with incident myocardial infarction\(^67,68\) beyond conventional cardiovascular risk factors and current algorithm models for CHD risk prediction.\(^64\) Conversely, those with baselines scores <100 and progression <15% are at lower risk.\(^57\) In a study of 422 patients, the highest rate of conversion from a CACS=0 was in the fifth year and was nonlinear (ie, 15% cumulative in the first 4 years and 25% in the fifth year), suggesting that 4 years might be the warranty period for a CACS=0, a period longer than the 2-year warranty period that is generally espoused for a normal stress perfusion study.\(^45\) However, at this time, repeat CACS testing is considered inappropriate for general use because of lack of data from large-scale randomized trials showing that this strategy reduces adverse events.\(^64\)

**Extracoronary Calcium**

Cardiac CT angiography (CCTA) is also able to identify noncoronary calcification. One example of this is mitral annular calcification (MAC), which has been shown to increase the risk of MACE. MAC increases with age and hypertension and is more common in women.\(^69\) On transthoracic echocardiography, the prevalence of MAC in women aged >65 years without evident cardiovascular disease is as high as 40%.\(^68,69\) MAC is also correlated with CACS,\(^70\) CAD,\(^71\) and vulnerable plaque\(^72\) and increases the risk of MACE.\(^73\) Other cardiac and vascular foci of calcification such as aortic valve calcification, intramyocardial calcification in healed infarct scars, and thoracic aortic calcium also provide additional risk information. However, in a recent analysis from the MESA trial, the addition of thoracic aortic calcium, aortic valve calcification, or MAC to the FRS did not improve cardiovascular risk prediction, and that CACS alone was the strongest factor to predict incident adverse events.\(^74\)

**Plaque Characterization**

Because CACS does not detect noncalcified plaques, contrast-enhanced CCTA is more ideally suited for noninvasive detection of noncalcified components of coronary atherosclerotic plaques and in the classification of plaques along the spectrum of stable to vulnerable.\(^75-79\) Current CT scanners are capable of visualizing not only the lumen for coronary stenosis assessment but also the vessel wall and providing information on plaque size, length, volume, geometry, composition, and adverse features. CCTA has shown its ability to effectively rule out obstructive and nonobstructive CAD with an exceptionally high negative predictive value, a finding associated with low incident MACE rates.\(^80,81\) CT harnesses the different tissue attenuation values of different plaque components, such as fibrous tissue, lipid core, and calcium, to characterize plaque as calcified plaque, noncalcified plaque (NCP), and mixed plaque (Figure 4).\(^82\)

Qualitative plaque measurements such as calcified plaque, NCP, and mixed plaque have been demonstrated to be consistent among readers, with good intra- and interobserver agreement (\(r>0.8\)).\(^83-87\) These 3 plaque types by CCTA have different compositions when validated against virtual histology intravascular ultrasound (IVUS) and may be able to effectively differentiate the risk state of specific plaque types. As an example, 32% of mixed plaques in a recent study were associated with TCFA.\(^88\) In a recent meta-analysis of 20 studies, CCTA had excellent accuracy in detecting plaque (area under curve, 0.94; sensitivity, 90%; specificity, 92%).\(^86\) Plaque area, volume, and
percent area stenosis on CCTA were similar to IVUS.\textsuperscript{59} CCTA demonstrated slight overestimation of lumen area compared with IVUS by 0.46 mm\textsuperscript{2} (6.7\%), likely because of partial volume effects from the contrast-filled lumen. Plaques with >10\% necrotic core on virtual histology IVUS had lower attenuation values by CT versus those that did not (43 versus 93 HU).\textsuperscript{84,90} Otsuka et al\textsuperscript{84} reported that CCTA overestimated calcified plaque volume by only 3\% but underestimated NCP by 17\%. Voros et al\textsuperscript{84-86} showed that lumen area was overestimated by 22\% on 64-slice CT compared with IVUS. Similarly, vessel area, NCP area, and calcified plaque area were also overestimated by 19\%, 44\%, and 88\%, respectively. NCP by CCTA correlated best with necrotic core plus fibrofatty tissue.

CCTA is also reproducible for the quantification of arterial luminal diameter and area, plaque size, volume, geometry, and features. Although there remains some variability at smaller plaque volumes (\(\approx 10\) mm\textsuperscript{3}) because of the limited spatial and temporal resolution of present-generation CT, CCTA measurements are robust with larger plaque volumes (\(\approx 100\) mm\textsuperscript{3}).\textsuperscript{82} Our group reported on the interobserver variability of plaque quantification measures, demonstrating good correlation between different observers.\textsuperscript{93,94} To further improve the reliability of measurements and make them less time-consuming, standardized automated software is capable of reducing interobserver variability and improving the limits of agreement.\textsuperscript{87} CT generally overestimates the minimum lumen area by 27\%, but area stenosis is only underestimated by 5\%.\textsuperscript{96}

