Published in final edited form as:

Atherosclerosis. 2008 October ; 200(2): 278–285. doi:10.1016/j.atherosclerosis.2007.12.057.

Incident Coronary Artery Calcium Among Postmenopausal Women

Lewis H. Kuller, MD, DrPH¹, Karen A. Matthews, PhD², Daniel Edmundowicz, MD³, and Yuefang Chang, PhD²

¹University of Pittsburgh, Department of Epidemiology, Pittsburgh, PA

²University of Pittsburgh, Department of Psychiatry, Epidemiology and Psychology, Pittsburgh, PA

³University of Pittsburgh, Department of Medicine, Pittsburgh, PA

Abstract

Recent studies have shown that individuals with 0 coronary artery calcium (CAC) scores have very low risk of coronary heart disease. In the Healthy Women Study, we evaluated development of new CAC among postmenopausal women (n=272) over a 6 year period, age 62 at the 1st and 68 at the 3rd electron beam tomography (EBT) examination. At the 1st EBT, 155 of 272 (57%) women had 0 CAC. By the 3rd, 56 (36%) of these women had developed new CAC, including 38 with >5 Agatston units. There was practically no regression from having CAC at with the 1st EBT to no CAC at the 3rd EBT. The risk of developing new CAC over 6 years among women with 0 CAC on their 1st EBT was strongly and significantly related to presence of both aortic calcium and carotid plaque at the time of 1st EBT. Baseline premenopausal risk factors, age 47, apolipoprotein B, body mass index (BMI) and triglycerides, were significant predictors of incident CAC as were the changes in BMI and low density lipoprotein cholesterol between premenopause and the 1st post exam, age 53. Risk factors measured premenopause and change in risk factors from premenopause to the 1st post exam and the extent of subclinical disease in other vascular beds are primary determinants of the risk of developing incident CAC in women over a 6 year period.

Introduction

There are very few longitudinal studies of changes in coronary artery calcium (CAC) over more than a few years. In this paper from the Healthy Women Study (HWS), we have evaluated change in CAC over a 6 year follow up by repeated electron-beam tomography (EBT). We believe that this is the first study in a defined population with long term measurements of risk factors and long follow up (6 years) of repeat CAC measurements.

Using data from the HWS, we hypothesized that measures of subclinical vascular disease in the carotid and aorta at the time of an initial EBT would predict the development of new CAC over a 6 year follow up period among women who had 0 CAC Agatston scores. Our rationale was that the extent of atherosclerosis and calcification is earlier and greater in the aorta than in the coronary arteries for women (5,6); and that the extent of carotid intimal medial thickness

Corresponding Author, Lewis H. Kuller, MD, DrPH, University of Pittsburgh, Department of Epidemiology, 130 North Bellefield Avenue, Room 550, Pittsburgh, PA 15213, (phone) 412-383-1895, (fax) 412-383-1956, (email) kullerl@edc.pitt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(IMT) and plaque in the carotid arteries is not dependent on presence of calcification, but was correlated with coronary atherosclerosis, and may be related to “soft noncalcified” plaque. We also hypothesized that risk factors measured prior to menopause or change in risk factors pre- to postmenopause predicted the risk of new or incident CAC among women with 0 CAC at their 1st EBT.

We have recently reported that risk factors measured premenopause were primary determinants of extent of coronary and aortic calcium independent of risk factor levels measured more proximately to the CAC evaluation. We have also reported that the amount of coronary or aortic calcification was a significant risk factor for incident coronary heart disease (CHD) in the HWS. (3)

In 2002, we presented the initial abstract on progression of coronary atherosclerosis over 2.8 years in the HWS. Of 86 women with 0 CAC at the 1st EBT, 19%, about 6% per year, had new CAC. The extent of CAC was the strongest predictor of increase in CAC over 2.8 years. (4) In 2006, we presented the preliminary 6 year follow up from the HWS. Among 81 women with 0 CAC at 1st EBT, 28 (35%) had CAC at 3rd EBT (6% per year). Risk factors at premenopause were predictors of new CAC. (5) Recently, the Multi-Ethnic Study of Atherosclerosis (MESA) has reported similar results for a relatively short term, 2.5 years of follow up. (6)

In recent years, the extent of CAC as measured by EBT was shown to be a very powerful predictor of clinical CHD risk. (7-10) The amount of CAC was determined by the levels of traditional risk factors. (11-14) The time from early development of atherosclerotic plaque to subclinical atherosclerosis and CAC (the incubation period) is probably long. Because of this prolonged incubation period, the association between concurrent measurement of risk factor levels and extent of subclinical disease may not correlate in so far as the current risk factor levels may not represent the longer term levels that resulted in the subclinical burden. Moreover, the levels of certain risk factors, such as inflammatory markers may be a function of the existing atherosclerosis and the subsequent inflammatory response to the atheroma, i.e. reverse causality.

