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Correlation between the Framingham risk score and intima media thickness: The *Paroi Artérielle et Risque Cardio-vasculaire* (PARC) study

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Abstract

Aims: Carotid intima media thickness (IMT) is associated with an increased risk of cardio-vascular events, but its correlation with the absolute cardio-vascular risk is not well known in large populations. The *Paroi Artérielle et Risque Cardio-vasculaire* (PARC) study was designed to evaluate the relationship between conventional assessment of the global cardio-vascular risk by means of the Framimgham score and measurement of IMT of the common carotid artery (CCAIMT).

Methods and results: About 246 French cardiologists selected 6416 subjects. CCAIMT measurements were performed using a specific methodology designed to harmonize the acquisition and processing of B-mode ultrasound images. The Framingham cardio-vascular score was determined for each individual. The relationship between CCAIMT and Framingham scores was evaluated using linear or polynomial models of regression. We found a significant correlation between CCAIMT and all components of the Framingham score ($p < 0.005$ for all parameters). The Framingham score and CCAIMT values were non-linearly related (coefficients of determination R^2 were 19% and 20% in men, 28% and 29% in women, for subjects with and without personal history of cardio-vascular disease, respectively). The younger the subjects, the steeper the relationship, when the analysis was performed according to decades.

Conclusions: The Framingham score and CCAIMT values were significantly correlated. However variations in CCAIMT only explained a modest part of the Framingham score and vice versa.

Keywords: Intima media thickness; Cardio-vascular risk factors; Framingham risk score; Carotid artery

1. Introduction

Many studies conducted in different countries have shown that Framingham score differ from one country to another [1]. This may partly account for the limitations of using Framingham score to evaluate global cardio-vascular risk worldwide. An association between intima media thickness (IMT) and cardio-vascular risk factors has been demonstrated in several epidemiological studies [2–6]. Ultrasound measurement of the two internal layers of the carotid artery is a validated technique [7]. IMT study has opened a broad field in clinical research because it detects early arterial disease in asymptomatic individuals and is significantly associated to a higher

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risk of incident myocardial infarction and stroke [8]. IMT measurements could constitute an important tool to identify and target intermediate risk subjects in preventive medicine.

The primary objective of the *Paroi Artérielle et Risque Cardio-vasculaire* (PARC) study was to evaluate, in a population aged 30 to 79, the relationship between conventional evaluation of global cardio-vascular risk using the Framingham score and the results obtained using IMT measurements of the common carotid artery (CCAIMT). The secondary objectives were to define normal CCAIMT values estimated from a large French population of subjects without modifiable risk factors and, second, to estimate the influence of the main risk factors for atherosclerosis on CCAIMT values.

2. Methods

2.1. Subject selection

The protocol, selection of subjects and the methods employed have been described in detail [9]. Briefly, this cross-sectional observational study involved 246 centres which were selected and certified after special training. The physicians were French cardiologists experienced in carotid ultrasound techniques. Each centre was required to include subjects aged 30–79 years with or without any modifiable atherosclerosis risk factor with a ratio of 4 to 1.

These subjects were referred to cardiologists for B-mode carotid examination because of cervical bruit, various non vascular symptoms (e.g., dizziness), planned surgery, detection of pre-clinical atherosclerosis, hyperlipidemia, diabetes etc. Documented results of lipid investigations within the past 6 months were required, including total cholesterol, triglycerides and HDL cholesterol. Non selection criteria were the following: subjects with a documented history of hyperhomocysteinemia [10], history of cervical radiotherapy, carotid or aortic dissection, carotid surgery, hypopituitarism and renal insufficiency. Subjects with plaque in the common carotid artery, making IMT measurements impossible, were not eligible.

2.2. Study design, medical history of subjects and standard biological procedures

After subjects were given relevant information regarding study conduct, medical information was recorded using a standardized questionnaire. Systolic and diastolic blood pressures were measured after a 10-min rest in a sitting position. Subjects receiving antihypertensive drugs or with systolic or diastolic blood pressures $\geq$140 and 90 mm Hg, respectively, were considered hypertensive. Subjects were deemed to be dyslipidemic by their physician according to NCEP-III guidelines or lipid-lowering therapy. Subjects were considered diabetic if they were being treated for diabetes.

