

Comparison of Coronary Risk Estimates Derived Using the Framingham and REGICOR Equations

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Introduction and objectives. To compare two equations for evaluating coronary risk, the Framingham-Wilson equation and the Framingham equation adjusted for the Spanish population (REGICOR), in a group of dyslipidemic patients in our healthcare area. In addition, the therapeutic implications of using the 2 methods were also evaluated.

Patients and method. The study included 815 dyslipidemic patients, aged 35-74 years, from our healthcare area. Coronary risk was determined using the 2 equations and subjects were categorized as either low-risk (0%-9%), moderate-risk (10%-19%), or high-risk ($\geq 20\%$). To compare the application of the 2 equations, we evaluated differences in derived scores, coronary risk category, and the number of patients regarded as potentially treatable with hypolipidemic drugs.

Results. The best correlation observed between the 2 methods was for quantitative scores ($r=0.983$; $P<.001$). The correlation was poorer when coronary risk categories were compared ($r=0.489$; $P<.001$). Overall, the concordance was poor ($\kappa=0.06$), and was only acceptable for low-risk patients ($\kappa=0.53$). The coronary risk estimates derived from the Wilson table were 2.4 times higher than those obtained using REGICOR. The main differences were for moderate and high-risk patients. In addition, the number of patients regarded as potentially treatable with hypolipidemic drugs was five times higher when the Wilson equation was used.

Conclusions. The overestimate of coronary risk obtained using the Framingham-Wilson equation leads to a greater number of patients being regarded as candidates for hypolipidemic treatment. Our data show the importance of using tables adjusted for the Spanish population.

Key words: *Coronary risk. Coronary risk equations. Hypolipidemic treatment.*

Ecuación de Framingham de Wilson y ecuación de REGICOR. Estudio comparativo

Introducción y objetivos. Comparar dos ecuaciones de valoración del riesgo coronario (RC), Framingham de Wilson y REGICOR, en una muestra poblacional de sujetos dislipémicos de nuestra área sanitaria. Valorar las posibles repercusiones terapéuticas derivadas de las mediciones obtenidas por ambos métodos.

Pacientes y método. La muestra poblacional estaba constituida por 815 pacientes dislipémicos de 35-74 años. Se determinó el RC mediante ambas ecuaciones y se compararon las puntuaciones obtenidas, la clasificación en las categorías de RC a los 10 años y el número de sujetos potencialmente tratables con medicación hipolipemiente en función de los resultados obtenidos con ambas escalas.

Resultados. Se observó una óptima correlación entre ambas mediciones al tener en cuenta los valores cuantitativos ($r = 0,983$; $p < 0,001$), aunque ésta disminuyó al valorar los resultados por categorías de RC ($p = 0,489$; $p < 0,001$). La concordancia fue mala en su conjunto ($\kappa = 0,06$) y sólo fue aceptable en el grupo de riesgo bajo ($\kappa = 0,53$). La tabla de Wilson proporcionó unos valores de RC global 2,4 veces superiores a los obtenidos con la calibración de REGICOR, y las diferencias se presentaron principalmente en las categorías de RC moderado y alto. El número de candidatos a ser tratados con hipolipemiantes fue 5 veces superior según la ecuación de Wilson que con la de REGICOR.

Conclusiones. La sobrevaloración que se obtiene al calcular el RC mediante la función de Framingham implica un mayor porcentaje de pacientes potencialmente tratables con fármacos hipolipemiantes. Este hecho apoya la necesidad de disponer de tablas de RC ajustadas para nuestra población.

Palabras clave: *Riesgo cardiovascular. Ecuaciones de riesgo cardiovascular. Tratamiento hipolipemiente.*

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ABBREVIATIONS

YLGAQ: years of life gained adjusted for quality.
 HDL-cholesterol: high density lipoprotein cholesterol.
 CVRF: cardiovascular risk factors.
 DBP: diastolic blood pressure.
 SBP: systolic blood pressure.
 REGICOR: Gerona Heart Register.

