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Subclinical atherosclerosis modeling: integration of coronary artery calcium score to Framingham equation.

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Abstract — **Medical prevention consists to identify as soon as possible apparently healthy individuals who develop a disease and to engage them for active preventive treatment. Several cross-sectional studies of general populations or high cardiovascular risk have shown that coronary calcium score (coronary artery calcium, CAC) was positively associated with traditional risk factors (hypertension, dyslipidemia, diabetes, and smoking) and some new risk factors (fibrinogen). In this work, we first calculated, among 618 men, the risk of 10-years cardiovascular heart disease (CHD) according to the Framingham risk model, and then we calculated the probability that the CAC score of an individual falls in all four CAC categories (0, 1-100, 101-400 and > 400). We obtained risk factors adjusted relative risk (RR) estimates from a meta-analysis comparing the risk of coronary heart disease in individuals with CAC scores of 1-100 (RR = 1.7), 101 - 400 (RR = 3.0) and> 400 (RR = 4.3) with the risk of a person with a CAC score zero. The new model for the risk of CHD for each CAC score category were then calculated assuming an average 1-year risk of CHD and risk assessment of the four CAC score categories, weighted by the probability that scores fall into each category. The combination of modeling the CCA with the modeling of conventional risk factors allows obtaining a remarkable predictive value that can improve the assessment of overall risk Framingham through the reclassification of the risk of CHD to an extent which may be clinically important.**

I. Introduction

ATHEROESCLEROSIS is the essential link between the risk factor and clinical cardiovascular disease as myocardial infarction, stroke or arteriopathy of the lower limbs [1]. It develops silently over many years before exteriorization of the clinical cardiovascular complication. Thanks to technological progress in the non-invasive exploration of human vessels, it is now possible to detect sub-clinical atherosclerosis and identification of subjects at risk, in the traditional sense, those with atherosclerosis silent and those who are diseased [2]. Coronary calcifications are a marker of coronary atherosclerosis and detectable by ultra fast scanner (EBCT) that can quantify their total deposit as a calcium score in which normal or pathological condition is not well standardized and should take into account, at least, age and sex. A mathematical model that incorporates all the classic risk factors and coronary calcium score in the equation of a risk model, where the calculated risk is expressed as a percentage that corresponds to a probability of occurrence of an cardiovascular event at 5 to 10 years, could have a remarkable interest in daily clinical practice so that we could predict the occurrence of cardiac diseases with higher precision than using the traditional risk factors.

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II. Material And Methods

A. Subjects

We used data from the PCV METRA cholesterol-screening program [3] conducted by occupational health physicians at the work site for Ile-de-France employees, and followed by in-depth evaluation of cardiovascular risk factors and non-invasive detection of sub-clinical atherosclerosis during 1-day hospitalization. Subjects included in the study were recruited between 1995 and 1996, were free of any history or symptoms of cardiovascular disease. Total blood cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured after 14 hours fasting in the supine position after 10 minutes resting. LDL-C was calculated by the classic Friedwald formula, and subjects whose triglyceride level was higher than 450 mg/dl were excluded from the study. Systemic blood pressure was determined in the arm as the mean of at least 3 measurements by sphygmomanometer procedure in the supine position after 10 minutes of rest. Hypertension was defined by systolic blood pressure (SBP) of 140 and/or diastolic blood pressure (DBP) 90 mmHg or above and/or presence of antihypertensive medication. Current smoker was defined as somebody who smokes at least five cigarettes per day for the previous 3 months. Blood glucose was measured after overnight fast and diabetes was defined by fasting blood glucose of 126 mg/dl or above and/or presence of antidiabetic medication. Ten-year CHD risk (% probability of CHD event in the next 10 years) was estimated with the Framingham risk model [4]. Peripheral atherosclerosis was detected by real-time B-mode ultrasound (Ultramark 4, Advanced Technology Laboratory) with a 3 MHz probe for the abdominal aorta and a 7.5 MHz probe for carotid and femoral arteries according to a procedure previously described [5]. Each of the three sites (abdominal aorta, carotid arteries, and femoral arteries) was considered as diseased if one or more plaque was found regardless the location. Peripheral atherosclerosis burden was expressed as the number of diseased sites from 0 to 3.

