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EARLY DETECTION OF CORONARY ARTERY DISEASE IN WOMEN

The Role of Coronary Artery Scanning With EBCT

INTRODUCTION:

The total number of men who develop clinically manifest heart disease during their lifetime is greater than that diagnosed in women and yet currently more women die as a result of coronary artery disease [CAD] than men. It has been estimated that 63% of these deaths occur in women who had no ante-mortem diagnosis of CAD.

These general facts have been established:

1. Women develop CAD symptoms later than men [on the average of 10 years];
2. Chest pain is generally a poor predictor of epicardial coronary disease in women;
3. And, women often have more extensive disease than their male counterparts when they do develop symptoms, thus their overall prognosis at presentation is worse than men.

The incidence of coronary disease in women increases dramatically after menopause, and this is NOT necessarily figured into the traditional Framingham risk assessment, which places chronologic age as the most powerful risk factor but considers female sex [regardless of age] as a separate and "negative" risk factor. Elevated total serum cholesterol is another important cardiovascular risk, but an HDL-C of >60 mg/dl is considered a "negative" [i.e. beneficial] for the population as a whole. However, there is emerging evidence suggesting that this may not always be true for women.[1]

Many cardiologists are therefore suggesting that clinicians consider testing women on an individual basis for signs of subclinical atherosclerosis, rather than relying on traditional broad based population NCEP or Framingham "risk equations" to identify those who may be at greatest risk. Current and emerging measures for clinicians to predict coronary plaque burden generally involve direct imaging of the vascular system and include direct coronary angiography, ultrasonography [carotid, peripheral, and intravascular], and quantification of coronary artery calcium by electron beam tomography [EBT].

Coronary artery calcium is intimately associated with mural atheromatous plaque[2-6]. A direct relationship has been established between coronary artery calcium as measured by EBT and both histologic[7,8] and in-vivo intravascular ultrasound[9,10] measures of atherosclerotic plaque on a heart-by-heart, vessel-by-vessel, and segment-by-segment basis. Additionally, there is increasing evidence that the common clinical measure of coronary calcium by EBT, the "calcium score"[11], has a significant predictive value for subsequent cardiac events in both symptomatic and asymptomatic patients[12-16], and has predictive value over and above traditional risk factors.[15] The discussion to follow will examine the role of EBT in the diagnosis of CAD in women.

CORONARY ARTERY CALCIUM

General Pathology of Coronary Calcium

Atherosclerosis is the only disease known to be associated with coronary calcification.[2,3,6] Recent studies have shown that calcium can be seen in all degrees of atherosclerotic involvement and is an active process.[17-20]

Coronary calcification is common in patients with known coronary artery disease[21-25], and is strongly related to age, increasing dramatically after age 50.[23-25] McCarthy[21] studied 65 consecutive autopsy derived hearts (death not necessarily of cardiac causes) and found 63% to have some coronary artery calcification, nearly always associated with some degree of luminal coronary artery disease. Ninety-four percent of the coronary arteries studied from patients older than 60 years demonstrated some degree of calcification. In a series of 360 (living) patients undergoing cardiac catheterization and coronary fluoroscopy, Bartel[26] found a 43% prevalence of calcification, and roughly 60% of patients studied over age 60 had some calcification noted by fluoroscopic examination. In a separate study of individuals from the general population not known to have coronary disease, the prevalence of calcification by fluoroscopy has been reported to be roughly 20%.[24] Since Faber[27] in 1912 noted that Mönckeberg's calcific medial sclerosis does not occur in the coronary arteries, atherosclerosis is the only vascular disease known to be associated with coronary calcification.

Many reports relate the amount of coronary calcification to the severity of stenoses. For example, in the autopsy series mentioned above[21], significant stenosis and/or occlusion was virtually certain if calcification was present in segments longer than 1 centimeter. This relation has been borne out by other studies as well.[2,3,28] Hamby[29] found that 81% of patients with angiographic two or three-vessel disease had coronary artery calcification. Mintz et al[30] studied 110 men and women undergoing coronary angioplasty for symptomatic coronary artery disease. The presence of target lesion calcification was identified in 75% of these individuals using intravascular ultrasound.

"Coronary remodeling" associated with the development and progression of atherosclerotic disease is a recently described phenomena whereby the luminal cross-sectional area and/or external vessel dimensions enlarge in compensation for increasing areas of mural plaque.[31] Coronary artery calcium is an intimate component of some plaques. Clarkson[32] in a histopathology investigation has shown that plaques with microscopic evidence of mineralization were much larger and were associated with much larger coronary arteries than those sections without microscopic evidence of calcification. This was true in humans and in non-human primates. The compensatory enlargement of atherosclerotic coronary segments may explain why coronary angiography frequently underestimates the severity of coronary disease as compared with histopathologic studies. Studies attempting to correlate the site and amount of coronary calcium with percent luminal narrowing at the same anatomic site have shown a positive but non-linear relationship with large confidence limits.[7] However, coronary plaque and its associated coronary calcification may have only a poor correlation with the extent of histopathologic stenosis,[32,33] which in turn is largely accounted for as a result of individual variations in coronary artery remodeling. In-situ coronary calcium, on the other hand, is associated with plaque size.[33]

A study by Rumberger et al[8] has emphasized that the total area of coronary artery calcification is correlated in a linear fashion with the total area of coronary artery plaque on a segmental, individual coronary artery, and whole coronary artery system basis. However, the areas of coronary calcification were on the order of 1/5 that of the associated coronary plaque. Additionally, there were clear areas of

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plaque without associated coronary calcium as detected with EBT. These data suggest that there may be a size of coronary plaque that is most commonly associated with coronary calcium but, in the smaller plaques, the calcium is either not present or is undetectable. However, coronary plaque disease is a diffuse process and although calcium may not be seen in one particular area, if the overall plaque burden is sufficient, coronary artery calcium will be identified.