INTRODUCTION

Cardiovascular diseases are associated with high morbidity and mortality.¹ In Spain, ischemic heart disease is the foremost cause of death in men and the third most important in women. Two thirds of all people who die of acute myocardial infarction do so before they reach a hospital.² However, some of these deaths could be avoided if preventive measures were taken to reduce the incidence of ischemic heart disease—a goal that might be better attained by trying to reduce the *overall coronary disease risk* than by acting against each cardiovascular risk factor (CVRF) in an isolated fashion.^{3,4} To this end, the overall coronary disease risk—the probability of suffering a coronary event in a certain period of time—is calculated using equations that evaluate the different CVRF in an associative fashion.⁵⁻⁷ Currently, the most commonly used equation is the Framingham-Wilson function, which estimates the risk of coronary disease over a period of 10 years.⁵ Although this equation allows coronary disease risk to be adequately calculated in most populations, it tends to overestimate it in some,^{6,8,9} mainly those in which the incidence of and mortality rate for coronary heart disease are low.⁶⁻⁸ For these populations, as indeed the authors of this equation^{5,6} and the European guidelines for the prevention of coronary heart disease³ point out, the function must be calibrated using specific population data.

In Spain, the number of coronary events observed for the level of exposure to CVRF is lower than expected,^{10,11} and the mortality rate for coronary heart disease is one of the lowest in the world¹²⁻¹⁴—a situation known as the Spanish paradox.

A number of efforts have been made to adapt the different types of equation used in the calculation of coronary disease risk for use with different populations.^{2,7} In this respect, the researchers involved in the REGICOR (*Registre Gironí del Cor*: the Gerona Heart Register) and Framingham studies calibrated the Framingham-Wilson⁵ equation bearing in mind the local prevalence of CVRF and the incidence of coronary events recorded in the REGICOR study.^{7,14} This study

compares the coronary disease risk ratings obtained with the Framingham-Wilson and Framingham-REGICOR equations for a sample of the population of our health district.

PATIENTS AND METHODS

The subjects selected for this descriptive, cross-sectional study were all 35-74 years old; of 5404 potential subjects in this required age range, 815 were eligible for final inclusion (15%). All subjects came to our center for blood tests and to have their blood pressure taken between January 1 and December 31, 2002; all were diagnosed with dyslipidemia (total cholesterol >200 mg/dL).¹⁵ Data was gathered from our center's computer database. The following variables were recorded for all subjects: age, sex, total cholesterol levels, high density lipoprotein cholesterol (HDL-cholesterol), diastolic blood pressure (DBP), systolic blood pressure (SBP) (both blood pressure readings were the mean of 2 consecutive readings), use of tobacco (according to the World Health Organization),¹⁶ and the presence of diabetes mellitus (according to the criteria of the American Diabetes Association).¹⁷ The most recent values for all variables were used in analyses.

Since it is unnecessary to perform cardiac risk calculations for patients with clinical symptoms of atherosclerosis,¹⁸⁻²¹ patients who came for consultation with any of the following conditions (according to the International Classification of Primary Care [ICAP])²² were excluded from the study: angina (K74), acute myocardial infarction (K75), other chronic ischemic diseases of the heart (K76), transitory cerebral ischemia (K89), cerebrovascular accident/apoplexy (K90), atherosclerosis other than cardiac or cerebral (K91), or other obstructive arterial or vascular diseases (K92). Patients who celebrated their 35th or 75th birthdays during the study period were also excluded, as were any for whom data were lacking.

The cardiac risk evaluation equations compared were the Framingham-Wilson equation and the same equation calibrated for the Spanish population using REGICOR study data^{5,7} (the Framingham-REGICOR equation). Both methods measure coronary disease risk as the probability of presenting with a fatal or non-fatal myocardial infarction or any type of angina within the next 10 years. The subjects were divided into the 3 risk categories (based on intention to treat) usually used in Spain²⁰: low (0%-9%), moderate (10%-19%), and high risk of coronary heart disease ($\geq 20\%$). Following the recommendations in the literature,³ coronary disease risk was calculated using the true age of the patient (no projections for age 60 years were made).

