Should all high-risk patients be screened with computed tomography angiography?

Screening High-Risk Patients With Computed Tomography Angiography

Ilan Gottlieb, MD; João A.C. Lima, MD

Earlier this year, among the usual menu of worrisome daily news, Americans woke up to learn that for the first time in the nation’s history, annual mortality caused by cancer had declined significantly. Cancer experts told us in addition that such decline resulted mainly from a reduction in smoking among American men but also as a consequence of successful screening programs for breast and colon cancers, 2 of the most important killers in industrialized countries. The American Cancer Society, American Heart Association, and American Diabetes Association have proposed joint efforts to prevent and foster the early detection of cardiovascular diseases, cancer, and diabetes. Specifically, the American Cancer Society recommends screening for breast cancer starting at age 20 years with annual mammography starting at age 40, screening for cervical cancer to begin at age 21, and screening for colon and prostate cancer to begin at age 50.

Screening Asymptomatic Individuals at Risk for Coronary Artery Disease Events: An Unmet Need

The approach to prevent cardiovascular diseases has, on the one hand, focused primarily on the control of new traditional risk factors and biomarkers identified at first by the Framingham study but since then characterized and refined by a multitude of other large prospective studies, clinical trials, and consensus panels involving scientists, physicians, educators, and other healthcare professionals all over the world. The latter effort has paid enormous dividends and is considered to be responsible in large part for the declining cardiovascular disease mortality seen in the United States.

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However, much too often, we learn of someone who died suddenly or suffered a large myocardial infarction or stroke at the prime of his or her life. This reflects the fact that coronary artery disease (CAD) remains the main cause of death among American men and women (1 in every 5 deaths) and that stroke remains not only the No. 3 killer behind CAD and cancer but also the leading cause of severe long-term disability in this country. In this regard, in some of the past surveys evaluating the perceived burden of different types of diseases by the general population, a disabling stroke is frequently listed as worse than death by the general population. Moreover, although overall mortality for cardiovascular diseases has declined in the United States, mortality due to sudden death has remained unaltered. In addition, although deaths caused by CAD or stroke in those aged ≤55 years account for only 4% of the total CAD or stroke deaths, it still represents a large number given that, in 2002 alone, 657 054 Americans died from CAD or stroke. Similar to the number of individuals who die from some of the most common cancers, such as 50 000 to 60 000 for colon cancer, 40 000 to 45 000 for breast...
cancer, and 30 000 to 35 000 for prostate cancer, the number of individuals who die from CAD or stroke before age 55 years is excessively high. It is no wonder that we often hear about them.

These and other considerations represent the rationale for the growing consensus that some form of screening for primary prevention of CAD should be instituted in combination with the Framingham Risk Score. Although there is no consensus yet on who should be screened for cardiovascular disease or which algorithms should be used for that purpose, several established methods to assess subclinical atherosclerosis have been proposed. They are based on previous prospective studies and clinical trials demonstrating the ability to assess subclinical disease and atherosclerotic plaque regression in response to therapy or lifestyle modifications. However, no previous randomized study has ever demonstrated the value or cost-effectiveness of widespread screening for CAD by imaging, biomarkers, or clinical/epidemiological evidence such as the Framingham Risk Score. We have implemented the latter on the basis of available clinical and epidemiological evidence, and it is intuitive to accept that at least part of the modern success in reducing CAD morbidity and mortality results from such implementation and its byproducts, including enhanced public education, health policy modifications, and the imposition of legal constraints, such as restrictions on cigarette smoking in certain public spaces. Similar types of evidence formed the rationale for the aforementioned cancer screening programs. Screening is appropriate when there is an asymptomatic stage of a particular disease that can be identified with a test and then treated to reduce subsequent morbidity and mortality. Recently, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force has proposed very specific algorithms (Figure 1) for screening asymptomatic men aged >45 years and women aged >55 years who would not otherwise be considered at high risk on the basis of the coronary heart disease risk equivalent criteria, ie, (1) patients with previous development of clinical atherosclerotic disease; (2) diabetics; (3) patients with evidence of myocardial ischemia; (4) patients with carotid or iliofemoral atherosclerosis; and (5) patients with ≥2 risk factors with a 10-year risk for clinical coronary heart disease event >20%. They propose the combination of clinical/epidemiological risk scores modified by carotid ultrasound imaging and/or computed tomographic (CT) coronary calcification measurements and estimate the potential impact of such a program in reducing sudden death.

Figure 1. SHAPE Task Force algorithm for screening asymptomatic men aged >45 years and women aged >55 years at low or intermediate cardiovascular risk. CACS indicates coronary artery calcium score; LDL, low-density lipoprotein; ABI, ankle-brachial index; CIMT, carotid intima-media thickness; and CRP, C-reactive protein.
smoking, and family history of CAD. Coronary calcium, density lipoprotein cholesterol, blood pressure, cigarette determination atherosclerosis such as total cholesterol, low-

Risk Assessment by Nonenhanced CT Measures of Coronary Calcification

The potential to quantify the burden of atherosclerosis by nonenhanced CT attracted the attention of cardiologists, radiologists, and epidemiologists early in the development of electron-beam CT. Both the power and main limitations of this approach to predict risk and quantify disease progression can be anticipated from current knowledge of the pathogenesis and epidemiology of atherosclerosis in industrialized populations. Coronary calcification as assessed by CT reflects only the calcified components of coronary atherosclerotic plaques involving epicardial coronary arteries. It is therefore proportional to total epicardial plaque burden but does not reflect microvascular disease. The magnitude of coronary calcification predicts the development of clinical events and is also related to most of the known etiologic factors that determine atherosclerosis such as total cholesterol, low-density lipoprotein cholesterol, blood pressure, cigarette smoking, and family history of CAD. Coronary calcification adds to the prediction of coronary events over and above the Framingham Risk Score. Greenland et al demonstrated that asymptomatic individuals with intermediate risk by Framingham criteria but calcium scores >300 had an annual hard event rate of 2.8% and would therefore be classified as high risk for CAD events (Figure 2). In that study, the best estimates of relative risk demonstrated that a calcium score >300 conferred a hazard ratio of ~4 compared with a 0 calcium score. This implies that the estimated risk in a Framingham intermediate-risk patient with 0 calcium score would be reduced 2-fold, whereas the corresponding risk for a similar Framingham intermediate-risk patient with a score >300 would be increased 2-fold, which would lead to reclassifying the latter patient into a high-risk group. On the other hand, although the evidence from prospective studies demonstrating the predictive power of coronary calcification to detect CAD events in asymptomatic individuals is compelling, there is no direct evidence that such screening will lead to reduced morbidity and mortality caused by CAD.