Molecular Biology of Coronary Calcium

Calcium phosphate, in the form of hydroxyapatite, and cholesterol accumulate in atherosclerotic lesions. Circulating proteins normally associated with bone remodeling play an important role in coronary calcification. Although the true role of calcium in the atherosclerotic process is unknown, new insights into the pathophysiology of coronary calcification have come within the past several years. Fitzpatrick et al[34] used in-situ hybridization to identify mRNA of matrix proteins associated with mineralization in coronary artery specimens. Specifically, they identified from autopsy coronary artery specimens a cell attachment protein (osteopontin), a protein associated with calcium (osteonectin) and a gamma carboxylated protein that regulates mineralization (osteocalcin). Similar studies have shown that osteopontin can be seen in tissue demonstrating atherosclerotic involvement and appears to be present only in sites of concomitant coronary atherosclerotic disease. Hirota et al[19] demonstrated by Northern blotting that osteopontin mRNA expression is related to the severity of the atherosclerosis. Additionally, osteonectin expression of mRNA decreased with the development of atherosclerosis. Shanahan[20] and Ideda[18] have independently demonstrated the predominant cell types in these areas are macrophage-derived foam cells, although some smooth muscle cells were also identified. Finally, Bostrom et al[17] recently identified bone morphogenetic protein-2a, a potent factor for osteoblastic differentiation, in calcified human atherosclerotic plaque. Cells cultured from the vascular wall formed calcified nodules similar to those found in bone cell cultures. The predominant cells in these nodules had immunocytochemical features characteristic of microvascular pericytes, which are capable of osteoblastic differentiation. These findings suggest that arterial calcium in atherosclerosis is a regulated process similar to bone formation rather than a passive precipitation of calcium phosphate crystals.

In summary, recent studies have confirmed that arterial calcium development is intimately associated with vascular injury and atherosclerotic plaque evolution and is largely controlled by common cellular and sub-cellular mechanisms. Calcium can be seen in all degrees of atherosclerotic involvement and is an active process; thus, the long held notion of so-called "degenerative" calcification of the coronary arteries with aging is not correct. Although there is an increasing incidence of coronary calcification in patients as one grows older, this simply parallels the increased incidence of coronary atherosclerosis with advancing age.

OVERVIEW OF EBCT:

Although it has been clinically available for 17 years, electron beam tomography [EBT - also referred to as "Ultrafast-CT", Imatron Inc., South San Francisco, CA] employs unique technology enabling ultrafast scan acquisition times of 50 to 100 msec per slice. EBT is distinguished by its use of a scanning electron beam rather than a traditional x-ray tube and mechanical rotation device used in current "spiral" scanners. The electron beam [cathode] is steered by an electromagnetic deflection system that sweeps the beam across the distant anode, a series of fixed tungsten "target" rings. Thus, as opposed to physically moving the x-ray tube in a circle about the patient, as is done by the so-called "subsecond" mechanical CT scanners, only the electron beam is moved in EBT.

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Current mechanical CT systems take images with scan times 3 to 10 times slower than EBT and may or may not also use retrospective "gating" of images and "post-processing" to attempt to mathematically or visually reduce cardiac motion artifacts. There are very few studies published with the use of these mechanical scanners and generally the information from them is considered by experts in cardiac CT to be limited with respect to reliable quantification of coronary artery calcium scores. The discussions to follow apply only to the EBT imaging system.

Standardized methods for imaging, identification and quantification of coronary artery calcium using EBT have been established.[6] The scanner is operated in the high resolution, single slice mode with continuous, non-overlapping slices of 3 mm thickness and an acquisition time of 100 msec per tomogram. Patients are positioned supine and, after localization of the main pulmonary artery, a sufficient number of tomographic slices are obtained to cover the complete heart through the left ventricular apex (usually 36 to 40 slices). Electrocardiographic triggering is done at end-diastole at pre-specified phase of the RR interval, determined from the continuous ECG recording. The presence of coronary calcium is sequentially evaluated in all levels. Coronary calcium is defined as a hyperattenuating lesion above a threshold of 130 "Hounsfield Units" with an area of 3 or more adjacent pixels [at least 1 mm^2.]. CT Hounsfield Unit densities range from -1000 [air], through o [water], and up toto +1000 [dense cortical bone]. Figure 1 show a representative EBT tomograms at the base of the heart demonstrating “ossification” of mural arterial segments in the left anterior descending coronary artery, left circumflex, and right coronary arteries of a 49 year old women with normal lipids, but a family history or premature CAD. To the right on the figure is also a 3-dimensional rendering showing the extent of coronary calcium in several vascular beds. The “calcium score”[6,11] is a product of the area of calcification per coronary segment and a factor rated 1 through 4 dictated by the maximum calcium CT density within that segment. A calcium score is reported for a given coronary artery and for the entire coronary system; however, most research studies have reported data related to the summed or total “score” for the entire epicardial coronary system.

CORONARY ARTERY CALCIUM BY EBT AND CORONARY DISEASE

Coronary Calcium, EBT, and Estimates of Atherosclerotic Plaque Burden

A fundamental requirement for the use of EBT coronary calcium quantification to define coronary artery plaque is to establish how these two measures relate to each other. Additionally, the potential for fundamental differences in plaque determination by EBT between men and women must be established before broad clinical application.

My colleagues and I initially examined random autopsy hearts and compared measures of coronary calcium using EBT as compared with direct histologic plaque areas, and percent luminal stenosis.[8,35,36] This study determined that the total area of coronary artery calcification quantified by EBT is linearly correlated (r=0.90) with the total area of histologic coronary artery plaque. Here, although the total atherosclerotic plaque burden was tracked by the total calcium burden, not all plaque was found to be calcified and the total calcium area was around 20% of the total atherosclerotic plaque area. An article by Baumgart et al[9] compared direct intracoronary ultrasound measures during angiography with EBT scanning and confirmed a direct association of coronary calcium score with localization and extent of atherosclerotic plaques, in vivo.

