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## Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women

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### Abstract

**Background:** Coronary heart disease (CHD) is the leading cause of death among American women. Currently, global risk assessment derived by Framingham risk equation (FRE) is used to identify women at increased risk for CHD. Electron-beam computed tomography (EBCT) derived coronary artery calcium (CAC) scores are validated markers for future CHD events among asymptomatic individuals. However, the adequacy of FRE for identifying asymptomatic women with CAC is unknown.

**Methods and results:** We studied 2447 consecutive non-diabetic asymptomatic females ( $55 \pm 10$  years). Based upon FRE, 90% were classified as low-risk (FRE  $\leq 9\%$  10-year risk of hard CHD events), 10% intermediate-risk (10–20%), and none were considered as high-risk ( $>20\%$ ). Coronary artery calcium was present in 33%, whereas CAC  $\geq 100$  and CAC  $\geq 400$  were seen in 10 and 3% of women, respectively. Overall, 20% of women had age-gender derived  $\geq 75$ th percentile CAC. According to FRE, the majority (84%) of women with significant CAC  $\geq 75$ th percentile were classified as low-risk. Approximately half (45%) of low-risk women with  $\geq 2$  CHD risk factors and a family history of premature CHD had significant CAC.

**Conclusion:** Framingham risk equation frequently classifies women as being low-risk, even in the presence of significant CAC. Determination of CAC may provide incremental value to FRE in identifying asymptomatic women who will benefit from targeted preventative measures.

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**Keywords:** Coronary artery calcification; Framingham risk equation; Subclinical atherosclerosis; Women

### 1. Introduction

Cardiovascular disease is the leading cause of death of women in the United States, with excess of 500,000 deaths annually [1]. Fifty percent of women will die of cardiovascular disease compared with 4% of breast cancer; yet, in a 1997 survey, only 8% of women considered cardiovascular disease to be their greatest health threat [2]. Whereas the

death rate from cardiovascular disease in men has declined steadily over the last 20 years, the rate has remained relatively the same for women [1]. At least 25% of patients with sudden death or nonfatal myocardial infarction experience no prior symptoms, which reinforces the importance of detecting individuals at-risk prior to an initial event to implement primary preventive therapy.

Improved precision in detecting early coronary disease may assist with more targeted preventive therapy. One way to detect subclinical atherosclerosis is by measuring the coronary artery calcium (CAC) using electron beam

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computed tomography (EBCT). As atherosclerosis develops within the coronary arteries, the majority of plaques become calcified. Because numerous histopathologic studies have shown that CAC linearly correlates with atherosclerotic plaque burden, EBCT is felt to be a useful tool in quantifying coronary atherosclerosis [3]. The CAC score has been shown to predict both the degree of stenosis seen at angiography, [4,5] as well as predict future cardiovascular events in both symptomatic and asymptomatic patients [6–9]. Asymptomatic individuals with increased coronary calcification have a greater burden of subclinical atherosclerosis and thus an increased likelihood of future cardiovascular events.

The American Heart Association's (AHA) Prevention V Conference, 'Beyond Secondary Prevention: Identifying the High Risk Patient for Primary Prevention', recommends all adults undergo an office-based risk assessment to first establish their 'global risk' as measured by a statistical model such as the Framingham risk equation (FRE) [10]. The traditional risk factors identified by the Framingham study include elevated total and LDL-cholesterol, low-HDL cholesterol, hypertension, cigarette smoking, diabetes, and age. Using the Framingham scoring table, a 10-year estimated risk of hard cardiovascular events can be predicted for a given patient based on these major risk factors [11,12]. Asymptomatic patients are categorized as low, intermediate, or high risk, based upon their respective scores, and then, ideally, subjected to an appropriate risk-modifying intervention. Low-risk patients can be reassured and followed with implementation of therapeutic lifestyle changes. Intermediate-risk patients may require further risk stratification, and high-risk patients should be considered candidates for aggressive intervention.

Lipid lowering trials such as the West of Scotland Coronary Prevention Trial (WOSCOPS) [13] and the Air Force/Texas Coronary Atherosclerosis Prevention Trial (AFCAPS/TexCAPS) [14] have demonstrated that primary prevention of coronary events is possible with statin therapy in patients with elevated cholesterol. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)-III guidelines use the FRE to set lipid treatment guidelines based on the FRE-determined 10-year global risk [12,15,16]. The NCEP guidelines assist with lipid management in intermediate and high risk women. However, the effectiveness of these guidelines to identify asymptomatic women at presumptively low-risk for a cardiac event is not clear. A small study of 304 asymptomatic women suggested that 47% of women classified as low-risk by NCEP had detectable subclinical atherosclerosis, yet would not meet criteria for pharmacologic therapy [17].