CT coronary calcium score measurements entail relatively low risks; the radiation exposure is limited to 1.0 to 2.0 mSv, and the test does not require the use of iodinated contrast agents. Conversely, the main intrinsic limitations of coronary calcification as a predictor of cardiovascular events relate to both the very high prevalence of coronary atherosclerosis in industrialized societies and the fact that coronary calcification represents only one of the components of atherosclerotic plaques that may develop late in the natural history of a single plaque. Therefore, the amount of calcium accumulated in any given coronary arterial segment reflects not only the magnitude of plaque burden but also the period of time during which plaques were exposed to the factors that underlie calcification. Although the potential contributions of inflammatory, hormonal, metabolic, and physical factors believed to underlie coronary calcification are still incompletely understood, the process is believed to represent a natural biological response to arterial wall injury, activated for the purposes of increasing arterial wall stiffness and theoretically rendering plaques less vulnerable to rupture or undue deformation caused by mechanical and biological stresses. This traditional viewpoint has, however, been challenged by empirical observations suggesting that, at least initially, plaque calcification could increase as opposed to reduce the risk of plaque rupture by creating high-stress interfaces with other less stiff plaque components. Given the aforementioned considerations, therefore, the risk associated with coronary calcification for any given individual is considered to be best represented when age and gender are taken into consideration. For example, a calcium score of 17 in a patient with a strong family history of premature sudden death caused by atherosclerosis has a completely different meaning if the patient is aged 27 (Figure 3) as opposed to 67 years. The coronary calcium score is calculated as a brightness index reflecting the magnitude of x-ray attenuation as it traverses the heart. It was pioneered by Agatston et al several years ago, and, although proportional to the number and severity of coronary stenoses in a particular arterial tree, it reflects atherosclerotic plaque accumulated within the vessel wall. The natural evolution of atherosclerotic plaques consists of outward growth initially with progressive encroachment of the vessel lumen later, leading to vessel narrowing and stenosis. However, because nonstenotic and noncalcified plaques may rupture and lead to infarction or sudden death, a
The ultimate demonstration of the superiority of this method in reducing catastrophic complications of CAD, particularly in young and middle-aged men and women (younger than 55 years for men and 65 years for women), would derive from randomized controlled trials of individuals at different levels of risk for CAD-induced cardiovascular morbidity and mortality, with the use of coronary artery calcium scores to assign different treatment strategies to patients. On the other hand, the continued refinement of risk assessment relative to other potential markers of CAD events in populations of different ethnic backgrounds and genetic profiles may lead to improved utilization of coronary calcification, placing it as the best CAD screening method in the future. The results of the Multi-Ethnic Study on Atherosclerosis as well as those from other ongoing prospective studies in the United States and abroad should provide important insight into this possibility. Finally, the concept of combining coronary calcification assessment with coronary MDCTA based on a preestablished algorithm that would take into consideration all of the aforementioned variables deserves serious consideration in future trials, as discussed below.

**Coronary Angiography by MDCTA:**

**Technological and Safety Considerations**

The technological evolution of MDCT has been informative in terms of obtaining an accurate coronary angiography by “stacking” cross-sectional tomographic imaging plans. Although the importance of slice thickness (spatial resolution on the Z direction) is undisputed, multiple simultaneous acquisitions of cross-sectional images (with the use of multiple detectors) have proven to be crucial to minimize motion and helical reconstruction artifacts, allowing for 3-dimensional spatial registration to be predicted with exquisite accuracy. Therefore, the possibility of imaging the coronaries reliably by MDCT became feasible only when at least 12 to 16 slices could be obtained simultaneously.

The governing influence of an appropriately long diastolic period has become obvious to those who perform coronary MDCTA, underscoring the importance of “freezing” the heart’s motion. The lower the patient’s heart rate is, the more accurate the angiogram will be if all other variables are kept constant. For the purpose of reducing the heart rate to <70 bpm (ideally <60 bpm), oral and/or intravenous β-blockade is routinely required in clinical practice. Moreover, sublingual nitroglycerin is also frequently administered to dilate epicardial coronary vessels and enhance coronary artery visualization. With these caveats in mind, the study is commonly performed after the injection of a bolus of iodinated contrast (60 to 120 mL) intravenously, and imaging begins after (or as soon as) the bolus reaches the coronaries. A series of 250 to 350 images is obtained with as perfect as possible ECG gating for retrospective image reconstruction. Each cross-sectional image is obtained by emitting x-rays from a source and capturing its intensity (inversely proportional to the degree of attenuation) from 16, 32, or 64 detectors located diametrically opposite to the tube in the CT gantry. Gantry rotation speed varies typically from 333 to 500 ms, depending on the instrument. Given that such imaging takes place as the patient’s body is displaced by the scanner table in the Z direction (helical mode), it is no surprise that in modern multidetector systems, image reconstruction (the assignment of certain images or section of that image to the right place in time) becomes crucial to the ability to generate a coherent ECG-gated 3-dimensional body of information reflecting the magnitude of attenuation as the x-ray beams.
traverse the heart. Image reconstruction is from information generated by the half-gantry rotation method (more commonly used) or by a subfraction of a gantry rotation (multi-segment reconstruction). Multisegment reconstruction is particularly desirable in patients with heart rates $>65$ bpm.

