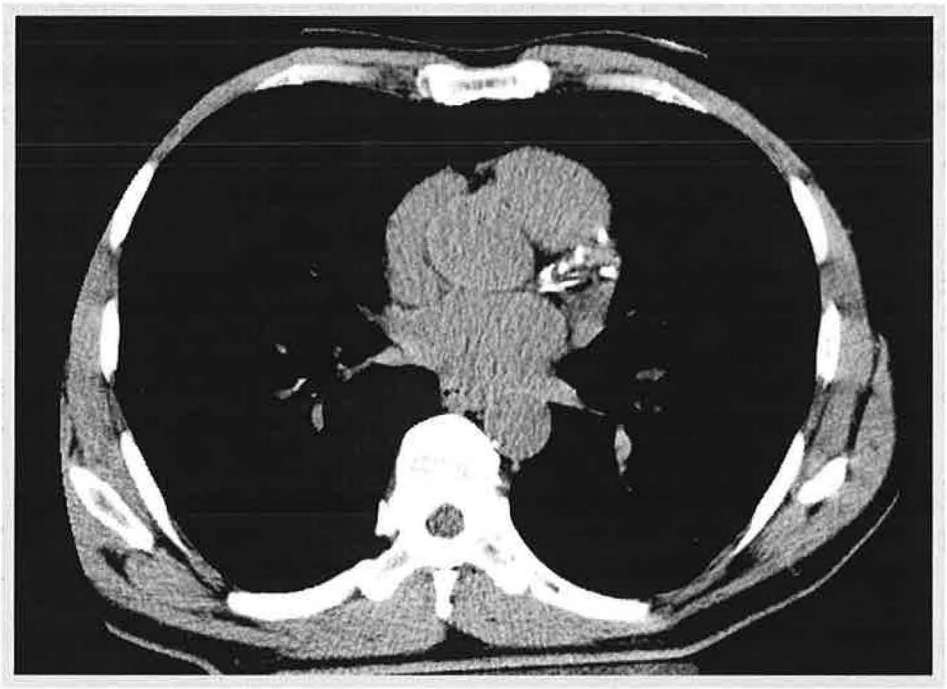
Screening for Heart Disease: The Promise and Pitfalls of Coronary Artery Calcium Scanning



"As I examin'd the external surface of the heart, the left coronary artery appear'd to have been chang'd into a bony canal, from its very origin to the extent of many fingers breadth, where it embraces the greater part of the basis. And part of that very long branch, also, which it sends down upon the anterior surface of the heart, was already become bony to so, great a space, as could be cover'd by three fingers plac'd transversely."[1]

—John Baptist, 1761

Amit Khera, MD, MSc

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Amit Khera, MD, MSc
Associate Professor of Medicine
Department of Internal Medicine
Division of Cardiology

Dr. Khera is Director of the Preventive Cardiology Program, Program Director of the Cardiology Fellowship Training Program, and Medical Director of Cardiac Rehabilitation at Parkland Memorial Hospital and University Hospital-St. Paul. His research and clinical interests involve the primary and secondary prevention of coronary artery disease, especially in those with premature or familial disease.

I. ASSESSING RISK- POPULATION AND PERSONAL APPROACHES

Broadly speaking, cardiovascular (CV) disease prevention involves two different but complementary approaches which were codified by Geoffrey Rose in 1985.[5] The population-based strategy attempts to shift the distribution of risk factors in the entire population to a lower average level (ie: shifting the mean blood pressure), often utilizing public health measures. This approach has been incredibly effective in improving CV disease outcomes over the last several decades but largely relies on public health measures targeting the masses.[6] A more individualized approach involves the high-risk strategy which focuses treatments on those exceeding a certain risk threshold thereby providing interventions that are appropriate to that individual and creating a more favorable risk-benefit ratio. A modern extension of the high-risk strategy is the concept of personalized medicine. As defined by the President's Council on Advisors on Science and Technology, "Personalized Medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."[7] Implicit in this definition is the ability to adequately assess risk (or susceptibility) for CV disease to make further therapeutic decisions.

Global risk assessment equations

Individual risk factors are poor predictors of CV risk as evidenced by the well known fact that rough half of all myocardial infarctions occur in individuals with "normal" cholesterol values.[8, 9] Thus, the currently recommended standard for assessing CVD risk involves predictive equations that are mathematical functions derived from multivariable modeling of several weighted well-established risk factors, which provide a probability estimates of developing CV diease events in a given time period. The most frequently used risk algorithm in the U.S. is the Framingham Risk Score which was endorsed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) report[23] and consists of a point scoring system based on categories of age, total cholesterol, HDL cholesterol, systolic blood pressure and smoking status. This Framingham Risk Score algorithm provides an estimate of the 10-year (short-term) absolute risk of "hard" coronary heart disease (CHD) endpoints (CHD death or myocardial infarction), but other more recent versions of the Framingham risk score algorithm derived from the same population can be used to determine the short term risk of CVD events (including heart failure and atrial fibrillation), or long-term (30-year) risk.[10, 11]

Despite the low-cost and ease of use of the Framingham algorithm, it has several inherent limitations. First, while the ability of this algorithm to discriminate between affected and unaffected persons (ie: c-statistic) is quite good at ~0.80, incorrectly assigning risk 20% of the time may be insufficient on an individual level.[12] In addition, several studies have demonstrated the inaccuracy of the Framingham Risk Score in young populations and in women.[13, 14] A study by Akosah et al. demonstrated these limitations of the Framingham Risk Score in a real-world setting.[15] The authors performed a retrospective study of 222 young men (≤55 years) and women (≤ 65 years) hospitalized in their institution with an acute myocardial infarction. After calculating 10-year risk based upon the FRS, only 12% of this cohort would have been considered

high-risk prior to their event, with 18% categorized as intermediate risk and 70% lower risk. Furthermore, only 25% of men and 18% of women would have been eligible for statin therapy prior to their event based upon their risk category and application of the NCEP ATPIII guidelines.

As the many limitations of current CV risk assessment strategies become increasingly evident, technological and scientific advances are providing promising new tools for improving risk prediction. Numerous candidates for improving risk assessment have been proposed and can generally be grouped into three broad categories: biomarkers, atherosclerosis imaging, and genetic markers. Of these new screening tests, imaging the coronary arteries for calcification using computed tomography (CT) scanning has currently been shown to result in the most meaningful change in risk categorization.