2.3. Ultrasound methodology

2.3.1. Ultrasound requirements

In order to harmonize data recordings and transfer, all centres, before being selected for the study, were required to have an ultrasound B-mode device no more than 7 years old, equipped with a probe with an emission frequency of at least 5 MHz. Details of ultrasound equipment have been previously described [9].

2.3.2. Data acquisition and recording

A dedicated software for image acquisition, measurements and storage was provided to all the centres (M'Ath^{TM} Std.). Images were stored on the hard disk of the computer, transferred to floppy disks, and then sent to a core laboratory for anonymous image analysis (CANEVAS, France).

2.3.3. Carotid ultrasound examination

The inner and outer walls of the mean right and left common carotid arteries were scanned longitudinally to assess the best incidence to obtain a clear image of this artery. Once the optimum view of the common carotid artery was obtained, the sonographer had to verify that the quality index (QI) was $\geq$0.5 for a measurement performed over a distance of 10 mm on the far wall of the common carotid artery. Since 150 values could be obtained automatically by edge detection over 10 mm, a QI $\geq$ 0.5 means that more than 50% of these measurements were available for IMT averaging. If this index was <0.5 the physician had to acquire another image of the common carotid artery so as to improve it above the threshold of 0.5. Images of the right and left common carotid arteries were then stored on a floppy disk and forwarded to the core laboratory. Inter reader variability has been published to be an intra-class correlation coefficient value of 0.97 [9]. The standard deviation of error measurement $\sigma_{IMT(ERROR)} = 0.0185$ mm reflected the high level of accuracy of the measurements, independently of the standard deviation of the mean CCAIMT value of the population [9].

2.3.4. Centre certification

Training sessions were organized to display and explain to the physician-sonographers the entire procedure for image acquisition, software use, and image storage. Prior to subject selection, each centre had to be certified. This certification was based on recordings of the carotid arteries of three subjects according to the procedure explained to the physicians during the training session. Physicians then had to send the floppy disks to Canevas (France). A precise chart analysis of the data received was used to certify each centre, which could only start selecting subjects once a validation certificate had been received. Most centres obtained certification at the first attempt. If they failed a second time, physicians were required to undergo a second period of training (explanations over the phone were usually sufficient). After three unsuccessful attempts, the centre was definitively excluded from the certification process.

2.4. Global cardio-vascular risk evaluation

The Framingham cardio-vascular score was determined for each individual. This was derived from the algorithm published in the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP-III) [11], and included age, gender, smoking, systolic blood pressure, use of antihypertensive treatment and total and high-density lipoprotein cholesterol.

2.5. Data management

During the study, demographic and clinical data were obtained from questionnaires and queries were regularly sent to physicians by Advance Drug Development Services-France (CRO) when data were missing or did not fall within the normal range. At the end of the study, when the databases obtained from questionnaires and the image analysis by the core laboratory were merged, the final database was cleaned (Orgamétrie-France) and sent for statistical analysis (J-JP, JL) under the SAS format.

2.6. Statistical analysis

The Framingham cardio-vascular score was determined for 5199 subjects. We studied the association between CCAIMT values and each component of the Framingham cardio-vascular score using linear regression. Relationships between CCAIMT values and the Framingham cardio-vascular score were analyzed by regression analyses, using either linear or polynomial models in both genders. Studentized residuals were calculated in order to evaluate model fit. In addition, because the NCEP-III Framingham score did not included the diabetes and was defined for subjects free of any cardio-vascular history, we conducted sensitivity analyses in the subset of patients free of diabetes and cardio-vascular history. In order to evaluate the impact of age on the relationship between the Framingham cardio-vascular score and CCAIMT, we calculated the mean Framingham score for each quartile of CCAIMT according to age category and gender.

Statistical tests were performed at the 2-tailed α-level of 0.05. Data were analyzed using SAS Version 8.2 (from SAS Institute).