Finally, postprocessing of the entire image data set is also of paramount importance in CT given that the typical difference in signal to noise among the different body tissues (or their ability to attenuate the x-ray beam relative to background noise) is not as great as with other imaging modalities, e.g., magnetic resonance imaging. Postprocessing played a major role in enabling MDCT to become useful to cardiologists and radiologists dedicated to imaging the heart. The final displays of source axial images or those generated from combined information obtained from parallel detectors or from images obtained at different times (but organized through ECG gating) are also complex and diverse, providing the physicians with a whole array of tools to examine the coronaries.

The main intrinsic limitations of MDCTA in terms of patient safety include the use of x-ray imaging with its accompanying risk of radiation-induced pathology as well as the iodinated contrast agents with their associated risk of allergic reactions and nephrotoxicity. The greater the tube voltage and the longer the radiation is applied, the greater is the risk of malignancies and other radiation-induced pathologies. These are crucial considerations for imaging children and adolescents, and they are particularly important for imaging young adults for whom coronary CTA may be contemplated as a screening tool for premature atherosclerosis. In addition, other factors that influence radiation risk for different individuals relate to differences in tissue susceptibility (for example, breast tissue in the case of coronary imaging) as well as the need to deliver a given amount of x-ray energy to create detectable differences in tissue attenuation at different chest depths in obese versus nonobese individuals. Centrally obese women (high body mass index as opposed to body surface area), for example, will receive a greater amount of breast radiation than leaner women for the same quality angiogram and will be at greater risk than other individuals of either gender for that reason. The risk of radiation-induced malignancies and other types of pathology was calculated from data obtained by the study of the tragic consequences of radiation released by the explosion of atomic bombs in Hiroshima and Nagasaki during World War II. The bulk of medical knowledge on radiation-induced pathologies comes from those studies. However, more recent studies clearly indicate that the risk of radiation-induced diseases associated with medical procedures (CT in particular) increases significantly in children and adolescents exposed to serial testing and should be an important consideration in the decision to use x-ray technology to screen large populations of asymptomatic individuals (for example, mammography, electron-beam CT, or MDCTA). The risk-benefit equation of potential CAD screening by employing these technologies becomes defined by the ratio by potential risks of radiation-induced diseases relative to the incidence and risk of CAD complications for a given individual or specific groups of asymptomatic individuals. The risk of nephrotoxicity associated with iodinated contrast agents is also an important consideration in screening asymptomatic individuals for CAD because some of the individuals at highest CAD risk may also be at an increased risk of developing nephropathies. In general, the larger the amount of contrast (or iodinated material) and the more impaired renal function is before contrast administration, the greater is the risk. Other factors such as contrast iodine concentration and potentially protective strategies of delivery may also play a role, but their importance is less certain at this point.

Performance Profile of Coronary MDCTA in Patients With Suspected CAD

The performance profile of MDCTA for scanners equipped with 16 detectors has been reasonably well established in the literature. Although some of the earliest studies reported very high values for both sensitivity and specificity for 16-detector MDCTA, it soon became obvious that although specificity estimates appeared to hold, those for sensitivity had wide limits of confidence associated with the type of population being examined (referral bias and spectrum bias), the techniques employed, the type of analytical comparisons made against the invasive coronary gold standard, and the rigor of control for other analytical biases.

Although this trajectory is not dissimilar from the introduction of other cardiovascular diagnostic tests ranging from the standard ECG exercise stress test to more recent stress echocardiography, nuclear cardiology tests, and coronary imaging by magnetic resonance angiography, it is important to note that the ability to exclude CAD as the cause of chest pain by 16-detector MDCTA in patients referred for elective invasive coronary angiography has been well documented. In this regard, a recent meta-analysis of 16-detector MDCTA studies analyzed on a per-segment basis, which included the most important single-center studies as well as the CATSCAN multicenter study, reported a pooled sensitivity of 76% with a confidence interval (CI) of 63% to 89% and specificity of 95% with a confidence interval of 94% to 97%. Moreover, less commonly used but potentially more informative indices of diagnostic testing performance were also calculated, which demonstrated a 22.7 (13.7 to 37.8) positive likelihood ratio, a 0.13 (0.05 to 0.34) negative likelihood ratio, and a 170.8 (57.1 to 510.5) diagnostic odds ratio. For the latter indices, a positive likelihood ratio of >10 and a negative likelihood ratio of <0.1 are considered reliable evidence of satisfactory diagnostic performance. The diagnostic odds ratio combines information from the positive and negative likelihood ratios and thus represents an estimate of how much greater the odds of having the disease are for patients with a positive test result compared with those with...
a negative test result.\textsuperscript{83} Using the area under the receiver operating characteristic (AUC) curve in a per-patient analysis from a single-center study, Hoffman et al.\textsuperscript{95} found AUC = 0.97 (95% CI, 0.90 to 1.00), indicating high discriminative power to identify patients who might be candidates for revascularization (\(>50\%\) left main and/or \(>70\%\) stenosis in any other epicardial vessel). Moreover, in the CATSCAN study,\textsuperscript{90} AUCs were reported for evaluable segments and only in the segment-based analysis. Values of AUC = 0.91 (95% CI, 0.86 to 0.96) and AUC = 0.97 (95% CI, 0.96 to 0.99) were found for 50% and 70% threshold stenoses by invasive angiography.

There are fewer studies performed with more modern >16-detector technology,\textsuperscript{96–105} although the pace of investigation remains fast, and additional results are likely to allow us a more complete evaluation of its capability in the near future. Most of the published studies were performed with technology that involved a moving or stationary x-ray source and 32 detectors (resulting in 64 slices covering 1.6 to 2.4 cm per acquisition) or a stationary source and 40 or 64 detectors (covering 2.8 to 4.4 cm per acquisition). The pooled sensitivity in a per-segment analysis was 87% (95% CI, 80% to 94%), whereas specificity was 96% (95% CI, 95% to 97%), with 22.5 (95% CI, 17.8 to 28.4) positive likelihood ratio, 0.10 (95% CI, 0.06 to 0.20) negative likelihood ratio, and 217.6 (95% CI, 117.6 to 402.7) diagnostic odds ratio according to the meta-analysis by Hamon et al.\textsuperscript{81} They also found a significant increase in the diagnostic odds ratio using 64 detectors compared with 16 in patient-based analysis. In addition, considering all studies performed with \(\geq 16\) detectors, the authors report the following on a patient-based analysis: 96% (95% CI, 94% to 98%) sensitivity, 74% (95% CI, 65% to 84%) specificity, 5.4 (95% CI, 3.4 to 8.3) positive likelihood ratio, 0.05 (95% CI, 0.03 to 0.09) negative likelihood ratio, and 133.05 (95% CI, 57.3 to 308.9) diagnostic odds ratio. Pooled positive predictive value for the per-patient analysis was 83% (95% CI, 76% to 90%), and pooled negative predictive value was 94% (95% CI, 89% to 99%).\textsuperscript{81}

