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Evaluation of cardiovascular risk profile: a comparative analysis between CUORE algorithm and the Framingham risk scores

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Abstract. – OBJECTIVE: Coronary heart diseases (CHD) are the leading cause of premature death and loss of disability adjusted life years in Europe. In order to implement appropriate health interventions as preventive tools, it is necessary to understand the epidemiological stratification of cardiovascular risk and the specific situation of each individual reality. This study investigates the reliability of two algorithms used to assess cardiovascular risk: the Framingham algorithm and the CUORE algorithm.

PATIENTS AND METHODS: Data specific on patients of General Practitioners working in the Province of Rome were considered, and a total of 996 subjects of both genders were evaluated. The goodness of fit of the regression model was evaluated using the R2 value.

RESULTS: The inferential analysis showed that the R2 value of the simple linear regression between CHD risk calculated according to the CUORE method (dependent variable) and CHD risk calculated according the Framingham method (independent variable), was initially equal to 0.350, and rose to 0.732 when the independent variables "Gender" and "Age" were added, thereby creating a multivariate regression. The R2 of the multivariate regression was 0.478 when using CHD Framingham as the dependent variable and CHD CUORE as the independent variable.

CONCLUSIONS: It emerged that the CUORE score was less reliable than the Framingham risk score; in fact, in the multiple linear regression model, the coefficient of determination was greater when the independent variable was the Framingham scale for CHD risk.

Key Words:
Cardiovascular risk, Framingham score, CUORE score, Algorithm, Prediction, Coronary disease, Primary prevention.

Abbreviations

CHD = Coronary Heart Disease, CVD = Cardio-Vascular Disease, DALY = Daily Adjusted Life Year, FPG = Fasting Plasma Glucose, HDL = High Density Lipoprotein, LDL = Low Density Lipoprotein, *SPSS* = Statistical Package for Social Science, Tot = Total, USA = United States of America, WHO = World Health Organization.

Introduction

Atherosclerotic cardiovascular diseases are the leading cause of premature death and loss of DALYs in Europe. These diseases are closely related to lifestyle habits (especially tobacco use, unhealthy diet, physical inactivity and the psychosocial stress[1]). Lifestyle is in turn responsible for the development of risk factors that predict the occurrence of cardiovascular diseases (hypertension, hypercholesterolemia and other lipid disorders, diabetes mellitus, overweight-obesity, thrombogenic factors[2,3]). The World Health Organization (WHO) stated that over three quarters of total mortality from CVD could be prevented by implementing appropriate lifestyle changes: therefore, a comprehensive national evaluation of cardiovascular risk factors, their control and their lifestyle determinants, are considered fundamental to the launching of realistic prevention programs[4].

In the clinical setting, the relationship between physician and patient cannot ignore information about an individual's cardiovascular risk. In order to adopt specific therapeutic interventions as part of primary prevention, it is useful to have a simple and immediate tool for evaluating an individual's coronary heart disease risk (CHD risk). In the literature, several cardiovascular risk scores can be found that aim to evaluate the probability of developing a cardiovascular event in the future. One such score is the Framingham Risk Score, published in 1998[5]. It is a scoring system used to determine an individual's chance of developing cardiovascular disease. This algorithm was developed based on data from the Framingham Heart Study,

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a long-term, ongoing cardiovascular cohort study on residents of Framingham town, (Massachusetts, USA).

The study began in 1948 with 5209 adults between 30-62 ages and is now on its third generation of participants[6]. The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by monitoring its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke[7]. Over the years, careful monitoring of the Framingham Study population has led to the identification of major CVD risk factors such as - high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity - as well as a great deal of valuable information on the effects of related factors such as blood triglyceride and HDL cholesterol levels, age, gender, and psychosocial issues[7]. On this premise, in 1998 Wilson et al[5] proposed a gender-specific score to evaluate the probability that an individual has of developing cardiovascular disease within 10 years of assessment. The Framingham Risk score has been validated in the USA, both in European Americans and African Americans[8]. After the first Framingham Risk Score, there have been two other versions, published in 2002 and in 2008, respectively[9]. Another score was also created in Italy and published in 2004: CUORE individual score[10]. It was a risk equation that used data from different populations living in the North, Center and South of Italy between the 80s and 90s. The endpoint was the probability of estimating a first event major coronary or cerebrovascular disease within 10-years of assessment. This study aimed to compare the reliability of these two scores used for assessing cardiovascular risk, i.e. the Framingham algorithm and CUORE algorithm, in an Italian population.