3. Results

3.1. Selected subjects

The subjects ($N = 6416$) were selected between September 15, 2000 and November 18, 2001. The reasons for not selecting subjects ($N = 983$) were: (1) file not reliable (0.2%), (2) deviation from the selection or non-selection criteria (3.2%), (3) quality index <0.5 (12.7%). Ultimately, the statistical analysis was performed on 5433 subjects representing 84.7% of those initially selected. Subject characteristics, including demographics data, risk factors and concomitant medications, are shown in Table 1. A Framingham score was not available for 234 subjects in whom at least one item was missing from the Framingham cardio-vascular score. Distributions of the Framingham score and CCAIMT values are shown for each gender in Fig. 1.

Table 1
Demographics and baseline characteristics of subjects selected in the PARC study

Subject demographics	
Age (years), mean ± S.D.	60.6 ± 11.6
Male sex (%) (*n*)	56.6 (3077/5433)
BMI (kg/m^2), mean ± S.D.	25.8 ± 4.1
Baseline risk factors	
Hypertension[a] (%) (*n*)	55.9 (3036/5430)
Dyslipidemia[b] (%) (*n*)	52.2 (2835/5433)
Diabetes[c] (%) (*n*)	12.5 (679/5421)
Tobacco use (%) (*n*)	14.9 (810/5429)
Personal history of CHD (%) (*n*)	27.3 (1484/5428)
Familial history of CHD (%) (*n*)	15.3 (826/5392)
Left ventricular hypertrophy (%) (*n*)	9.0 (468/5215)
Early menopause[d] (%) (*n*)	4.6 (107/2349)
Total cholesterol (g/l), mean ± S.D.	2.15 ± 0.42
LDL cholesterol (g/l), mean ± S.D.	1.34 ± 0.37
HDL cholesterol (g/l), mean ± S.D.	0.56 ± 0.17
Systolic BP (mm Hg), mean ± S.D.	136 ± 16
Diastolic BP (mm Hg), mean ± S.D.	80 ± 9
Concomitant medications	
Antihypertensive treatment (%) (*n*)	38.9 (2095/5392)
Lipid-lowering treatment (%) (*n*)	39.2 (2125/5414)

CHD, coronary heart disease; BP, blood pressure.
[a] Systolic BP ≥ 140 or diastolic BP ≥ 90 or on antihypertensive treatment.
[b] Known dyslipidemia or HDL-C < 0.35 g/l or on lipid-lowering treatment.
[c] Medical history of diabetes with or without medication.
[d] Data in women.

3.2. Relationship between CCAIMT and each component of the Framingham score

As shown in Table 2, each component of the Framingham score was significantly associated with CCAIMT after adjustments for age and gender. In addition, in both genders, all these components were found to be independently associated with CCAIMT in the multivariate regression analysis (with the exception of women in whom total cholesterol and tobacco did not reach the significance level, with $p = 0.14$ and 0.17, respectively).

3.2.1. Relationship between CCAIMT and the Framingham cardio-vascular score

Scatter plots for Framingham scores and CCAIMT values are presented in Fig. 2. The Framingham score increased significantly with CCAIMT in both men and women ($p < 0.0001$). However, these plots showed a wide dispersion between these values. It should also be noted that variance in the Framingham score decreased as CCAIMT values increased. When considering different models of regression,