II. CALCIFICATION AND ATHEROSCLEROSIS

Historical perspective

The presence of calcium within the coronary vasculature was reportedly first described in the late seventeenth century, but was not appreciated as a marker of advanced atherosclerotic disease until the early 1900's (**Table1**).[16] Although it has been detected roentgenographically for over a hundred years,[16] it was not until the last several decades that significant advances in radiographic techniques, including the use of image intensifiers, fluoroscopy, cine imaging and tomography, that coronary artery calcium (CAC) been able to be routinely detected non-invasively.[17, 18] The appreciation for the potential clinical use of CAC scanning lead to the development in the late 1980's of an ultrafast high-resolution CT, or electron-beam CT (EBCT) that could be used primarily for the purpose quantifying coronary calcifications.[19]

Year	Contributors	Contribution
Late 17th century	Bellini	First documented evidence of coronary
Early 18th century	Thebesius	calcification
1761	Morgagni, John Baptist	Further studies of coronary artery calcification
1936	Leary and other pathologists	Established calcification as a hallmark of advanced atherosclerosis
1959	Blankenhorn et al	Detection of coronary calcification on fluoroscopy
1961	Lieber et al	Correlation of coronary calcification with clinical atherosclerotic disease
1965	Eggen et al	Correlation of coronary calcification on autopsy with increased CAD mortality
1988	Janowitz et al	Use of EBCT for detection of coronary calcium
1990	Agatston et al	Scoring system for quantifying coronary calcium
2002	Kopp et al	Use of MDCT for measuring coronary calcium

Table 1. Historical perspective on coronary calcification and atherosclerosis. Adapted from Ref[2]

Pathobiologic relationship

Calcium deposits within the vasculature are mainly in the form of calcium hydroxyapatite.[20, 21] Coronary calcifications are essentially atherosclerotic in nature with rare exception, and calcification occurs primarily in the intimal layer in a structured fashion, very analogous to the physiological formation of bone.[22] Several proteins involved in bone formation, such as osteopontin and bone morphogentic protein-2, have been demonstrated to be present in atherosclerotic plaque.[21, 23, 24] There is evidence that smooth muscle cells within the vasculature have the capacity to transform into osteoblast-like cells under the appropriate conditions and the presence of these cells within the atherosclerotic plaque appears to precede the deposition of calcium.[24-26] Inflammatory mediators, high density lipoprotein, and growth factors appear to play a key role in their transformation and calcium deposition.[27-32]

From a lesion specific view, the relevance of calcifications in plaque is controversial. Specifically, there is some question as to whether the presence of calcification leads to increased or decreased biomechanical stability of the plaque. In a study evaluating for CAC with intravascular ultrasound, Beckman *et al.* found that that the amount of calcium content was less in plaques of patients with myocardial infarctions and unstable angina than in patients with stable angina.[33] Another intravascular ultrasound study found that patients with stable angina had the most extensive calcifications and the greatest size of calcium deposits compared with those with acute coronary syndromes.[34] In addition, patients with acute myocardial infarction more commonly had 'spotty' calcification, occurring in 51% of such culprit lesions. Another study using combining coronary CT angiography and intravascular ultrasound demonstrated that lesions commonly responsible for acute coronary syndromes, the thin cap fibroatheroma, were most prevalent in mixed or partially calcified plaque compared to non-calcified or heavily calcified plaque.[35] In order to study the biomechanical impact of calcifications, Huang *et al.* used computational analysis of 10 ruptured coronary lesions and 10 stable coronary lesions and determined that calcification did not appear increase fibrous cap stress.[36] In contrast, a more recent *in vitro* study using confocal microscopy with

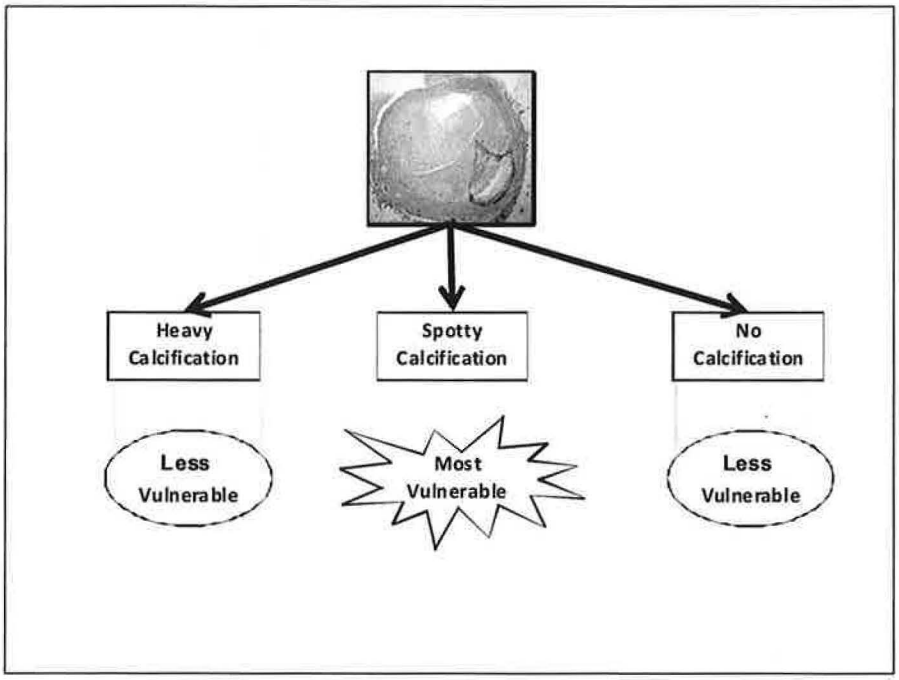

Fig 1. Calcification patterns and lesion stability. Plaques with spotty calcification maybe most vulnerable compared with those with no or heavy calcification

calcium staining and microcomputed tomography to evaluate for calcifications that are too small to be seen with conventional imaging techniques, found that microcalcifications did in fact lead to increased local stress and destabilized thin fibrous cap atheroma.[37] Therefore, it appears that although large deposits of calcium may have a stabilizing effect on coronary plaques, small deposits theoretically may make the plaque more vulnerable to rupture (**Figure 1**).

