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Coronary age as a risk factor in the modified Framingham risk score

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Abstract

Background: Clinical guidelines emphasize risk assessment as vital to patient selection for medical primary intervention. However, risk assessment methods are restricted in their ability to predict further coronary events. The most widely accepted tool in the United States is the Framingham risk score. In these equations age is a powerful risk factor. Although the extent of coronary atherosclerosis increases with age, there is large inter-individual variability in the rate of development and progression of this disease. This fact limits the utility of Framingham scoring when applied to individuals. Electron beam tomography (EBT), which measures coronary calcium, provides a non-invasive method for assessing coronary plaque burden, thus offering the possibility of providing a more accurate estimate of an individual's "arterial age" than from chronological age alone.

Methods: In this paper we discuss a new and simple method for incorporating the coronary calcium score (CCS) to modify the Framingham Risk Assessment (FRA). Using this method, a coronary artery calcium (CAC) age equivalent is generated that replaces chronological age in Framingham scoring.

Results and discussion: Using a percentile table of CCS scores by age group and sex, individuals are matched to the age group whose calcium score most closely approximates their own individual score. The original 10-year absolute risk score of a 65-year old man with a CCS of 6 based on chronological age is 10%, whereas the modified absolute risk score based on CAC age equivalents is 2%.

Conclusion: Our approach of replacing chronological age with CAC age equivalents in the Framingham equations possesses simplicity of application combined with precision. Physicians can easily derive adjusted Framingham risk scores and prescribe intervention methods based on patients' ten-year risks. The adjusted ten-year risks are likely to be more accurate than unadjusted risks since they are based on coronary calcium score information. The modified FRA approach not only may increase the predicted risk for some patients, but also may decrease the predicted risk for others, making it a more precise adjustment than other methods.

Background

Effective medical interventions to reduce risk for coronary heart disease (CHD) have brought the issue of primary prevention with drug therapies to the fore. There is growing evidence that both cholesterol-lowering drugs and anti-platelet drugs will reduce risk for new onset CHD in otherwise asymptomatic persons. The selection of patients for medical intervention for primary prevention therefore has assumed increasing importance in clinical practice. Current clinical guidelines stress risk assessment as the key to selection of persons for medical primary prevention. Unfortunately, current risk assessment tools are limited in their power to predict further major coronary events. The most widely accepted tool in the United States is the Framingham risk score. This scoring is based on summing the risk of the major, independent risk factors. Most investigators agree that while Framingham risk scoring is useful, its predictive power is limited.

One concept that is gaining favor worldwide is that asymptomatic patients whose risk for major coronary events equals that of patients with established CHD deserve preventive therapies similar to the latter. Most patients with established CHD have a 10-year risk for major coronary events (myocardial infarction + coronary death) of >20%. Patients in this high-risk category generally will be treated with a cholesterol-lowering drug and an antiplatelet drug. However, recent guidelines have identified many persons in the "intermediate" risk range (i.e., 10-year risk 10–20%) as potential candidates for these agents. The National Cholesterol Education Program (NCEP) reported that cholesterol-lowering drugs are "cost-effective" for persons in this range in whom serum cholesterol levels are elevated. In addition, the American Heart Association has recently recommended that low-dose aspirin therapy be instituted in persons whose 10-year risk for major coronary events is ≥ 10%. For these reasons, the identification of persons at "intermediate" risk has become clinically important beyond the identification of high-risk patients.

All of the major cardiovascular risk factors, except advancing age, are believed to be primary causes of coronary heart disease (CHD). Strong evidence exists that these factors directly promote atherosclerosis and thus can lead to major coronary events. Advancing age is a risk factor of a different sort. It is well known that the likelihood of developing CHD increases with aging. The rationale for this is clear; throughout life there is a slow but progressive accumulation of atherosclerotic plaque in coronary arteries. Thus, age as a risk factor is an indicator of population plaque burden. Moreover, the probability of experiencing an acute coronary event is directly proportional to the total burden of coronary plaque [1-3].