### Table. Summary of Accuracy Results From a Meta-Analysis Including Studies With \(\geq 16\) Detectors Comparing Invasive Coronary Angiography With CTA\textsuperscript{83}

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Likelihood Ratio (95% CI)</th>
<th>Negative Likelihood Ratio (95% CI)</th>
<th>Diagnostic Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per segment</td>
<td>0.81 (0.72–0.89)</td>
<td>0.93 (0.90–0.97)</td>
<td>21.54 (13.07–35.48)</td>
<td>0.11 (0.06–0.21)</td>
<td>189.32 (93.47–383.43)</td>
</tr>
<tr>
<td>Per vessel</td>
<td>0.82 (0.80–0.85)</td>
<td>0.91 (0.90–0.92)</td>
<td>11.8 (6.75–20.64)</td>
<td>0.08 (0.02–0.32)</td>
<td>146.45 (31.95–671.21)</td>
</tr>
<tr>
<td>Per patient</td>
<td>0.96 (0.94–0.98)</td>
<td>0.74 (0.65–0.84)</td>
<td>5.36 (3.45–8.33)</td>
<td>0.05 (0.03–0.09)</td>
<td>133.05 (57.29–308.98)</td>
</tr>
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</table>

Some considerations regarding patient selection are also important, such as the fact that, for practical reasons, most published studies included patients referred for invasive coronary angiography (thus deemed at high risk for having CAD), which represent a different patient population than the one usually thought to benefit the most from screening with CTA, ie, patients at intermediate risk assessed with clinical scores such as the Framingham Risk Score. Most of the trials have also limited the inclusion of very obese patients (body mass index >40), making it difficult to generalize the results to this group of patients, commonly associated with poorer image quality studies.

Imaging patients with lower prevalence of disease should yield lower positive predictive values and increase the negative predictive value, a beneficial effect for a screening test. Another important open question is whether patients with very high coronary artery calcium should have a CTA because the test accuracy decreases with increasing coronary artery calcium scores and the prevalence of disease increases, diminishing the utility of CTA.

In summary, results from studies performed thus far indicate that although coronary CTA has room to evolve and improve relative to invasive coronary angiography, its sensitivity and negative predictive value are high enough to indicate that the test can certainly be used as a tool to exclude...
the presence of significant coronary stenoses in patients without severe coronary calcification.

**Combined Coronary Angiography and Perfusion Imaging by MDCT**

The current management of symptomatic patients with suspected CAD entails the detection of atherosclerotic lesions that cause a myocardial perfusion defect or ischemia indexed by contraction abnormalities or ECG changes at rest, during stress, or both. The identification of such lesions generally leads to invasive coronary angiography for further documentation of vessel stenosis, anatomic characterization, and suitability for catheter-based intervention or surgery if clinically indicated. On the other hand, the possibility of coupling anatomic and functional information in a single test could have important implications for screening older individuals at high risk for coronary events, those with calcified arteries, or those with suspected microvascular disease.

The idea that CT could provide information on myocardial perfusion has been explored in the past by investigators using electron-beam CT. However, the combination of a reliable coronary angiogram with stress-induced myocardial perfusion assessment had to wait until spiral CT technology progressed sufficiently to enable the acquisition of 64 slices simultaneously. This technology, although still in its developmental stage, offers a glimpse of what the workup of patients with suspected CAD could look like in the future. At present, the greatest limitations to coronary CTA are the presence of severely calcified coronary segments, stents, or other artifacts (Figure 4). Patients with calcified arteries tend to be older and/or have advanced CAD. Their studies are challenging from a diagnostic viewpoint because vulnerable plaques and stenotic lesions may be hidden underneath large amounts of calcium accumulated in the outer portions of atherosclerotic plaques encompassing ≥1 segment. Although progress in multidetector technology has improved our ability to study such patients, greater coverage and improved temporal resolution are unlikely to eliminate the problem, which is in large part intrinsic to the pathogenesis of atherosclerosis, ie, plaques grow outwardly first and tend to accumulate calcium as part of the healing process, therefore creating a natural shield to x-ray penetration. This is a particular limitation for the study of older individuals, those with advanced CAD, those who underwent coronary artery bypass grafting or multiple stent implantation, and patients with disease states that accelerate plaque calcification such as chronic renal failure.

Initial clinical studies documenting the possibility of translating these methods to humans (Figure 5) indicate that the combination of coronary angiograms with measurements of relative differences in myocardial blood flow during stress is feasible with current 64-detector MDCT technology. In this regard, the main obstacle for full implementation of this methodology has been the magnitude of radiation that would be needed for the acquisition of myocardial perfusion information not only during stress but also at rest. Although previous work using cardiovascular magnetic resonance imaging to measure myocardial perfusion suggests that most of the needed information is provided by the stress images, differentiation between stress-induced perfusion defects and myocardial scar–like old infarcts (Figure 6) or myocardial fibrosis secondary to previous myocardial damage due to other disease processes would be hampered by the absence of perfusion studied at rest. In this regard, the development of CT technology that would allow complete myocardial imaging during 1 gantry rotation (Figure 7) combined with the capability of programming such gated image acquisitions to occur only during specific portions of a given cardiac cycle, has created a new horizon of possibilities to reduce radiation exposure enough to enable the performance of combined angiography and myocardial perfusion assessment at rest and during stress. Such techniques would be ideal for the assessment of patients with chest pain who also have calcified coronary arteries, as well as the follow-up of patients with advanced heart disease after coronary artery bypass surgery or multiple stent implantations. It is reasonable to expect that the addition of perfusion information to the angiography would increase the test sensitivity to flow-limiting lesions, a salutary effect when the use of this method is considered for screening purposes.