B. Modeling

We use a two-stage modeling approach. We first applied a logistic regression to model the probability of a non-zero CAC score, and then used linear regression to model the actual CAC score, log-transformed, for the set of patients with non-zero values. Using this methodology, we assessed the independent effects of CHD risk factors on both the presence and extent of CAC.

We considered for the logistic and linear model the following set of predictors: age (in decades), hypertension (SBP ≥ 140 mmHg or DBP ≥ 90), high cholesterol (LDL cholesterol ≥ 129 mg/100 ml), smoking (1, Yes; 0, No) and diabetes (1, Yes; 0, No). Prevalence of any CAC score for the logistic model is described in Eq. 1:

$$f(\beta_1,\cdots,\beta_6)=\frac{1}{1+e^{-(\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6)}} \quad (1)$$

The linear regression to model the actual CAC score after exclusion the zero values in the log –transformed CAC score values is given by Eq. 2:

$$g(\gamma_1,\cdots,\gamma_6)=\gamma_1 x_1+\gamma_2 x_2+\gamma_3 x_3+\gamma_4 x_4+\gamma_5 x_5+\gamma_6 \quad (2)$$

where the β_i and γ_i for $1\le i\le 5$ are the estimated logistic and linear parameters, for the predictors x_1:age; x_2: hypertension; x_3: diabetes; x_4: high cholesterol; x_5: smoking and β_6 and γ_6 are the intercepts.

The probability that a given subject has a CAC score between two levels CAC_1 and CAC_2 is

$$P\{CAC_1<CAC<CAC_2\}=F(CAC_2)-F(CAC_1) \quad (3)$$

where:

$$F(x)=\frac{1}{\sqrt{2\pi}\sigma}\int_{-\infty}^{x} e^{-\frac{(x-\bar{x})^2}{\sigma^2}}dx \quad (4)$$

The CAC probability ranges for a particular subject with a mean CAC score $\bar{x}$ and deviation of the residuals σ given by the linear regression of Eq. 2 and using Eq. 4 are:

$$\begin{aligned}
&P\{1<CAC<100\}=F(\ln(100))\\
&P\{1<CAC<400\}=F(\ln(400))\\
&P\{100<CAC<400\}=F(\ln(400))-F(\ln(100))\\
&P\{CAC>400\}=1-F(\ln(400))
\end{aligned} \quad (5)$$

For the same particular subject, the prevalence for any CAC score using Eq. 1 is:

$$\text{Prev\_any\_CAC}=\frac{e^{(\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6)}}{1+e^{(\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\beta_6)}} \quad (6)$$

Consequently, and using Eq. 5 and Eq. 6, the overall predicted prevalence based on all CHD risk factors for an individual in each of the four standard CAC score categories (0, 1-100, 100-400 and >400) is:

$$\begin{aligned}
&\text{P_CAC}_0=1-\text{Prev_any_CAC}\\
&\text{P_CAC}_{1-100}=\text{Prev_any_CAC}\cdot P\{1<CAC<100\}\\
&\text{P_CAC}_{101-400}=\text{Prev_any_CAC}\cdot P\{100<CAC<400\}\\
&\text{P_CAC}_{>400}=\text{Prev_any_CAC}\cdot P\{CAC>400\}
\end{aligned} \quad (7)$$