Using a much larger population, we hypothesized that the Framingham risk score and the NCEP ATP III guidelines may fail to identify a sizeable portion of asymptomatic women with low-risk FRE scores but with detectable and significant subclinical atherosclerosis, who may benefit from more aggressive primary prevention.

## 2. Methods

### 2.1. Subjects

This is a cross-sectional study on a consecutive sample of 13,389 physician-referred individuals who presented to a single EBCT scanning facility (Columbus, OH) between the dates of July 1999 and June 2003 for CHD risk stratification. We excluded patients who reported any personal history of CHD defined by prior myocardial infarction or coronary/peripheral revascularization ( $n=322$ ) or any current symptoms potentially suggestive of angina ( $n=4518$ ) defined by self-reports of chest pain, chest pressure, or chest tightness. We excluded men ( $n=5931$ ). Thus, our study sample consisted of 2618 asymptomatic women free of known CHD. Since the FRE from ATP III [12] counts diabetics as a CHD-risk equivalent, we excluded individuals with diabetes ( $n=171$ ) from our analysis.

### 2.2. Risk factor assessment

All individuals provided details of their demographics, medical history, medication usage, current symptoms, and involvement in leisure time physical activity. A history of cigarette smoking was considered present if a subject was a current or former smoker. Dyslipidemia was coded as present for any individual self-reporting a history of high total cholesterol, high LDL, low HDL and/or high triglycerides, or currently using lipid-lowering therapy. Patients were considered to have diabetes if they reported using oral hypoglycemic agents, insulin sensitizers, or subcutaneous insulin. Patients were considered to have hypertension if they reported a history of high blood pressure or used antihypertensive medications.

Body mass index (BMI) was calculated from individuals who provided a self-report of height and weight. Individuals with  $BMI \geq 30 \text{ kg/m}^2$  were considered as obese. A family history (FH) of premature CHD in parents and siblings was obtained by asking patients whether any member in their immediate family (parents or siblings) experienced a fatal or non-fatal myocardial infarction and/or coronary revascularization before the age of 55 years.

### 2.3. Framingham global coronary risk scores

Framingham sex-specific risk equations were used to predict the risk of developing hard coronary disease events (myocardial infarction or CHD death) over the next 10 years as previously described [11,12]. These traditional risk assessment scores were estimated based on the subject's description of their reported lipid profile, smoking, age, current blood pressure and whether they were receiving antihypertensive therapy. The *estimated* risk scores did not differ significantly from the *calculated* risk scores in approximately 150 individuals, as such that it did not change the risk category. The individuals were divided into three groups: Low-risk ( $\leq 9\%$

risk of developing a hard CHD event over the next 10 years), intermediate-risk (10–20% risk) and high-risk (>20% risk).

#### 2.4. Electron beam tomography

Each patient underwent EBCT scanning using an Imatron scanner (Imatron, South San Francisco, CA). Coronary arteries were imaged with rapid acquisition of approximately 30–40 contiguous images of 3 mm slice thickness (with a 26 cm field of view) during end-diastole using ECG-triggering during a single 30–35 s breath hold. CAC was quantified using the previously described Agatston scoring method [18]. Calcium was considered present in a coronary artery when a density of >130 Hounsfield units (HU) was detected in >3 contiguous pixels (>1 mm<sup>2</sup>) overlying that coronary artery.

The CAC score was computed from the product of the attenuation factor and the area of calcification (mm<sup>2</sup>), with the total CAC score of each coronary artery being equal to the sum CAC of all the lesions from that artery. The total calcium score was calculated by summing CAC scores from the left main, left anterior descending, left circumflex, and right coronary arteries.