Means and standard deviation (SD) were calculated for the different variables recorded. Means were com-

pared using the Student *t* test. The χ^2 test was used to compare the number of subjects in the different coronary disease risk categories and the proportions of patients who were potentially treatable. The correlation between the 2 studied methods was determined by calculating the Pearson correlation coefficient for continuous quantitative variables, and the Spearman Rho coefficient for categorical variables. The agreement between the classifications of coronary disease risk determined by the 2 methods was evaluated by calculating the Cohen Kappa index.²³ All calculations were performed using SPSS v.10.0 software.

RESULTS

The study population (n=815) was composed of 56.1% women and 43.9% men. In total, 16.4% had diabetes mellitus and 22.3% were smokers. With respect to tobacco use, a significant difference was seen between the sexes: 39.1% of men were smokers compared to 9.2% of women ($P<.0001$). Table 1 shows the means for age, total cholesterol levels, HDL-cholesterol levels, SBP, and DBP.

According to the Framingham-Wilson equation (Figure), 55.8% of subjects had a low risk of coronary disease, 29.8% had a moderate risk, and 14.4% had a high risk. These results were significantly different to those obtained with the Framingham-REGICOR equation, which gave figures of 92%, 7.4%, and 0.6%, respectively ($P<.05$). The Pearson correlation coefficient for the scores obtained with the two methods was 0.983 ($P<.001$), indicating a very strong, positive and practically linear relationship between the 2 equations (each score obtained with the Framingham-Wilson function corresponding to a lower Framingham-REGICOR score). However, when the resulting stratifications of coronary disease risk (low, moderate, and high) were taken into account, the degree of correlation diminished significantly (Spearman Rho coefficient 0.489; $P<.001$). The same was seen for both sexes separately and combined.

The Kappa index for the agreement between the 2 methods was 0.06 (95% CI, 0.04-0.08). The value obtained for this index depends strongly on the number

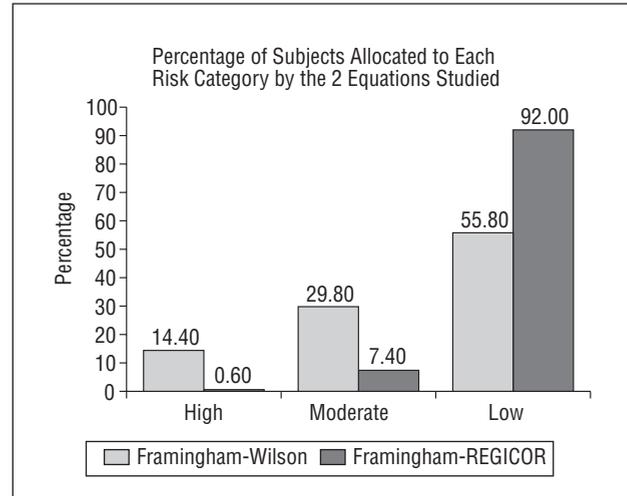


Figure. Risk stratifications obtained with the 2 study equations.

of categories employed, and tends to become smaller as it increases. Therefore, when there are more than 2 categories, it is a good idea to compare the coronary risk for each of them with the sum of all the others (specific agreement).²³ The Kappa index between both methods with respect to the classification of low risk was 0.53 (95% CI, 0.49-0.57); this value shows that agreement between the 2 methods was moderate. For the moderate and high risk groups, however, the indices were -0.12 (95% CI, -0.22 to -0.02) and 0.07 (95% CI, -0.11 to 0.25) respectively.