From a patient level view, calcified plaque quantity is strongly correlated with the overall atherosclerotic plaque burden. As such, higher CAC scores are accompanied by greater total plaque quantity and numerically increased number of vulnerable plaques, thus resulting in higher risk of myocardial infarction. In a seminal study by Rumberger *et al.*, in which 38 coronary arteries from 13 autopsied hearts underwent calcium measurements by EBCT scanning and atherosclerotic plaque measurement by direct histological assessment (**Figure 2**).[38] Each artery was sectioned into 3mm segments and the sum of calcium areas and sum of histological plaque areas were highly correlated (r=0.90). Importantly, a few arteries had evidence of atherosclerotic plaque, but no corresponding calcium, consistent with the knowledge that not all coronary plaque is calcified. In fact, it has been estimated that the area of CAC by EBCT is approximately one-fifth the size of total plaque area.[38]

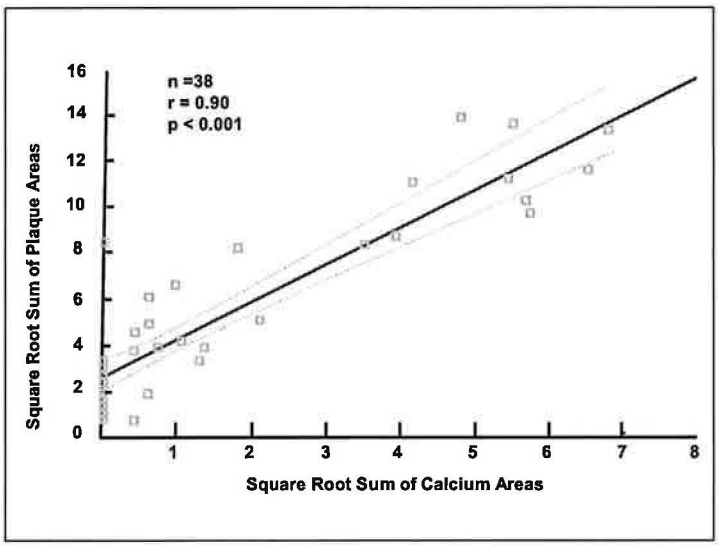

Fig. 2 Close correlation between EBCT measured coronary artery calcium and atherosclerotic plaque in 38 coronary arteries.

III. CT IMAGING OF CORONARY CALCIFICATION

Imaging of the beating heart using CT requires fast scanning times and high temporal resolution which can be accomplished by two different methods, EBCT and multidetector CT (MDCT).[39, 40] EBCT or ultrafast-CT was the initial method that was used in the clinical development of CAC scanning. This technology involves an electron beam emitted from an electron gun and directed at tungsten rings encircling the patient to create X-rays that pass through the patient and reach the detector on the opposite side. Since the only moving part of the scanner is the patient table rather than rotating x-ray tubes, EBCT provides for very rapid image acquisition times and fewer motion artifacts.[40] In MDCT or helical CT scanning, x-rays tubes mounted on a rotating gantry and can acquire multiple (commonly 64 and up to 256) slices simultaneously. These two techniques correlate reasonably well, although there may be some discrepancies at lower levels of calcium.[40],[41] Another use of MDCT is to perform coronary CT angiography (CTA) which involves the injection of iodinated contrast to opacify the coronary arteries and can be used to assess for both calcified and soft coronary

atherosclerotic plaque, evaluate for obstructive coronary artery disease, and delineate cardiac structures and myocardial function.[39] Given the increased radiation exposure and need for intravenous contrast, coronary CTA is currently used in the evaluation of symptomatic patients rather than for screening of asymptomatic individuals.

Radiation exposure is an important consideration for CAC screening of symptom free individuals. The effective radiation dose for CAC scanning using EBCT scanners is approximately 0.7-1.3mSv, and slightly higher with MDCT methods, approximately 1.0-1.8 mSv.[42, 43] By comparison, the effective radiation dose is approximately 0.05mSv for a PA and lateral chest x-ray, 8-11 mSv for an abdomen and pelvis CT, and 3.6 for the average annual background radiation in the US.[43] Coronary CT angiography, in contrast, currently involves approximately 10 fold higher radiation exposure, 9-12mSv, although new techniques are evolving such as dual source CT that use considerably lower doses. A recent report estimated the lifetime risk of radiation induced cancers from a single CAC screening exam, and revealed higher estimates when scanning occurred at younger ages, and in women partly due to excess breast cancer risk.[44] A single scan at age 40 years could result in 9 and 28 excess cancers per 100,000 men and women respectively; the corresponding values at age 80 are 3 and 6 per 100,000 respectively.

IV. CORONARY ARTERY CALCIUM AND PROGNOSIS

Several retrospective[45-47] and more recently, prospective studies[48-54] have evaluated the predictive ability of CAC scanning for CV events. The South Bay Heart Watch Study, started in 1990, is a large study of predominantly male subjects with the longest prospective follow up to date.[49] 1461 subjects >45 years of age (mean 66 years) with at least one coronary risk factor and no know CHD underwent CAC scanning at baseline, with 84 of them experiencing CHD death or MI in 8.5 years of follow-up. The hazard ratio for CHD events in those with CAC scores >300 compared with a score of 0 was 3.9 (95% CI 2.1-7.3). Moreover, higher CAC scores were able to stratify CHD risk within categories of risk determined by the Framingham Risk Score, particularly the intermediate risk group (10-20% 10-year risk) ($p<0.001$). Another larger prospective study of 4613 subjects, the St. Francis Heart Study, evaluated an apparently healthy cohort that was not required to have risk factors as inclusion criteria.[48] In 4.3 years of follow-up, a CAC score ≥100 compared with <100 conferred a relative risk of CHD death or MI of 9.2 (95% CI 4.9-17.3), and the relationship between CAC and CV events persisted after adjusting for traditional risk factors and C-reactive protein (CRP) ($p=0.01$). Similarly, CAC scores were able to further stratify risk amongst each category of Framingham Risk Score determined risk. The Aerobics Center Longitudinal Study (ACLS) is a prospective study of CAC scanning in 10,746 adults and included a wide age range (22-96) and separate analyses of men and women.[50] After an average of 3.5 years of follow-up, the hazard ratio for hard CHD events in the highest tertile of CAC compared with a score of 0 was 20.0 (95% CI 5.8-69.6) in men and 9.3 (1.2-18.9) in women. These associations persisted after adjustment for or stratification by risk factors.