#### 2.5. Statistical analysis

Continuous variables are expressed as mean ± S.D. Descriptive statistics were used to summarize patient characteristics. The distribution of values was assessed by the Kolmogorov–Smirnov test for homogeneity of variances. Distribution of CAC scores in various risk groups was tested by Kruskal–Wallis and Mann–Whitney *U*-test. The prevalence of any coronary calcium (positive scores >0), as well as the prevalence of CAC ≥ 100 (moderate calcification) [19] and CAC ≥ 75th percentile matched for age and gender, [20,21] were determined in the population and compared to FRE scores. CAC ≥ 75th percentile for age and gender based data was considered ‘significant CAC’ as it has been suggested as a criterion warranting more aggressive risk factor intervention [12]. Logistic regression was used to assess the association of increasing FRE risk category with any CAC as well increasing burden of CAC.

### 3. Results

The final study population consisted of 2,447 asymptomatic non-diabetic women (55 ± 10 years). None of the

women were considered high risk (FRE > 20%). Based upon FRE, 10% (*n* = 249) were candidates for further evaluation (intermediate-risk) and 90% (*n* = 2198) were classified as low-risk requiring no further intervention. Detectable CAC (>0) was observed in 33% (*n* = 803) of the cases, whereas moderate (CAC ≥ 100) and severe (CAC ≥ 400) was seen in 10% (*n* = 247) and 3% (*n* = 83) women, respectively. Overall, 20% of the women (*n* = 489) had age and gender derived ≥ 75th percentile CAC, which is a marker for future CHD events [7].

Baseline characteristics according to significant CAC are outlined in Table 1. The asymptomatic patients with significant subclinical atherosclerosis ≥ 75th age-gender percentile compared to subjects < 75th percentile had a higher prevalence of known risk factors such as cigarette smoking, hypertension, obesity, dyslipidemia, and FH of premature CHD.

In this study population, women classified as intermediate-risk were more likely to have greater coronary atherosclerosis as compared to those at low-risk as shown in Table 2. The median (interquartile range) of CAC was 0 (0–3) in low-risk women as compared to 6 (0–131) in those classified as intermediate-risk (*p* = 0.0001). The odds ratio for presence of any CAC among intermediate-risk women was 3.1 (95% CI: 2.4–4.0) compared to women in low-risk group. In a similar fashion, a higher odds ratio with each increasing burden of CAC was observed among intermediate-risk women (Table 2).

On the other hand, the majority of the women having a higher degree of CAC were still classified as low-risk. As seen in Table 3, 84% of these women with significant subclinical atherosclerosis (CAC ≥ 75th percentile) were classified as low-risk, while only 16% were considered intermediate-risk. Thus, despite having significant burden of subclinical disease, these 408 ‘low-risk’ women would not be considered candidates for known proven primary preventative therapies such as aspirin or lipid lowering agents. Using absolute CAC scores, 72% of women with advanced CAC ≥ 100 and 64% of women with severe atherosclerotic plaque burden (CAC ≥ 400) would also be classified as low-risk.

Among women classified as low-risk (FRE < 10% 10-year hard CHD risk), those with significant CAC were more likely to be hypertensive, dyslipidemic, current smoker, and obese (Fig. 1). Nearly a quarter of women (24%) in the low-risk group with a FH of premature CHD had significant CAC ≥ 75th age-gender percentile, as compared to 15% observed in those without a FH (*p* < 0.0001). In order to identify which low-risk women would likely benefit from CAC screening,

Table 1  
Baseline characteristics of the study population

Risk factor	CAC ≥ 75th percentile ( <i>n</i> = 489)	CAC < 75th percentile ( <i>n</i> = 1958)	<i>p</i> -value
Cigarette smoking	15%	8%	<0.0001
Hypertension	39%	24%	<0.0001
FH of premature CHD	43%	29%	<0.0001
Obesity	30%	20%	<0.0001
Dyslipidemia	27%	17%	<0.0001

Table 2  
Odds ratio for presence of CAC for intermediate risk women

CAC	Odd ratio	95% CI	p-value
>0	3.1	2.4–4.0	<0.0001
≥100	4.4	3.2–5.9	<0.0001
≥400	5.7	3.6–8.9	<0.0001
≥75th percentile	2.1	1.6–2.8	<0.0001

Low risk women were used as a reference group.