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Our original autopsy study evaluating EBT consisted of 13 hearts included those from 5 women and 8 men. In this study, the 3 major epicardial arteries were dissected, each artery straightened, and scanned using EBT in contiguous 3 mm thick cross sections. After imaging, histologic sections were prepared at corresponding intervals and luminal area obstruction determined by planimetry. A total of 522 [182 in women and 340 in men] histologic specimens were examined and paired with corresponding EBT scans. Receiver-operating characteristic (ROC) analysis was used to define site specificity of calcium area for luminal area narrowing by atherosclerosis.[36] ROC curve areas for segmental EBT calcium and prediction of mild (maximum lumen stenosis <50% diameter narrowing), moderate (maximum stenosis at least 50% diameter narrowing), and severe (maximum stenosis at least 75% diameter narrowing) were, respectively, 0.712, 0.843, and 0.857 for women and 0.732 (p=NS), 0.793 (p=NS), and 0.841 (p=NS) for men. Curves relating false-positive rate sclerotic narrowing versus EBT quantified coronary calcium area were curvilinear. Examples of those data for women are shown on Figure2. Figure 2, left is the ROC curve for women based upon calcium area and the presence in the same histologic region of varying luminal stenoses. Figure 3, right represents the linear measure of the calcium area in a given histologic section and the false positive rate [defined as {1-specificity}]. In both men and women, an EBT measured coronary calcium area of 1 mm^2 in any histologic specimen gave a false positive rate of 0%. For both men and women a segmental calcium area of 2.0-2.5 mm^2 by EBT showed no false positives for the presence of moderate coronary stenoses, while a segmental EBT calcium area of 3.0-3.5 mm^2 was associated positively with the presence of severe luminal disease at the same anatomic site.

Angiographic Correlates

The direct pathologic study noted above thus suggested that coronary artery calcium defined by EBT had similar predictive values for similar extents of coronary disease, regardless of gender. The next step was then to assess the effect of patient sex on EBT studies done in patients undergoing direct coronary angiography.

We studied 50 women and 89 men who had EBT scans done 1 day after cardiac catheterization. The women were roughly a decade older than the men, but were matched for clinical indications for angiography and extent of luminal disease as confirmed by angiography. Sixteen women (32%) had normal coronary arteriograms; 6 women (12%) had trivial stenoses (maximum <20%); 10 women (20%) had moderate stenoses (>20% but <50%); and, 18 women (36%) had significant stenoses (>50%) [p=NS for all compared to men]. Sensitivity, specificity, and positive and negative predictive values for coronary calcium were nearly identical for men and women regardless of the degree of angiographic stenoses [see Table 1]. Overall negative predictive values were 91% in women for any angiographic disease and 100% in women for significant angiographic disease. Receiver operating characteristic curve areas in women for prediction of any angiographic disease using EBT was 0.92 ± 0.02; in women for prediction of significant angiographic disease using EBT the ROC curve area was 0.83 ± 0.06 [p=NS for both compared to men].

Based upon this study, we concluded that in this middle-aged population, noninvasive definition of coronary calcium by EBT had similar predictive value for angiographic coronary artery stenoses in men and women.

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CLINICAL EPIDEMIOLOGY, RELATIONSHIPS TO RISK FACTORS, AND PREDICTION OF RISK OF FUTURE CARDIAC EVENTS

Epidemiology of Coronary Artery Calcium by EBT

A prospective study of >14,000 men and women found that CAD risk increases with age, and that this increase is more dramatic in women. Most of the risk factors were more favorable in women, but the gender effect on risk factors diminishes with increasing age.[38] Another study found that the incidence of CAD is lower in premenopausal women compared with men. However, following menopause, the risk of mortality from CAD increases in women.

The incidence of coronary artery calcium by EBT as a function of age has been shown to mimic that of the incidence of cardiovascular atherosclerotic disease in men and women. Figure 3 shows the incidence of coronary calcification by EBT in an unselected patient population of men and women between the ages of 20 and 80.[39] These data show the following: a) the incidence of coronary artery calcium increases from only a few percent in the second decade of life to nearly 100% by the 8th decade in men and women; b) the general incidence of coronary artery calcium in women is similar to that in men who are a decade younger; c) however, this separate in incidence with age is eliminated by approximately age 65-70, when the incidence of coronary calcium is similar to that of men of the same age.

Coronary artery calcium score, as a measure of the extent of coronary disease also increases with age, but the magnitude of the estimated atherosclerotic plaque burden by EBT is quite different in men versus women. Table 2 shows calcium scores in a large group (9728) of unselected, consecutive male and female adults seen at one EBT scanning center.[40] Data are given as a function of age, gender, and percentile rank of EBT calcium scores. The median coronary calcium score is zero for women until their mid to late 50's. In men of similar ages, already moderate EBT calcium scores are noted – again consistent with an overall low prevalence of advanced coronary atherosclerotic disease in men and especially women until the 5th decade of life.

EBT Coronary Calcium and Risk Factors in Women

Kuller and colleagues recently examined coronary and aortic calcification by EBT in a group of postmenopausal women in relationship to premenopausal risk factors.[41] From the Healthy Women Study, Dr. Kuller measured conventional risk factors in 169 women at age 48 and then followed up with an EBT scan done at age 59. Thirty-seven percent of these healthy women, with no known heart or vascular disease, had positive EBT coronary scans; the 75th percentile score was 13, the 90th percentile score was 138, and the 95th percentile score was 332. These calcium scores are consistent with the data obtained in a separate asymptomatic female population between the ages of 50 and 59, as given in Table 2.

Coronary and aortic calcification [an indicator of extra-cardiac atherosclerosis] was positively associated with each other. There were very strong associations between LDL-C and coronary calcification. Among women with premenopausal LDL-C <100 mg/dl only 9% has a calcium score above 100 compared with 30% of women with an LDL-C >160 mg/dl. Approximately 5% of women with an HDL-C >60 mg/dl had coronary calcium and the level of HDL2-C was especially strongly inversely related to coronary calcium scores. Other premenopausal risks that were associated with postmenopausal coronary calcium [coronary plaque] were cigarette smoking, higher

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systolic blood pressure, serum triglycerides levels, and 2-hour post-prandial serum glucose. These data strongly indicated that premenopausal risk factors were powerful predictors of postmenopausal coronary and aortic calcification by EBT. However, despite the general linear association, risk factors values on an individual basis were only moderate predictors of the extent of coronary plaque.

EBT Coronary Calcium and Risk of Future Cardiac Events

Since EBT calcium scores do relate to conventional risk, but also provide an assessment that cannot be obtained by a blood test, that is the actual site and severity of atherosclerotic plaque disease, it is important to explore how EBT might be an "independent" predictor of risk.