Individuals with no CAC have very low risk over time of clinical CHD. (15) Recent studies have also shown that asymptomatic individuals with no CAC have a low prevalence of significant noncalcified atherosclerotic soft plaque and stenosis (16,17), rarely have decreases in coronary flow reserve as measured by magnetic resonance imaging (MRI) (18), and have a low prevalence of coronary perfusion abnormalities after exercise. (19) Many individuals with high CAC, however, have no perfusion abnormalities on exercise SPECT. (20)

Methods

The HWS began in 1984-85 selecting a sample of 541 women, all premenopausal, who did not have diabetes or clinical hypertension. The study has been previously described in detail. (21-26)

Women after the menopause were followed yearly by mail and telephone follow up and at their 1st postmenopausal examination (post exam) defined as 12 months amenorrhea or 12 months of combination of amenorrhea and hormone therapy (HT) and again at their 2nd, 5th and 8th post exams. Telephone and mail contact was done at between visits. The evaluation of carotid IMT began in 1995 at the 5th post exam, and EBT in 1997, including both coronary and aortic studies. We subsequently repeated the EBT and carotid studies 3 years and 6 years after the 1st exam. To date, i.e. January 2007, 363 women had 1st EBT (67% of the 541 original sample) and 272 (75%) had a 3rd EBT approximately 6 years later. (Table 1)

The time between 1st and 2nd CAC score was 3.19 years, median of 3.06 and between the 1st and 3rd EBT was 6.44 years with a minimum of 4.48, maximum 8.82 and median of 6.50.

Of the 363 women who had a 1st EBT and did not have a 3rd EBT, 23 (25%) had a time period too short for their 3rd EBT, 9 (10%) of the women moved out of the area, 17 (19%) can only be followed by mail follow up only, 4 of the women are deceased (4%) and 38 (42%) of those who missed their 3rd EBT and have refused to continue to participate. Thus, of the 363 who had a 1st EBT, 272 (75%) have now had their 3rd EBT. Only 12% have been refusals to continued follow up.

The characteristics of women who had no EBT and those who had at least one EBT only were similar. A higher proportion of blacks did not have an EBT but there was no difference by race between those who had 1st only or 3 EBT examinations. Systolic blood pressure (SBP) was lower among women who had 1st, 2nd and 3rd EBT as compared to no EBT and higher prevalence of smoking among those who did not have any EBT (35%) versus 29% for those who had 3 EBTs. None of the other biological variables were different between women who had no EBT, 1 EBT or 3 EBT examinations. (Appendix Table 1)

Measurement of calcification was performed using a GE-Imatron C-150 (Ultrafast CT®) scanner (Imatron, South San Francisco, CA). For evaluation of the coronary arteries, 30 to 40 contiguous 3-mm thick transverse images were obtained from the level of the aortic root to the apex of the heart. Images are obtained during maximal breath holding using ECT triggering so that each 100-millisecond exposure are obtained at 60% of the R-R interval. During a second pass, 6-mm contiguous images of the aorta are obtained from the aortic arch to the iliac bifurcation using a 300-millisecond exposure time. The radiation exposure associated with the coronary scan is 407 millirads and with the aortic scan is 2,200 millirads. The study protocol was reviewed and approved by the Radiation Health Committee of the University of Pittsburgh.

Calcium scores for both the coronary arteries and aorta are calculated by the method of Agatston resulting in both a total score and a total number of calcifications and volume scores. Calcification was considered present in the coronaries or aorta when at least 3 contiguous pixels of 130 Hounsfield Units were present on a 30-cm matrix. Initial image analysis was performed with a densitometric program available on the Imatron C-150 workstation. Repeat scans were performed on a DICOM workstation using software provided by AcuImage, Inc. The total calcium score determination was identical for the two software packages.

Measurement variability over time and between readers was evaluated in a small sample of HWS participants. (27) Eighty of these women at that time had a 2nd EBT 18 months apart. We did duplicate readings to evaluate effects of reading variations on CAC scores. The average CAC change was 11 Agatston units and in the aorta, 112 Agatston units. Reading variability did not contribute significantly to the variation of CAC scores. The interclass correlation for replicate scans defined by time was .98 for the coronaries and .99 for the aorta. Measurement error was extremely small in this study. Spearman correlation between the Agatston scores and volumetric scores was 0.99 for the aorta and 0.94 for the coronaries. The correlation between the 1st, 2nd and 3rd EBT is also very high, Pearson correlation between the 1st and 2nd was 0.94 and the Spearman 0.85; and correlation between the 1st and 3rd was 0.896 and 0.833.