Table 3  
NCEP classification according to CAC burden

CAC	Intermediate risk FRE	Low risk FRE
<100 (n = 2200)	180 (8%)	2020 (92%)
<400 (n = 2364)	219 (9%)	2145 (91%)
<75th (n = 1958)	168 (9%)	1790 (91%)
>100 (n = 247)	69 (28%)	178 (72%)
>400 (n = 83)	30 (36%)	53 (64%)
≥75th (n = 489)	81 (16%)	408 (84%)

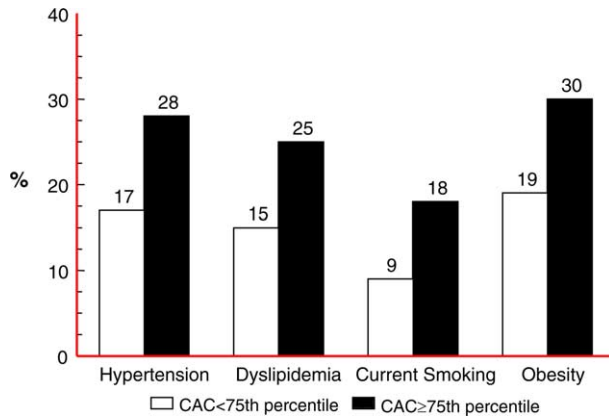
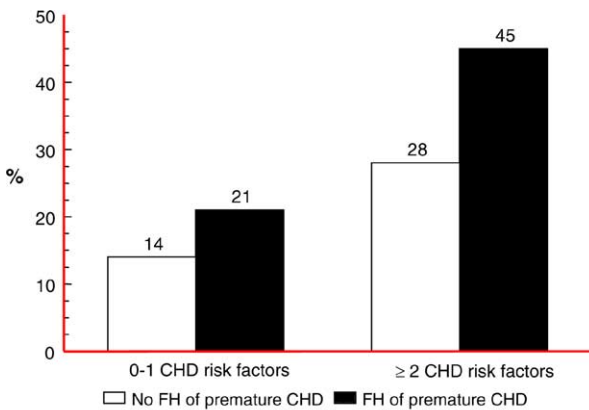


Fig. 1. Risk profile of low-risk women (FRE <10%) according to significant CAC.

we divided them according to FH of premature CHD, as well as presence of 0–1 or ≥2 CHD risk factors (hypertension, dyslipidemia, smoking, and obesity). Fig. 2 demonstrates that those with 0–1 CHD risk factors without any FH of



\*CHD risk factors: hypertension, dyslipidemia, current smoking and obesity

Fig. 2. Prevalence of significant CAC (≥75th percentile) according to family history of premature CHD and multiple CHD risk factors in low-risk women.

premature CHD had the least prevalence of significant CAC (14%), whereas nearly half (45%) of low-risk women with ≥2 risk factors as well as a FH of premature CHD had significant CAC ≥75th percentile.

#### 4. Discussion

In our study population, 90% of the women had 10-year global risk for hard events less than 10%, but we found that over a third had detectable coronary atherosclerosis. Twenty percent of the population had significant subclinical atherosclerosis ≥75th of the percentile for their age and gender, despite the fact that 84% of these women were classified as low-risk by FRE. As per AHA primary prevention guidelines, these patients would not have been eligible for low dose aspirin therapy [22].

The FRE is also used to stratify individuals for pharmacological lipid lowering therapy in the third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) guidelines [12]. These guidelines suggest that low-risk individuals (FRE <10%) with ≥2 risk factors and 0–1 risk factors should be considered for drug therapy at LDL ≥160 and ≥190, respectively [12]. However, recent publications have questioned the adequacy of those guidelines.

In a study of 304 asymptomatic women, 47% of the women who had atherosclerotic disease as measured by detectable CAC on EBCT scan were considered low risk by NCEP guidelines (LDL <130, HDL >35) and thus not candidates for treatment [17]. In another study of 222 patients (25% women), none of the women <65 years of age who presented with their first myocardial infarction had a prior 10-year Framingham risk of >20%; only 5% had an intermediate risk FRE 10–20%, and only 18% of them met criteria for lipid lowering therapy per NCEP guidelines [23]. Yet, despite their low FRE scores, clearly these women were at increased risk because they presented with a myocardial infarction [23]. These studies, as well as our findings, all suggest that a substantial number of women at higher CHD risk would not have met criteria for primary prevention therapy.