EBT coronary calcium scores have been shown to be predictive of cardiac and coronary vascular events in several studies. The data discussed so far are consistent with the "area" or "score" for coronary calcification quantified by EBCT being viewed as a surrogate for the overall atherosclerotic plaque burden. Although calcification may be a histologic feature of "stable" as well as "unstable" plaques, it is reasonable to assume that a greater overall plaque burden increases the likelihood of greater proportions of both plaque subtypes. Indeed, the extent of coronary atheromatous disease remains the most powerful predictor of subsequent or recurrent cardiac events.[42] The implications for prognostication using quantification of coronary calcium by EBT should not be predicated solely on the site and severity of the calcified plaque per se or even the likely severity of luminal narrowing, but by the fact that the extent of atherosclerotic disease and the presence of plaques of variable morphologic characteristics increase in direct proportion to the amount of detectable calcified plaques.

There have been several studies most recently published regarding cardiac prognosis and EBT calcium score. Arad and colleagues[13] initially reported a follow up study of 1173 initially asymptomatic patients (average age 53 $\pm$ 11 years) who had no known coronary disease for a mean of 19 months after a screening EBCT coronary calcium scan. The magnitude of the coronary calcium score at the time of the index EBCT scan was highly predictive of subsequently developing symptomatic cardiovascular disease during follow up. Odds ratios ranged from 20:1 for a calcium score of 100 to 35:1 for a calcium score of 160. This study has now been carried out for a total of 3.6 years of follow up. [16] Complete follow up was available in 99.6% of the original 1,177 patients. There were a total of 39 subjects with coronary events [only 1 event per patient was considered, even if some had multiple events] and included 3 coronary deaths, 15 nonfatal MIs, and 21 coronary artery revascularization procedures. For the prediction of "hard" events only [nonfatal MI or coronary death], areas under the ROC curve was 0.86 and a coronary calcium score above 160 was associated with an odds ration of 22.2. The odds ratios for all cardiac events remained high (14.3 to 20.2) after adjustment for self-reported cardiovascular risk factors. However, the study by Arad did not specifically evaluate risk in women and, in fact, 71% of the participants were men.

Wong et al. have reported on a group of 926 initially asymptomatic men (n=735) and women (n=191) followed up for cardiovascular events a mean of 3.3 years after a baseline EBT scan.[12] Although there were a total of 41 new cardiovascular events reported by the patients, only 28 could be verified by careful review of medical records and included 6 myocardial infarctions, 2 strokes, and 20 coronary revascularization procedures. Cox proportional-hazards regression showed coronary artery calcium by EBT to be associated with a greater risk for a cardiovascular event INDEPENDENT of age, gender,

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and other risk factors. Importantly, the RR (relative risk) for any cardiovascular event increased with the numerical value of the calcium score. Compared to scores of 1-15, those with scores exceeding 271 [highest quartile of "plaque burden"] were 8.8 times higher. The finding that these data were independent of gender at least is consistent with the data suggesting that, at a given EBT calcium score, women have similar disease extents as compared to men and thus should be expected to have similar numbers of events based upon estimates of total atherosclerotic plaque burden.

The magnitude of the risk to an individual with moderate or greater coronary artery calcium, viewed as a surrogate to measures of total coronary atherosclerotic burden, is underscored when one considers relative risks of developing symptomatic coronary disease using conventional risk analysis. Exercise thallium scintigraphy was recently shown to predict coronary death and nonfatal MI with an odds ratio of 4.4 at six years in an already high-risk cohort.[43] Bostom[44] reported a 15-year follow up in 2191 middle-aged initially asymptomatic men (20 to 54 years old at entry) as part of the Framingham database. The relative risk of developing symptomatic coronary artery disease in this group was 1.9:1 (95% CI, 1.2-2.9) for an elevated Lp(a), 1.8:1 (95% CI, 1.2-2.6) for total cholesterol >240 mg/dL, 1.8:1 (95% CI, 1.2-2.6) for an HDL < 35 mg/dL, 3.6:1 (CI, 2.2-5.5) for cigarette smoking, and 1.2:1 (CI, 0.8-1.8) for systolic hypertension. Thus, based upon these comparisons, EBCT calcium score alone appears to be more predictive of cardiac events than traditional risk factors individually, and as the only non-invasive method to localize and quantitate the extent of the total coronary atherosclerotic plaque burden, offers a measurable tool for improved risk stratification and prognosis.

CLINICAL APPLICATIONS:

EBT is totally non-invasive, requires no injections, and scanning of the entire heart is completed in a single breathhold. Coronary calcium scanning [CAS] using EBT is intended to assist clinical decision making and to thus improve outcomes in patients with suspected coronary disease and in those "at risk" for its development. Based upon the discussions above, EBT has applications in women with and without cardiovascular symptoms.

Symptomatic Women

Women with a variety of symptoms [chest pain/pressure, unusual dyspnea with effort, etc.] may have angina. The objective of cardiac testing in most symptomatic individuals is to rule in or rule out the presence of obstructive coronary artery disease. The usual clinical scenario is to perform a provocative "stress" test to determine if there is inducible ischemia. If the test is abnormal, further testing, treatment, or intervention is indicated. If the test is normal or negative, the patient is reassured or sent for further testing looking for a non-cardiac cause for their symptom. However, not all patients with symptoms are alike and conventional as well as Radionuclide stress testing in women is notoriously imprecise, mainly due to issues related to pre- and post-test likelihood of obstructive disease as well as the issues of referral bias which cloud the issues of sensitivity and specificity related to conventional stress testing in men and women. A decision for determining which investigations [if any] are needed beyond the initial history and physical examination requires the physician first to estimate the "likelihood" that the patient does or does not have "angina".

Age, gender, contributing risks, and the nature or severity of symptoms are the usual clinical variables that provide useful clues to the need for additional testing. The commonly employed

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terms "atypical chest pain" versus "typical angina" imply a low to intermediate likelihood of ischemic disease versus a high likelihood of ischemic disease, respectively.