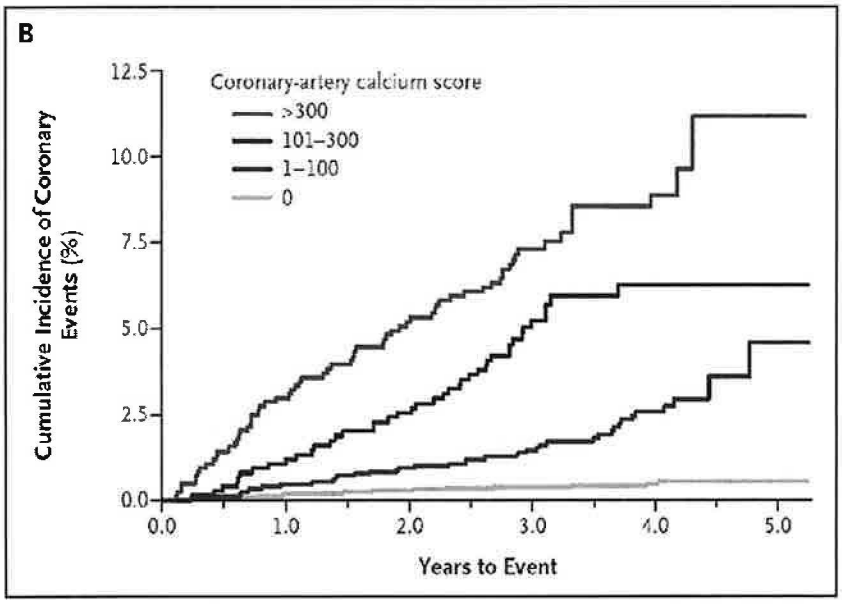

Fig. 3 Association between CAC scores and coronary events in 6722 subjects from the multiethnic MESA study

More recently, the Multiethnic Study of Atherosclerosis (MESA) investigators evaluated the predictive ability of CAC scanning in a cohort of 6722 individuals ages 45-85 including a reasonable proportion black, Hispanic, and Chinese subjects.[53] Over a median follow up of 3.8 years, calcium scores >300 were associated with a greater than 9 fold increased risk of coronary events after risk factor adjustment compared with the absence of calcium (**Figure 3**). Further, each doubling of the calcium score resulted in a 15-35% increased risk of such events, and this pattern was consistent across all racial and ethnic groups. Similar associations between CAC and CHD events have also been observed in prospective studies in Europe[52] and in cohorts of younger subjects.[50, 51]

Metrics to assess clinical value

Several metrics can be used to assess the value of a novel risk stratification tool.[55] The incremental value relative to traditional CV risk factors is commonly gauged using the change in c-statistic (or area under the receiver operator curve). Compared with the Framingham Risk Score variables, the addition of CAC improved the c-statistic in the South Bay Heart Watch Study (0.63 to 0.68, $p<0.001$)[49], the Rotterdam Study (0.749 to 0.774, $p=0.02$),[52] the St. Francis Study (0.68 to 0.79, $p<0.001$),[48] and in the MESA Study (0.79 to 0.85, $p=0.006$).[53]

An emerging statistical metric termed the net reclassification improvement (NRI) appears to be a better measure of the clinical utility of a new test in that it assess the ability of such tests to appropriately reassign clinical risk category compared with standard techniques (ie: the Framingham Risk Score).[56] Specifically, it measures the extent to which subjects with and without events are appropriately reclassified into clinically accepted higher or lower risk categories with the addition of a new test. The MESA investigators reported an NRI of 25% when CAC was added to the Framingham variables compared with Framingham alone for their entire cohort, and 55% amongst those initially classified as intermediate risk by Framingham (10-20% 10-year risk).[57] Similar NRI values for CAC scanning have been reported in other cohorts.[54, 58] These NRI values are significantly higher than any current emerging CV risk assessment tool including carotid intima-media thickness and C-reactive protein testing, which have

reported NRI values of 9.9% and 5.7% respectively,[59, 60] and speak to the potential clinical value of CAC scanning (**Table 2**).

	NRI	NRI (Intermediate Risk)	Δ C-stat	Study
CAC	**25%**	**55%**	**+**	**MESA**
Carotid IMT	**9.9%**	**21%**	**+**	**ARIC**
CRP	**5.7%**	**15%**	**-**	**WHS**

Table 2. Comparison of net reclassification improvement (NRI) and change in c-statistic for CAC, carotid intima-medial thickness, and C-reactive protein

V. CLINICAL APPLICATIONS OF CAC IMAGING

Based upon the evolving supportive evidence, a recent guideline report from the American College of Cardiology and American Heart Association (ACC/AHA) on Cardiovascular Risk Assessment provided a IIA recommendation (ie: reasonable to perform) for CAC measurement in asymptomatic adults at intermediate risk for coronary events (10-20% 10-years risk) and a IIb recommendation (ie: may be considered) for those at low to intermediate risk (6-10% 10-year risk).[61] Despite this endorsement, the interpretation and clinical response to a score result are not well defined, particularly as there are few randomized outcomes data involving therapeutic interventions for elevated CAC scores. Various clinical scenarios can occur with CAC results, some with greater consensus on therapeutic response than others.

High absolute scores

One scenario where the clinical interpretation is less controversial involves intermediate risk patients who are found to have high CAC scores (ie: >400). In MESA, 8.8% of subjects with 10-20% risk by the Framingham Risk Score have calcium levels above this threshold.[62] Corresponding percentages from the younger Dallas Heart Study population is 7.3% percent in men and 5.2% in women.[63] Several studies have demonstrated that such subjects with scores >400 have greater than a 2% annualized risk of CVD events which can be extrapolated to high risk status (ie:>20% 10-year risk) (**Table 3**).[48, 49, 52] Although there are a paucity of data on therapeutic interventions in patients with high CAC, it would be reasonable to initiate statin medications and low dose aspirin in these individuals.[64-66] In the only large randomized trial of statin use and clinical events in those with CAC, the St. Francis Study investigators found that the pre-specified subgroup with CAC >400 had an 42% reduction in CV events with statin use compared to placebo (p=0.046).[48]

	Risk	1-99	100-400	>400
South Bay	Intermediate	8.5%	12.2%*	21.4%**
St. Francis†	Low-Intermed	2.3%	12.8%	32.6%
Rotterdam	Intermediate	3.0%	8.7%	21.6%
Heinz-Nix	Intermediate	2.8%	5.6%	17.4%
MESA	Low	5.3%	7.9%	15.8%

Table 3. Extrapolated absolute 10-year risk of coronary events by CAC score category. *indicates CAC 100-300, **>300; † indicates all cardiovascular events. Framingham risk indicates average risk category of the cohort.