In a comparison of CCTA with optical coherence tomography, Kashiwagi et al\textsuperscript{95} observed several indices of plaque instability by CCTA to be associated with TCFA, including increased remodeling indices in TCFA (1.14 versus 1.02) and lower attenuation values (35 versus 62 HU). In addition, ring-like enhancement (also referred to as a napkin-ring sign), characterized by contrast accumulation in the periphery of the plaque but not in the central core, is observed in 44\% of plaques with TCFA versus only 4\% in plaques without TCFA. As opposed to these technologies (IVUS and optical coherence tomography), which allow morphological assessment, near-infrared spectroscopy uses the infrared light absorption spectrum of cholesterol to identify the cholesterol content of plaques in the artery. CCTA has shown good correlation of plaque features compared with this newer technology also. Voros et al\textsuperscript{84} demonstrated good spatial correlation between cholesterol localization on the block chemogram on near-infrared spectroscopy and the presence of NCP as well as the plaque burden on CCTA. The advantage of CCTA is that it is noninvasive and lends itself to serial follow-up to assess changes in plaque geometry and composition as compared with the other 3 invasive modalities.\textsuperscript{96}

**Prognosis**

Given the relationship of CCTA artery and plaque features with measures of plaque stability, an abundance of recent data has examined the prognostic use of CCTA-identified stenosis and plaque constituents. In a recent meta-analysis of 18 studies with 9592 patients with suspected CAD, CCTA robustly predicted MACE as well as all-cause mortality during a median follow-up of 20 months.\textsuperscript{97} When stratified according to tertiles of no stenosis versus <50\% stenosis and >50\% stenosis, the annualized rates of MACE were 0.17\% versus 1.4\% versus 8.8\%. Rates for all-cause mortality were 0.15\% versus 0.75\% versus 2.2\%. Further similar results have been reported for MACE in a large, prospective, multinational, multicenter Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) study of 15187 patients without previous known CAD.\textsuperscript{86} Among these patients, 595 MACEs (3.9\%) occurred at 2.4±1.2 years of follow-up. In multivariable analyses, an increased risk of MACE was observed for both nonobstructive (hazard ratio [HR], 2.43; \(P<0.001\)) and obstructive CAD (HR, 11.21; \(P<0.001\)) when compared with patients with normal CCTA. Risk-adjusted MACE increased in a dose–response relationship based on the number of vessels with obstructive CAD ≥50\%, with increasing hazards observed for nonobstructive (HR, 2.54; \(P<0.001\)), obstructive 1-vessel (HR, 9.15; \(P<0.001\)), 2-vessel (HR, 15.00; \(P<0.001\)), or 3-vessel or left main (HR, 24.53; \(P<0.001\)) CAD. Among patients stratified by age <65 years versus ≥65 years, older individuals experienced higher risk-adjusted hazards for
MACE for nonobstructive, 1-, and 2-vessel, with similar event rates for 3-vessel or left main (P<0.001 for all) compared with normal individuals aged <65 years.

Our group has also examined the prognosis of CCTA luminal stenosis by a modified Duke CAD index, which integrates not only stenosis severity but also the distribution and location of plaque. Using this measure, stenosis findings by CCTA offer improved risk stratification. Survival worsens with higher Duke score (96% survival for 1 stenosis >70% dropping to 85% survival for left main stenosis >50%).

Measures of stenosis severity as a function of prognosis transcend conventional definitions of anatomically severe. Lin et al studied the presence and extent of nonobstructive CAD and showed that the presence of any plaque increased the risk of death beyond clinical risk factors (Figure 5). Hazard ratios for all-cause mortality over 3 years in this study increased from 1.98 for the presence of any plaque to 5.12 when >5 segments were involved with nonobstructive plaque.

In addition to measures of stenosis severity, CCTA offers prognostic power by atherosclerotic plaque features. As an example, culprit lesions at the time of acute coronary syndrome demonstrate higher plaque volume, remodeling indices, larger vessel areas, less overall calcification, more low-attenuation plaques (<30 HU), spotty calcifications, and ring-like enhancement patterns. In a prospective study of 1059 patients undergoing CCTA for the evaluation of chest pain, 4% of patients possessed plaques with both low-attenuation plaque and spotty calcification. Among this subset, 22% developed acute coronary syndrome at 27 months of follow-up. In contrast, only 0.5% of patients without either of these features developed acute coronary syndrome, providing preliminary evidence that these atherosclerotic plaque features are infrequently seen in stable outpatients, but if seen can portend a worse downstream event rate.

CCTA offers prognostic value beyond that of CAC. This is true even in patients with a zero CACS. Furthermore, the burden of atherosclerotic involvement by CCTA correlates well with mortality and cardiac event rate. The worst prognosis is observed in left main and in 3-vessel coronary disease, and then there is a graded decrease in risk with proximal left anterior descending artery disease and further lower risk with 1-vessel disease. Nonetheless, even patients with nonobstructive disease (≤50%) fare worse compared with those with normal CTAs, indicating that the total plaque burden bears a close relationship to cardiac event rate and prognosis. The segment involvement score and segment stenosis score and Duke CT jeopardy score are 3 different ways of quantifying the degree of atheroma burden and stenosis, respectively, in the entire coronary arterial tree.