The issue of using EBT as a probabilistic model for examining the "likelihood" of obstructive disease in women [and in men] was recently presented by Bielak and colleagues.[45] A total of 213 clinical patients were examined with clinically indicated coronary angiography, based upon symptoms or results of prior conventional stress examinations. Each of these individuals had an EBT scan on the order of 1 day after the angiogram. An additional 765 research patients were examined with EBT alone to assist in refining issues of "referral" [or verification] bias. Referral bias is a common problem with conventional stress testing as sensitivity for obstructive disease as compared with angiography is falsely elevated, since mostly only "abnormal" stress results end up with requests for confirmatory angiograms. However, in general, the specificity of stress tests is actually falsely lowered, since "normal" patients do not generally get referrals for angiography. To adjust for the potential for bias, data on sex, age, and calcium scores from the research participants were incorporated into the overall sensitivity and specificity analysis.

In the angiography group, 53.6% had at least one obstructive lesion and only 1 patient [0.9%] with obstructive CAD had a calcium score of zero. Conversely, 46.4% of the patients with obstructive CAD had a calcium score >500, but few [3 of 101, 3%] without obstructive CAD had a calcium score >500. Among patients >50 years old, 39 women were in the angiography group and 196 women were in the nonangiography group. Among patients <50 years old, 12 women were in the angiography group and 194 women were in the nonangiography group. After adjustments for verification bias, the overall sensitivity of EBT for obstructive disease for men and women was 97% and the specificity was 73%. Four optimal strata were then identified for men and women based on age and EBT calcium score for the diagnosis of obstructive CAD.

The Likelihood Ratio [LR] reflects the odds that a given test result will occur in an individual with the disease as opposed to an individual without the disease and values can range from zero to infinity. In women >50 years old a calcium score of zero gave an LR close to zero [0.07], where calcium score >200 gave an LR of 12.85. In women <50 a calcium score equal to zero again had an LR 0.29, where for the same age group a calcium score of >100 was found to be optimal with an LR of 189.69.

Figure 4 shows the probabilistic curves for women based upon the above information. Likelihood ratios were constructed for each of the strata. For a specific pretest probability, the vertical distance between a point on the line indicating the posttest probability and the equity line indicates the size of the difference between the pretest and posttest probabilities as well as the direction of the revision. As can be noted, when the pretest probability of obstructive disease [based upon clinical information such as history, physical, and laboratory work] is close to zero or close to 1 [i.e. 100%], the gain in information from the EBT examination is small, as is the case with any specific test which fits into a probabilistic model and Bayesian statistics. However, the most "incremental" value is in the patient with an intermediate pretest likelihood of obstructive disease, where, specifically in the case for women both above and below the age of 50, the use of the EBT scan result can help determine if further testing may be indicated or if no further testing is needed.

Two recent studies using EBT have confirmed that its use in those patients with an intermediate pretest probability as a clinical test is highly cost effective.[46,47] Furthermore, recent studies have

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confirmed that a zero calcium score is associated with a 95%-98% event free survival at a median follow up of 3.5 years.[16]

A "positive" coronary calcium scan indicates unequivocally that there is coronary atherosclerotic plaque disease present. Although one cannot use the magnitude of the calcium "score" to define percent luminal stenosis on a one-to-one basis, the calcium score can be used to define the likely severity of associated coronary luminal disease.[48] In a symptomatic patient with an abnormal EBT scan, further cardiac testing is indicated. Low to moderate scores [10 to 400] increases the likelihood of disease from low/intermediate to intermediate/high and provocative stress testing would be a reasonable next step. A high coronary calcium score [>400] in a patient with "chest pain" however increases the likelihood of obstructive disease significantly and in some cases direct coronary angiography may be the most prudent next step in the workup.

Asymptomatic Women

Traditional cardiac risk factors predict coronary disease in only 50% of cases. Although a traditional determination of "risk" is clinically useful, the most powerful predictor of coronary events is a measure of current disease severity. EBT can determine the calcium score, which measures the overall atherosclerotic plaque burden.[8]

Coronary artery disease is a complex process and results from a combination of environmental, hereditary, habitual, and perhaps infectious influences that affect its occurrence and severity in an imprecise manner. However, heart disease is not inevitable. There are effective means to reduce the chances of developing manifest heart disease, but truly determining the magnitude of the "risk" in any given patient has traditionally been difficult. A decision to use or not use expensive drug therapy in very high versus very low risk patients is relatively straightforward in clinical practice. However, these decisions in individuals at "intermediate" risk are clinically difficult. Overtreatment of truly low risk patients with drugs such as "statins" is not cost effective and subjects them to a low but real long-term risk of harmful side effects. Undertreatment of true high-risk patients with such drugs may limit the potentially life saving benefits verified in multiple treatment trials.

EBT and coronary artery calcium scanning can determine the severity of atherosclerotic plaque disease. Based on the magnitude of the "calcium score", clinical treatment and/or additional work up guidelines have been put forward.[49,50] Details of recommendation based upon absolute as well as relative calcium scores [base upon age and gender] are given in Figure 5. Grundy[51] has more recently put forward an alternative approach to incorporate EBT calcium score into the traditional Framingham analysis. Since chronologic age has the most dominant effect on the actual risk calculation, he has suggested using coronary calcium percentile ranking, as a more precise measure for atherosclerotic plaque burden. In this way, the 'intermediate" risk patient might benefit from a refinement in risk stratification to determine if they are indeed at "median" risk or fall at a calcium score which would suggest that they more properly belong in the "low" or alternatively "high" cardiac risk subclasses.

EBT has also the potential to follow the progression and/or regression of atherosclerotic plaque disease.[52,53] Thus, repeat scanning, when recommended, may provide information to the clinician and the patient which may indicate if the disease process is under control. Such information can also provide motivation to the patient to follow a healthy lifestyle or continue to take prescribed medications. The sad statistics are that up to 4 out of 5 patients without known heart disease started on lipid lowering medications will stop them within the first one to two years.

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The woman with a negative EBT scan can be reasonably reassured that there is no detectable disease and no further testing is presently indicated. Furthermore, in such patients in whom there is a borderline elevation of cholesterol, diet and exercise is the most prudent and cost-effective first line of therapy, reserving pharmacologic therapy for those with abnormal scans. This has important implications for overall costs for preventive therapies. A negative EBT scan in a woman may allow deferring the initiation of statin therapy based on the absence of detectable disease. Utilization of repeat scanning at a later date may allow this issue to be re-addressed with indications for drug therapy reserved for those who have developed measurable disease since the last scan.