The extent of coronary calcium in the arteries correlates with the severity of coronary atherosclerosis, as shown by autopsy studies and angiographic measurements [1,2,4]. Electron beam tomography (EBT), which measures coronary calcium, provides a non-invasive method for assessing coronary plaque burden. This offers the possibility of providing a more accurate estimate of an individual's "arterial age" than from chronological age alone.

An accepted method for estimating absolute risk for CHD is to use Framingham risk equations. In these equations age is a powerful risk factor. Although the extent of coronary atherosclerosis increases with age, there is large inter-individual variability in the rate of development and progression of this disease. This fact limits the utility of Framingham scoring when applied to individuals. The weakest component of Framingham scoring for individuals is age. This is because a fixed value for age does not take into account the individual variation in accumulation of coronary atherosclerosis with advancing age. Grundy [5] and Greenland *et al*. [6] therefore proposed using coronary calcium scores (CCS) to estimate the individual's "coronary artery calcium (CAC) age equivalent "; as such, the accuracy of risk assessment could be improved by substituting CCS for age as a risk factor in Framingham risk scoring.

The purpose of this study is to investigate a new and simple method for incorporating the CCS to modify the Framingham Risk Assessment (FRA) on the basis of the concept "you are as old as your arteries" [7].

Risk score calculation

Framingham risk assessment

For estimation of absolute 10-year risk for hard CHD events (CHD death + myocardial infarction), we utilized a point system based on the Framingham Heart Study and updated for NCEP guidelines [8,9]. Published tables (Tables 1 and 2) can be used for computation of Framingham risk assessment (FRA) for men and women [8,9]. To illustrate, consider the calculation of 10-year risk of experiencing cardiac death or MI for a 55-year-old man who is a non-smoker with systolic BP of 125, total cholesterol of 275 and HDL of 35. For every risk factor, points are assigned according to the level of associated risk. Using Framingham scoring, this patient receives 8 points for his age, 0 points for blood pressure, 4 points for total cholesterol, 3 points for HDL, for a total of 15 points and, from the same table, corresponding to a 10-year risk of hard events of 20%.

"CAC age equivalent" calculation method

In recent years, coronary calcium scores have been widely measured in asymptomatic men and women. These scores can be arranged in percentiles according to age and sex [10-12]. On the basis of reported data, we developed a

Table 1: Framingham point system for men

Risk factor		Age range									
		20–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Age		-9	-4	0	3	6	8	10	11	12	13
Total Cholesterol	<160	0		0		0		0		0	
	160–199	4		3		2		1		0	
	200–239	7		5		3		1		0	
	240–279	9		6		4		2		1	
	≥ 280	11		8		5		3		1	
Smoking	*Nonsmoker*	0		0		0		0		0	
	Smoker	8		5		3		1		1	
HDL	<40					2					
	40–49					1					
	50–59					0					
	≥ 60					-1					
-Treatment status-		*Untreated*						*Treated*			
Systolic blood pressure	<120	0						0			
	120–129	0						1			
	130–139	1						2			
	140–159	1						2			
	≥ 160	2						3			

Total points	<0	0–4	5–6	7	8	9	10	11	12	13	14	15	16	≥17
10-Year risk (%)	<1	1	2	3	4	5	6	8	10	12	16	20	25	≥30

method of using the coronary calcium score to generate a CAC age equivalent [11]. By means of the available data and interpolation between medians we created bounds that define mutually exclusive adjusted-age categories that are then utilized to replace chronological age in Framingham scoring. Using table 3, which displays CCS scores by age group and sex, individuals are matched to the age group whose calcium score most closely approximates their own individual score. Each age group comprised a 5-year age range. In this manner, CCS is utilized to define an individuals' CAC age equivalent (table 3); subsequently, this CCS-determined coronary age is used in place of chronological age in FRA.