A significant difference was found between the means of the absolute values for coronary disease risk as determined by the 2 methods ($P<.001$). The mean value provided by the Framingham-Wilson equation was 11.36 ± 8.45 while that of the Framingham-REGICOR equation was 4.78 ± 3.2 . When the risk of coronary disease was stratified, the difference between the two equations was not uniformly distributed, but mainly affected the moderate and high risk groups. All patients classified at low risk by the Framingham-Wilson equation were also classified as such by the Framingham-REGICOR equation, but only 60% of those classified at low risk by the Framingham-REGICOR equa-

TABLE 1. Patient Characteristics*

| Variable | Women | Men | Total |
|--|--------------------|--------------------|--------------------|
| Age, years (mean \pm SD) | 55.33 \pm 12 | 54.56 \pm 11.55 | 54.86 \pm 1.90 |
| Total cholesterol, mg/dL (mean \pm SD) | 234.86 \pm 36.73 | 226.38 \pm 41.85 | 231.13 \pm 39.26 |
| HDL-cholesterol, mg/dL (mean \pm SD) | 67.85 \pm 17.13 | 57.65 \pm 14.99 | 63.37 \pm 16.99 |
| DBP, mm Hg (mean \pm SD) | 77.36 \pm 8.72 | 79.38 \pm 9 | 78.25 \pm 8.91 |
| SBP, mm Hg (mean \pm SD) | 133.29 \pm 15.57 | 132.60 \pm 14.5 | 132.99 \pm 15.1 |
| Diabetes, n (%) | 65 (14.2) | 69 (19.3) | 134 (16.4) |
| Smokers, n (%) | 42 (9.2) | 140 (39.1) | 182 (22.3) |

*SD indicates standard deviation; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2. Pharmacologically Treatable Patients (semFYC)

| According to the Framingham-REGICOR Equation | According to the Framingham-Wilson Equation | | |
|--|---|--------------|--------------|
| | Yes | No | Total |
| Yes | 36 (4.42%) | 146 (17.91%) | 182 (22.33%) |
| No | 0 (0%) | 633 (76.67%) | 633 (76.67%) |
| Total | 36 (4.42%) | 779 (95.58%) | 815 (100%) |

tion were thus classified by the Framingham-Wilson equation. All patients classified as being at moderate risk by the Framingham-Wilson equation were classed as being at low risk by the Framingham-REGICOR equation. Finally, the Framingham-Wilson equation classified 117 patients (14.4%) as being at high risk, while the Framingham-REGICOR equation found only 5 (0.6%). The remaining patients were classified by the latter method as being at moderate (n=60) or low risk (n=52) ($P<.001$). This great variability in the categories determined by the two methods agrees with that expressed by the Kappa index (Figure).

Finally, taking into account the factors indicating the reduction of lipidemia published by the semFYC dyslipidemia group²⁴ (according to which all patients with a high risk of coronary heart disease, plus those with a moderate risk who also have diabetes, should be treated pharmacologically in the primary prevention setting if they do not respond to non-pharmacological treatment), only 36 of the present patients (4.42%) would require treatment as indicated by their Framingham-REGICOR classification, whereas 182 (22.33%) would require treatment as indicated by their Framingham-Wilson classification ($P<.001$; Table 2).

DISCUSSION

The Framingham-Wilson and Framingham-REGICOR equations correlate perfectly in terms of absolute coronary disease risk. This is to be expected since the Framingham-REGICOR equation is based on the Framingham-Wilson equation but takes into account the CVRF prevalence and coronary event data of the REGICOR study.⁷ Because of this calibration, the Framingham-REGICOR^{7,14} equation gives lower cardiac disease risk values than the Framingham-Wilson equation for the same patients. Thus, the Framingham-Wilson equation overestimates the risk of coronary heart disease in the Spanish population; too many people are placed in moderate and high risk categories, and this translates into a larger number of people being treated.^{24,25} Among the present subjects, 37.2% descended to a lower risk category when the Framingham-REGICOR equation was used, and 6.4% actually

descended 2 categories. The practical implications of these results are important. The Framingham-Wilson equation doubles the overall risk rating for coronary heart disease compared to the Framingham-REGICOR equation for the same CVRF (comparison of absolute means), and multiplies by 5 the number of patients treated if the semFYC lipid group recommendations are followed (these state that pharmacological treatment should be given to patients at high risk of developing coronary heart disease, i.e., those with $\geq 20\%$ risk of developing this within 10 years according to the Framingham-Wilson equation).²⁴