Patients and Methods

Setting

Data were pooled on a needs basis, and were selected taking into account a sample of individuals from the general population. The patients were selected from a large database (DATAMeG, Rome, Italy, auth. ec 456/12) containing anonymous clinical records of patients living in the Province of Rome. A total of 996 clinical records were retrieved, regarding patients of both genders, containing all the variables collected within a year.

Variables Examined

In this study, we analyzed the following variables: age, sex, systolic and diastolic blood pressure, hypertension treatment, total cholesterol, LDL cholesterol, HDL cholesterol, diabetes mellitus, smoking habits (as self-reported by the subject). Missing data were unavailable in the above mentioned archive.

Tools to Estimate Cardiovascular Risk

Cardiovascular risk Estimation According to the Framingham risk Score

The Interpretation of risk estimates for CHD requires a precise definition of CHD. The Framingham score, in particular the prediction of total CHD, includes angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency (unstable angina), and CHD deaths.

Based on available data, taken from Millewin archive, we calculated a Score to estimate a 10-year cardiovascular risk in the general population, adopting the mathematical equation reported by Wilson et al[5]. Biochemical and clinical data were converted into points and added together: these determined the total Score, which was then converted into a percentage of projected cardiovascular risk for the successive 10 years (CHD Risk). Age was categorized into 9 classes: ≤ 34, 35 – 39, 40 – 44, 45 – 49, 50 – 54, 55 – 59, 60 – 64, 65 – 69, ≥ 70. Lipemia was categorized into 5 classes and took into account the following cut-offs:

- Total Cholesterol: <160, 160 – 199, 200 – 239, 240 – 279, ≥ 280 mg/dL;
- LDL-C: <100, 100 – 129, 130 – 159, ≥ 160 mg/dL;
- HDL-C: <35, 35 – 44, 45 – 49, 50 – 59, and ≥ 60 mg/dL.

LDL cholesterol values were obtained using the Friedewald equation [LDL (mg / dL) = Tot Cholesterol (mg / dL) - HDL (mg / dL) - Triglycerides (mg / dl) / five] though this is not reliable if the triglycerides are > 400 mg / dL. So, in order to determine the risk of a coronary event within 10 years, we chose to use the score obtained using the total cholesterol values instead of LDL cholesterol values, as reported by Wilson et al[5]. Blood pressure was also categorized into 5 classes:

- Optimal: systolic <120 mm Hg and diastolic <80 mmHg;
- Normal: systolic 120-129 mmHg and diastolic 80-84 mmHg;

- At the higher limits of the standard: systolic 130-139 mmHg and diastolic 85-89 mmHg;
- Hypertension Stage I: systolic 140-159 mmHg and diastolic 90-99 mmHg;
- Hypertension Stage II-IV systolic ≥ 160 or diastolic ≥ 100 mmHg.

When the systolic and diastolic blood pressure fell into different categories, the upper category was selected for classification purposes. The categorization was carried out without considering the use of antihypertensive medications.

As for dichotomous variables "diabetes" and "smoke", the categories were interpreted as follow:

- Diabetes was considered present if the participant was undergoing treatment with insulin or oral hypoglycemic agents or if the FPG was ≥126 mg / dl;
- Smoking habit was considered present or absent on the basis of self-reported information.

The CHD risk score, thus obtained, was interpreted as described by Wilson et al[5]. For example, a score of 5 corresponds to a cardiovascular risk (CHD risk) at ten years of 8% in males and 4% in females. Statistical analysis was performed using the SPSS 23.0 statistical package (SPSS Armonk, NY,USA).

Cardiovascular risk Estimation According to the Cuore Individual Score

The individual cardiovascular risk score according to the CUORE algorithm is applicable to men and women who haven't had a previous cardiovascular event, provided that the risk factors are measured by adopting standardized methodologies. Inserting in the questionnaire proposed by Palmieri et al[10], the variables sex, age, cigarette smoking, systolic blood pressure, total and HDL cholesterol, the presence of diabetes and regular intake of antihypertensive drugs, made it possible to calculate the individual score. The first major coronary event (recognized acute myocardial infarction and CHD deaths), over the next 10 years, was considered as the endpoint[10].

The following mathematical function was used to estimate the probability of a first major cardiovascular event:

$$1 - [S(t)] \text{ ^ } \{EXP [\beta1 \times age + \beta2 \times PAS + \beta3 \times COL + \beta4 \times HDL + \beta5 \text{ (if SMOKER)} + \beta6 \text{ (if DIABETIC)} + \beta7 \text{ (if TREATED with antihypertensive drugs)} - G(\mu)]\}$$

In this function, S(t) is the survival at 10 years evaluated for the average value of the factors; βi are the risk factor coefficients; G(μ) is the linear combination of the mean of the factors or prevalence in each category for the respective coefficients βi[10].