Images were taken from the near and far walls of the distal common carotid artery (one centimeter proximal to the carotid bulb), and the far walls of the carotid bulb (the point where the near and far walls of the common are no longer parallel, extending to the flow divider) and the internal carotid artery (from the flow divider to 1 cm distal to this point). IMT measures were performed by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1 cm segment. The computer then generated one measurement for each pixel over this area, for a total of about 140 measures. The mean of all average readings across the

8 locations (4 on each side) comprised the average IMT. We calculated the mean of the maximum reading from each segment. All readings of 1st, 2nd and 3rd EBT were blinded to previous readings and to other subclinical measurements and risk factors.

Statistical Analysis

We studied the association of risk factors measured at premenopausal or at the 1st, 5th, 8th post exams with extent of CAC with focus on women with 0 CAC score at 1st or 3rd EBT examination using both univariate and multivariate analyses. All of the continuous variables were examined for normality prior to the comparisons. Analysis of variance (for continuous variables) and Chi-square test (for categorical variables) were used to determine if the risk factors differed between women who progressed from 0 CAC to new CAC. Changes in risk factors from baseline to first post exam were also compared among the outcome groups while adjusting for baseline risk factor values by analysis of covariance. Multivariate analyses by logistic regressions with stepwise selection of risk factors were used to identify the factors that were significantly related to the outcome. For the model of predicting progression of CAC from 0 to greater than 0, we included the aortic calcium, carotid IMT and plaque measurement before the 3rd EBT as covariates.

Results

Subclinical Disease

At baseline, the mean CAC was 47, standard error 8, and median of 0; at 2nd CAC the mean was 60, standard error 10, and median of 1; and 3rd CAC, mean was 128, standard error 20, and median 7.3. At the 1st EBT, 155 (57%) of the women had 0 CAC. At the 2nd EBT, 121 (44.2%) had 0 CAC and at 3rd EBT, 103 (37%) had 0 CAC. Among women at the 1st EBT who had 0 CAC, 56 (36.1%) had CAC at their 3rd EBT (Table 2). The mean age at 1st EBT was 62 and 68 at the 3rd EBT, 6 years later. Two hundred twenty-seven of the 272 women who had 3rd EBT (83.5%) were between the ages of 65-70. The prevalence of CAC was much higher among participants who reported at the time of the 3rd EBT were on drug therapy for diabetes (17%), on lipid lowering drug therapy (33%), on antihypertensive medication (31%), or on antidepressant therapy (16%).

Practically all of the women who had any CAC at 1st EBT had progression in their CAC scores between 1st - 3rd EBT over 6 years. There were 4 participants who had a 0 CAC score at their 3rd EBT and had CAC present 6 years previously on their 1st EBT. Their 1st CAC scores were: 1, 2, 2.7 and 6.5. Two had no CAC at their 2nd EBT, i.e. at their 1st they had 1.0 and 2.7. Furthermore, the individual who had CAC of 6.5 on the 1st and 0 on the 3rd had substantial weight loss due to illness between the 1st and 3rd EBT. Among women who had CAC at both baseline and at Year 6, only 22 had regression of CAC scores. It is extremely unlikely that CAC scores regress or disappear over time.

Predictors of New CAC

About 36% of the women (56 of 155) converted from 0 CAC at 1st EBT to some CAC, 31% to >3 and 25% to >5 Agatston units. (Table 2) Body mass index (BMI), apolipoprotein-B (ApoB) and triglycerides were determinants of any new CAC (Table 3). BMI and triglycerides were significant predictors of conversion to CAC >3, and triglyceride levels were the only significant predictor of the conversion to CAC >5 Agatston units. There was no evidence that use of HT at 1st post exam was related to development of new CAC, 35% of women not on HT and 36% on HT developed new CAC between the 1st and 3rd EBT.

In multiple logistic regression analyses to predict the development of new CAC, only baseline triglyceride levels were significantly related to the development of new CAC, odds ratio (OR)

2.76 (95% CL: 1.15-6.6). The association of triglycerides and increased risk of development of new CAC was noted for both those on or not on HT at 1st post exam.

The changes in weight and LDL cholesterol from baseline to 1st post exam were significant determinants of incident CAC. These associations were found only for women who were not on HT at the 1st postmenopausal visit. (Table 4) Among women not on HT, triglyceride levels also increased in women with new CAC, 21 mg/dl versus 9 mg/dl ($p=0.07$) for those without new CAC. There was no significant relationship between changes in risk factors from baseline to the 5th or the 8th post exam and new CAC irrespective of HT use at the 5th or 8th post exam. (not shown) Much of the risk factor changes, however, occurred between the premenopause to the 1st post exam.

Very few women who had 0 CAC on the 1st EBT were cigarette smokers and most stopped smoking before the 3rd EBT exam. There are only 5 continuing smokers between baseline and 1st CAC study among those who had 0 CAC at the 1st EBT. Therefore, the effect of smoking cessation and the development of new CAC cannot be evaluated in this study.

There was no relationship between the use of lipid lowering drug therapy at the time of the 3rd EBT and the development of new incident CAC for women with 0 CAC at their 1st EBT. The risk of new CAC 1st to 3rd EBT was 36% for those who were not on lipid lowering therapy (43 of 119) and 36% (13 of 36) who were on lipid lowering drug therapy.