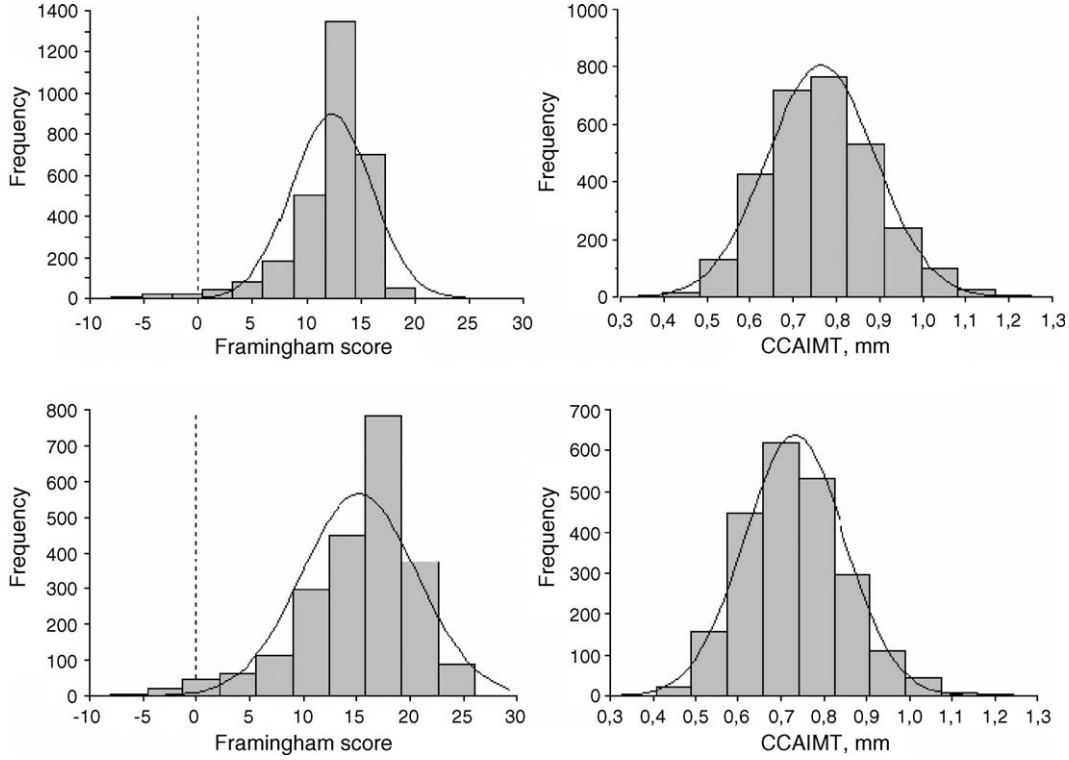

Fig. 1. Statistical distributions of Framingham cardio-vascular scores (left panels) and CCAIMT (right panels) in men (upper panels) and women (lower panels).

Table 2
Association between the components of the Framingham score and CCAIMT ($N = 5199$)

	b (S.E.)	*p*
Age (years)	0.0051 (0.0001)	<0.0001
Male sex	0.0415 (0.0030)	<0.0001
Tobacco use	0.0272 (0.0042)	<0.0001
Total cholesterol (g/l)	0.0123 (0.0035)	0.0005
HDL cholesterol (g/l)	−0.0373 (0.0094)	<0.0001
Systolic BP (mm Hg)	0.0010 (0.0001)	<0.0001
Antihypertensive treatment use	0.0253 (0.0031)	<0.0001

This table shows the linear regression coefficient *b* adjusted on age and gender and its S.E. (between brackets) for each component of the Framingham score and CCAIMT.

it appeared that the best fit for the relationship between the Framingham score and CCAIMT was achieved using a third order polynomial model (Fig. 2). With this model, the R-square value (i.e., that part of the variance explained by the model) was 19% in men and 28% in women. Sensitivity analyses conducted in subjects free of diabetes or cardio-vascular history produced similar results (Table 3).

3.3. Relationship between CCAIMT and the Framingham cardio-vascular score according to age category

As shown in Fig. 3, the Framingham score increased with quartiles of CCAIMT (p for trends <0.001) for each

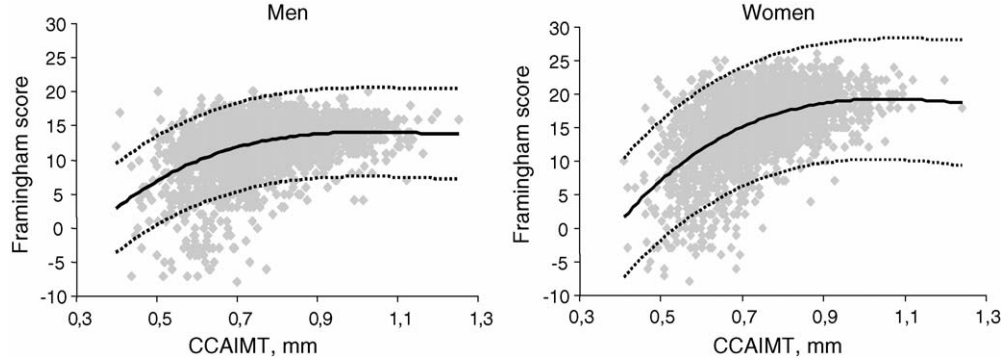

Fig. 2. Plots of Framingham scores vs. CCAIMT in men (left panel) and women (right panel). Regression lines of the third order polynomial model were plotted (solid lines) with 95% CI (dotted lines) for predictive value.