Since the type of antihypertensive treatment potentially taken was not present in our database, two different CUORE risk scores were estimated:

- CHD Risk CUORE0 = 10-year cardiovascular risk estimated by assuming that no one was subjected to antihypertensive treatment.
- CHD Risk CUORE1 = 10-year cardiovascular risk years estimated by assuming that each individual was subjected to antihypertensive treatment.

In this way we obtained two values, the first (CHD Risk CUORE0) underestimates cardiovascular risk, the second (CHD Risk CUORE1) overestimates it. From the average of the two values, we derive a reliable estimate of cardiovascular risk calculated by the CUORE method.

Statistical Analysis

The frequency distributions of the variables of interest were evaluated using measures of central tendency (mean and median) and dispersion (standard deviation, minimum and maximum).

A bivariate analysis was conducted to assess the relationship between both CHD (Framingham and CUORE) risk scores. This was visualized using a scatter plot. The relationship between the two scores, moreover, was evaluated through a linear regression analysis, using univariate and multivariate models. For the latter we introduced age and gender as independent variables.

The goodness of the regression model was evaluated using the R^2 value (square of the correlation coefficient). Statistical analysis was performed using the SPSS 23.0 statistical package (SPSS Armonk, NY, USA). The level of significance was set at $p < 0.05$.

Results

When the Dependent variable was CHD CUORE

The inferential analysis was undertaken using CUORE CHD risk as the dependent variable and Framingham CHD risk as the independent variable, in order to obtain a correlation. Both univariate and then second multivariate analysis were carried out.

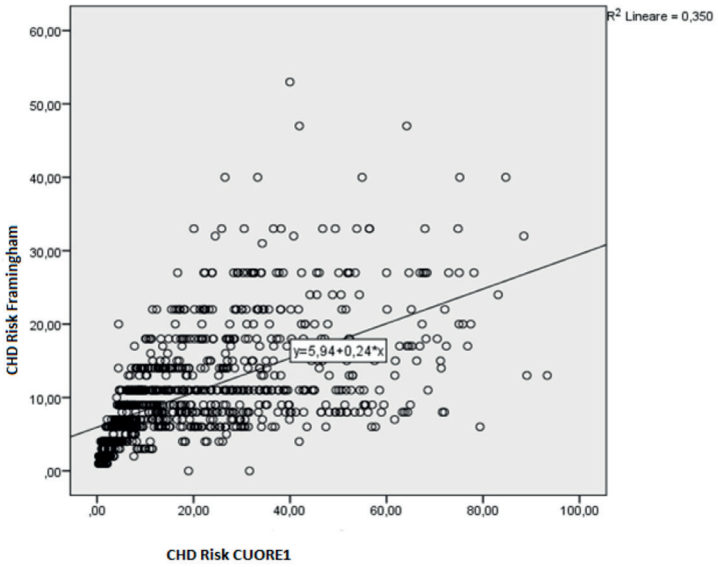

Figure 1. Scatter PLOT, with the regression line, shows pairs of values of the two variables that identify the risk (Framingham and CUORE) of 996 individuals.

Univariate Analysis

The equation for the univariate analysis (Y = a + b1x1) is as follows:

CHD Risk CUORE = 3.744 + 1.485 (CHDRisk Framingham)

The goodness of the model is described by the coefficient of determination $R^2 = 0.350$. The proportion of variance between the two variables, in this model, is low: it emerged that, by comparing the individual scores obtained with the CUORE algorithm and the Framingham risk score, there was poor correlation between the two algorithms (Figure I).

Multivariate Analysis

The equation for the multivariate analysis (Y = a + b1x1 + b2x2 + b3x3) is as follows (Table I):

CHD Risk CUORE = -47,758 + 0822 (CHDRisk Framingham) + 0.884 (age) + 6,122 (gender)

Two independent variables were included in the model: age, multiplied by a coefficient b = 0.884, and gender, multiplied by a coefficient b = 6.122.

The goodness of the model is described by the coefficient of determination $R^2 = 0.732$. The proportion of variance between the two variables, in this model, is much higher than in the previous model. The R^2 value of the multivariate analysis was in fact double that of the univariate analysis.

When the Dependent variable was CHD risk (Framingham)

We operated a second inferential analysis of setting representing the general population, using the Framingham CHD risk as the independent variable and CHD Risk CUORE as the dependent variable. Even in this case two analyses were carried out, an initial univariate followed by a second multivariate.