Taking into account the overall 10-year CHD Framingham risk estimate ($FCHD_{10Y}$) and the corresponding 1-year risk estimate assumption with equal event rate each year given by:

$$\text{FCHD}_{1Y}=1-(1-\text{FCHD}_{10Y})^{1/10} \quad (8)$$

Consequently and using relative risk estimates from a meta-analysis [6] (RR=1.7 for CAC 1-100; RR=3 for CAC 101-400 and RR=4.3 for CAC>400), new CAC score categories were obtained with these relative risks:

$$\begin{aligned}
\text{CAC}_0&=\text{FCHD}_{1Y}/(\text{P_CAC}_0+\text{P_CAC}_{1-100}\cdot\text{RR}_{1-100}+\cdots\\
&\cdots+\text{P_CAC}_{101-400}\cdot\text{RR}_{101-400}+\text{P_CAC}_{>400}\cdot\text{RR}_{>400})\\
\text{CAC}_{1\text{-}100}&=\text{CAC}_0\cdot\text{RR}_{1-100}\\
\text{CAC}_{101\text{-}400}&=\text{CAC}_0\cdot\text{RR}_{101-400}\\
\text{CAC}_{>400}&=\text{CAC}_0\cdot\text{RR}_{>400}
\end{aligned} \quad (9)$$

Finally, the new 10-year model risk estimates were calculated as:

$$\begin{aligned}
&\text{Post_test_CAC}_0=1-(1-\text{CAC}_0)^{10}\\
&\text{Post_test_CAC}_{1\text{-}100}=1-(1-\text{CAC}_{1-100})^{10}\\
&\text{Post_test_CAC}_{101\text{-}400}=1-(1-\text{CAC}_{101-400})^{10}\\
&\text{Post_test_CAC}_{>400}=1-(1-\text{CAC}_{>400})^{10}
\end{aligned} \quad (10)$$

C. Statistics

Logistic, linear regressions and receiver opearating characteristics (ROC) were performed with JMP (SAS NC USA) software. Statistical significance was set at $p<0.05$ and area beneath the ROC curves were compared by c-statistic.

III. Results

Six hundred and eighteen male subjects were selected in the present study, with a high prevalence of hypertension (52%), smoking (38%), and coexistence of ≥2 major non-LDL-C risk factors (69%). Also, 39% of the population had 2 or 3 extra-coronary diseased-sites and 13 % had 3 or 4 extra-coronary and coronary diseased-sites. Distribution of CAC score categories by age range was not normal with greater proportion of zero CAC score than of highest score (>400) but this difference was attenuated in older subjects as it can be seen in Figure 1.

Table 1 shows the estimated logistic and linear parameters for the logistic and linear models tanking into account the 618 subjects under the present studio.

The calculated CAC model evidenced a higher remarkable predictive value than Framingham risk model ($p<0.05$), to predict atherosclerosis with a value of 0.74 of the area under the ROC curve in terms of number of sites of the extra

coronary atheroma plaques, including sites carotid, femoral and abdominal aorta (with codifications 0-1 site = 0; 2-3 site = 1).

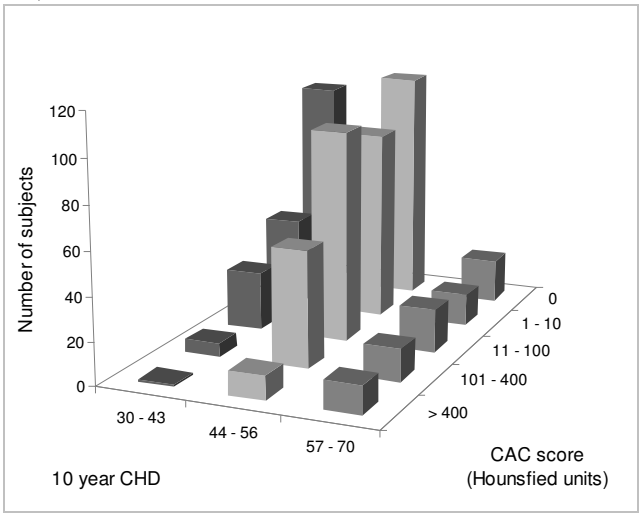

Fig. 1. Number of subjects by class of age according to CAC score category in the study population

Framingham and post CAC risks models were not normally distributed and histogram of the CAC risk model was shifted on the left as compared to Framingham risk histogram resulting in lower post CAC test risk level than Framingham risk (Figure 2).