Whether lower thresholds of CAC, >300 or even >100, translate into high risk status is unclear. In South Bay Study., CAC scores >300 resulted in a risk of CHD of 13.6% over 6.3 years, which can be extrapolated to 21% 10-year risk.[49] One AHA scientific statement on CT imaging published in 2006 recommended that a score >100 be considered high risk with corresponding intensification of lipid lowering therapy.[39] However, a subsequent ACC/AHA document from 2007, stated "that for a score greater than or equal to 400, the patient's 10-year CHD risk would achieve risk equivalent status similar to that noted with diabetes or peripheral arterial disease…thus, clinical decision-making could potentially be altered…"[67]

It is important to note that absolute CV risk conveyed by a CAC score is conditioned on the pretest risk. Specifically, most studies have shown that absolute risk of those with moderate or high CAC scores is higher among those at high Framingham 10-year risk than those at low Framingham risk.[48, 49, 52, 54] In the South Bay Heart Watch Study the observed absolute 7 year risk of CHD with CAC >300 was 5.2% in those at low Framingham risk compared with 32% in those at high risk. Thus, while a patient categorized as low risk by Framingham would certainly be considered higher risk with a CAC scores >100 or >400, their absolute risk may not exceed 10% and 20% 10-year CHD risk, respectively.

High percentile scores

The extensive databases amassed with CAC scoring information has allowed for age, sex, and race specific normograms for CAC scores.[68] The MESA investigators have published an online calculator to determine an individual's CAC percentile relative to others in their demographic group (http://www.mesa-nhlbi.org/Calcium/input.aspx). Applying these normograms can be very informative, but also leads to the challenging scenario of a patient with low absolute but high percentile score. For example, a 45

year old man with a CAC score of 40 would be considered at low short-term (10-year) risk for CV events, but would also be in 90th percentile for his age and sex, with a likely worse long-term prognosis. Potential divergent responses to his result are to label the patient with a disease or to offer reassurance, neither of which seem wholly appropriate.[69] It is also unclear when or if to initiate statin therapy in such an individual. Following NCEP recommendations, statin therapy would not be recommended for such an individual unless his LDL levels were significantly elevated (>190 mg/dl). However, if this patient remained at the 90th percentile for CAC, his predicted score at the age of 60 would be approximately 500. Thus, earlier intervention is appealing, particularly as there is growing appreciation for the long term effects of modestly lower cholesterol earlier in life.[70] Alternatively, one could defer statin use until his risk exceeded a certain threshold, but the exact timing of this intervention is unclear, and whether serial CAC scanning can help in decision making is also currently unknown.

Some have suggested the concept of vascular age where the CAC score could be extrapolated to the patients "arterial age," either by determining the age where a certain CAC value is the median score, or the age at which the risk of CHD was equivalent to the risk with this CAC score.[71-74] This arterial age could then be entered into the Framingham equation to provide a modified risk estimate. While a valuable patient communication tool, the proposed arterial age calculators have not been validated in external datasets and the accuracy of modified Framingham estimates are unclear.

Zero score

Coronary artery calcium scans are often performed to assess for unsuspected or higher CV risk in excess of that predicted by standard risk factors. However, an equally or perhaps more valuable use of these tests is to convey a very low risk of events in patients with a score of zero. An evolving literature base surrounding the zero score suggests that in *asymptomatic* individuals without any detectable calcium, the annual probability of CV events is exceedingly low (0.1% per year or less) (**Table 4**).[3, 75] In a recent meta-analysis involving 71,595 asymptomatic subjects from 13 studies, 41% (range 22-80%) were found to have a CAC score of 0.[75] In a mean follow up of 50 months, the CV event rate in those without CAC was 0.47%. Another group compiled data from 44,052 subjects from 3 centers and demonstrated that among the 45% of subjects with a CAC score of 0, the annualized all-cause mortality rate was 0.87 deaths per 1000 person-years, or ~1% probability of death over 10-years.[76] Of note, scores from 1-10 have been associated with a 2 to 3 fold higher relative risk of CV events compared to scores of 0, but the absolute risk of cardiovascular events in subjects are still quite low (<0.5% per year).[77]

A critical point in interpreting CAC scores of zero is the concept of conditional probability or Bayes Theorem. Here, the pretest probability of CV events has implications for the post-test risk assessment, and the negative predictive value of a score of zero is not the same for asymptomatic and symptomatic patients.[3] In addition, the absence of CAC does not mean the absence of any atherosclerotic plaque. In a recent registry study of 10,037 symptomatic patients referred for coronary CT angiography, 51% were found to have a CAC score of 0.[78] Among these subjects, 13% had some degree of non-obstructive coronary plaque, and 4% had coronary stenoses of greater than 50%. The CV event rates in those with a CAC score of 0 and obstructive CAD was 3.9% over 2.1

year of follow up compared with 0.8% for those without obstructive CAD. However, most of the CV events in those with obstructive CAD were coronary revascularization procedures, which may have been in response to the CT findings rather than spontaneous events. Another prior smaller study of 291 symptomatic subjects

Study	No of Patients in Full Study	Follow-up Duration, y	Annual Event Rate in CAC=0 Patients, Per 100 Individuals
Georgiou et al	192	4.2	0
Rozanski et al	1,153	2.7	0.47
Greenland et al	1,312	7	0.63
Arad et al	1,173	3.6	0.11
Raggi et al	632	2.7	0.13
Wong et al	926	3.3	0
Arad et al	4,613	4.3	0.12
Kondos et al	5,635	3.1	0.09
Anand et al	510	3	0.12
Taylor et al	2000	3	0.04
Church et al	10,746	3.5	0.04
Becker et al	1,726	3.3	0

Table 4. Annual CV event rate per 100 individuals among those with CAC=0
Adapted from Ref [3]

undergoing coronary CT angiography reported the prevalence of obstructive CAD (>50% stenosis) in those with a CAC score of 0 of 19%.[79] In contrast, the probability of having any atherosclerotic plaque detected by CT in *asymptomatic* subjects with a CAC score of 0 is quite low (<5%).[80] While CAC scanning may have some role for risk assessment in symptomatic patients, including those evaluated in the emergency room, these data suggest that the greatest utility of this test is in asymptomatic individuals.