Univariate Analysis

The equation for the univariate analysis (Y = a + b1x1) is as follows:

Framingham CHD Risk = 5.943 + 0.236 (CHDRisk CUORE)

The goodness of the model is described by the coefficient of determination $R^2 = 0.350$. The proportion of variance between the two variables, in this model, is obviously equal to that emerged from the univariate analysis previously exposed by reversing the two variables (dependent and independent). It is, therefore, low.

Multivariate Analysis

The equation for the multivariate analysis (Y = a + b1x1 + b2x2 + b3x3) is as follows (Table I):

Framingham CHD Risk = 13.636 + 0.278 (CHDRisk CUORE) + (-0.072 * age) + (-6.985 * gender)

Two independent variables were included in the model: age, multiplied by a coefficient b = -0.072, and gender, multiplied by a coefficient b = -6.985.

The goodness of the model is described by the coefficient of determination $R^2 = 0.478$. The proportion of variance between the two variables, in this model, is slightly higher than in the previous model. The R^2 of the multivariate analysis was slightly greater than the R^2 of the univariate analysis.

Discussion

The aim of the study was to assess the reliability of scores used to estimate cardiovascular risk, and to study which explanatory variables significantly improve the goodness of fit in the multiple regression models. This method has already been used in several studies in order to evaluate the trustworthiness of assessment tools[11-13] and it can be considered a good way of obtaining an estimate of relative reliability between two or more analogous scoring systems[14]. This analysis showed that the coefficient of determination in a univariate regression (with CUORE CHD risk as the dependent variable and Framingham CHD risk as the independent variable) was $R^2 = 0.350$. The concrete meaning of this result is that there is a difference in reliability between the two scores analyzed. In fact, the linear regression (used to describe the relationship between the two scores) is a statistical model of poor goodness, and consequently this relationship is weak. The relative discrepancy between the two classifications, since the indication about the adoption of which one was not coded, poses the risk of causing a significant clinical issue relative to behavioral, diagnostic and treatment strategies that the physician must define for the patient. This can leave him/her rather disoriented about which is the best tool to use. However, it is historically established that for the correct adoption of prevention strategies it is necessary to have previously obtained a correct interpretation of the individual cardiovascular health status of each patient[15,16], with particular attention to the evaluation of those subjects considered at "high risk" (defined by the US National Cholesterol Education Program (NCEP) guidelines as individuals having a 10-year absolute risk for CHD events of ≥ 20%, on the basis of the presence of various risk factors[17]). However, unambiguous indication about which is the best algorithm to use for obtaining a valid and coherent estimate of individual cardiovascular risk is still unavailable[18]. Even if there is some evidence of effectiveness of new cardiovascular risk factors[19], and the availability of new techniques, such as modalities of ultrasound-based intima-media thickness, arterial stiffness and non-coronary vascular calcifications detection to assess cardiovascular risk[20], the use of traditional cardiovascular risk factors[21] and related algorithms is fundamental for an easy and reliable assessment of both individual and populations risks. Basing treatment decisions on predetermined levels of a risk score potentially replace arbitrary decisions with transparency, consistency and potential for audit. It may maximize the efficient use of limited resources and imply fairness in ensuring equitable distribution. Determining by score, those whose condition warrants treatment eliminate many possible sources of bias[15]. The inferential analysis in this study also showed that the coefficient of determination is more than doubled if the independent variables "Gender" and "Age" are added to the analysis, thereby creating a multivariate analysis. In this way, R^2 was 0.732. Conversely, in a multiple linear regression considering the Framingham CHD risk as the de-

Table I. Values of the coefficients for the inferential analysis.

Independent Variables	Dependent variable	
	CUORE B* (p)	Framingham B* (p)
Age	0.884 (< 0.001)	-0.072 (0.006)
Gender Female	6.122 (p< 0.001)	-6.985 (<0.001)
CHD risk	0.822 (< 0.001)**	0.278 (<0.001)***
Constant	-47.758	13.636
Goodness of fit – R2	0.732	0.478

* non standardized coefficients; **Framingham CHD risk; *** CUORE CHD risk.

pendent variable and the CUORE CHD risk as independent variables, and by adding age and gender, R^2 is 0.478. This suggests that the CUORE score is less reliable than the Framingham score; in fact, in the multiple linear regression model, the coefficient of determination was higher when the independent variable was the Framingham CHD risk and lower when the independent variable was the CUORE CHD risk.

Conclusions

Considering the increased reliability of the Framingham algorithm, it is, therefore, advisable to use this latter one, to estimate a 10-year cardiovascular risk for a patient, and even more so when the appropriate biochemical and clinical parameters are available.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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