CONFIRM is a 27,000-patient international CCTA registry involving 12 centers in 6 countries that is tracking patients who underwent a clinically indicated CTA between 2005 and 2009 and following them prospectively for cardiac events. It has yielded a wealth of information about the relationships and interactions between risk factors and scoring systems (including FRS), lipid levels, and the extent and distribution of plaques as well as clinical events. Given its unparalleled large patient cohort size and prospective design with cumulative follow-up, it exists as a robust database to evaluate the relationships between various aspects of CAD, including sex, lipids, treatment patterns, and prognosis. Its limitations are that it is not a randomized comparison but rather an observational registry and is, therefore, subject to referral and treatment biases.

Serial Progression

Data on serial coronary plaque progression evaluation by CCTA are scant, but general thematic lessons are emerging. Early studies have determined that <1 to 2 years there is an observable increase in plaque volume and extent by CCTA. In a single-center study of 50 patients followed for 17 months who were not treated with medical therapy for CAD, noncalcified plaque volume in the left main and proximal left anterior descending artery increased from 91 to 115 mm³. In contrast, in a separate study of patients on statin therapy, no significant changes in overall plaque volume were observed at 18 months. These neutral findings were nevertheless accompanied by a decrease in the noncalcified portion of the plaque from 42 to 30 mm³. Concordant with this study is another investigation that comprised patients without any specific intervention to assess the natural history of plaque progression, demonstrating an increase in noncalcified plaque from

![Figure 5. Presence of nonobstructive coronary artery disease is associated with poorer survival compared with patients who have no visible plaque on coronary computed tomographic angiography. In this study of 2583 patients, the presence of any nonobstructive plaque carried a 1.98-fold higher risk of death at 3.1 y; compared with the group without any plaque. This risk increased further if more vessels were involved; when all 3 major epicardial coronaries showed nonobstructive plaque, the hazard ratio for death increased to 4.75, after adjustment for coronary artery disease risk factors.](image)
27% at baseline to 35% at 1 year of follow-up, with a decrease in minimum luminal area. This study advances the notion that the percent atheroma volume may be a better parameter to evaluate changes in plaque volume over time relative to the extent of arterial remodeling and may be a useful adjunct to conventional measures of luminal stenosis severity.

Role of CCTA in Symptomatic Patients With Acute Chest Pain
In patients presenting to the emergency department with acute chest pain, the evidence for CCTA has grown rapidly and now includes 4 randomized trials that have convincingly shown that a negative CCTA is associated with a low cardiac event rate, shorter length of stay, and lower rates of hospital admission as well as cost savings (Goldstein et al., Coronary Computed Tomography for Systematic Triage of Acute Chest Pain Patients to Treatment [CT-STAT]. American College of Radiology Imaging Network [ACRIN]). Rule Out Myocardial Infarction by Cardiac Computed Tomography (ROMICAT II). As such, CCTA allows busy hospital emergency departments to safely discharge such patients as opposed to the conventional strategy of admitting these patients for a rule-out myocardial infarction protocol followed by stress testing, all while decreasing resource utilization and improving efficiency. Given these data, the appropriate use criteria now classify CCTA as an appropriate test for such patients who have a low to intermediate pretest probability of having CAD.

Future Developments in CT
The recently completed HeartFlow Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (HeartFlow NXT) trial enrolled 254 patients and demonstrated the potential of fractional flow reserve derived from CT angiography (FFRct) to correctly identify patients with ischemia better than a purely anatomy-based evaluation. All patients underwent CTA, FFRct invasive angiography, and also invasive FFR as the gold standard. FFRct had a specificity of 79% to rule out myocardial ischemia compared with 34% for CTA and 54% for invasive coronary angiography. Sensitivity to detect ischemia was 86%. Similar to the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) trial, the area under curve for FFRct was ≥20% better at 0.82 versus 0.63 for CCTA, signifying the ability of FFRct to better discriminate lesion-specific ischemia. A strategy of revascularization based on FFR evaluation has been shown to decrease cardiac event rate, mortality, and reduce costs by $30,000 per patient.

Other advantages of FFRct are that it does not require additional contrast and that analysis can be performed on the same data set as acquired during the CCTA without any additional modification of the scanning protocol.

Summary
In recent years, CT has emerged as a robust technology with demonstrable utility in the evaluation of asymptomatic and symptomatic patients with suspected CAD. A plethora of population-based studies has confirmed the usefulness of CACS to offer improved risk stratification, discrimination, and reclassification compared with conventional risk assessment of CAD. CCTA has been introduced as a more contemporary adjunct to CACS, offering the ability to determine measures of stenosis severity and atherosclerotic plaque features. In large-scale studies, these findings may enable improved risk stratification than even CACS and may hone the ability to identify individuals at risk of incident myocardial infarction or death.

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