Moreover, recent attention to patients with chest pain but no obstructive epicardial CAD (syndrome X) has demonstrated that in a substantial proportion of these individuals, microvascular processes can be identified by perfusion reserve measurements in association with traditional CAD risk factors such as hypercholesterolemia, hypertension, and smoking, as well as with diabetes. The possibility of quantifying epicardial coronary plaque burden while also assessing microvascular disease during maximal vasodilatation by MDCTA would have profound implications for the future.
evaluation of asymptomatic individuals at risk of developing complications of CAD. However, it is the ability to quantify and characterize epicardial coronary atherosclerosis (macrovascular disease) that imparts this method with its unique and undisputed potential for risk stratification of asymptomatic patients susceptible to coronary events.

Atherosclerotic Burden Measured by Coronary CTA

Abrupt coronary occlusion with its often disastrous consequences is commonly caused by plaque rupture and exposure of the lipiddic core to blood components in the vessel lumen, leading to thrombus formation and vessel occlusion. The culprit plaque does not necessarily need to be obstructive before rupture, and evidence that nonstenotic plaques are vulnerable to rupture is firmly established. Plaque rupture is thought to be mediated by inflammation, mechanical stress, and a propensity to thrombus formation, among other factors. Vulnerability to plaque rupture can therefore be assessed by the presence of specific risk factors in addition to plaque morphological characterization.

The detection and quantification of plaque components other than calcium would theoretically increase the ability of coronary MDCTA to assess the risk of cardiovascular complications among asymptomatic individuals, particularly young or middle-aged men and women. Recent studies have demonstrated the ability of coronary CTA to measure plaque size accurately and distinguish between calcified and noncalcified plaque components compared with intravascular ultrasound. On the other hand, attempts to further distinguish fibrotic from lipidic noncalcified components have not been conclusive, possibly because the technique does not possess sufficient contrast-to-noise capability to provide such distinction, and spatial resolution may still not be high enough to differentiate small lipid pools from the surrounding fibrous tissue. Furthermore, there have not been animal or human systematic studies comparing in vivo plaque assessment by coronary CTA against ex vivo histopathology. Other methodological challenges to plaque characterization include finding the thresholds for lipid and fibrous tissue, which may vary from patient to patient because radiation penetration and intracoronary contrast concentrations are not constant for every patient. The identification of a reliable reference against which signal intensity of the different noncalcified plaque components are compared becomes paramount; luminal contrast signal intensity is commonly selected as the reference.

Despite these and other potential limitations, there are few doubts that the ability to measure and characterize coronary atherosclerosis is far greater with coronary MDCTA than with nonenhanced CT measures of coronary calcification. On the basis of the data supporting this premise, practicing cardiologists and internists have referred patients perceived to be at high risk to develop CAD complications but not at the level at which cardiac catheterization with angiography would be indicated. Such patients are generally not completely asymptomatic and frequently have a strong family history for premature atherosclerosis among other risk factors. For example, Figure 3 shows the left descending coronary artery of a 27-year-old man whose father died of premature CAD at age 27 years. The patient saw his internist with vague symptoms, and, except for hypertension and mild obesity, he had no other risk factors for CAD. His total calcium score was 17, placing him at high risk for complications of CAD on the basis of the calcium score alone, when adjusted for age.
and gender. In addition, the presence of 2 soft plaques located in the proximal and mid left anterior descending coronary artery further strengthens the notion that this patient was at risk for plaque rupture over and above risk factors and calcium score. Similarly, the presence of a completely calcified plaque in the distal portion of the left main artery (Figure 8) in an asymptomatic 40-year-old man whose brother died in his 40s from coronary occlusion indicates that his risk for coronary complications is high and supports the notion that the patient should be treated aggressively.

In this regard, Hausleiter et al. in a recent study involving 161 consecutive patients with intermediate risk of CAD to rule out significant coronary stenoses, found that 29.8% of all coronary plaques seen by MDCTA were not calcified. Mixed plaques consisting of plaques with noncalcified and calcified portions were present in 23.6%. In addition, 10 of the 161 patients (6.2%) had noncalcified plaques only. These data correlate with previous studies documenting myocardial infarction and sudden death in patients with a calcium score of 0. More recently, studies relating the presence of plaque burden measured by coronary CTA with morbidity and mortality by CAD in mostly symptomatic patients underscore the ability of this method to forecast coronary events. Recently, a study evaluating a treatment strategy

Figure 6. Cardiac MDCT study at rest showing hypoperfusion in the apical and apical-septal walls (arrows). Differentiation between stress-induced perfusion defects and myocardial scar-like old infarcts or myocardial fibrosis secondary to previous myocardial damage due to other disease processes would be hampered by the absence of rest perfusion studies.

Figure 7. Coverage of the heart with a 64-slice scanner compared with a 256-slice scanner. With the latter technology, the entire heart is covered in 1 gantry rotation.

Figure 8. Example of an asymptomatic 40-year-old man whose brother died in his 40s from coronary occlusion. The presence of a calcified plaque in the distal portion of the left main artery indicates that his risk for coronary complications is high and supports the notion that the patient should be treated aggressively.
based on the result of CTA was published, in which patients referred for invasive coronary angiography were asked to have a CTA first, and in case the CTA demonstrated <50% lesions only, the patients had the invasive procedure canceled and were followed clinically and were demonstrated to have low incidence of cardiovascular events (0.7% at a mean follow-up of 15 months).125 This study showed for the first time that a strategy based on CTA results is effective and could be refined still further to differentiate patients with any plaque from those with no detectable plaque.