Results

The utility of the proposed method is best displayed by example. Consider a 65-year old man with a CCS of 6; from table 3, a CCS of 6 for males corresponds to the 45–49 age group (by virtue of being between 1.8, the lower bound and 7.9, the upper bound for the age group). In this example coronary age is lower than chronological age. After determining the CAC age equivalent, we substitute it for the chronological age and apply it to the Framingham scoring system. Chronological age, however, is utilized for age-specific risk factors. The absolute risk for this asymptomatic 65-year old man is calculated in Table 4. Along with his calcium score of 6, his total cholesterol is 180, HDL is 52, systolic blood pressure is 117 without using medications, and he does not smoke. The original 10-year absolute risk score of this individual based on chronological age is 10%, whereas the modified absolute risk score based on CAC age equivalents is 1%.

Conversely, a 37-year old male's age can be increased substantially if his calcium score is high. Accordingly, a 37 year old man with risk factors equivalent to those of the previous example (TC = 180, HDL = 52, SBP = 117, nonsmoker) and calcium score of 100 has a CAC age equivalent of 65–69 and has a modified absolute risk score of 20%, whereas the original absolute risk score for this individual would be less than 1%. For instances where the individual's CCS falls on the bound (e.g. a 57 year old man with CCS = 7.9, or a 43 year old woman with CCS = 0) the age category closest to the chronological age should be selected as the coronary age (i.e. 50–54 for our 57 year old man and 40–44 for our 43 year old woman). Individuals with CCS above the maximum values in tables (i.e. men with CCS > 648, women with CCS > 148) are considered to have a CHD risk equivalent (i.e. risk of event equal to that of established CHD) implying absolute 10-year risk > 20%, based on NCEP guidelines [8,9]. The same procedure applies for women.

The effect of this new method on risk stratification is exhibited more generally for males and females, in Figures 1 and 2 respectively. The modified 10-year risk is displayed as a function of both CCS and the resultant CAC age equivalent, with varying levels of risk by FRA. For both men and women, low risk and intermediate risk by FRA may be reclassified as high risk when incorporating this

Table 2: Framingham point system for women

Risk factor		Age range									
		20–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Age		-7	-3	0	3	6	8	10	12	14	16
Total Cholesterol	<160	0		0		0		0		0	
	160–199	4		3		2		1		1	
	200–239	8		6		4		2		1	
	240–279	11		8		5		3		2	
	≥ 280	13		10		7		4		2	
Smoking	*Nonsmoker*	0		0		0		0		0	
	Smoker	9		7		4		2		1	
HDL	<40					2					
	40–49					1					
	50–59					0					
	≥ 60					-1					
-Treatment status-		*Untreated*						*Treated*			
Systolic blood pressure	<120	0						0			
	120–129	1						3			
	130–139	2						4			
	140–159	3						5			
	≥ 160	4									

Total points	<9	9–12	13–14	15	16	17	18	19	20	21	22	23	24	≥25
10-Year risk (%)	<1	1	2	3	4	5	6	8	11	14	17	22	27	≥30

Table 3: CAC[a] age equivalents as a function of coronary calcium score in men and women

Males CCS		Females CCS		CAC age equivalent
Lower Bound	**Upper Bound**	**Lower Bound**	**Upper Bound**	
0	0	0	0	20–34
0	0.4	0	0	35–39
0.4	1.8	0	0	40–44
1.8	7.9	0	0	45–49
7.9	29	0	0.125	50–54
29	75	0.125	1.62	55–59
75	148	1.62	12.5	60–64
148	614	12.5	148	65–70
614	-	148	-	>70

[a]Coronary artery calcium, CAC

new method. Reclassification can also occur in the opposite direction. With sufficiently low CCS, men with high risk by FRA may be considered of intermediate risk, and both men and women with intermediate risk by FRA may be reclassified as low risk.