Table 3
Polynomial regression model of order 3 of the Framingham score on CCAIMT by gender

	Men		Women	
	b (S.E.)	*p*	*b* (S.E.)	*p*
Whole population				
CCAIMT	105 (27)	<0.001	152 (43)	<0.001
$CCAIMT^2$	−90 (34)	0.008	−122 (57)	0.031
$CCAIMT^3$	25 (14)	0.076	32 (24)	0.194
	$R^2 = 19\%$		$R^2 = 28\%$	
	$n = 2943$		$n = 2256$	
Subjects free of diabetes				
CCAIMT	96 (29)	0.001	163 (45)	0.003
$CCAIMT^2$	−78 (38)	0.038	−137 (59)	0.020
$CCAIMT^3$	20 (16)	0.209	38 (25)	0.130
	$R^2 = 20\%$		$R^2 = 29\%$	
	$n = 2507$		$n = 2038$	
Subjects free of cardio-vascular history				
CCAIMT	102 (37)	0.005	144 (48)	0.002
$CCAIMT^2$	−85 (48)	0.076	−112 (63)	0.074
$CCAIMT^3$	23 (20)	0.261	27 (27)	0.315
	$R^2 = 20\%$		$R^2 = 29\%$	
	$n = 1877$		$n = 1892$	

b (S.E.) indicates the regression coefficient associated with each polynomial order; *p* the probability associated with the test of each regression coefficient; R^2 is the part of the variance of the Framingham score explained by the model.

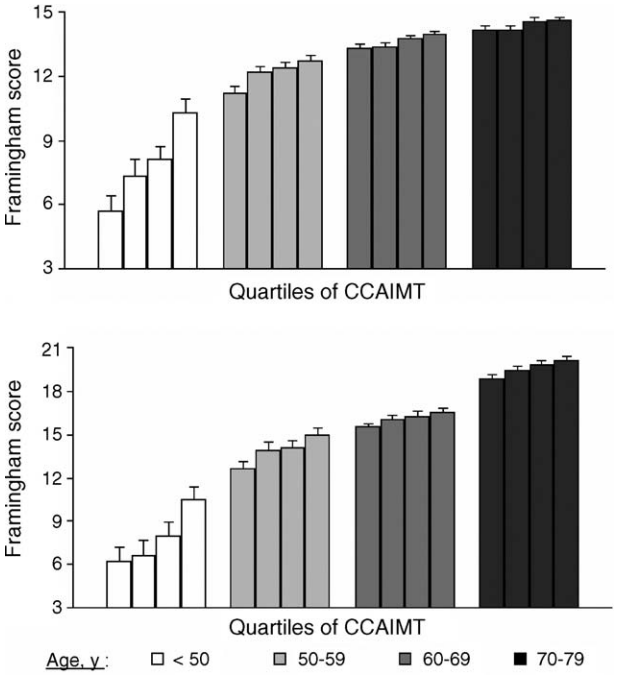

Fig. 3. Means of Framingham scores by each quartile of CCAIMT according to age in men (upper panel) and women (lower panel). Uppers bounds of 95% CI are indicated. Quartiles of CCAIMT were calculated for each age category and each gender.

age–gender strata, with a greater slope for the lowest age group (i.e., below the age of 50 years).

4. Discussion

In this large cross-sectional study of 5199 subjects, we found that the Framingham score and CCAIMT values were significantly correlated. The variances explained by each other were 19% in men and 28% in women. Interestingly, the increase in Framingham scores with quartiles of CCAIMT was more marked in the lowest age group.

NCEP-III guidelines recommend Framingham risk scoring for assessment of the absolute CHD-risk [11]. Although CCAIMT and coronary plaque burden increase with age, rates of accumulation vary greatly from one individual to another. Thus, imputation of the same number of points to all individuals in the same age group does not reflect the reality observed by non-invasive imaging of the carotid or coronary arteries. What is true for large populations is not so for individuals. Since the Framingham score provides only a limited part of the real prediction, additional tools are required to enable a clearer discrimination between subjects at an intermediate cardio-vascular risk in large populations. Currently, the main candidates are CRP levels, the coronary artery calcification (CAC) score and CCAIMT values. In this study, CCAIMT was shown to be a simple, non-invasive test with a low cost and a high level of accuracy, which provided information that was not redundant with the Framingham score.