Furthermore, a recent study by Min et al124 demonstrated that prognosis (defined by absolute mortality) could be assessed on the basis of the MDCTA coronary interpretations, with an increasing risk of death being associated with higher-grade stenosis and proximal lesions in a continuous pattern, as shown in Figure 9. Importantly, negative MDCTA results (defined as <50% coronary stenosis) conferred a very low risk of death at follow-up, confirming the results of other cohorts.122–125 Although these first studies are valuable and informative, they represent only the beginning of efforts directed at assessing the prognostic value of cardiac MCTA. Patient selection and limited follow-up are still limitations to generalization of these early findings, which are nonetheless promising. Moreover, there is no evidence from studies examining the prognosis of asymptomatic individuals selected for MDCTA for screening purposes only.

**Summary and Conclusions**

Coronary MDCTA is currently used to assess the severity of atherosclerosis in middle-aged men and women who have vague symptoms but have unusually elevated risk factor profiles. A strong family history of premature CAD causing sudden death or nonfatal infarction is commonly part of the risk profile that has prompted referral to noninvasive coronary angiography. Until we have data from randomized studies indicating that such a course of action is useless or harmful, clinical “common sense” based on what we know and have experienced in taking care of patients with CAD should be exercised on a patient-by-patient basis. In these individuals, however, the typical dilemma relates to the decision to repeat the test or not after medical intervention such as aggressive lipid-lowering therapy, frequently involving multiple agents. The radiation dose delivered during coronary MDCTA currently falls between a standard sestamibi perfusion test and a dual-isotope procedure, now uncommonly used in clinical cardiology. The latter realization is of paramount importance in performing the test in the first place but also in deciding to repeat it. Moreover, in large part because of such radiation requirements but also because of the possibility of contrast-induced allergic reactions and kidney injury, the widespread use of coronary MDCTA in asymptomatic individuals at risk to develop coronary atherosclerosis is not yet warranted.

In the not so distant future, however, the risk-benefit equation may change substantially by the use of CT technologies that require much lower radiation doses (1 to 2 mSv) by gated exposure during helical imaging or by the use of devices that provide complete myocardial coverage during a single gantry revolution. In that scenario, risk factor assessment combined with novel biomarkers and/or ultrasound imaging could be used to trigger coronary CTA for epicardial coronary atherosclerotic burden quantification and vessel stenoses. In older asymptomatic individuals or in those with propensity for premature coronary calcification, calcium score determination could further trigger the performance of a combined angiogram/perfusion stress test. In any scenario,
the need to obtain data from prospective studies with the use of coronary CTA to screen asymptomatic individuals at risk of developing symptomatic CAD cannot be overemphasized given the rapid adoption and accelerated development of this technology. In this regard, coronary CTA could be conceptualized as a potential addition to an ideal algorithm designed to prevent the complications of CAD and eliminate CAD-induced sudden death and nonfatal infarctions in women younger than 65 years and men younger than 55 years, as a first step. It is hoped that the clever combination of epidemiological data, biomarkers, and imaging will allow us to reach that goal way before the end of this century.

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**Response to Gottlieb and Lima**

*Christopher M. Kramer, MD*

I am grateful to my colleagues Drs Gottlieb and Lima for their excellent review. I see no need for a rebuttal as they state the following in their conclusion: “Moreover, in large part because of such radiation requirements but also because of the possibility of contrast-induced allergic reactions and kidney injury, the widespread use of coronary MDCTA in asymptomatic individuals at risk to develop coronary atherosclerosis is not yet warranted.” Thus, we are in agreement that CTA is an exciting technology that is finding its place in the armamentarium of the cardiac imager, but it is not presently useful as a screening tool because of its higher risk-benefit ratio in asymptomatic individuals. Changes in the risk side of the equation may ultimately change this, but in 2008, CTA for screening is not ready for prime time.
Should all high-risk patients be screened with computed tomography angiography?

All High-Risk Patients Should Not Be Screened With Computed Tomographic Angiography

Christopher M. Kramer, MD

On the basis of the most recent American Heart Association/American College of Cardiology guidelines for assessment of cardiac risk,1 high-risk patients are defined as those with a 10-year coronary heart disease risk of >20% based on Framingham risk criteria or the presence of diabetes mellitus. The major independent risk factors for coronary heart disease comprising the Framingham Risk Score are cigarette smoking, hypertension, elevated total cholesterol and low-density lipoprotein cholesterol, low serum high-density lipoprotein cholesterol, diabetes mellitus, advanced age, and male gender.1 Derived from National Health and Nutrition Examination Survey statistics from 1999 to 2000,2 the prevalence of risk factors in patients aged 20 to 74 years is 17% for total cholesterol ≥240 mg/dL, 14.9% for hypertension, 26.4% for smoking, and 8% for diabetes (including undiagnosed). Data from the 2003 Behavioral Risk Factor Surveillance System survey of 103 191 adults aged >18 years3 show that >37% of the population surveyed had ≥2 risk factors for coronary heart disease and thus are considered to be at high risk. These figures together suggest that the number of high-risk patients who are potential candidates for screening programs is quite high.

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The Clinical Role of Computed Tomographic Coronary Calcium Scoring

Multiple studies over the last 2 decades have confirmed the prognostic utility of coronary artery calcium (CAC) measurements primarily with electron-beam computed tomography (EBCT) and more recently with multidetector CT (MDCT) technology (Figures 1 and 2). The 2 techniques are fairly equivalent as long as the latter is performed with at least a 4-detector scanner.4,5 The reproducibility of MDCT, however, may not be as good as EBCT at lower calcium scores.4 CAC is an indicator of atherosclerotic plaque burden, and very high levels confer an increased risk of future cardiac events. The absence of CAC confers a very low but still measurable cardiac risk,6 whereas its presence confers an increased relative risk of hard events. However, absolute event rates are relatively low (1% to 2% per year) even in the highest-risk group, and thus the routine clinical use of CAC scoring has yet to be defined clearly. There is no correlation between CAC and physiological or anatomic significance of a stenosis.7 In addition, there can be significant heterogeneity between the extent of plaque calcification even within an individual subject, independent of age, gender, or number of plaques. Ethnic heterogeneity must also be taken into account when CAC results are interpreted. The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that CAC is most prevalent in whites, with a lower risk of calcification (between 23% and 31% lower) for those of black, Hispanic, or Chinese descent.8