Discussion

NCEP ATP III guidelines recommend Framingham risk scoring in assessing absolute risk for CHD events [8,9]. Framingham scoring is used to inform clinical management of asymptomatic patients for primary prevention. As people age, chronological age becomes the predominant risk factor [13]. Age as a risk factor is largely a "surrogate marker" for atherosclerotic burden. Certainly, coronary plaque burden accumulates progressively with age, but rates of accumulation vary greatly from one person to another. Thus, assigning the same number of Framingham risk points to all individuals of the same chronological age does not take into account the variation in plaque burden at a given age. An alternate surrogate for plaque burden is the CCS. Several studies show that amounts of coronary calcium correlate strongly with total plaque burden [14-17]. We therefore postulate that replacing chronological age in Framingham equations with the calcium-

Table 4: Calculation of absolute risk of a 65 year-old with a calcium score of 6.

Risk Factor	Standard Framingham scoring	Coronary calcium modified Framingham scoring
CAC age equivalent (from table 3)	11	3
Total Cholesterol (180 mg/dl)	1	1
HDL (52 mg/dl)	0	0
Smoking (non-smoker)	0	0
Systolic blood pressure (117 mmHg)	0	0
Total points	12	4
10-year absolute risk	10%	1%

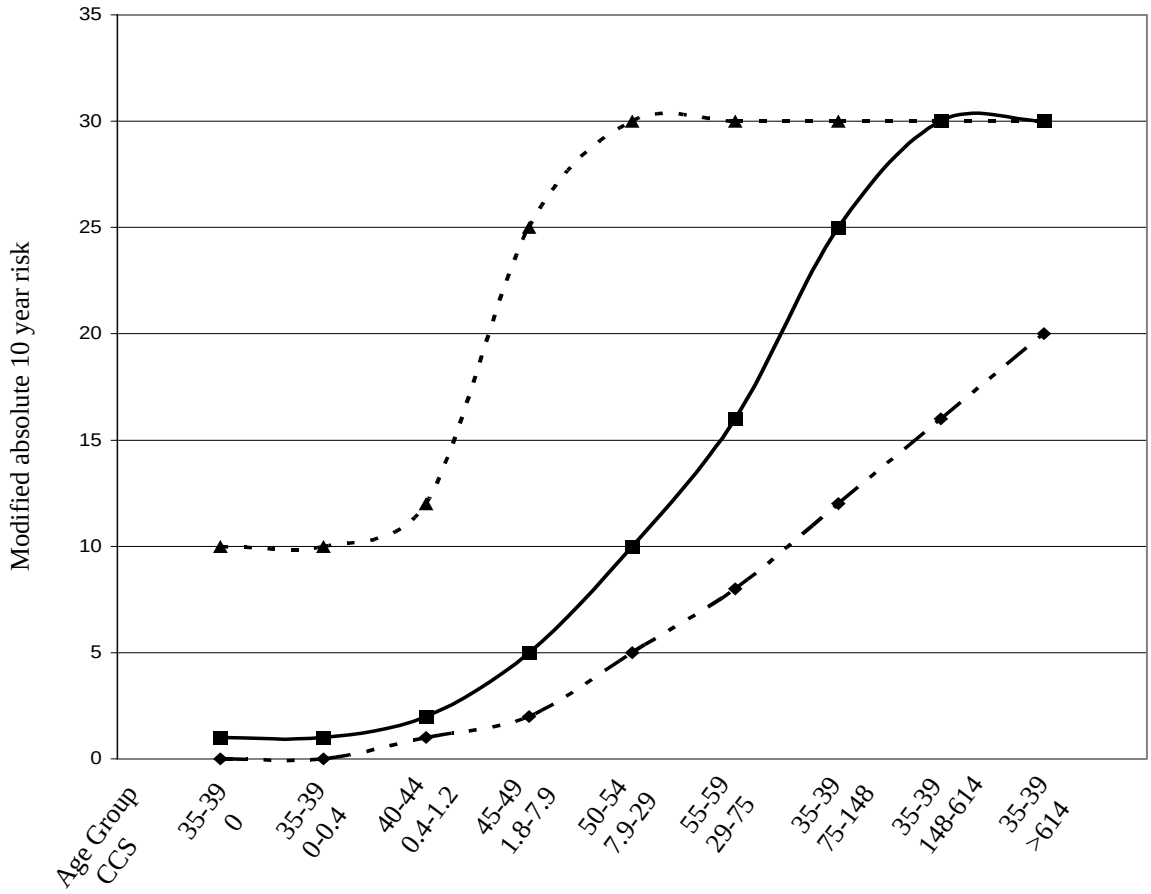

Figure 1
Absolute 10-year risk for low, intermediate, and high risk 50-year-old men by CAC age equivalent adjusted age group.

adjusted coronary age will better account for intra-individual variability in disease progression. More accurate estimates of plaque burden should improve risk prediction, and consequently, improve selection of patients for medical intervention in primary prevention.