There was no significant difference in C-reactive protein (CRP) measured at approximately the time of the 1st EBT exam and subsequent new CAC. The mean CRP was 2.3 for those without new CAC and 3.2 for those who developed new CAC ($p=0.12$). Furthermore, dividing by below and above CRP of 3.0, 25 of 69 with CRP <3 or 36% had new CAC as compared to 13 of 35 (37%) with CRP >3 ($p=0.9$). Not all women had CRP measurements.

Subclinical Disease Predicts New CAC

We then asked the question, are measures of subclinical disease in other vascular beds related to the development of new CAC? The analysis was restricted to women who had both coronary and aortic calcium (149 of 155) at 1st and 3rd EBT. The presence of 1st aortic calcium was independently related to the risk of development of new CAC. The relationship with carotid plaque index and new CAC was weaker. (Table 5) We combined the presence of a carotid plaque index >1 and 1st aortic calcium >100 . There was a significant linear trend for the development of both >3 and >5 CAC by having 1 or both positive as compared to both being negative. For example, for development of CAC >3 , if both were negative, 25% converted; if 1 was positive, 40%; and if both were positive, 47%, (p for trend = 0.04). Likewise for >5 CAC, prevalence went from 19% to 35% to 42.9%, p for trend = 0.02. The addition of carotid IMT did not substantially improve prediction. The measurements of subclinical disease 6 years previously in other vascular beds were an independent predictor of the risk of developing CAC, especially >3 or >5 Agatston scores at follow up EBT, Year 6.

If the CAC scores were 0 at both the 1st and 2nd EBT, would presence of vascular disease in other beds be a predictor of CAC at the 3rd EBT? The length of follow up was restricted to 3 years since women had to have 0 CAC at both their 1st and 2nd CAC. The numbers are very small but the trends are consistent with the previous analyses for >3 , both plaque and CAC scores were negative, 17% converted; 1 positive 23%; and 2 positive, 30% (p for trend was not significant because of the small sample size). Likewise for >5 , it went from 11% to 16% to 30% with a $p=0.01$ but the numbers were very small.

There were 20 (7%) of the 272 women at 3rd EBT who had no coronary or aortic calcium. These women had very low risk factors at baseline compared with 253 who had some calcium

in any bed: 0 smokers versus 27% ($p=0.005$), ApoB was 83 mg versus 94 mg ($p=0.992$), BMI 23 kg/m² versus 25 kg/m² ($p=0.06$), triglycerides 63 mg% versus 83 mg% ($p=0.06$), SBP 103 mmHg versus 108 mmHg ($p=0.09$) and HDL cholesterol 69 mg% versus 59 mg% ($p=0.002$). Waist circumference (WC) was not measured at baseline in most women but was 72 cm versus 79 cm. There were only 8 (3%) women who had 0 CAC, 0 aortic calcium and no plaque by the 3rd EBT. Their risk factors at baseline in 1982-83 were strikingly different than for the remaining sample. None were cigarette smokers, their LDL cholesterol was 78 mg% versus 109 mg%, their HDL cholesterol was 73 mg% versus 59 mg%, their triglycerides were 83 versus 59, their insulin was 37 versus 50, ApoA-1 was 160 versus 141, ApoB was 78 versus 94, BMI was 22 versus 25, WC 72 cm versus 80 cm, all of those differences even with just 8 people were statistically significant.

Discussion

We estimated that new CAC develops at about 6% per year in postmenopausal women. The MESA study recently reported a similar, about 6%, risk of new CAC over a short term, 2.5 year follow up. (6)

Our initial hypothesis was that measurement of the amount of subclinical disease in other vascular beds, i.e. aortic calcium and carotid IMT and plaque, measured at the time of the 1st measurement of CAC by EBT would predict the development of new CAC, i.e. among those who had 0 CAC at 1st EBT. This hypothesis was partially supported by the results of this study. Aortic calcium measured at the 1st EBT was a significant predictor of incidence of new CAC and was strongly related to the progression of CAC among those who had some CAC at the 1st EBT. Carotid plaque was also associated with the likelihood of developing new CAC but the association was weaker than for aortic calcium. In part, this was due to the low prevalence of carotid plaque among relatively young women (mean age 62) at the time of their 1st EBT. This observation makes good biological sense since the amount of aortic atherosclerotic disease is similar in men and women while coronary atherosclerosis is much lower in women than in men. The aortic calcium at the 1st EBT is likely marking the developing CAC over this 6 years of follow up. There is a strong correlation between amount of coronary and aortic calcification and carotid calcification or IMT. (28-30) The amount of aortic calcium could be used as a marker of atherosclerosis among younger women with very low prevalence of CAC.