VI. SERIAL CAC SCANNING

Atherosclerosis is a dynamic process and imaging of the blood vessels at a single point in time may not capture the temporal and variable aspects of this disease. Two natural questions that evolve from the clinical CAC scanning scenarios presented are: 1) what is the warranty of a zero score, and 2) what is the significance of a change in CAC score?

Warranty of a zero score

A CAC score of 0 in asymptomatic patients conveys an excellent short term prognosis. However, whether to rescan or when to rescan such individuals is unclear. There are currently few data to help answer these questions, but a study by Gopal *et al* did help to define the natural history of a zero score.[81] In this observational study from 710 physician-referred patients with no CAC at baseline, follow up scans were performed after 1-3 years in 35%, 3-5 years in 36%, and >5 years in 29% (mean interscan interval 4±2 years). In the entire cohort, 62% did not develop any CAC on the repeat scan, and

only 2% developed a score >50 (**Figure 4**). Even among those with >5 years of follow up, 54% remained free of CAC and only 4% developed CAC score >5. Based upon these results, the authors concluded that in individuals without CAC, a repeat scan should not be performed within 5 years.

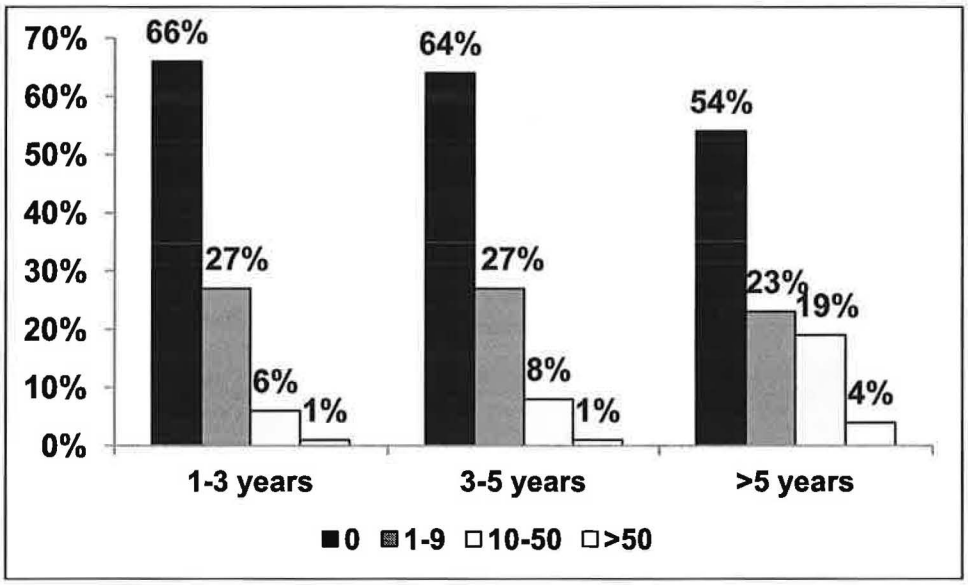

Fig. 4 Progression of calcium score of 0. Cohort of 710 subjects with CAC=0 and subsequent CAC imaging at 1-3, 3-5, or >5 years. Proportion of subjects with follow up CAC score in each CAC category, of those with CAC=0 at baseline

Progression of CAC

There are currently no published prospective, population-based studies evaluating the relationship between progression of CAC scores and clinical events. However, in a retrospective study of 495 subjects with serial CAC scans an average of 1.9 years apart, the change in CAC score was significantly greater in those who subsequently developed an MI than those that remained event-free. In fact, the odds ratio for MI in those whose CAC score increased ≥15% per year was 17-fold greater than those that progressed <15% per year.[82] Further analyses revealed that the baseline CAC score was only related to CV events in those who subsequently had CAC progression (≥15% per year), but not in those without progression (**Figure 5**). An additional study involving the same cohort reported that when baseline CAC values and change in CAC were assessed jointly in multivariable analyses, only CAC progression was associated with CV outcomes.[83] These findings suggests that 1) for every level of atherosclerotic burden, there are varying rates of atherosclerosis progression, and 2) that atherosclerosis progression may be a better indicator of adverse clinical events.

Supporting data come from an observational study by Budoff *et al* that included 4,609 physician referred subjects with repeat CAC scanning performed an average of 3.1 years apart.[84] In this cohort, progression of CAC was strongly associated with all cause mortality independent of baseline CAC score and cardiovascular risk factors. More recently, the MESA investigators presented the preliminary results of their CAC progression dataset at the AHA Scientific Sessions 2011 confirming an independent association of CAC progression with clinical CV events. However, the optimal scoring method to define and quantify CAC progression remains unclear, and at least 4 different methods have been proposed.[84, 85] In addition, the threshold of CAC change that warrants therapeutic intervention and the nature of this intervention has not been defined. Ongoing studies, including projects in the Dallas Heart Study and the Cooper Center Longitudinal Study, will help to answer these questions.