The use of the Framingham-REGICOR equation could lead to a reduction in the pharmacological treatment of men and its almost complete disappearance in women. However, this does not seem acceptable since hypercholesterolemia on its own is an important risk factor in Spain.²⁶ In addition, despite the fact that few women are usually included in clinical trials, a recent meta-analysis has shown a reduction in coronary events among women receiving primary prevention treatment (at least when the ALLHAT study is excluded),²⁷ especially among diabetic women.²⁸

The Framingham-REGICOR equation shows the need to establish a new threshold for the high risk category of coronary heart disease in the Spanish population, as do the results of clinical trials showing reduction in the number of coronary events in patients in lower risk categories receiving primary prevention treatment (15.2% in the WOSCOPS study,²⁹ 5%-8% in the AFCAPS study,³⁰ 9% in the ASCOT study,³¹ and 11.6% in the CARDS study).²⁸ The use of the "20% in 10 years" level as the threshold for considering a patient at high risk of coronary heart disease is relatively arbitrary and based on cost-effectiveness. In fact, not all dyslipidemia guides use this threshold; a range of 15% to 30% is seen.^{3,18,20,21,32} In addition, the overall number of patients treated at each center also depends on whether pharmacological treatment is regarded as indicated for patients at moderate or even low risk.¹⁸ It should also be remembered that cost-effectiveness studies have their limitations. Though some evaluate the cost of treatment with respect to reductions in lipid parameters,³³ it would seem much more robust to express the cost per year of life gained adjusted for quality (YLGAQ).³⁴

It is thought that pharmacological treatment has a good cost-effect relationship in patients in secondary prevention but that in primary prevention this is only true in certain patients. Nonetheless, the range for the cost of YLGAQ is greater in primary than in secondary prevention, and does not depend on the patient's risk of coronary disease alone, but also on age, the efficiency and especially the cost of the drug used. In a recent study in which it was considered that the figure of \$60 000 per YLGAQ at 35 years of age showed good cost-effectiveness, a risk threshold of as low as 4.8% in 10 years for men, and of 4% in women, was considered acceptable.³⁵

A limitation of the present study is the inclusion of patients who were probably undergoing pharmacological treatment with either anti-hypertension or blood lipid reducing agents. This implies that the calculation of coronary disease risk for these patients is biased and that lower risk values were obtained. However, since each patient was his/her own control (i.e., their data were processed by both equations) the overall comparison does not suffer. Had there been no patients already undergoing treatment, it is likely that both equations would have indicated more patients should begin therapy.

Caution should be exercised when extending the validity of the Framingham-REGICOR equation to other areas of Spain since the incidence of ischemic heart disease differs from one region to another, as shown by the IBERICA (*Investigación y Búsqueda Específica y Registro de Isquemia Coronaria Aguda*—Acute Coronary Ischemia Research and Specific Search Registry)¹² study. Further, any new calibration should be validated by collecting data from representative samples of new populations in a prospective fashion. With the aim of solving some of these problems, the REGICOR team undertook a prospective verification study with the participation of multiple patient cohorts from around the country.

Since the incidence of angina and silent acute myocardial infarction in the population of Gerona is unknown, the authors of the Framingham-REGICOR equation used the Framingham values. This probably confers a conservative nature upon this new equation since it is unlikely that the true values for Gerona are higher than those for the American city of Framingham. In any event, it is important to remember that medicine is still (at least in part) an art, and that the use of coronary disease risk equations and the recommendations accompanying them should be considered only an aid when making decisions on treatment.

CONCLUSION

The coronary disease risk results obtained with the Framingham-Wilson equation can lead to the overuse of pharmacological treatment. The correct use of the calibrated Framingham-REGICOR equation, along with a reconsideration of the risk threshold above which treatment should begin in primary prevention, could be of great use in determining the correct course of clinical action.

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