The risk factors for aortic calcium were similar to those for CAC. Aortic calcium was also a predictor of risk of clinical CHD over time. (31) We do not know whether nonpharmacological or pharmacological therapies to change key risk factors in younger women with aortic calcium or carotid plaque but no CAC would reduce the risk of progression of coronary atherosclerosis to CAC. We also do not know whether women with aortic calcium or carotid plaque but no CAC have soft plaques in the coronary arteries on multi-slice CT.

An alternative hypothesis was that the new incident CAC identified over the 6 years is due to measurement error correlated with the extent of aortic calcium. Aortic calcium is highly correlated with the amount of CAC. Therefore, the probability of having CAC on the 3rd EBT and be missed on EBT would be a function of the amount of aortic calcium. However, as noted, the number of women in this study who had CAC on their 1st EBT and no CAC on their 3rd EBT, i.e. either regression or due to measurement error is extraordinarily small and practically no women with CAC as high as 5 on their 1st EBT regressed to 0 by their 3rd. Measurement error, therefore, would be extremely unlikely to explain these observations, especially for women who have >3 or >5 Agatston units. Also, among participants who had 0 CAC at both the 1st and 2nd EBT, aortic calcium at the 1st EBT was related to their risk of developing CAC on their 3rd EBT. The development of atherosclerosis and calcification occurs over a long period of time (incubation period).

We have previously shown that the measurements of risk factors at premenopausal when the women were 42-49 is the primary determinant of the risk of having any coronary or aortic calcium 14-20 years later. (3) The recent report from the Coronary Artery Risk Development in Young Adults (CARDIA) Study was consistent with these findings. (32) They showed that risk factors measured 25 years previously among young adults were the primary determinants of the extent of CAC and that concurrent or even more recent measurements were less powerful predictors of CAC. The long incubation period for the development of atherosclerosis and calcification is likely the major reason for these observations. Studies have also shown that risk factors measured earlier, i.e. in midlife, were powerful determinants of the risk of disease, even to older ages, independent of changes in risk factors over time. (33-37)

It is likely but unproven that if we could prevent the development of new CAC during the pre-to postmenopause that incidence of CHD among postmenopausal women would be substantially reduced, even to very old age (Cardiovascular Health Study). (38) There is little evidence, however, that lipid lowering therapies slow the progression of CAC, at least in the short term. Evidence from intravascular ultrasound (IVUS) and from studies of coronary artery stenosis (coronary angiography) suggest that aggressive lipid lowering therapy and substantial decrease in LDL cholesterol may slow the progression of subclinical disease and reduce the risk of heart attack. (39)

The successful prevention of new coronary atherosclerotic lesions among women with minimal atherosclerotic disease from the pre-through the postmenopause would more likely have a greater impact on CHD and perhaps other vascular disease in women than treatment aimed at older women who already have extensive vascular disease. (40,41)

Important research questions, therefore, are: 1) can we prevent the development of atherosclerosis prior to menopause by maintaining or reducing risk factor levels, especially ApoB, LDL cholesterol or LDL particles, BP, obesity and low HDL cholesterol. Does the LDL cholesterol need to be as low as 70 mg%? There is no clinical trial evidence that risk factor reduction from the pre- or perimenopause reduces the risk of subsequent CHD among women; 2) can risk factor modification during premenopausal years reduce the likelihood of developing incident new CAC during the postmenopause, i.e. as a measure of atherosclerosis, and how aggressive does the risk factor modification need to be to prevent the development of new CAC or atherosclerosis? There is limited clinical trial evidence for women on the benefits of lipid lowering drug therapy in the primary prevention of CHD among postmenopausal women. (42) Primary and secondary prevention trials among men and somewhat older women suggest that fairly substantial reductions in LDL cholesterol may be required to reduce the risk of CHD, obtainable by lipid lowering drug therapy in the population. (43,44) A large number of women would be needed to be treated by pharmacological or nonpharmacological approaches. It is also likely that fairly extensive reduction of LDL cholesterol, ApoB or LDL particles, increases in HDL cholesterol and substantial weight loss would be required. These therapeutic approaches would have to be safe, be relatively low cost and, most important, would have to be shown to be efficacious in clinical trials. Can we identify women who are more or less susceptible to the higher risk factor levels in terms of the development of atherosclerosis and clinical CAD through genomic analysis? (45-47)

Most likely, the prevention of the development of atherosclerosis from premenopause through the postmenopause would reduce the incidence and disability due to CHD and probably other vascular diseases among women. Thus, prevention of atherosclerosis and subsequent CVD among women may need to focus on the pre- to perimenopause than on the postmenopause. (48-50)

Appendix 1

Appendix Table 1
Characteristics of Participants (at Baseline) with 3rd EBT vs. No EBT, 1st EBT