TABLE 1.
PARAMETER ESTIMATION FOR LOGISTIC AND LINEAR MODELIZATION

	Logistic model parameters	Linear regression model parameters
Age/10 years	-0,8521	0,9311
Hypertension (1,0)	-0,2849	0,1255
Diabetes (1,0)	-0,6261	-0,1140
High cholesterol (1,0)	-0,7256	-0,0947
Smoking (1,0)	-0,2361	0,3915
Intercept	4,4434	-1,7033
Standard deviation of the residuals		1,8495

Both Framingham risk and post CAC risk models were positively associated with the number of extra-coronary diseased-sites and with the number of extra-coronary and coronary diseased-sites ($p<0.001$)

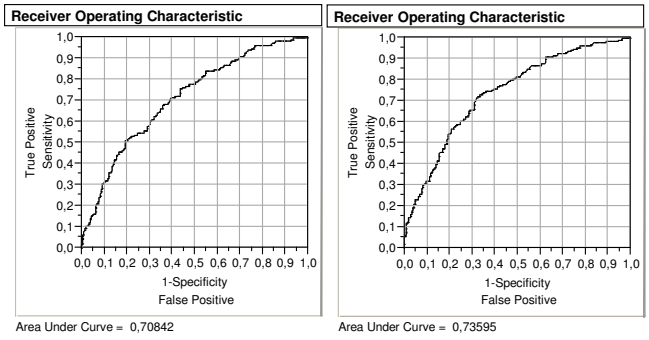

Fig. 2. Receiver operating characteristic curves for Framingham study and CAC Framingham addition

Our atherosclerosis model has no significantly differences respect to Pletcher's model [7] (similar approach using 9341 asymptomatic subjects) as it can be seen in Figure 4.

In our population, CAC model risk was on average lower than Framingham risk and provided different proportions of risk categories from those obtained with Framingham risk, consisting of 10% more low risk and 10% less intermediate risk. CAC-based reclassifications of risk were bidirectional since 30% of high Framingham risk and 30% of intermediate Framingham risk were downgraded to intermediate and low risk categories while 11% of low Framingham risk and 14% of intermediate Framingham risk were upgraded to intermediate and high risk categories.

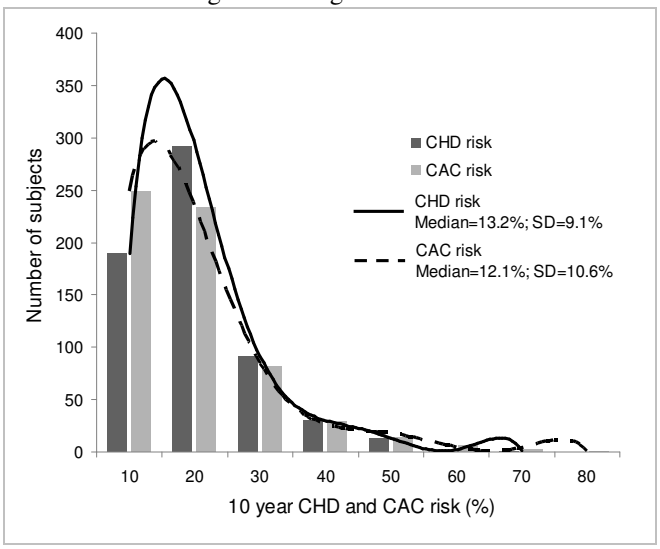

Fig. 3. Histogram of distribution of Framingham risk and post CAC test risks in the study population. CAC = coronary artery calcium; CHD = coronary heart disease.

IV. DISCUSSION

The goal of primary prevention is to detect and deal with cardiovascular risk factors and to develop therapeutic measures dietary or medication and to prevent, limit or delay the development of cardiovascular disease. Secondary prevention seeks to prevent the occurrence of complications and recurrences.

These preventive interventions based on demonstrated efficacy involving a change in attitudes and lifestyles (e.g. smoking cessation, regular physical activity, dietary rules) and drug treatments (antihypertensive, cholesterol-lowering, antiplatelet, antidiabetic).