Recent studies suggest that the utility of CAC may be highest in patients who are at intermediate risk according to the Framingham risk data; CAC levels can place such patients into low-risk categories.
higher or lower risk categories6 (Figure 3). For high-risk patients who would be candidates for screening (Framingham Risk Score >20%), a CAC score >300 raised the risk of coronary death or nonfatal myocardial infarction to nearly 20% over 7 years. The St Francis Heart Study, a prospective, population-based EBCT study of 4903 asymptomatic individuals between ages 50 and 70 years,9 showed that after >4 years of follow-up, CAC predicted coronary artery disease events independently of either standard risk factors or CRP and was a better predictor than the Framing-

Accuracy of CT Coronary Angiography

CT to perform noninvasive coronary angiography is in rapid evolution. It has long been an excellent technique for diagnosing anomalous coronary arterial anatomy in adults (Figure 4), and its accuracy for detecting stenoses in patients with coronary artery disease has progressed rapidly. Initially, EBCT was the technique of choice because of excellent temporal resolution, but as the number of detectors for MDCT angiography (MDCTA) has increased rapidly in the new millennium, it has all but replaced EBCT. In the first multicenter study of 16-detector scanners, 29% of segments were unable to be evaluated.12 The negative predictive value
(99%) compared with x-ray angiography was outstanding, but the positive predictive value was poor because of both the high number of segments that could not be evaluated and false-positives, which were primarily due to the presence of coronary calcification.

Scanners with 64 detectors (Figure 5) and now dual-source 64-detector scanners13,14 (Figures 6 and 7) are becoming more widely available; thus, temporal and spatial resolutions are steadily improving with a concomitant reduction in unreadable segments and false-positive studies. In an initial published single-center 64-detector study of 70 patients with exclusions for atrial fibrillation but not for calcified arteries, heart rate, or obesity, only 12% of segments were excluded for inadequate image quality. Per-segment values were impressive for sensitivity (95%), specificity (96%), and positive (66%) and negative (98%) predictive values. On a per-patient basis, the values were also high for sensitivity (92%), specificity (91%), and positive (80%) and negative (97%) predictive values. Subsequent moderate-size studies (52 to 67 patients) have demonstrated sensitivities on a per-segment basis ranging from 85% to 99%, specificities from 93% to 99%, negative predictive values from 95% to 99%, and positive predictive values from 76% to 97%.16–20 In these studies, the greatest number of segments excluded from analysis was 6%, and some did not exclude any segments. Clearly, 64-detector CT has developed into an excellent test for excluding significant coronary artery disease. Heavily calcified coronary arteries remain the principal cause of false-positive studies.21

Studies are under way to determine which patient populations are best served by CT angiography (CTA). To date, it has shown to be useful in the following groups: low-to intermediate-risk patients seen in the emergency department with acute chest pain22; patients with left bundle-branch block23; and patients before cardiac valve surgery.24 A positive test in symptomatic patients is predictive of cardiovascular events, primarily revascularization, whereas a negative test in the same patient population is an excellent marker of a good prognosis over 1 year of follow-up.25 The only study in asymptomatic patients completed to date was in patients before cardiac valve surgery.24

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Figure 4. Multiplanar reformat from a contrast-enhanced 16-detector CT angiogram demonstrating an anomalous right coronary artery originating from the left coronary cusp and coursing posteriorly between the aorta and pulmonary artery.

Figure 5. Multiplanar reformat of a contrast-enhanced 64-detector CT coronary angiogram (C) demonstrating a tight stenosis of the right coronary artery distal to the marginal branch as well as more proximal calcifications in the artery wall and the corresponding x-ray angiogram (E). Adapted from Raff et al,15 with permission.
CTA for Identification of Soft Plaque

A promising potential use of MDCTA is the differentiation of atherosclerotic plaques based on their density, as measured by Hounsfield units. An early study examined 34 plaques in 15 patients with intravascular ultrasound used as the gold standard and differentiated plaques into categories of soft, intermediate, and calcified. Subsequently, larger studies demonstrated significant overlap of the CT attenuation pattern of intravascular ultrasound–defined hypoechoic plaque (lipid-rich soft plaques) and hyperechoic plaques (fibrous plaques). Thus, MDCT may be best at differentiating calcified from noncalcified plaques, and interobserver variability for this application is excellent. More research is required to determine the utility of differentiating lipid-rich from fibrous plaque with the use of MDCT.

In a study of 161 intermediate-risk patients, MDCT with the use of a 64-detector scanner identified noncalcified plaques in 48 (30%) of the patients. Noncalcified plaque was the sole manifestation of coronary artery disease in 10 (6%) of the patients. Generally, these soft plaques were nonobstructive. Long-term follow-up of these patients is not yet available to show whether identification of soft plaques is prognostically important. Some authors have suggested that the identification of noncalcified plaque may be most important in patient populations for whom calcium scoring is less accurate, eg, younger patients and those with a history of smoking. However, patients without coronary calcification (some of whom have soft plaque) have an extremely low event rate. In the St Francis Heart Study, only 8 of 1504 patients (0.5%) without calcium had a coronary event over 4.3 years, leading to an event rate of 0.1% per year. Another large study of >10,000 subjects quantified the risk of those without calcium as 0.4 events per 1000 person-years of observation. Thus, further risk stratification in this population does not appear necessary. In a study of younger patients (mean age, 43 years), the event rate in those without calcium was only 0.05% per year, further limiting the potential additive value of MDCT in patients without coronary calcification.

Potential Risks of MDCTA

Efforts are being made to limit the radiation dose from MDCTA because its widespread use as a screening examination may expose the population studied to a significant burden of excess radiation. One method for limiting radiation exposure is tube current modulation, which limits the full radiation exposure to certain critical portions of the R-R interval. For comparison purposes, the dose range for invasive x-ray angiography is on the order of 2 to 5 mSv. Early publications with 64-detector scanners showed that radiation dose without tube current modulation was as high as 13 mSv in men and 18 mSv in women. More recent estimates in studies using tube current modulation range from 5.4 to 9.4 mSv.