Baseline Variable	No EBT 268	1 st EBT only 90	1 st and 3 rd EBT 272
Age	47	47	47
Race: Black, %	12	06	06*
High School Only	32	32	26
Married	71	82	74
HT at 1 st Post	27	38	37
Antihypertensive therapy at 1 st Post	04	01	02*
SBP mmHg	111	110	107*
Smoker	35	33	29*
Waist Circumference cm	80	78	79
Kilocalories Exercise: last week	1362	1715	1483
Alcohol gm/day	8.2	8.0	8.8
HDL cholesterol mg/dl	59	61	60
LDL cholesterol mg/dl	108	110	108
Triglycerides mg/dl	85	79	81
Glucose mg/dl	88	87	88
2 hr Glucose mg/dl	94	88	93
ApoA1mg/dl	144	147	143
ApoB mg/dl	94	93	93

* $P < .05$

References

1. McMahan CA, Gidding SS, Fayad ZA, et al. Risk scores predict atherosclerotic lesions in young people. *Arch Intern Med* 2005;165:883–90. [PubMed: 15851639]
2. McMahan CA, McGill HC, Gidding SS, Malcom GT, Newman WP, Tracy RE, Strong JP, for the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. PDAY risk score predicts advanced coronary artery atherosclerosis in middle-aged persons as well as youth. *Atherosclerosis* 2007;190:370–7. [PubMed: 16530772]
3. Matthews KA, Kuller LH, Chang Y, Edmundowicz D. Premenopausal risk factors for coronary and aortic calcification: A 20-year follow-up in the Healthy Women Study. *Prev Med*. In Press
4. Kuller L, Edmundowicz D, Sutton-Tyrrell, Matthews KA. Galloping atherosclerosis among postmenopausal women. *Circulation* 2002;105:86–119. Abstract #13
5. Kuller LH, Matthews KA, Edmundowicz D, Sutton-Tyrrell K. Incidence and determinants of coronary calcium among postmenopausal women over 6 years: the Healthy Women Study. *Circulation* 2005;111:204. [PubMed: 15642766] Abstract #P53
6. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects. Results from the Multi-Ethnic Study of Atherosclerosis. *Circulation* 2007;115:2722–30. [PubMed: 17502571]
7. Folsom AR, Evans GW, Carr JJ, Stillman AE, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Association of traditional and nontraditional cardiovascular risk factors with coronary artery calcification. *Angiology* 2004;55:613–23. [PubMed: 15547647]
8. Raggi P, Shaw LJ, Berman DS, Callister TQ. Gender-based differences in the prognostic value of coronary calcification. *J Womens Health* 2004;13:273–83.
9. Detrano RC, Guerci A, Carr JJ, Bild D, Burke GL, Folsom AR, Liu K, Shea S, Szklo M, Bluemke D, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal R. Coronary calcium predicts near-term coronary heart disease events in major American ethnic groups: the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2007;49:101A. Abstract #811-3
10. Arad Y, Spadaro LA, Goodman K, et al. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000;36:1253–60. [PubMed: 11028480]
11. Gidding SS, McMahan CA, McGill HC, Colangelo LA, Schreiner PJ, Williams OD, Liu K. Prediction of coronary artery calcium in young adults using the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score. *Arch Intern Med* 2006;166:2341–7. [PubMed: 17130387]