Women between the ages of 45 to 70 with no known heart disease and at least one more significant conventional risk factor are potential candidates for EBT scanning. Advise on scanning younger patients would depend on mitigating factors [e.g., history of very early heart disease in a first or second-degree relative, familial hypercholesterolemia, juvenile onset diabetes].

CONCLUSIONS

EBT is a method that can be used to estimate the overall coronary atherosclerotic plaque burden in women. It can be used to diagnose its presence and determine its extent; furthermore, the information from the calcium score can be used to assess the likelihood of advanced obstructive disease and to provide prognostic information, and as discussed, these finding appear to be gender independent. Finally, it has the potential to determine the consequences of therapeutic interventions regarding progression, stabilization, or regression of coronary atherosclerotic disease.

The application of EBT is seen in both symptomatic and asymptomatic women, but the clinical questions vary between these individuals. In the symptomatic woman, the clinical question is *"Does this patient have obstructive coronary disease?"* In older and younger women it can function as a low cost and convenient alternative to conventional stress testing in those with a low to intermediate pre-test likelihood of ischemic heart disease. Additional considerations for EBT in lieu of conventional stress testing could also be in those with pre-existing resting ECG abnormalities, those unable to adequately exercise, those with a question of non-cardiac caused of chest pain, and in those with "equivocal" prior stress test results. If negative, no further cardiac testing is recommended. If positive for coronary calcium, then the magnitude of the total score can be used as a guide for further testing. In any regard, even if further testing does not confirm the presence of advanced obstructive coronary disease, the presence of sub-threshold coronary plaque can be used to address the need for intervention with respect to risk factor modification.

In the asymptomatic woman, EBT is most useful in the "intermediate" risk patient in whom there is often a clinical conundrum as to the need or level of aggression for risk factor intervention. Traditional estimates of “risk” for women such as lipids and even the use of age adjusted Framingham estimates cannot provide a measure of current plaque "disease" severity, as can be done with EBT. Currently there are published guidelines in men and women for the use of EBT.

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TABLE 1**:** Sensitivity, specificity, predictive values, and standard errors for EBCT detection of coronary calcium and angiographic disease severity. (based upon data presented in Reference 37)

	Any Arteriographic Disease		Significant Arteriographic Disease	
EBT and Coronary Calcium	Women	Men	Women	Men
Sensitivity	97±3%	94±3%	100±0%	98±2%
Specificity	38±12%	35±10%	66±8%	57±8%
Positive Predictive Value	85±6%	89±4%	46±8%	66±6%
Negative Predictive Value	91±9%	79±9%	100±0%	95±5%

Any angiographic disease - presence of at least minimal luminal irregularities.
Significant angiographic disease - presence of any luminal stenosis representing ≥50% diameter narrowing.

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Table 2:

Age/ Men Percentile Rank	35-39	40-44	45-49	50-54	55-59	60-64	65-69
25th	0	0	0	0	3	14	28
50th	0	0	3	16	41	118	151
75th	2	11	44	101	187	434	569
90th	21	64	176	320	502	804	1178

Age/ Women Percentile Rank	35-39	40-44	45-49	50-54	55-59	60-64	65-69
25th	0	0	0	0	0	0	0
50th	0	0	0	0	0	4	24
75th	0	0	0	10	33	87	133
90th	4	9	23	66	140	310	362

Age = chronologic age in years
Adapted from data presented in reference 40

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Legends for Figures:

Figure 1 Non-contrast EBT of a 49 year old, asymptomatic woman who has an extensive family history of premature coronary disease. The image on the right is a single tomogram at the base of the heart and shows prominent calcification in the left anterior descending [LAD] and left circumflex [LCX] arteries. The image on the left is a three-dimensional volume rendering which shows the extent of calcification in both the LAD and LCX. Additionally, there is prominent calcification of the proximal, mid, and distal (lower arrow) right coronary arteries [RCA] that was evident when the entire scan set was reviewed.

Figure 2: Top: ROC [receiver operating characteristic] curves for EBT coronary calcium area in predicting mild, moderate, and severe luminal atherosclerotic disease in coronary artery pathologic specimens from women [adapted from data presented in reference 36, see text for details]. False positive rate is defined as the quantity [1-Specificity]. Each of these ROC curve areas indicates the positive association between EBT calcium area and coronary disease.

Bottom: False positive rate versus area of coronary artery calcium from pathologic specimens in women, as related to the prediction of mild, moderate, and severe luminal atherosclerotic disease [adapted from data presented in reference 36, see text for details]. A false positive rate of 0.5 corresponds to a 50% specificity, while a false positive rate of 0 [zero] corresponds to a specificity of 100%.

Figure 3: Incidence of coronary artery calcium by EBT as a function of age and gender [adapted from data presented in Reference 39]

Figure 4: Pre- and Post-test likelihood of obstructive coronary artery disease using EBT calcium score strata [adapted from data presented in Reference 45]. Individuals with low to moderate pre-test likelihood of obstructive disease are the ones most likely to have that estimate of likelihood significantly reduced or increased, depending on the corresponding EBT calcium score strata. [see text for discussion]

Figure 5: Overview of suggested interpretation of EBT calcium scoring in women and men – based upon the total or absolute calcium score as well as the percentile rank, which is depending on both age and gender.