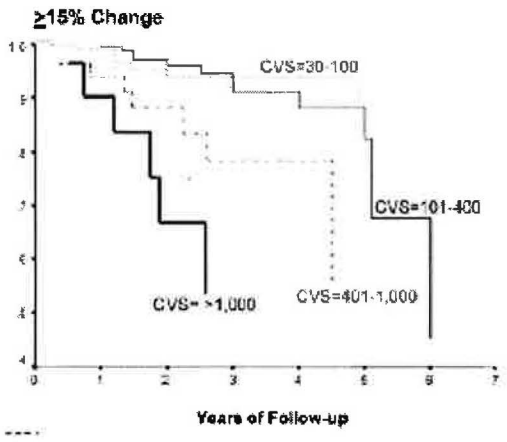

Fig. 5a Baseline CAC scores (CVS) and risk of MI with CAC progression

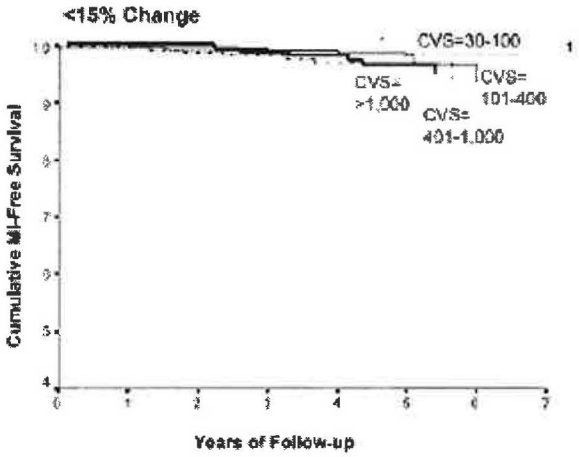

Fig. 5b Baseline CAC scores (CVS) and risk of MI without CAC progression

Statins and CAC progression

It was previously thought that statin use may slow or halt the progression of CAC. This belief came from early retrospective studies,[86] but has since been refuted by several recent prospective studies.[64, 87-89] In a nested prospective study within the larger randomized Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression (SALTIRE) trial assessing the effect of statins in patients with early aortic valve stenosis, 88 subjects underwent serial CAC scanning with a median interval of 2 years.[89] Subjects assigned to 80mg of atorvastatin (n=38) witnessed a 53% reduction in LDL-C levels and 49% reduction in CRP ($p<0.001$ each) compared with no statistical change in either parameter in the placebo group (n=49). Despite marked differences in LDL and CRP during the study period, there was no difference in change in CAC score between the two groups (**Figure 6**). In the larger St. Francis Heart Study, subjects who had CAC scores >80th percentile (n=1005) were enrolled in a prospective, randomized trial of atorvastatin 20mg daily in addition to vitamins C and E vs. matching placebos. After a mean follow up of 4.3 years and reduction in LDL of 43% in the atorvastatin arm, there was no difference in change in CAC scores between this group and those receiving placebos[64] Similarly, in two prospective randomized trials of intensive vs. standard statin therapy, there was no significant difference in CAC progression based upon statin potency.[87, 88]

The lack of effect of statins on progression of CAC is in sharp contrast to the well known effects of statins on reducing clinical CV events.[90] One explanation for these seemingly contradictory observations is that statin use and potent lipid lowering result in delipidation of atherosclerotic plaques,[91] but do not reduce the calcified components.[92] In fact, some studies have found progression of calcification with diet induced regression of plaque volume in animals, which occurs as part of the healing process, with replacement of necrotic debris by fibrous tissue and calcification.[93] Statins themselves may also promote calcification in some tissues.[94] As such, changes in calcification which occur during statin use may have different clinical implications from those that occur without such therapy. One can infer from this line of reasoning that there is limited utility for repeat CAC scanning once the decision to initiate statin therapy has occurred.

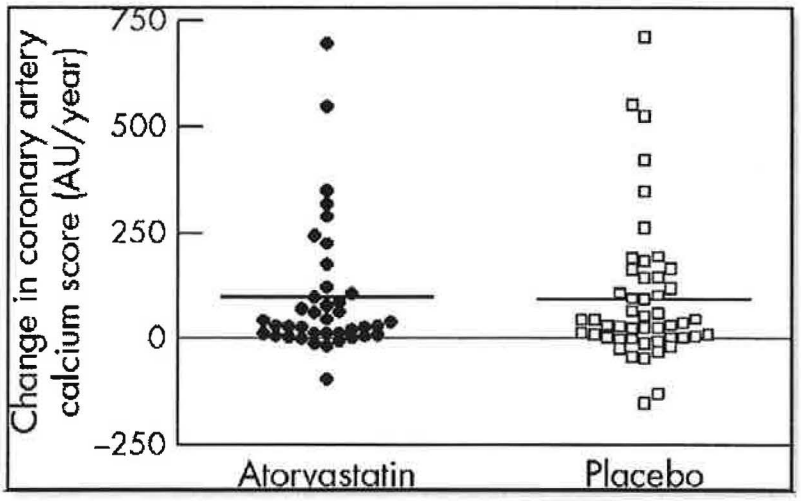

Fig. 6 Change in CAC score with statin therapy. There was no difference in change in CAC in subjects randomized to atorvastatin 20mg (n=39) or placebo (n=49) (p=NS) after a median follow up of 24 months.

VII. POPULATION SCREENING USING CAC SCANS

While CV disease remains the leading cause of death in the United States, and numerous studies have convincingly demonstrated that higher CAC scores are associated with increased CV event rates, there still remain several areas of uncertainty before CAC scanning can be recommended for broad population screening. Notably, there are currently no randomized trials to date demonstrating that a *strategy* incorporating CAC scanning is superior to current standard of care in improving clinical outcomes. Indeed, enhanced disease detection does not necessarily equate to improved rates of morbidity and mortality.[94] In addition, as outlined in this manuscript, there are several practical questions regarding thresholds for treatment, interpretation of high percentile scores, and need for repeat scanning which must be addressed. Without such answers, there is the potential for both inappropriate over and undertreatment of individuals. Finally, although conceptually the intermediate risk group is the appropriate target for such a screening test based upon Bayesian principles, alternative definitions of the "intermediate risk group" may actually have higher yield and efficiency in detecting those at increase risk for CV disease.[63]

Proving a potential benefit of CAC scanning beyond quantifying risk

As mentioned, there is currently only one large, prospective, randomized study evaluating the effect of a therapeutic intervention (ie: statins) on clinical outcomes in those deemed at higher risk based upon CAC.[64] In the entire St. Francis Heart intervention study of 1005 subjects with a median CAC score of approximately 370 and mean LDL-C of 147mg/dl, the group assigned to 20mg of atorvastatin trended towards a

reduction in CV events compared with the placebo arm (6.9% vs. 9.9%, p=0.08), with a more robust reduction in the pre-specified subgroup with CAC >400 (8.7% vs. 15.0%, p=0.046). While the data are not definitive for a beneficial role of statin use in those with a high burden of CAC, there may no longer be equipoise for such a randomized trial.

Another potential benefit of atherosclerosis imaging tests is to encourage adherence to preventive therapies, and thus improve CV risk factors. Two prospective, randomized trials have assessed the association between CAC scanning and risk factor levels.[95, 96] In one study of 450 healthy, male, military recruits (Prospective Army Coronary Calcium, or PACC study), providing CAC results did not translate into improvement in CV risk factors at one year compared to usual care.[95] However, in this cohort, 85% of subjects had no detectable CAC, so the motivating potential of CAC only applied to a small proportion of the overall trial population. In the recently published Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study of 2,137 participants randomized to risk factor counseling with or without CAC scanning, those that underwent CAC imaging had greater improvements in systolic blood pressure, LDL-C, and Framingham risk score compared to the no-imaging group ($p<0.05$ each).[96] Furthermore, there was a graded response between reduction in lipids, blood pressure, glucose, weight and Framingham score with higher CAC scores among the scanned group. The proportion of subjects with non-zero scores was much greater in EISNER (52%) than in the PACC study.