Some investigators have expressed skepticism about the utility of CCS in risk prediction and especially whether they provide predictive power independently of the major risk factors. What is really being questioned is whether it is a better predictor than age as a risk factor. The claim is

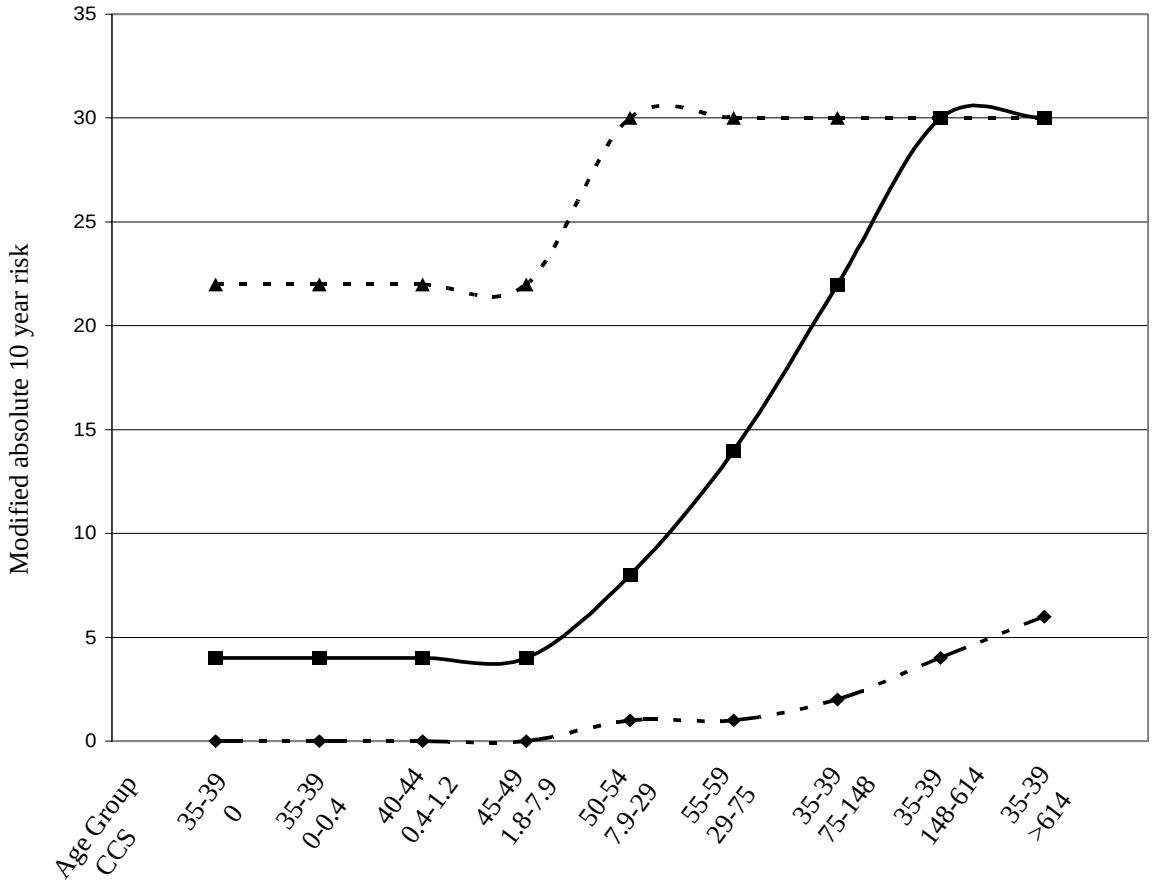

Figure 2
Absolute 10-year risk for low, intermediate, and high risk 50-year-old women by CAC age equivalent adjusted age group.