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Figure 1:

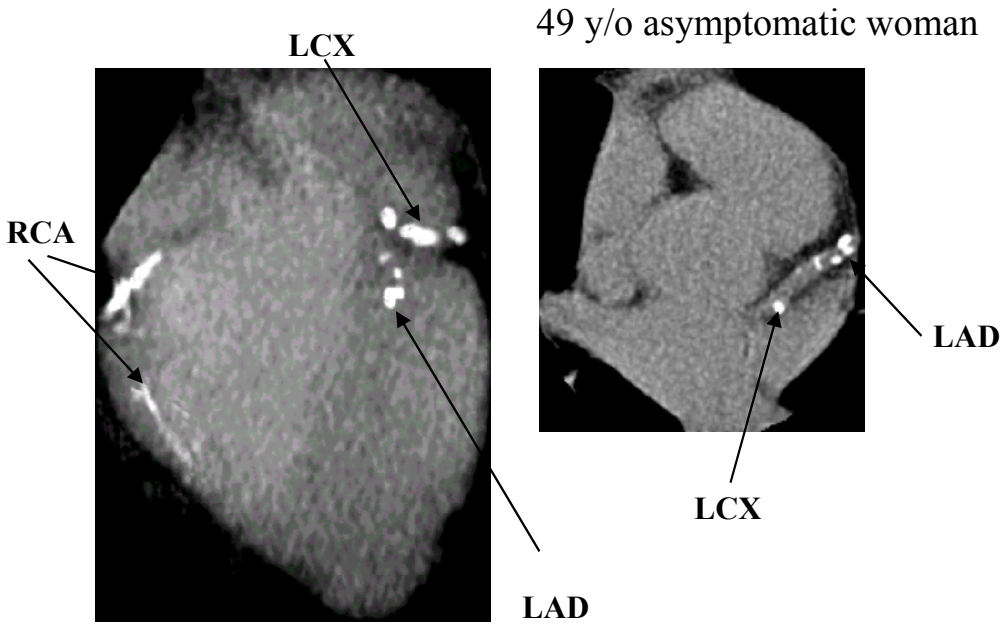
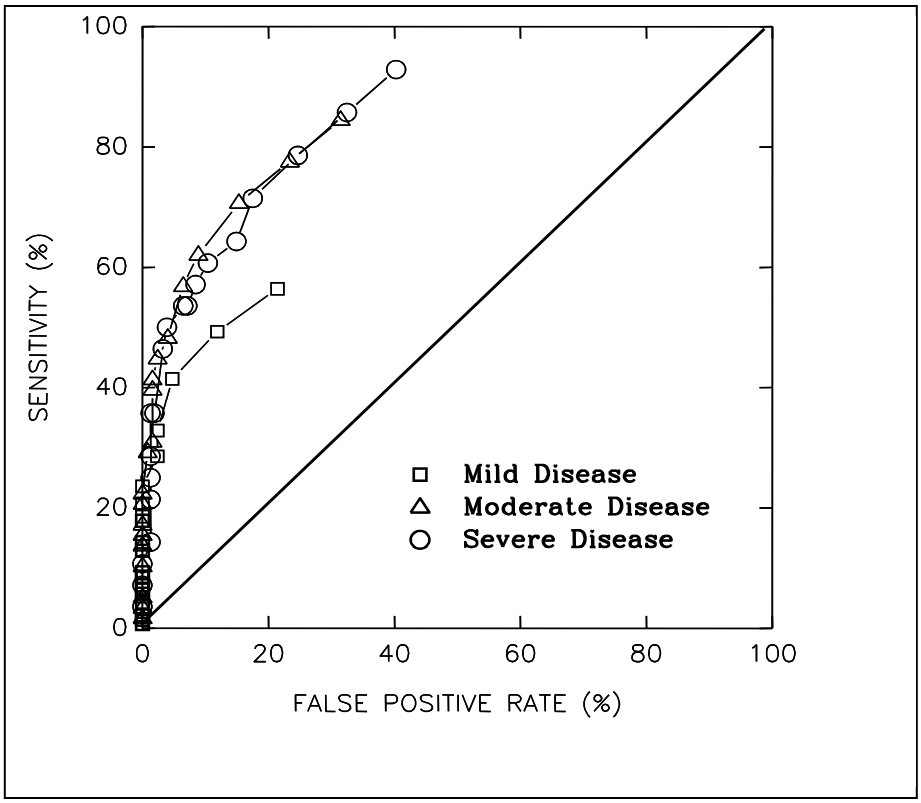


Figure 2



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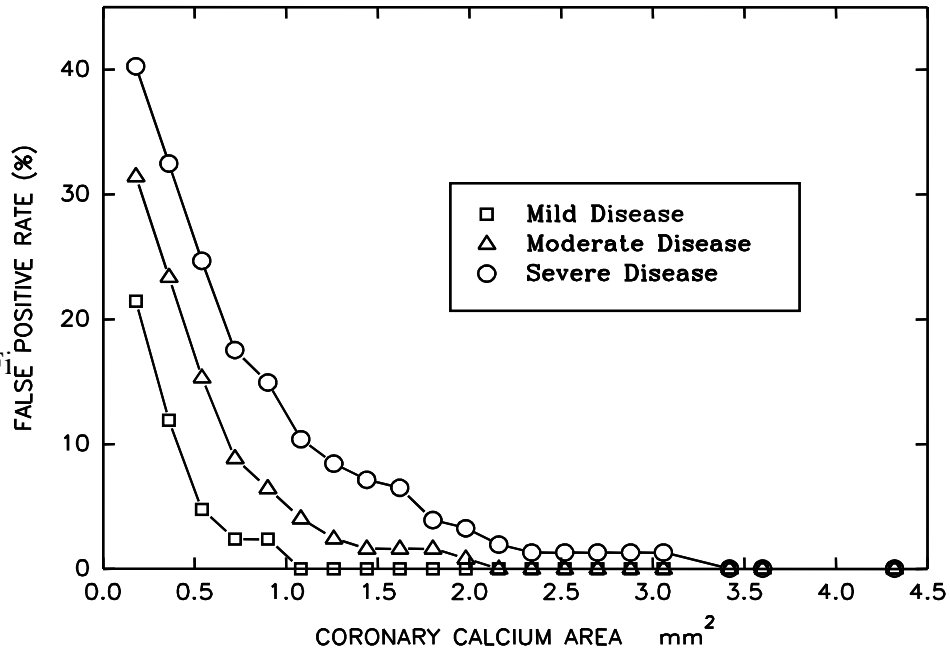