A cross-sectional study of 1666 individuals free of cardio-vascular disease showed a significant correlation between CRP levels and the 10-year Framingham CHD-risk categories [12]. However, CRP levels correlate only minimally with the components of the Framingham score. In the PARC study, CCAIMT was significantly correlated with each component of the Framingham score (Table 2).

However, longitudinal studies including additive potential indicators of the global cardio-vascular risk and cardio-vascular events as outcomes are required to demonstrate the predictive value of these markers and their possible integration in clinical practice for individual assessments. Links between IMT and coronary heart disease [13] or stroke [14] are well known. The cardio-vascular health study has already shown the specific value of IMT measurements in the prediction of cardio-vascular risk. However, the population in this study was skewed towards healthy elderly subjects aged 65 or over [8] as 1389/5888 subjects with established vascular disease were eliminated from the analysis. In the nested case-control study comprising 374 subjects with either an incident stroke or a myocardial infarction and 1496 controls participants of the Rotterdam study [15]. with a mean follow-up of 4.2 years, the addition of IMT to a risk function for coronary heart disease and cerebrovascular disease did not result in a substantial increase in the predictive value. In that population, the mean age of the populations was 70, and the predictive value was mainly driven by age.

More recently the carotid atherosclerosis prevention study [16] (CAPS) demonstrated in a large population (5096) aged 19–90 (mean age 50.1 years) that IMT at all carotid segments was highly predictive of myocardial infarction, cerebrovascular disease and death. Moreover the HRs per 1 S.D. were considerably higher in the younger group (<50 years old).

By improving population screening methods, IMT measurements could help in selecting and targeting subjects at intermediate risk in primary prevention, thus lowering costs, increasing efficiency and hastening interventional trials.

The PARC study is the first large study to evaluate the correlation between CCAIMT and the Framingham score in a countrywide population with and without risk factors for atherosclerosis. This study has been reproduced in Asia, Latin America and Middle East in PARCAALA [17] and CARMELA [18] Studies with the same methods. It is likely the meta-analysis of these three studies will enable to correlate Framingham risk to a given IMT range in these populations.

Our study has certain strengths and limitations. We used a dedicated methodology to secure the acquisition and collection of ultrasound data in a study involving the largest number of centres ever included in an IMT study. The procedures applied concerned all stages of data collection: (1) centre selection criteria, (2) physician training, (3) centre certification, (4) use of a quality index for B-mode acquisition, and (5) centralized readings. Inter-observer variability in IMT measurements were analysed using an intra-class correlation coefficient in order to define and ensure data reliability [9]. During this study, we were able to evaluate the standard deviation of error measurement $\sigma_{IMT(ERROR)} = 0.0185$ mm [9] reflected the high level of accuracy of the measurements, independently of the standard deviation of the mean CCAIMT value of the population.

As a regular structure delimited by two parallel lines in the validation studies, IMT was evaluated on the common carotid artery in this protocol. The presence of carotid plaque precluded ultrasound examination because the definition and recording of plaque would have required highly experienced sonographers, and ultrasound acquisitions would have been less likely to provide sensitive information in the setting of the 246 centres. In the EVA study, high IMT values were associated with a higher prevalence of plaque at the bifurcation [19]. Diabetes was not assessed in this correlation, because this risk factor identifies a high-risk population, which was not likely to be of help for intermediate risk evaluation. Moreover, diabetes is not a component in the NCEP-III Framingham score table. Our study showed the broad heterogeneity of the Framingham score for each CCAIMT value. This observation was confirmed by the weakness of the explained variance, independently of the statistical model.

This weakness of variance may be partly due to the differences between the components. IMT components include not only modifiable and non-modifiable factors (mainly age and gender-related risk factors) like the Framingham score does, but also genetic, biological and other unknown factors which may play a specific role in different individuals. The possibility cannot be excluded that in addition to the Framingham score and IMT, other markers – such as carotid plaque – may explain part of the risk.

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