12. Goff DC Jr, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY, Psaty BM. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. *Circulation* 2006;113:647–56. [PubMed: 16461837]
13. Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, Blumenthal RS. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis* 2006;184:201–6. [PubMed: 15907856]
14. Post W, Bielak LF, Ryan KA, Cheng Y-C, Shen H, Rumberger JA, Sheedy PF II, Shuldiner AR, Peyser PA, Mitchell BD. Determinants of coronary artery and aortic calcification in the Old Order Amish. *Circulation* 2007;115:717–24. [PubMed: 17261661]
15. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JAC, Rader DJ, Rubin GD, Shaw LJ, Weigers SE. Assessment of coronary artery disease by cardiac computed tomography. A scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006;114:1761–91. [PubMed: 17015792]
16. Cheng VY, Lepor NE, Madyoon H, Eshaghian S, Naraghi AL, Shah PK. Does absence of coronary calcification predict the absence of coronary plaque or significant luminal stenosis on 64-slice computed tomographic coronary angiography? *Circulation* 2006;114(Suppl II):II-725. Abstract 3490
17. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schomig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006;48:312–8. [PubMed: 16843181]
18. Rosen BD, Lima JAC, Nasir K, et al. Lower myocardial perfusion reserve is associated with decreased regional left ventricular function in asymptomatic participants of the Multi-Ethnic Study of Atherosclerosis. *Circulation* 2006;114:289–97. [PubMed: 16847154]
19. Ramakrishna G, Breen JF, Mulvagh SL, McCully RB, Pellikka PA. Relationship between coronary artery calcification detected by electron-beam computed tomography and abnormal stress echocardiography. *J Am Coll Cardiol* 2006;48:2125–31. [PubMed: 17113002]
20. Shavelle DM, Budoff MJ, LaMont DH, Shavelle RM, Kennedy JM, Brundage BH. Exercise testing and electron beam computed tomography in the evaluation of coronary artery disease. *J Am Coll Cardiol* 2000;36:32–38. [PubMed: 10898409]
21. Kuller LH, Matthews KA, Sutton-Tyrrell K, Edmundowicz D, Bunker CH. Coronary and aortic calcification among women 8 years after menopause and their premenopausal risk factors: The Healthy Women Study. *Arterioscler Thromb Vasc Biol* 1999;19:2189–98. [PubMed: 10479662]
22. Park HA, Lee JS, Kuller LH. Relationship between premenopausal dietary intake and postmenopausal subclinical atherosclerosis. *Atherosclerosis* 2006;186:420–7. [PubMed: 16182299]
23. Matthews KA, Kelsey SF, Meilahn EN, et al. Educational attainment and behavioral and biologic risk factors for coronary heart disease in middle-aged women. *Am J Epidemiol* 1989;129:1132–44. [PubMed: 2729252]
24. Mackey RH, Kuller LH, Sutton-Tyrrell K, Evans RW, Holubkov R, Matthews KA. Hormone therapy, lipoprotein subclasses, and coronary calcification. *Arch Intern Med* 2005;165:510–5. [PubMed: 15767525]
25. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol* 1996;143:971–8. [PubMed: 8629615]
26. Matthews KA, Meilahn E, Kuller LH, et al. Menopause and risk factors for coronary heart disease. *N Engl J Med* 1989;321:641–6. [PubMed: 2488072]
27. Sutton-Tyrrell K, Kuller LH, Edmundowicz D, Feldman A, Holubkov R, Givens L, Matthews KA. Usefulness of electron beam tomography to detect progression of coronary and aortic calcium in middle-aged women. *Am J Cardiol* 2001;87:560–4. [PubMed: 11230839]
28. Odink AE, van der Lugt A, Hofman A, Hunink MGM, Breteler MMB, Krestin GP, Witteman JCM. Association between calcification in the coronary arteries, aortic arch and carotid arteries: The Rotterdam Study. *Atherosclerosis*. 2006Epub ahead of print
29. Allison MA, Criqui MH, Wright CM. Patterns and risk factors for systemic calcified atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004;24:331–6. [PubMed: 14656730]

30. Newman AB, Naydeck BL, Sutton-Tyrrell K, Edmundowicz D, O'Leary D, Kronmal R, et al. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. *Arterioscler Thromb Vasc Biol* 2002;22:1674–9. [PubMed: 12377748]
31. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DAM, Witteman JCM. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction. The Rotterdam Study. *Circulation* 2004;109:1089–94. [PubMed: 14993130]
32. Carr JJ, Person S, Sidney S, Evans G, Colangelo L, Jacobs D, Liu K, Lewis CE, Schreiner P, Loria C, Hulley S, Williams OD. Coronary artery calcified plaque in individuals 38 to 50 years old and cardiovascular risk factors measured 5 years earlier: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Circulation* 2007;115:25. Abstract #10
33. Daviglus ML, Pirzada A, Liu K, et al. Comparison of low risk and higher risk profiles in middle age to frequency and quantity of coronary artery calcium years later. *Am J Cardiol* 2004;94:367–9. [PubMed: 15276108]
34. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2005;352:1293–304. [PubMed: 15753114]
35. Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, Berger K, Buring JE. Healthy lifestyle and the risk of stroke in women. *Arch Intern Med* 2006;166:1403–9. [PubMed: 16832006]
36. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006;113:791–8. [PubMed: 16461820]
37. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors. Comparison of African American with White subjects-Atherosclerosis Risk in Communities Study. *Arch Intern Med* 2007;167:573–9. [PubMed: 17389288]
38. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. *Arterioscler Thromb Vasc Biol* 2002;22:424–30. [PubMed: 11884285]
39. Berry C, L'Allier P, Gregoire J, Lesperance J, Levesque S, Ibrahim R, Tardif J-C. Comparison of intravascular ultrasound and quantitative coronary angiography for the assessment of coronary artery disease progression. *Circulation* 2007;115:1851–7. [PubMed: 17389269]
40. Napoli C, Lerman LO, de Nigris F, Gossel M, Balestrieri L, Lerman A. Rethinking primary prevention of atherosclerosis-related diseases. *Circulation* 2006;114:2517–27. [PubMed: 17146003]
41. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;115:1481–501. [PubMed: 17309915]
42. Walsh JME, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA* 2004;291:2243–52. [PubMed: 15138247]
43. Nissen SE, Nicholis SJ, Sipah I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. *JAMA* 2006;95:1556–65. [PubMed: 16533939]
44. Michos ED, Vasamreddy CR, Becker DM, et al. Women with a low Framingham risk score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. *Am Heart J* 2005;150:1276–81. [PubMed: 16338271]
45. Nicholls SJ, Wolski K, Sipahi I, Schoenhagen P, Crowe T, Kapadia SR, Hazen SL, Tuzcu M, Nissen SE. Rate of progression of coronary atherosclerotic plaque in women. *J Am Coll Cardiol* 2007;49:1546–51. [PubMed: 17418293]
46. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in *PCSK9*, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264–72. [PubMed: 16554528]
47. Ginsburg GS, Donahue MP, Newby LK. Prospects for personalized cardiovascular medicine: the impact of genomics. *J Am Coll Cardiol* 2005;46:1615–27. [PubMed: 16256859]
48. Stamler J. Low risk-and the “no more than 50%: myth/dogma (Editorial). *Arch Intern Med* 2007;167:537–9. [PubMed: 17389284]
49. McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science* 2007;316:1488–91. [PubMed: 17478681]
50. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007;316:1491–3. [PubMed: 17478679]