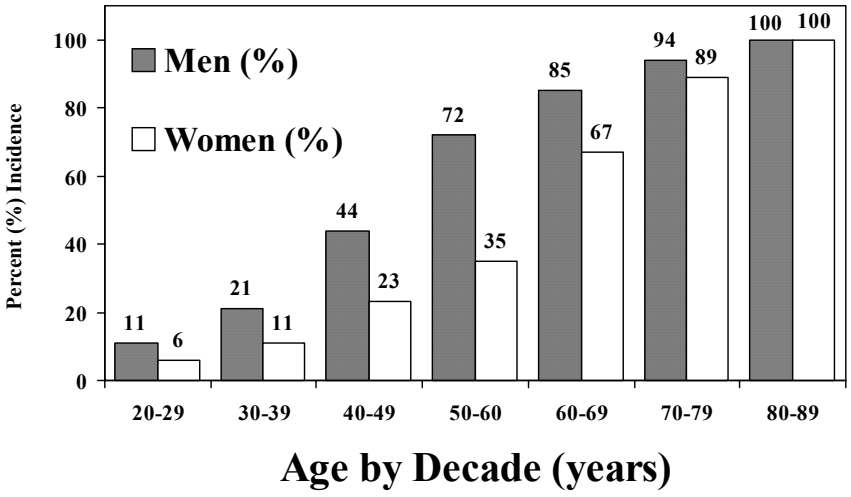

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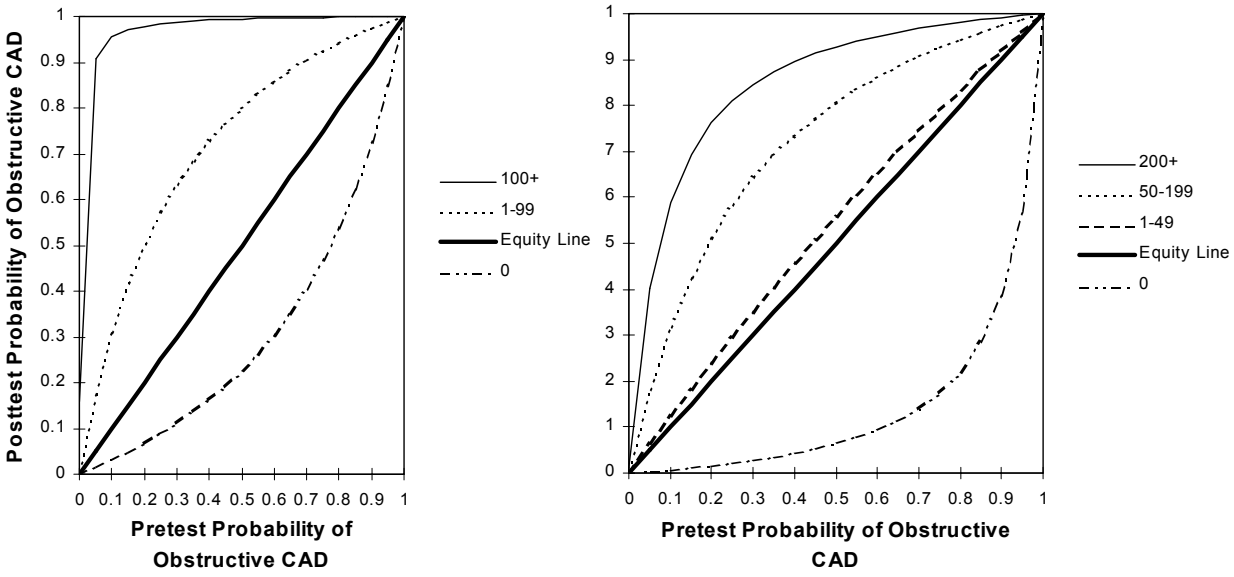
Figure 4:



Women <50 y/o

Women >50 y/o

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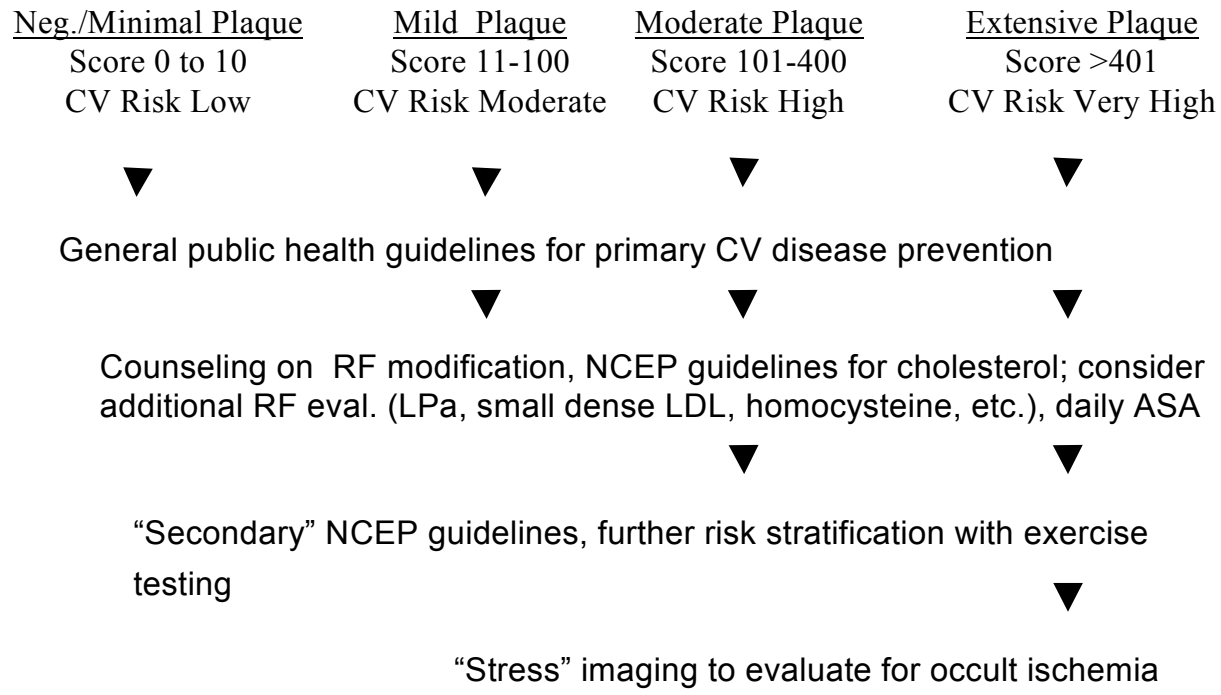
Figure 5:



Caveat: If calcium score >75th percentile for age or gender - *move to next level*