The risk of radiation exposure in the general population is calculated as $5 \times 10^{-5}$ Sv$^{-1}$ for lifetime cancer mortality. According to a recent review, typical doses for MDCTA yield lifetime risks of 0.07% for inducing a fatal cancer in the general (ie, age- and gender-averaged) population. This risk has been further quantified on an age basis in a phantom study that estimated a lifetime attributable risk of cancer of 1 in 1911 for a 60-year-old man and 1 in 715 for a 60-year-old woman. In a symptomatic patient, this stands in contrast to a 0.1% risk of death, myocardial infarction, or stroke from x-ray angiography. In an older population, the lifetime risk is substantially less. However, in an asymptomatic high-risk patient, often a younger individual, this potential risk is substantially higher than for other types of screening examinations.

The iodinated contrast dye used in MDCTA poses an additional risk. Nonionic contrast media cause severe allergic reactions in 0.2% to 0.7% of patients. Nephrotoxicity is yet another potential risk, one that can be lowered by the use of
nonionic low-osmolar contrast media and by avoiding a dose >100 mL of contrast.\(^{42,43}\) Another risk that is difficult to quantify is the risk of further x-ray angiography and interventional procedures that may not be necessary or indicated, which are triggered by a screening examination.

### Does Screening High-Risk Patients Change Behavior?

An important question in regard to any screening test is as follows: Does the test change either behavior or outcome in an individual patient? This question has been addressed in several studies of CAC, and the findings are somewhat at odds. In a study of 450 asymptomatic active-duty US Army personnel (aged 39 to 45 years), 15\% of whom had CAC, the finding of CAC did not motivate them to modify known cardiac risk factors over the course of 1 year.\(^{44}\) In contrast, a study of patients already on statin therapy demonstrated that knowledge of higher baseline CAC scores was associated with improved statin compliance on multivariable analysis.\(^{45}\) It is unclear whether knowledge of the extent of underlying coronary artery disease based on MDCTA will be more of a motivational factor than the presence of CAC alone. An incomplete understanding of the difference between CAC scoring and MDCTA in the eyes of the lay public could mitigate any improvement in patient behavior based on the latter.

### Does Screening High-Risk Patients Change Outcome?

Whether screening examinations can be used to monitor effects of therapies to reduce atherosclerosis burden and improve outcomes remains an open question. A nonrandomized study suggested that lower low-density lipoprotein levels in patients on statins was associated with lowering of CAC scores.\(^{46}\) Other studies suggest little relationship between CAC progression and changes in lipid status.\(^{47}\) Recent work using intravascular ultrasound suggests that noncalcified plaques respond better to therapies aimed at plaque regression than do calcified plaques.\(^{48}\) This suggests the theoretical possibility that identifying noncalcified plaques with the use of MDCTA might lead to a greater ability to identify patients with the type of atherosclerosis which may respond to therapy. However, no studies exist to date that link improved clinical outcomes with response to atherosclerosis therapies applied as a result of CAC or MDCTA.

### Is Screening High-Risk Patients Cost-Effective?

The most recent American College of Cardiology Foundation/American Heart Association Consensus Document on CAC scoring\(^{11}\) states that data were lacking to apply to cost-effectiveness models. The incremental cost-effectiveness ratio is dependent on the annualized risk of the patient being screened and the effectiveness of primary prevention strategies, both of which use multiple assumptions and are thus problematic. One study suggested a range from $500 000 for a patient with a risk of 0.6 events per year (intermediate risk) to $30 742 if the event rate was 2\% per year (high risk).\(^{49}\) The incremental cost-effectiveness ratio would certainly be higher for MDCTA than for CAC scoring given the higher cost of the procedure as well as the additive potential risks of increased radiation burden of angiography and the use of iodinated contrast.

### Why CTA Should Not Be Used for Screening

Much of this discussion leads to the conclusion that, in its present form, MDCTA should not be used for screening asymptomatic high-risk patients. To summarize:

1. CAC scoring alone, which is associated with lower cost, lower radiation exposure, and no contrast dye, has not been endorsed in the latest guidelines for high-risk patients\(^{11}\) because they should have their risk factors treated aggressively regardless of outcome of further screening.
2. Patients with calcium scores of 0 have an extraordinarily low risk of events, and thus the theoretical value of identifying noncalcified plaque appears quite limited.
3. The risks of MDCTA may outweigh the potential benefits in asymptomatic patients.
4. Even for CAC scoring, it is not entirely clear that knowledge of the result changes behavior in terms of risk factor modification.
5. No study to date has demonstrated an association between change in coronary plaque burden by MDCTA and improved outcome.
6. Given the prevalence of individuals being assessed as high risk on the basis of risk factors alone and the high cost of MDCTA relative to other potential screening techniques, the cost-effectiveness of screening with this technique is likely to be poor.

Indeed, a recent president of the Society for Cardiovascular Computed Tomography has stated that “screening applications of coronary CTA in asymptomatic individuals currently are not backed by clinical data.”\(^{50}\) An article by another prominent individual in the field has stated that “the use of contrast CT for risk stratification of the asymptomatic patient is problematic.”\(^{51}\) In summary, in 2008, MDCTA should not be used for screening asymptomatic high-risk individuals.

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### Disclosures

None.

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Response to Kramer

Ilan Gottlieb, MD; João A.C. Lima, MD

Great advances in cardiology during the 20th century led to unprecedented improvement of outcomes in the acute care of patients with cardiovascular diseases. We cardiologists learned to become effective hospitalists, with a wide array of medicines and gadgets at our disposal. Once the patient arrives at the emergency department, we usually can define the best way to treat her or him. The flip side of this coin, preventive cardiology, has gained much less attention, although it has equal or even greater potential for reducing cardiovascular morbidity and mortality. The reasons underlying such disparities are multifold and beyond the scope of this commentary. Among them is the fact that cardiovascular science is in large part organized to examine the impact of 64x0.5-mm MDCT technology on the prognosis of diabetic individuals are just beginning participant enrollment, and the future looks promising as new techniques to improve image quality while minimizing radiation dose emerge. We badly need data on the safety and effectiveness of screening CAD in the asymptomatic patient population by better methods, as our colleagues in oncology have recently taught us.


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