made that what is needed is a new Framingham Heart Study in which CCSs are included in a prospective study along with other major risk factors. The Framingham Heart Study was carried out over a period of many years; risk factors were identified and quantified at the beginning and were left untreated over the duration of study. Any prospective study that adds CCSs to the mix of predictive risk factors is unlikely to be feasible since major coronary risk factors can no longer be left untreated for long periods in a study population. A current long-term program, the Multi-Ethnic Study of Atherosclerosis is designed to address the role of subclinical atherosclerosis in risk prediction; this study however must evaluate the predictive power of coronary calcium and other subclinical surrogates indirectly. Findings furthermore will not be available for many years. The purpose of our study is to provide a means to employ estimates of subclinical atherosclerosis in quantitative risk prediction at the present time. It does this by linking CCS directly with Framingham risk scoring.

There is increasing recognition that CCS has useful predictive power for major coronary events. The potential for this purpose was noted in the American Heart Associations Prevention V conference, in an American Heart Association/American College of Cardiology report on EBT, and in the recent NCEP ATP III report [9]. These reports indicate that EBT is a clinical option for risk assessment for evaluation of individuals to adjust absolute risk estimates. However, none of these reports specified how CCS information could be used for this purpose. Subsequently, several studies have reported the power and/or independence of CCS in risk prediction. However, these studies collectively do not provide a guide for integrating CCS into absolute, quantitative risk assessment. The

present report proposes a method to get around this impasse.

Alternative approaches to risk assessment

Greenland *et al*. [6] have proposed an alternate approach for incorporation of CCS into the Framingham Risk Index. In this method, all individuals of intermediate risk, defined in this report as Framingham Risk of 5–20%, and a CCS greater than 80 are raised to the high-risk category (> 20%). This particular CCS score pertains to only to published data in middle-aged men whose Framingham risk scores are in this range; it does not hold for women or older men. The advantage of this method lies in its parsimony; clinicians could easily be expected to apply this simple evaluation for middle-aged men with two or more risk factors.

However, this simplicity may come at a cost, as it does not take into account much available information. Because coronary calcium varies greatly with age and is impacted by gender, a one-size-fits-all cut point will be limited in effectiveness. Additionally, this method fails to consider the information garnered from a negative scan; those individuals with intermediate to high risk by FRA and little to no subclinical disease by EBT are not reassigned to lower risk categories. Because ATP III guidelines draw a distinction between low risk and intermediate risk individuals for treatment, the unidirectional risk adjustment has real clinical implications [8,9].

Our proposed method is more quantitative and based on a continuum of risk. This more linear relation may possess greater accuracy in representing risk. While more complex than the approach suggested by Greenland *et al*. [6], use of calcium-adjusted coronary age can be easily incorporated into Framingham risk scoring and NCEP guidelines.

Similarly, the proposed method may add information missing from the current guidelines in ATP III [9]. These guidelines suggest interchangeability between FRA and count of risk factors. They suggest that few individuals with 0–1 risk factors will be in the higher risk categories, i.e., 10-year risk ≥ 10%. Such lower risk individuals thus are not good candidates for EBT screening. However, men older than 70 have a baseline Framingham 10-year risk of 10%; assessing CAC age equivalent in these individuals may be of particular utility for risk stratification.

Potential advantages of age adjustment by coronary calcium

Our approach of replacing chronological age with CAC age equivalents in the Framingham equations possesses simplicity of application combined with precision. Physicians can easily derive adjusted Framingham risk scores and prescribe intervention methods based on patients' ten-year risks. The adjusted ten-year risks are likely to be more accurate than unadjusted risks since they are based on coronary calcium score information. The modified FRA approach increases the risk for some patients and decreases the risk for others, making it a more precise adjustment than other methods.