Table 1**Age Distribution of Study Subjects**

N		Mean	Age S.D.	Median
541	Baseline - Premenopausal (1984-85)	47	2	47
331	1 st Postmenopausal exam*	53	3	53
339	5 th Postmenopausal exam	57	2	57
303	8 th Postmenopausal exam	60	2	60
363	1 st EBT	62	2	62
275	2 nd EBT	65	2	65
272	3 rd EBT	68	2	68
343	1 st Carotid	58	2	58
202	2 nd Carotid	61	2	61
288	3 rd Carotid	68	--	68

* Drop between baseline and first postmenopausal exam due to end of initial grant.

Table 2

Comparison of CAC in 1st and 3rd EBT

1 st EBT	0	1-5	5-10	11-100	>100	T
3 rd EBT						
0	99	18	12	25	1	155
1-5	03	03	04	14	--	24
5-10	01	--	05	05	03	14
11-100	--	--	02	16	27	45
>101	--	--	--	--	34	34
T	103	21	23	60	65	272

Table 3
Relationship of Baseline Risk Factors to Development of New CAC Among Women With 0 CAC at 1st EBT

Baseline Risk Factor	Zero CAC 1 st + 3 rd EBT n = 99	Zero CAC 1 st CAC Present on 3 rd EBT n = 56	P value *
BMI kg/m ²	23.3	24.6	.013
LDL cholesterol mg/dl	100	107	.06
ApoB mg/dl	86	94	.04
HDL cholesterol mg/dl	63	60	.26
Triglycerides mg/dl	69	84	.02
SBP mmHg	106	106	.93
Glucose mg/dl	85	87	.27
Insulin Iu/U	7.1	7.5	.66
% Smoking	16	21	.43

* In multi-logistic regression only triglyceride levels were significant, O.R. 2.76 (1.15- 6.61)

Table 4
Change of Risk Factors (Baseline to 1st Post) Among Women with 1st CAC Score = 0 and No HT Use at 1st Post Exam

Change - Baseline to First Post	3 rd Scan CAC Score								p-value *
	0				> 0				
	n	Mean	SD	Median	n	Mean	SD	Median	
Age	62	5.9	2.7	5.8	33	5.9	2.7	6.3	
BMI	62	0.8	1.5	0.6	32	1.9	1.8	1.4	
Weight	62	3.4	9.4	3.5	33	8.0	11.3	6.5	
LDL cholesterol mg/dl	60	18.7	24.2	19.5	30	30.3	19.9	32.5	
HDL cholesterol mg/dl	61	1.1	9.0	1.7	30	0.1	14.9	-0.4	
Triglycerides mg/dl	60	8.5	29.9	8.0	30	20.9	33.9	11.5	
SBP mmHg	62	0.5	10.4	-0.5	33	2.9	9.4	4.0	
DBP mmHg	62	-1.5	9.1	-1.0	33	-0.0	7.6	1.0	
Glucose mg/dl	61	-1.7	10.8	-3.0	30	-1.1	9.6	-0.5	
Insulin Iu/U	49	4.9	5.8	4.1	24	4.6	4.6	5.4	

* p-values adjusted for baseline value

Table 5
Risk of New CAC by Extent of Aortic Calcium at 1st Exam 6 Years Previously:
0 CAC at 1st EBT

3 rd CAC					3 rd CAC*						
Score					Score						
0 >0					0 >3						
1 st Aortic	0	41 (71.9%)	16 (28.1%)	57	1 st Aortic	0	41 (77.4%)	12 (22.6%)	53	1 st Aortic	0
Calcium	>0	53 (57.6%)	39 (42.2%)	92	Calcium	>0	53 (60.2%)	35 (39.8%)	88	Calcium	>0
T		94	55	149	T		94	47	141	T	
p = 0.078					p = 0.037						

* Excludes women with increase in coronary calcium from 0 to 3 (n=8)

** Excludes women with increase in coronary calcium from 0 to 5 (n=18)