In recent years, there is considerable supportive evidence in the literature that CAC is an independent predictor of events and mortality, beyond traditional risk factor assessment. In a retrospective analysis, Kondos et al. found in 5,635 asymptomatic, predominantly low to moderate risk, largely middle-aged individuals followed for 37 ± 12 months, that the presence of any CAC by EBCT was associated with a relative risk for events of 10.5, compared to 1.98 and 1.4 for diabetes and smoking, respectively [24]. In women, only CAC was linked to events, with a relative risk of 2.6, and risk factors were not related. The presence of CAC provided prognostic information incremental to age and other risk factors. Women with CAC scores in the highest age-sex quartile accounted for 50% of the hard and 58% of the soft events, respectively [24].

Perhaps the best data regarding the prognostic yield of CAC scoring in women comes from Raggi and co-workers

[25,26]. Shaw et al. reported on all-cause mortality in the largest cohort studied to this date, consisting of 10,377 asymptomatic individuals (40% women,  $n = 4191$ ), followed for an average of  $5 \pm 3.5$  years. In both genders CAC was an independent predictor of death ( $p < 0.001$ ) with 21.5% of mortality information or incremental value attributable to CAC beyond traditional risk factor assessment, and the risk increased proportionally to the baseline calcium scores [26]. In the same population, when men and women were evaluated separately, a disproportionately higher mortality for women compared to men at each level of calcification was observed [25].

The finding of higher event rates among women compared to men within each level of absolute calcium scores suggest that age-gender based CAC percentiles may be more useful for risk stratification [25]. Asymptomatic patients who appear to be at a low to intermediate risk based on FRE could be elevated to a higher risk category if they have elevated CAC that is above the 75th (and certainly above the 90th) percentile for their age [10]. It has been proposed in the literature to use the amount of plaque burden measured by CAC scoring to modify the number of points assigned to chronological age when determining global risk assessment using the Framingham model for more accurate prediction of 10-year cardiovascular risk [27].

Typically, those classified as low-risk by the FRE would be recommended for lifestyle modifications, but otherwise would be reassured because of their low-risk status without further risk assessment testing. If that were the case, one would miss a substantial number of women who have significantly higher baseline risk, and thus miss an opportunity to initiate aggressive preventive strategies to reduce the possibility of CHD events in these women. Unlike with the trend in men showing a decline in CHD death, there has actually been an increase in the incidence of cardiovascular mortality in women [1]. Our findings contribute to a growing body of evidence that suggest traditional risk factor assessment may not be adequate enough to identify women at risk for CHD events [28,29].

Although the majority of women are classified as 'low risk' by global risk assessment, screening every woman in this group may not be feasible. As a result, it is vital to identify a subset of women within the low-risk group that have an increased likelihood of having higher burden of coronary atherosclerosis. We have previously demonstrated that both men and women with a known FH of premature CHD had higher degrees of CAC at every level of CHD risk [30]. In this study, we extend this finding to show that nearly half (45%) of the low-risk women with a FH of premature CHD as well as presence of  $\geq 2$  CHD risk factors had CAC  $\geq 75$ th percentile. Based upon our data, we believe it is reasonable to consider selective non-invasive quantification of subclinical atherosclerosis in low-risk women who have a known FH of premature CHD in the presence of multiple CHD risk factors for further risk stratification. This strategy will allow us to identify potential candidates that may benefit from more ag-

gressive preventive pharmacotherapy such as aspirin, statins, and possibly anti-hypertensive medications.

## 5. Limitations

The results of our study should be interpreted in the context of several limitations. The authors acknowledge that the purpose of risk assessment in NCEP is to predict CHD events and not coronary atherosclerosis. However, recent studies have provided strong support for the relationship between increasing CAC and risk of future CHD events. In our study, CHD risk factors were self-reported. However, the validity of self-reported histories of hypercholesterolemia, diabetes, and hypertension in self-referred individuals for EBCT scanning has been previously described [21]. Since the CHD risk factors were self-reported, the potential for 'residual confounding' cannot be ruled out. Also, the study population was mainly composed of Caucasians, and the findings may not apply to other ethnic groups.

## 6. Conclusion

FRE scoring based on traditional risk factor assessment frequently classifies women as being low-risk CHD status, even in the presence of moderate burden of subclinical atherosclerotic disease as measured by CAC. Assessment of CAC burden may provide incremental value to global risk assessment in identifying asymptomatic women who may benefit from more aggressive primary preventive therapy. Low-risk women with multiple CHD risk factors, especially in presence of a FH of premature CHD, are potential candidates for additional risk stratification by CAC screening. Further studies are needed to address this issue, which has enormous implications for the identification of asymptomatic women at risk for CHD.

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