Implications of the modified risk assessment approach in differing risk groups

Modifying risk assessment methods has important implications for patient management as well as for cost effectiveness of treatments. In the low risk categories, it is clear that CAC age equivalent is very close to chronological age, as indicated by the high concordance between Framingham and our modified Framingham risk scores. This may imply that EBT is not warranted for routine risk assessment in individuals with low Framingham risk scores. In the high-risk category (10-year risk > 20%), CAC age equivalent may only reclassify a small percentage of individuals. This implies that EBT may be more effective in this group for monitoring progression of disease and effectiveness of therapy [18-25].

Use of calcium-adjusted coronary age in place of chronological age will have the greatest impact on persons determined to be in the 10-year risk range of 10–20% by standard Framingham risk scoring. The approach employed assumes that for any Framingham risk score low levels of coronary artery calcium justify reducing a person's risk estimate whereas high levels warrant raising the risk. In the current subjects with 10–20% risk, our method results in a high rate of reclassification of patients, both to higher and lower risk categories. This group of subjects thus should benefit the most from EBT. Evidence of advanced subclinical disease otherwise not detected may identify individuals who are not receiving appropriate treatment. For others, EBT may identify patients in whom aggressive medical therapy is unneeded and not cost-effective.

Limitations of age adjustment

A limitation of this study is that the data utilized to generate the coronary age equivalent algorithm comes from patients who may not be representative of the general population [11]. These individuals were likely mostly self-referred and were recruited from seven centers located across the US. Unlike the Framingham cohort, this sample was clinic based rather than population based. Nevertheless, comparison of major risk factors between the Framingham cohort and a sample of the calcium screening cohort suggests a similar risk level [26,27]. If other baseline factors related to development of CAC are unequally distributed in the study populations, the age-CCS relation presented herein may require modification. The precise relation between CCS and Framingham points is an

aspect of the described method that must be validated in appropriate settings. However, the mostly asymptomatic nature, the geographical diversity and large size of the study sample (59,289 patients), may allow for valid comparisons. Moreover, this group is a good representation of the individuals that pursue calcium screening.

Notably, outcome data were not available for this study, so the efficacy of this method of assessment cannot be evaluated presently. We strongly encourage investigators with access to data including Framingham risk factors, CCS and CHD outcomes to do so. Our method fails to adequately take into account elevations of risk in patients with marked elevation of coronary calcium scores since age scores are available up to age 75 in the FRA. Longitudinal studies that include both measurements of coronary calcium scores and have outcomes of CHD events are needed to better evaluate the different methods of adjusting age in the Framingham equations.

Conclusion

Use of CAC age equivalent has the potential to improve global risk prediction for primary prevention of CHD. CCS may be effectively used by replacing age as a risk factor in Framingham risk equations; such scores are a more direct measure of coronary plaque burden than chronological age. Use of the modified Framingham risk score should make it possible to integrate CCS with other risk factors to obtain quantitative risk estimates. The modified FRA method may not only improve the efficacy of intervention, but may also do so without greatly increasing the cost of preventive medical therapies. However, coronary calcium measurements need not be done routinely in risk assessment. They appear to be indicated only for those individuals whose Framingham risk scores are ≥ 10%. This approach will reduce the number of subjects who will require assessment of subclinical atherosclerosis, and it will provide more precise information for cost-effective and efficacious intervention with drug therapy. We encourage investigators with access to data including Framingham risk factors, CCS and CHD outcomes to evaluate this method to determine if its use in practice proves as effective as in theory.

List of abbreviations

electron beam tomography, EBT; coronary calcium score, CCS; coronary artery calcium, CAC; Framingham risk assessment, FRA; coronary heart disease, CHD; myocardial infarction, MI; low density lipoprotein, LDL; high density lipoprotein, HDL; National Cholesterol Education Program, NCEP; Adult Treatment Panel III, ATP III

Competing interests

None declared.

Authors' contributions

ES and BW contributed equally to the preparation of the manuscript

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