The overall cardiovascular risks can be estimated by a mathematical modeling that integrates all the risk factors and takes into account the actual value of each of these risk factors (blood pressure, cholesterol, ...); the calculation of the CHD risk uses either the global equation of a risk model (e.g., the Framingham equation) or a score that is derived (European SCORE), the risk is calculated as a percentage which corresponds to a probability of occurrence of a cardiovascular event within the next 5 to 10 years.

A new paradigm is to assign to the sub clinical atherosclerosis, the ability to better predict cardiovascular

events than traditional risk factors. This explains that, currently intense research is devoted to the development of new models of sub clinical atherosclerosis, noninvasive assessed to asymptomatic subjects in primary prevention. Several vascular anomalies represent sub-clinical atherosclerosis can be diagnosed in individuals at high risk, including coronary artery calcification visible scanner and thickening of arterial walls extra measurable coronary ultrasound. We chose the calcium score because it is a more powerful risk mark that the classic intima-media widely adopted by the medical community [7].

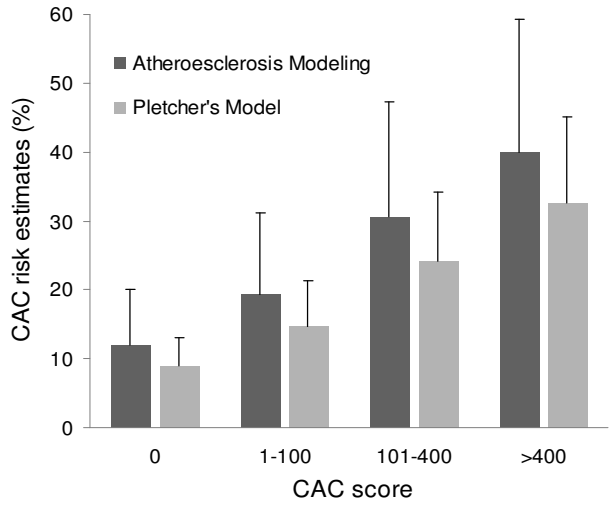

Fig. 4. Comparison between Pletcher's model and atherosclerosis model ($p<0.05$) ANOVA for repeated measurements.

The measurement of intracoronary calcium and their use in an equation of global cardiovascular risk was previously developed by Pletcher in 9347 patients [8]. We developed a model of sub-clinical atherosclerosis assessed in 618 patients yielding the same CAC risk estimates than Pletcher, demonstrating that our model has a higher predictive value than Framingham risk model to characterize the presence and extent of peripheral atherosclerosis burden.

This supports the clinical relevance of the present recalibration of risk prediction with CAC and suggests that such CAC-based risk index may better reflect subclinical atherosclerosis burden, and consequently better predict future CHD event, than the Framingham risk alone.

Our major finding was that post CAC test risk calculation changed CHD risk categorization obtained with Framingham assessment. So, we found that adding CAC test to conventional risk factors stratification induced much more risk downgrading than risk upgrading, partly because in our study population the prevalence of zero CAC score that conveys a low risk was higher than prevalence of highest CAC score (> 400) that is a powerful indicator of high risk.

Further studies will be necessary in order to evaluate if the CAC model can include the location of calcification in the arterial wall.

V. Conclusion

A new CAC risk model was calculated by means of an algorithm previously published by Pletcher et al [8] and based on a mathematical model taking into account the Framingham risk, the expected distribution of CAC scores adjusted for conventional risk factors, and the relative risk associated to CAC score categories. This analysis confirms that conventional CHD risk factors (hypertension, diabetes, smoking and high cholesterol, and the increase of age and sex) were independent predictors of coronary artery calcification. Our analysis suggests that a two-step modeling approach (with the aid of a first logistic regression and then using a linear regression) will allow the multivariate analysis of the interval data provided by the CAC score without violating the basic assumptions of parametric statistics.

In conclusion, the calcium score is a numerical information to quantify the extent of coronary atherosclerotic lesions and provides predictive information independent of traditional risk factors on overall mortality. The combination of modeling the CAC with the modeling of conventional risk factors leads to a remarkable predictive value that improves the assessment of Framingham overall risk through the reclassification of the risk of atherosclerosis to a point which may be clinically essential.

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