SHAPE Society recommendations

In contrast to the more conservative recommendations for CAC scanning endorsed by the AHA/ACC,[61] other groups have advocated more broad application of atherosclerosis imaging. The Society for Heart Attack Prevention and Education (SHAPE) is an independent group of prominent cardiovascular specialists that published their own clinical practice recommendations for screening in an industry sponsored supplement in 2006.[97] These "guidelines" call for atherosclerosis imaging tests in all asymptomatic men ages 45-75 and women ages 55-75 with at least one atherosclerotic risk factor with LDL-C targets determined by the test results. The authors estimated a 10% reduction in CVD deaths and 25% reductions in myocardial infarctions by applying their screening algorithm, and suggested that there would be a 50-65% increase in the statin eligible population.

There have been no prospective studies validating these recommendations or their implications. However, we evaluated the effects of applying the SHAPE recommendations on lipid lowering therapy eligibility in subjects ages 30-65 in the Dallas Heart Study.[98] Compared with the NCEP-ATPIII guidelines, application of SHAPE would result in bidirectional reclassification such that 6.3% of the population would be newly deemed not at LDL-C goal, while 2.7% of the population would be reclassified as at goal. Thus, there would be a 3.6% absolute and 12.8% relative increase in population eligible for lipid lowering therapy using SHAPE recommendations in Dallas County.

Texas Atherosclerosis Imaging Bill

On September 1st, 2009, Texas implemented to first law in the nation mandating insurance coverage for imaging tests used in cardiovascular disease (CVD) screening. The legislation, known as HB1290, contains provisions for both CVD screening of the general population as well as bariatric surgery coverage for state employees.[99] The CVD screening component mandates insurance coverage of up to $200 for coronary artery calcium scanning (CAC) or carotid intima-media thickness (CIMT) testing every five years in an accredited laboratory for men between the ages of 45-75 years and women 55-75 years who are also 1) diabetic or 2) have "a risk of developing coronary heart disease, based on a score derived using the Framingham Heart Study coronary prediction algorithm, that is intermediate or higher." The bill's sponsor, Representative Rene O. Oliveira, introduced the legislation after undergoing a "screening" CAC scan that indicated significant coronary artery disease, resulting in coronary artery bypass surgery. After an unsuccessful attempt in the 2007 legislative session, the bill finally passed and was signed into law in June 2009. The unique aspect of this bill is that it did not emanate from major specialty societies such as the AHA or ACC and was not developed with their input and endorsement, but did involve collaborations with SHAPE.

		Men	Women
Total Adult Population of Texas		**8,676,003**	**8,789,633**
Men ages 45-75 and Women 55-75		**3,359,622**	**1,902,552**
	Intermediate Risk by FRS	**1,325,973**	**151,866**
	Diabetic	**423,494**	**252,690**
TOTAL ELIGIBLE		**1,749,467**	**404,556**
Screening Costs		**$350 million**	**$81 million**

Table 5. Estimates of population eligible for atherosclerosis imaging screening and screening costs for HB1290.[4]

Despite the broad target group of this legislation, there had been no published detailed assessment of its potential implications prior to its implementation. In a recent manuscript, I evaluated the impact of implementation of HB1290 in the target population.[4] Using Texas population estimates from 2007,[100] data from the Texas Behavioral Risk Factor Surveillance Survey,[101] and the National Health and Nutrition Examination Survey,[102] an estimated 2.2 million people in Texas would currently be eligible for these CVD screening imaging test under this legislation (**Table 5**). At $200 per exam, the one-time cost of screening all eligible individuals would be approximately $430 million, although usually only a fraction of eligible individuals elect to undergo routine screening tests. In addition, one time screening of the current eligible population of Texas with CAC imaging would result in approximately 180 new cancers, while

screening every five years could cause as many as 1000 new cancers.[44] Conservative estimates also suggest approximately that 150,000 incidental findings requiring follow up will be discovered,[103] with higher end estimates of 300,000.[104]

Changing paradigms for CAC screening

Current recommendations[67, 105] advocate the use of CAC screening among individuals estimated to be at intermediate risk (10-20% by the Framingham risk score) based on Bayesian probability theory that post-test risk assessments are more likely to be influenced by test results among subjects whose pre-test risks are intermediate, rather than low or high.[106] However, while theoretically sound, the utility and efficiency of such recommendations when applied on a population basis remain unclear. In the Dallas Heart Study, we evaluated the impact of CAC scanning recommendations in adults ages 30-65 in the Dallas County population and discovered that only 1.0% of women and 15.4% of men were at intermediate risk by Framingham and thus eligible for imaging, and less than 0.1% of women and 1.1% of men changed from intermediate to high risk categories.[63] Importantly, greater than 100 women and 14.3 men would need to be scanned to reclassify risk in one subject. Thus, current CAC screening recommendations would have low yield and poor efficiency when applied to a population.

Reclassification of risk among lower risk subjects may have greater clinical ramifications than reclassification among intermediate risk individuals, because lower risk subjects are presently ineligible for more intensive primary prevention strategies, such as the use of statins with aggressive LDL-C goals (< 100 mg/dL) and the use of aspirin, which are already options for all intermediate and high risk subjects.[107, 108] Indeed, at the present time, the key distinction between preventive strategies targeted toward intermediate and high risk subjects are optional LDL-C treatment goals of < 100 mg/dL versus < 70 mg/dL, respectively.[107] In a secondary analysis, of the Dallas Heart Study data, we found that 3.2% of all men and 2.9% of all women were classified as low risk but with CAC scores >100. We evaluated various eligibility criteria to target CAC screening in select low risk subjects and found that age and subcategories of the Framingham risk score (ie: 3-6, 6-9% risk) could efficiently identify seemingly low risk subjects with high CAC. Using these two criteria, a simple CAC screening strategy for low risk subjects was developed that captured 51.1% of men and 84.2% of women with CAC scores out or proportion to their Framingham risk category from the entire cohort, and detected one subject with CAC >100 for every 6.8 for men and 5.2 for women screened. Further studies are needed to refine the optimal group for screening using CAC.

VIII. CONCLUSIONS

Coronary artery calcium scanning is a valuable tool to refine CV risk estimates and to detect those at higher risk than suggested by risk factors levels alone. On an individual level, it can help guide therapeutic decision making in select patients, particularly for those with very high scores and scores of zero. While calcium scanning holds great promise for broad population screening, several remaining questions must be addressed before this it can be endorsed for this purpose.

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